The FIGO Textbook of

Pregnancy Hypertension

An evidence-based guide to monitoring, prevention and management

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Edited by

Laura A. Magee MD, FRCPC, FACP,
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Incorporating the key findings of the PRE-EMPT global studies

With Forewords by the President of FIGO
and by the Immediate Past President of FIGO

Published by
The Global Library of Women's Medicine

Dedicated to the memory of ***Sabrina Dwan*** *– and with gratitude to the* ***Sabrina's Foundation*** *for the financial support generously provided to assist in the publication of this book*

Published by
The Global Library of Women's Medicine
9 Provost Court
London NW3 4SR

ISBN: 978-0-9927545-5-6

This book is published on a not-for-profit basis and is also available at www.glowm.com

Typeset by AMA DataSet Ltd, Preston, UK
Printed in the UK by CPI Group (UK), Croydon CR0 4YY, UK

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Abbreviations

ABPM	ambulatory blood pressure monitoring
ACE inhibitor	angiotensin converting enzyme inhibitor
ACOG	American College of Obstetricians and Gynecologists
ACR	albumin : creatinine ratio
AFI	amniotic fluid index
AFLP	acute fatty liver of pregnancy
ANC	antenatal care
AOM	Association of Ontario Midwives
APTT	activated partial thromboplastin time
ARB	angiotensin receptor blocker
AST	aspartate transaminase
BEmONC	basic emergency obstetric and neonatal care
BID	twice daily dosing
BMI	body mass index
BP	blood pressure
BPP	biophysical profile
CBC	complete blood count
CEmONC	comprehensive emergency obstetric and neonatal care
cGMP	cyclic guanosine monophosphate
CO	carbon monoxide
CPG	clinical practice guideline
CSE	combined spinal–epidural analgesia
CVP	central venous pressure
DASH	dietary approaches to stop hypertension
dBP	diastolic blood pressure
DIC	disseminated intravascular coagulation
EmONC	emergency obstetric and neonatal care
eNOS	endothelial nitric oxide synthase
GDM	gestational diabetes mellitus
GH	gestational hypertension
GMP	guanosine monophosphate
GRADE	grades of recommendation, assessment, development and evaluation
GSNO	S-nitrosoglutathione
GTP	guanosine triphosphate
HDL	high-density lipoprotein
HDP	hypertensive disorder of pregnancy
HELLP syndrome	haemolysis, elevated liver enzymes and low platelets syndrome
HIC	high-income country
HR	heart rate
IM	intramuscular
INR	international normalised ratio
IOL	induction of labour

ISSHP	International Society for the Study of Hypertension in Pregnancy
IUGR	intrauterine fetal growth restriction
IV	intravenous
LDH	lactate dehydrogenase
LDL	low-density liporotein
LMICs	low- and middle-income countries
LMP	last menstrual period
MEOWS	modified early obstetric warning systems
MRI	magnetic resonance imaging
NICE	National Institute for Health and Clinical Excellence
NICU	neonatal intensive care unit
NO	nitric oxide
NSAIDs	non-steroidal anti-inflammatory drugs
NST	non-stress test
NVOG	National Obstetrics and Gynaecology Society, The Netherlands
PCA	patient-controlled labour analgesia
PDE5	phosphodiesterase-5
PET	pre-eclampsia
PLGF	placental growth factor
PO	per os – by mouth
pRBCs	packed red blood cells
PrCr	protein : creatinine ratio
PRECOG	pre-eclampsia community guideline
PRES	posterior reversible leukoencephalopathy syndrome
QID	four times daily dosing
QLD	Queensland Maternity and Neonatal Clinical Guidelines Program
RCT	randomised controlled trial
RDA	recommended daily allowance
sFlt-1	soluble fms-like tyrosine kinase-1
sBP	systolic blood pressure
sEng	soluble endoglin
SFH	symphysis–fundal height
SGA	small for gestational age
sGC	soluble guanylate cyclase
SOGC	Society of Obstetricians and Gynaecologists of Canada
TID	three times daily dosing
TTE	transthoracic echocardiography
UNFPA	United Nations Population Fund
US	United States
VEGF	vascular endothelial growth factor
WHO	World Health Organization

Foreword by the Immediate Past President of FIGO

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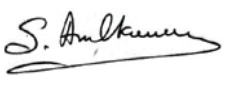
Hypertension in pregnancy is a major contributor to maternal and perinatal mortality and morbidity. Every year 70,000 women die and there are half a million stillbirths or neonatal deaths owing to hypertensive disorders of pregnancy – the vast majority being in the developing world. Those who survive, especially those who had preterm pre-eclampsia, face the issues of hypertensive, cerebro- and cardiovascular events in the future resulting in premature deaths. The International Federation of Gynecology and Obstetrics (FIGO) have responded to this important issue by commissioning *The FIGO Textbook of Pregnancy Hypertension*. It provides an evidence-based guide to monitoring, prevention and management of this common disease that affects 5–10% of pregnant women.

Our sincere gratitude to the editors Laura Magee, Peter von Dadelszen, William Stones and Matthews Mathai – as well as to the international team of authors all of whom have first-hand clinical experience of this condition; together they have produced a book that should be immensely useful to health care personnel whatever the setting they work in. The main section of the book consists of a clinical review that covers the knowledge needed to provide the best care for women. It deals with hypertension; measurement of proteinuria; classification of hypertensive disorders; epidemiology; risk factors; diet, lifestyle and care; fluids, drugs and transfusion; timing and mode of delivery; anaesthesia; and immediate postpartum and long-term management. This is a complete review of the subject and it incorporates the important findings from the global PRE-EMPT studies. Section 2 is devoted to the appendices and provides extensive, additional information.

This monograph on pregnancy hypertension endorsed by FIGO should be available to all health care personnel caring for pregnant mothers globally. We are grateful for the kind generosity of Paula and David Bloomer, for making this useful resource available free of charge to everyone including women, health care personnel, advocates and administrators through the free web resource – *The Global Library of Women's Medicine* (www.glowm.com), which acts as the Official Educational Platform for FIGO. I am sure this book will help to reduce the maternal and perinatal mortality and morbidity.

Yours truly,



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May 2016

Foreword by the President of FIGO

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The International Federation of Gynecology and Obstetrics (FIGO) has a longstanding commitment to initiatives devoted to the improvement of maternal morbidity and mortality – fortunately in recent years there has been some improvement in their incidence but much more urgently needs to be done. The quality of care provided to pregnant women in different locations still varies markedly and far too many women's lives are still lost that might have been saved if their carers had been better informed and better trained, which explains why effective knowledge transfer of current best practice is so important.

FIGO has placed a very high priority on improving education and training in maternal medicine and that is why I am particularly pleased to welcome this new *FIGO Textbook of Pregnancy Hypertension – an evidence-based guide to monitoring, prevention and management*. It is a landmark volume that provides a definitive clinical guide to the diagnosis and management of pre-eclampsia, one of the principal, worldwide, causes of maternal mortality. Pre-eclampsia is a condition that often seems symptomless in its earliest stages but which can develop in a surprisingly rapid, complex and life-threatening manner if not diagnosed promptly and treated appropriately.

What makes this volume particularly important is that it incorporates many of the key findings of the PRE-EMPT global studies – a major, 7-year, multicountry programme led by Professor Peter von Dadelszen to investigate pre-eclampsia and the most effective methods of managing it both in the community and in tertiary care settings. This book draws on the studies as well as on wider research plus the best practice protocols produced by a number of leading authorities to produce a guide that is clear, specific and immediately practical. I would like to thank all the editors and authors for the work that they have undertaken to produce such a valuable aid to clinical practice and I welcome its timely and well-presented publication.

C. N. Purandare
President of FIGO
May 2016

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Introduction

LA Magee, P von Dadelszen, W Stones, M Mathai

Hypertensive disorders complicate 5–10% of pregnancies worldwide, with limited data suggesting an upward trend in incidence most likely related to increasing maternal weight and sedentary lifestyle (Chapter 4). With few differences, all international societies define the hypertensive disorders of pregnancy as chronic hypertension, gestational hypertension and pre-eclampsia (Chapter 3). Although women with pre-eclampsia have the greatest risk of maternal and perinatal complications, what constitutes pre-eclampsia is controversial, and diagnostic distinctions are often blurred. As such, it is important to view all women with a hypertensive disorder of pregnancy and their babies as being at increased risk of mortality and morbidity, and act accordingly.

Pre-eclampsia remains one of the top five causes of maternal and perinatal mortality worldwide. Our best estimate is that pre-eclampsia claims the lives of more than 70,000 women per year and more than 500,000 of their fetuses and newborns; this is equivalent to the loss of 1600 lives per day[1]. More than 99% of these losses occur in low- and middle-income countries (LMICs), particularly those on the Indian subcontinent and sub-Saharan Africa[2]. For every woman who dies, it is estimated that another 20 suffer a life-altering morbidity[3,4].

Given that maternal (and perinatal) deaths and sequelae result primarily from delays in triage, transport and treatment, it would seem important for the global community to turn its attention to community-based care[1]. A community-focused approach could include community engagement and use of innovative technologies, like smartphone applications could be used to support community-based health workers. In addition, however, care at facility must be of high quality in order for outcomes to be improved, a point that has been highlighted by the move towards encouraging more facility births and concerns about the quality of care received there. In the World Health Organization Multicountry Survey on Maternal and Newborn Health (WHOMCS) that covered 357 health facilities in 29 countries, high coverage of essential interventions was not associated with reduced maternal mortality[5]. As such, attention must also be focused on strengthening provision of evidence-based comprehensive emergency obstetric care (CEmOC)[6], conducting maternal death and near-miss morbidity surveillance and response (www.who.int/mdsr), and performing large-scale effectiveness evaluations, with the district as the unit of design and analysis and the clear message that there is local ownership, by women, communities, care providers and government[7].

Knowledge is power, and the impact that evidence-based knowledge can have on practice and policy is highlighted by the WHO IMPAC (Integrated Management of Pregnancy and Childbirth) guidance documents (2000) (www.who.int/preadolescence/topics/maternal/impac/en/). These were among the first WHO documents to recommend $MgSO_4$ for eclampsia prevention and treatment. The information was adopted in national guidelines in many African and Asian countries, and formed the core of EmOC training packages, as well as led to policy changes in countries on use of $MgSO_4$ as reflected in national medicines lists.

In the 1980s, it was noted that the dramatic decline in maternal mortality over the prior 50 years in Britain was related to the standard of maternity care, even in the face of ongoing social deprivation:

> "In obstetrics the difference between a careful doctor (or midwife) and a careless one can be very large indeed. The introduction, therefore, of an ordinary standard of good obstetric practice, not necessarily at the level of the hospital specialist, can be expected to have a profoundly beneficial effect in societies that still suffer high maternal mortality."
>
> Irvine Loudon, British Med J 1986[8]

The purpose of this book is to promote evidence-based maternity care for all women, regardless of where they live. This text covers all clinical aspects of hypertensive disorder of pregnancy diagnosis and management of women in both well- and under-resourced settings. Each chapter begins with a synopsis of the material, followed by a summary of the evidence. Best practice points are designed to provide practical advice; the evidence on which the recommendations are based, and the strength of each recommendation, is presented in appendix tables for readers interested in more detail. There is specific discussion of priorities for under-resourced settings, what international guidelines say, and logical future directions. Each chapter includes material in the appendices, ranging from the evidence grading for recommendations (mentioned above) to internal guideline recommendations and policy brief templates (e.g., Chapters 1 and 2) and practice drills (Chapter 8).

Chapters 1 and 2 address the diagnosis of hypertension and proteinuria, the two most common diagnostic criteria for pre-eclampsia and the only ones for which there is international agreement.

The diagnosis of hypertension is based on systolic and diastolic blood pressure values, taken in any setting by auscultatory or oscillometric (automated) devices. In LMICs, the assessment of service gaps and programmatic responses to ensure access to blood pressure measurement are a priority, supported where appropriate by implementation research.

Increasingly, it is recognised that proteinuria is not essential for the diagnosis of pre-eclampsia, which can be based on other end-organ complications (such as elevated liver enzymes). Although heavy proteinuria has been linked with an increased risk of stillbirth in a 'signs and symptoms only' model of maternal risk (i.e., miniPIERS), we lack the ability to identify a level of proteinuria above which maternal and/or perinatal risk is heightened. Therefore, at present, we rely on the detection of proteinuria that exceeds what is normally excreted by healthy pregnant women. Proteinuria detection methods are also a matter of keen debate, with all available methods having advantages and disadvantages.

Chapter 3 presents the classification of the hypertensive disorders of pregnancy, relating categories directly to maternal and perinatal complications and recommendations for surveillance. In addition to the universal categories of pre-existing (chronic) hypertension, gestational hypertension and pre-eclampsia, other categories of white coat and masked hypertension are also discussed. Of note, there is tremendous controversy over whether the term 'severe' pre-eclampsia should be used and, if so, how it should be defined. We endorse the 2014 Canadian approach of defining 'severe' pre-eclampsia according to the presence of severe complications that mandate delivery so timing of delivery is clear to those with less experience with the disease[9].

The distinction between identification of women at increased risk of pre-eclampsia (Chapter 5) and the identification of women at increased risk of complications once a hypertensive disorder of pregnancy has been diagnosed (Chapter 3) is an important one. The potential for accurate prediction of pre-eclampsia lies in multivariable models, with the most promising predictors being the angiogenic factors and uterine artery Doppler velocimetry combined with other biochemical factors. There is an urgent need to evaluate how new diagnostic and risk-stratifying biomarkers can be incorporated into existing protocols and to improve both prediction of pre-eclampsia itself among women who are well, as well as the prediction of complications among women who already have pre-eclampsia. Having these biomarkers available as point-of-care tests in all clinical settings would be the ultimate goal.

Preventative strategies for pre-eclampsia and its complications are based on risk (Chapter 6). Women are classified as being at 'low' or 'increased' risk of pre-eclampsia most commonly by the presence or absence of one or more of the risk markers discussed in Chapter 5. There is strong evidence that low risk women who have low dietary intake of calcium (<600 mg/d) may benefit from calcium supplementation (of at least 1 g/d, orally) to prevent pre-eclampsia. High risk women are recommended to take calcium supplementation (of at least 1 g/d) if calcium intake is low, and are also recommended to initiate low-dose aspirin (75–100 mg/d) at bedtime before 16 weeks' gestation, when most of the physiologic transformation of uterine spiral arteries occurs, or even before pregnancy; such early intervention has the greatest potential to decrease the early forms of

pre-eclampsia that are associated with incomplete transformation of uterine spiral arteries. Widespread implementation of these interventions is recommended to help prevent pre-eclampsia and its complications.

The management of hypertensive disorders of pregnancy involves non-pharmacological (Chapter 7) as well as drug, blood product and fluid administration (Chapter 8).

Although widespread, use of lifestyle (e.g., stress reduction, increased rest at home, or bed rest) to manage women with pre-eclampsia is based on a lack of high quality evidence, as are dietary interventions (e.g., salt reduction). There is also little information about the relative benefits and risks of place of care if delivery is deferred. In under-resourced settings, addressing a lack of safe and available transport from community to facility has enormous potential to address maternal and perinatal mortality and morbidity. Also, communities have a critical role to play in ensuring that women and their families are prepared for birth and any complications that may arise, from the hypertensive disorders of pregnancy or other conditions that may arise.

Women with pre-existing or gestational hypertension are at risk of any of the hypertensive disorders of pregnancy evolving into pre-eclampsia, a multisystem disorder of endothelial dysfunction. As such, attention must be paid to judicious fluid management, antihypertensive therapy of severe and non-severe hypertension with oral or parenteral agents, magnesium sulphate ($MgSO_4$) for eclampsia prevention and treatment as well as fetal neuroprotection with birth at <34 weeks, antenatal corticosteroids for acceleration of fetal pulmonary maturity, and various therapies for HELLP syndrome (haemolysis, elevated liver enzyme, low platelet), including transfusion of blood products and, possibly, corticosteroids. The WHO Model List of Essential Medicines includes all of the aforementioned interventions other than fluid therapy for pregnant women. We must advocate for use of effective interventions whether we practice in well- or under-resourced settings.

The phrase, "planned childbirth on the best day in the best way," alludes to the fact that there is a myriad of considerations regarding timing (and mode of) childbirth in women with a hypertensive disorder of pregnancy, particularly pre-eclampsia (Chapter 9). Complicating this decision-making is inaccurate determination of gestational age, difficulty identifying those women who are at particular risk of an adverse outcome if pregnancy is prolonged, and the fact that 'severe' pre-eclampsia has been variably defined by international organisations and, yet, all list 'severe' pre-eclampsia as an indication for delivery. Regardless, the past decade has seen publication of a significant body of work that informs our decisions about timing of delivery in women with a hypertensive disorder of pregnancy, particularly pre-eclampsia. Childbirth is recommended for women with pre-eclampsia or gestational hypertension at term for maternal benefit, although expectant care is recommended for women with any hypertensive disorder of pregnancy at late preterm gestational ages to reduce neonatal respiratory morbidity (associated with labour induction and Caesarean delivery). Small trials suggest that expectant care of women with pre-eclampsia from fetal viability to 33^{+6} weeks reduces neonatal morbidity, but the magnitude of maternal risk has not been fully quantified. There are no trials to inform timing of delivery determination of women with chronic hypertension, but observational literature suggests that the optimal period is between 38^{+0} and 39^{+6} weeks.

Mode of delivery is usually determined by usual obstetric indications (Chapter 9). However, if there is evidence of fetal compromise at a gestational age remote from term, women with a hypertensive disorder of pregnancy may benefit from delivery by Caesarean. It is particularly important for women with a hypertensive disorder of pregnancy to have the third stage of labour actively managed, particularly in the presence of thrombocytopoenia or coagulopathy. Ergometrine maleate should not be administered to women with any hypertensive disorder of pregnancy given its potential to precipitate severe hypertension.

No text on a common and dangerous pregnancy-related complication would be complete without discussion of the anaesthetic issues. Chapter 10 presents a focused discussion of anaesthetic issues specifically related to parturients with a hypertensive disorder of pregnancy. Early consultation and involvement of anaesthesia will result in the best possible outcome for these women and their babies. Provision of effective analagesia for labour will not only decrease pain, but also attenuate its effects on blood pressure and cardiac output. In addition,

epidural analgesia benefits the fetus by decreasing maternal respiratory alkalosis, compensatory metabolic acidosis and release of catecholamines. An effective labour epidural can be used should a Caesarean delivery be required, avoiding the need for general anaesthesia. Both neuraxial (epidural, spinal, continuous spinal and combined spinal epidural) and general anaesthesia are appropriate for Caesarean delivery. The choice of technique will depend on the overall condition of the parturient, the urgency of the situation, and whether there are contraindications to any particular technique. Challenges associated with anaesthesia include maintaining haemodynamic stability during laryngoscopy and intubation with general anaesthesia, or after sympathetic block secondary to neuraxial anaesthesia. Although neuraxial anaesthesia is preferred to general anaesthesia, owing to potential problems with the airway in the woman with pre-eclampsia, neuraxial anaesthesia may not be possible in the presence of a low platelet count or other coagulation abnormality. The interaction of non-depolarising muscle relaxants (as part of general anaesthesia) and $MgSO_4$ will limit their use in the woman with pre-eclampsia. Adequate analgesia and ongoing monitoring are important components of overall postpartum management.

Chapter 11 emphasises the importance of postpartum care, to prevent short-term complications, as well as initiating thoughts about the implications for future pregnancy and long-term health in an evolving circle of life (below). In the immediate postpartum period, hypertension may worsen transiently, especially between days 3 and 6 when blood pressure peaks. Hypertension and pre-eclampsia may even develop for the first time postpartum. Hypertension, proteinuria and the biochemical changes of pre-eclampsia begin to resolve by 6 weeks postpartum but may persist for longer, especially when those changes have been extreme (e.g., nephrotic-range proteinuria). Care in the 6 weeks postpartum includes management of hypertension, ensuring resolution of biochemical changes, and screening for secondary causes of hypertension in women with resistant hypertension, impaired renal function, or abnormal urinalysis. Care providers must be aware of the mental health implications of the hypertensive disorders of pregnancy, such as anxiety, depression and post-traumatic stress disorder. The hypertensive disorders of pregnancy are also associated with a number of long-term complications and the postpartum period provides an ideal window of opportunity to address these risks, such as premature cardiovascular disease and chronic kidney disease. Women with a history of a hypertensive disorder of pregnancy should adopt a heart-healthy lifestyle and should be screened and treated for traditional cardiovascular risk factors according to locally accepted guidelines.

It is hoped that this text will play a role in promoting high-quality, evidence-based care of women with the hypertensive disorders of pregnancy, because none should die or become seriously ill owing to their own ignorance or that of their care providers.

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1

Hypertension

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SYNOPSIS

Defining hypertension in pregnancy is challenging because blood pressure levels in pregnancy are dynamic, having a circadian rhythm and also changing with advancing gestational age. The accepted definition is a sustained systolic (sBP) of ≥140 mmHg or a sustained diastolic blood pressure (dBP) ≥90 mmHg, by office (or in-hospital) measurement.

Measurement of blood pressure in pregnancy should follow standardised methods, as outside pregnancy. Blood pressure measurement may occur in three types of settings, which will dictate in part, which measurement device(s) will be used. The settings are (1) health care facility; and two types of settings outside the facility: (2) 'ambulatory' blood pressure measurement (ABPM); and (3) home blood pressure measurement (HBPM). Furthermore, blood pressure can be measured using auscultatory (mercury or aneroid devices) or automated methods.

Factors to consider when selecting a blood pressure measurement device include validation, disease specificity, observer error and the need for regular recalibration. The accuracy of a device is repeatedly compared to two calibrated mercury sphygmomanometers (the gold standard), by trained observers, over a range of blood pressures and for women with different hypertensive disorders of pregnancy; only a few devices have been validated among women with pre-eclampsia.

This chapter discusses the advantages and/or disadvantages of the various settings and devices.

Low- and middle-income countries (LMICs) bear a disproportionate burden of maternal morbidity and mortality from the hypertensive disorders of pregnancy. While regular blood pressure monitoring can cost-effectively reduce this disparity, LMIC-health systems face unique challenges that reduce this capacity. Assessment of service gaps and programmatic responses to ensure access to blood pressure measurement are a priority, supported where appropriate by implementation research.

DEFINING HYPERTENSION

Defining what represents hypertension in pregnancy is complicated by the fact that blood pressure levels in pregnancy are even more dynamic than they are in non-pregnant women. Blood pressure levels in pregnancy vary according to gestational age, and the circadian rhythm in women with a hypertensive disorder of pregnancy may differ by more than in normotensive pregnant women and non-pregnant women.

Outside pregnancy, both sBP and dBP peak in the afternoon and drop in the evening and during the night. However, this pattern tends to be blunted in women with gestational hypertension and pre-eclampsia among whom it tends to peak in the evening and overnight[1,2]. Proposed theories to explain this include a compensatory mechanism to maintain organ blood flow during sleep in response to ischaemia, or a disturbance in hypothalamic pituitary adrenal periodicity and in sympathetic nervous system activity[3].

Blood pressure tends to reach its nadir during pregnancy just before or at 20 weeks' gestation, with some variation by parity. In nulliparous women, sBP reaches its nadir at 17 weeks, and dBP at 19 weeks. These troughs in blood pressure are slightly later in multiparous women – 18 weeks for sBP and 20 weeks for dBP[4].

KEY POINT

Hypertension in pregnancy is a sustained sBP ≥140 mmHg or dBP ≥90 mmHg by office (or in hospital) measurement

Hypertension is defined according to systolic and diastolic criteria, with either needing to be sustained (i.e., present on repeat measurement): sBP ≥140 mmHg or a dBP ≥90 mmHg. A dBP of 90 mmHg represents a level that is both: (1) two standard deviations above values at any point in normal pregnancy, and (2) associated with increased perinatal morbidity in non-proteinuric hypertension. Systolic blood pressure is included in the definition, recognising that it is more susceptible to environmental influences and an inferior predictor of adverse pregnancy outcomes than is dBP[5–7]. Furthermore, a focus on sBP is appropriate given that inadequate treatment of severe systolic hypertension has been recognised as a major failing in the care of women who died with pre-eclampsia[8]. A conservative diagnostic approach is particularly important where ANC follow-up may be less reliable, as illustrated by the following quote:

> "If they feel there is any fluctuations or rise in blood pressure, immediately they should refer to the primary health center or directly refer to the gynecologist . . . then the initial proper treatment can be started to the hypertension with the help of the gynecologist then they can continue treatment until delivery."
>
> Health Administrator, Bagalkot, India

On average, obese women have higher blood pressure in each trimester compared with those who are not obese, even when an appropriately sized cuff is used. The difference is about 10 mmHg for sBP and 8 mmHg for dBP[4].

The importance of repeat measurement

It is important to remember that blood pressure, whether systolic or diastolic, must be confirmed to be elevated on repeat measurement before the woman can be considered to be hypertensive to reduce the potential for misdiagnosis based on a spurious reading or the patient's anxiety during the consultation. The first auscultatory measurement should be discarded (as the first is *in lieu* of taking blood pressure by palpation), and two additional measurements should be taken and averaged to get the blood pressure for that visit. Ideally, repeat measurement should be at least 15 minutes apart at that visit.

Up to 30–70% of women with an office blood pressure of ≥140/90 mmHg are found to have normal blood pressure on subsequent measurements on the same visit, or after serial measurement by ABPM (i.e., serial measurements by a portable recording device over 24 hours) or HBPM (i.e., measuring the blood pressure at home)[5,9–12]. Whether the woman is reassessed in hours, days, or weeks will depend on the level of the blood pressure and the underlying hypertensive disorder of pregnancy diagnosed or suspected, as the elevated office blood pressure may be owing to a situational rise, the 'white coat' effect, or early manifestations of pre-eclampsia[13,14].

Severe hypertension

Severe pregnancy hypertension is defined as sBP ≥160 mmHg or a dBP ≥110 mmHg. The systolic value was reduced from 170 mmHg by most international societies after recognition that a sBP ≥160 mmHg is associated with an increased risk of stroke in pregnancy[15,16].

KEY POINT

Severe hypertension in pregnancy is a sustained sBP ≥160 mmHg or dBP ≥110 mmHg

What is not included in the definition of pregnancy hypertension

A relative rise in blood pressure of 30 mmHg in sBP or 15 mmHg in dBP is *not* part of the definition of a hypertensive disorder of pregnancy, given that it is within the variation seen in all trimesters of pregnancy, and there is a high false positive rate if it is taken as a diagnostic criterion for pre-eclampsia[17].

Mean arterial pressure (MAP) is not part of the definition of hypertension in pregnancy as there are no clinical studies that relate MAP levels to risk and outcomes.

Blood pressure measurements taken in the community

Outside pregnancy, a widely accepted threshold for normal (daytime) ABPM or HBPM is <135/85 mmHg[18]. As such, a diagnosis of hypertension in pregnancy is *consistent with* a daytime ABPM or average HBPM of sBP ≥135 mmHg and/or dBP ≥85 mmHg[19,20].

KEY POINT

A diagnosis of hypertension in pregnancy in a community setting is consistent with a daytime ABPM or average HBPM of sBP ≥135 or dBP ≥85 mmHg

It is recommended that given issues with automated blood pressure machines in pregnancy and/or self-monitoring techniques, that elevated values outside the office be confirmed in the office/clinic setting. (These issues are discussed in detail under blood pressure measurement devices and HBPM sections, below.)

There can be discordance between blood pressure values taken in the office/clinic compared with those taken in the community. When the discordance cannot be attributed to the blood pressure machine and/or the measurement technique, two patterns of discordance are widely recognised. 'White coat' effect is defined as an elevated blood pressure in the health facility (i.e., ≥140/90 mmHg), but a normal measurement in the community (i.e., average daytime ABPM or average HBPM values <135/85 mmHg). 'Masked' hypertension is defined as a normal blood pressure in the health facility (i.e., <140/90 mmHg), but an elevated measurement in the community (i.e., average daytime ABPM or average HBPM values ≥135/85 mmHg). Outside pregnancy, it is widely recognised that patients with 'white coat' effect are at lower, but not baseline, risk of adverse cardiovascular outcomes related to hypertension (such as cardiac or renal disease)[21–28]. Also, patients with 'masked' hypertension (i.e., normal office blood pressure but elevated ABPM) are at similar cardiovascular risk to patients who are hypertensive in both the facility and community settings[29,30]. Both 'white coat' effect and 'masked' hypertension are discussed in detail, along with the implications for pregnancy outcome, in Chapter 3.

BLOOD PRESSURE MEASUREMENT TECHNIQUE

Blood pressure measurement in pregnancy should follow the same standardised technique as outside pregnancy[18,31,32] and the 'Best Practice Points' below for recommendations specific to pregnant women. In brief, the following steps should be taken:

1. The woman must be **positioned** appropriately: seated, still, and with her legs uncrossed, feet flat on the floor, and her back resting on the back of the chair. Women should be in the sitting position that gives a blood pressure reading that reflects the true value; supine positioning has the potential to cause hypotension, and left lateral positioning has the potential to give a spuriously low reading, because the right arm is frequently elevated above the level of the heart during blood pressure measurement[33].
2. The woman **should not talk, read, look at her phone/computer, or watch television**.
3. The woman's **arm should be resting at the level of her heart**. This may require use of a pillow.
4. The woman should **rest for 5 minutes** before her blood pressure is taken.
5. The **blood pressure cuff should be placed on the woman's bare upper arm**, and not over clothing.
6. The **blood pressure cuff must be the right size**. It must be long enough and wide enough. The length should cover two-thirds of the distance between her shoulder and elbow; the bottom should end up about 1–2 cm above the elbow. The width must be such that the

inflatable part of the blood pressure cuff should go around about 80% of the woman's upper arm where the blood pressure is being measured. If the cuff is too small (e.g., a 22–32 cm cuff used on a 35 cm circumference arm), it will overestimate sBP by 7–13 mmHg and dBP by 5–10 mmHg.

7. The blood pressure should be measured using **appropriate technique for the machine in use**.
   a. Use of **auscultatory techniques** requires a stethoscope and special training. Blood pressure is taken at least three times, with the first measurement discarded as it is the range-finding measurement; the second and third measurements are taken one minute apart and the average is the measurement for that visit. Korotkoff phase V (marked by the disappearance of Korotkoff sounds) should be used for designation of dBP; compared to phase IV (marked by muffling of Korotkoff sounds); identification of phase V is more reliable[34] than that of phase IV and pregnancy outcomes are similar when either is used[35]. Korotkoff phase IV should be used for dBP only if Korotkoff sounds are audible as the dBP level approach 0 mmHg.
   b. Use of **automated devices** requires the operator to follow the manufacturer's instructions carefully. Two measurements are taken 1 minute apart and the average is the measurement for that visit.

Blood pressure measurement devices

Blood pressure can be measured using auscultatory devices (mercury, aneroid, or liquid-crystal sphygmomanometer) or automated methods. Mercury devices have largely been removed from clinical areas owing to safety concerns. Table 1.1 outlines the advantages and disadvantages of auscultatory and automated methods[36].

Auscultatory methods

Auscultatory methods are used primarily in the health facility (i.e., office/clinic or hospital) setting (with health care personnel trained to use stethoscopes), as discussed below.

Aneroid devices appear to give more variable blood pressure readings; one study found that 50% of aneroid devices had at least one reading that was more than 10 mmHg different from others, compared with only 10% of mercury devices[37].

The liquid-crystal device is a hybrid sphygmomanometer developed as an alternative to mercury; in an initial study in pregnancy, this hybrid device appears to be accurate and may be a reasonable alternative to mercury sphygmomanometry (or an automated device)[38].

Table 1.1 Blood pressure measurement methods[36]

	Auscultatory methods	*Automated**
Method	Observer uses a stethoscope and a mercury, aneroid, or crystal device to directly identify Korotkoff sounds reflecting sBP and dBP	Oscillometric: proprietary algorithms use maximal oscillations during cuff inflation or deflation to *estimate* sBP and dBP Ultrasonographic: ultrasound transducer uses Doppler principles to estimate sBP and dBP
Advantages	Uniformly available in all clinical settings	Widely available for purchase at reasonable prices Avoids observer bias
Disadvantages	Observer bias and observer error related to external noise or auditory acuity	Sensitive to physical movement
Comments	Mercury devices have been removed from most clinical settings Aneroid devices require recalibration every 2 years	Require validation in pregnancy and pre-eclampsia specifically Most devices used in ABPM or HBPM are oscillometric

ABPM, ambulatory blood pressure monitoring; dBP, diastolic blood pressure; HBPM, home blood pressure monitoring; sBP, systolic blood pressure

* List of validated automated blood pressure devices is available at http://www.bhsoc.org/default.stm

Automated devices

Automated machines may be used in the office/clinic, community, or home settings, as discussed below. A comprehensive list of automated devices approved for HBPM can be found at http://www.dableducational.org and http://www.bhsoc.org/default.stm.

When choosing an automated blood pressure measurement device, considerations include validation, disease specificity, observer error (largely eliminated with automated devices), and the need for regular recalibration. A key issue is that ideally, women who are pregnant or postpartum should use devices that are accurate for use in both pregnancy and pre-eclampsia. First, detection of pre-eclampsia is a major objective of all antenatal care as maternal and perinatal complications are focused in this group of women. Second, women with chronic or gestational hypertension are at increased risk of pre-eclampsia[39–49]; women with pre-existing hypertension have an approximately 20% risk of pre-eclampsia[39–43], and women with gestational hypertension have a risk as high as 35% if they present with gestational hypertension prior to 34 weeks[44–49]. Unfortunately in practice, there may be no pregnancy and pre-eclampsia approved device available locally in well- or under-resourced settings, making calibration a particularly important concept to understand (see below).

The accuracy of a device is repeatedly compared with two calibrated mercury sphygmomanometers (the gold standard), by trained observers, over a range of blood pressures and for women with different hypertensive disorders of pregnancy. This must be done for pregnant women compared with non-pregnant subjects, as well as specifically for women with pre-eclampsia. Pre-eclampsia is associated with decreased vessel wall compliance and increased interstitial oedema that can lead to under-reading of blood pressure by the algorithm used by any given automated device; on average, the under-reading is by 5 mmHg in systolic and diastolic, although there is wide variation[50]. A device that is accurate for measurement of blood pressure in a healthy pregnant woman may be inaccurate in a woman with pre-eclampsia.

Although automated blood pressure measurement devices will eliminate some observer error, only some devices have been validated in pregnancy[51–53] and in pre-eclampsia, specifically[54,55]. It should be noted that in a randomised controlled trial of 220 hypertensive pregnant women, approximately 20% of whom had pre-eclampsia, management using a mercury sphygmomanometer or a validated automated electronic blood pressure device (Omron HEM-705CP) was associated with similar maternal and fetal outcomes[1]. If anything, severe hypertension was more common in the group that had blood pressure measured by the automated device, possibly related to a reduction in observer error associated with use of an automated device.

Recalibration involves comparing readings from an aneroid or automated blood pressure machine with those taken with a mercury manometer. As most mercury manometers have been removed from clinical settings around the world, most clinics will have available to them only aneroid devices. Aneroid devices require the most frequent calibration in comparison with automated devices[56]. As the devices that women use will be compared with the clinic aneroid device in many settings, it is critical to understand that aneroid devices must be recalibrated every 2 years against mercury devices, usually by the hospital biomedical department; this must be arranged separately by practitioners with private offices. In under-resourced settings, procurement processes will need to be strengthened to specify devices that are amenable to calibration and adjustment, together with a means of tracking device maintenance within health facilities over months and years of use.

Blood pressure measurement settings

The settings will drive (in part) the choice of blood pressure measurement devices, as discussed above[19]. Table 1.2 outlines which devices are used in which settings.

Health facility blood pressure measurement

Health facility blood pressure measurement is usually undertaken by a physician, nurse, or other trained health care provider in an office, clinic, or hospital setting. It involves use of any of the aforementioned blood pressure measurement devices, although most clinics and hospitals use aneroid or automated devices. The potential for 'white coat' effect is reduced when multiple readings are taken, using proper technique (see

Table 1.2 Blood pressure measurement devices used in various settings

	Mercury or liquid-crystal sphygmomanometer	*Aneroid device*	*Automated device*
Office/clinic/hospital	✓	✓	✓
Out-of-office			
Community			
Obstetric day unit	✓	✓	✓
24 hour ABPM	–	–	✓
Home	–	–	✓

ABPM, ambulatory blood pressure monitoring

'Blood pressure measurements taken in the community', above), and by either trained non-physician health care providers or using a fully automated machine that takes multiple readings[57–59].

The fact that health facility blood pressure measurements may also be falsely normal in the approximately 10% of patients with 'masked' hypertension[60] underscores the need for community-measurement, by either ABPM or HBPM.

Ambulatory blood pressure measurement

ABPM is a process by which blood pressure readings are obtained either in a community setting (serially over a 24 hour period using an automated measuring device) or by serial blood pressure measurements in an obstetric or maternal health ambulatory care setting. This could be in a specialised day unit where women can be monitored over several hours without facility admission, or a formal programme in which health care workers visit women in their homes.

ABPM has the advantage of reducing errors associated with clinic measurements[61]. Also, ABPM in the community provides a more comprehensive, actual blood pressure profile of a patient's blood pressure during daily activities and at night during sleep during which women with pre-eclampsia may have a diminished decrease in their blood pressure or an actual rise[36]. The addition of ABPM to health facility measurements may be of particular value when women have non-severe hypertension in the office or other facility setting and pre-eclampsia is not suspected, particularly if office blood pressure values are fluctuating.

Pregnant women with elevated office blood pressure measurements but normal ABPM (i.e., 'white coat' effect) are at lower risk of adverse maternal and perinatal complications such as severe hypertension, preterm delivery and admission to neonatal intensive care[9,49,54,62,63]. However, studies have demonstrated that ABPM has only modest predictive value for adverse outcomes such as severe hypertension, preterm delivery and admission to the NICU[9,19,49,63]. Therefore, the service priority is to assure comprehensive conventional measurement of blood pressure in pregnancy during clinical encounters.

Home blood pressure measurement

HBPM is undertaken by the woman in a home environment using an automated blood pressure device. Several proposed monitoring schedules have been recommended. All involve duplicate measurements taken at least twice daily over several monitoring days[18,64]. When HBPM values are normal but health facility blood pressure is elevated, repeated HBPM (or ABPM) are recommended outside pregnancy[18].

Regardless of the brand of automated device used by the woman, or the chosen system of measurement (ABPM or HBPM), the woman should be educated about the appropriate blood pressure monitoring procedures and interpretation

of the values recorded, including when and whom to call about blood pressure values of concern.

Which is best – ambulatory blood pressure measurement or home blood pressure measurement?

In the past two decades, both ABPM and HBPM have gained popularity in confirming diagnosis and improving blood pressure monitoring, compliance with antihypertensive medication, and achievement of blood pressure targets[27]. Evidence from cross-sectional studies shows that HBPM and ABPM have modest diagnostic agreement[65] and they are similar in identifying patients with 'white coat' effect and 'masked' hypertension. However, HBPM offers some advantages. HBPM is economical, comfortable, engages the patient and is easy to repeat when disease evolution is suspected, a particularly important issue in pregnancy[66]. Also, pregnant women and practitioners prefer HBPM to ABPM[67]; a Canadian survey on the practices surrounding the use of ABPM by maternity care providers to diagnose hypertension and to rule out the 'white coat' effect indicated that the majority preferred to use HBPM, while only a minority used ABPM[68]. ABPM is less comfortable; up to 15% of patients enrolled in ABPM may discontinue the process because of discomfort[69]. There is an important cautionary note about HBPM, however; HBPM values have not been validated against adverse pregnancy outcomes, and, to date, no randomised trial has assessed the impact of either HBPM or ABPM on maternal or perinatal outcomes[17].

Literature from outside pregnancy suggests that addition of ABPM or HBPM to office/clinic measurements is cost-effective[19,70]. However, further implementation research will be needed in pregnant women before we can be confident that the favourable outcomes seen outside pregnancy can be generalised to pregnancy.

UNDER-RESOURCED SETTINGS

Regular blood pressure monitoring is an essential, cost-effective intervention for early identification and management of the hypertensive disorders of pregnancy[71]. Regular blood pressure monitoring may reduce the burden of maternal morbidity and mortality from the hypertensive disorders of pregnancy that disproportionately affect women in LMICs[72–75]. The obvious priority is the availability of functioning equipment to measure blood pressure. Additional challenges to address include a lack of good quality antenatal care, inadequate staffing of health facilities, and gaps in health care worker competency.

Availability of equipment in good repair

A service challenge in many LMIC health facilities, including maternity wards, is poorly functioning or absent equipment that prevents health care workers from taking blood pressure measurements (or those that are accurate) and acting on the results[71,76,77]. For example, the Malawi Demographic Health Survey (DHS) reports that only 64% of health centres offering ANC services were equipped with blood pressure measurement apparatus[78]. The following quotes serve to further highlight this from the perspectives of both health care workers and women:

> "You must make equipment available, like the sphygmomanometer, just ordinary sphyg . . . is not available until a patient just throws a fit that you know that the problem is high. So, making sure simple, simple, things that can save life are available, like I said sometimes, the sphygmomanometer to monitor blood pressure . . ."
>
> Focus Group Discussion participant from SOGON (Society of Gynaecology & Obstetrics of Nigeria (SOGON)

> "Even sometimes you find out that in a health center that there is no appropriate instrument to take blood pressure. You get to a primary health centre and find out that there is nothing."
>
> Focus Group Discussion participant from SOGON (Society of Gynaecology & Obstetrics of Nigeria (SOGON)

There are several novel technologies that may improve access to accurate blood pressure measurement at community and health facility levels[80,81,83–87]:

1. *A semi-automated blood pressure device and vital signs early warning tool*[83–85] This device is unique for many reasons, most importantly because it is one of a few to be accurate in

pregnancy and pre-eclampsia, and it is the only device known to be accurate at the low blood pressure values seen commonly in pregnancy. The 'traffic light' early warning system alerts untrained health care workers to the need for urgent intervention and referral of women with hypertension or shock (secondary to obstetric haemorrhage or sepsis), even if the vital sign thresholds are not well understood by that health care worker. In addition, the device achieves the criteria stipulated by WHO for use of automated devices in low-resource settings. These features include the following: (a) reliance on manual inflation (deflating automatically), limiting the power requirements; (b) use of sealed lithium batteries that are charged through a micro-USB port, a method that is ubiquitous even in low-resource settings; and (c) the low cost of only $19 USD. The device is being evaluated at both community- and institutional-levels in a number of LMIC sites; qualitative evaluation to date of both trained and untrained health care users has been overwhelmingly positive. A randomised controlled trial is underway to assess the ability of the device to reduce maternal mortality and morbidity in under-resourced settings.

2. *An interface connecting blood pressure devices to mobile smartphone and tablet technology*[86] This technology is currently under development. An audio-based interface allows for blood pressure readings (amongst other vital signs) to be automatically recorded for tracking and trending. Furthermore, there is potential for further transmission of advice from a central facility to minimally trained health care workers based on the blood pressure values.
3. *A solar panel-powdered blood pressure device*[87] A semi-automated blood pressure device designed for under-resourced settings charges using a solar panel and fulfills other WHO criteria for use of devices in LMICs. Furthermore, qualitative evaluation has demonstrated acceptability by non-physician health care workers. Although the device has been validated as accurate for use in a non-pregnant population, it has not been validated for use in pregnancy, and so cannot be used in a pregnant population at the current time.

In summary, the current priority is the procurement, distribution and maintenance of standard blood pressure apparatus of robust manufacture that can withstand heavy use. Innovative blood pressure measurement devices for low-resource settings have great potential to reduce maternal mortality from pre-eclampsia and eclampsia in LMICs. With an emphasis on task-sharing, blood pressure measurement devices must not rely on knowledge of proper auscultation with a stethoscope in order that more workers can use the devices correctly (Figure 1.1). Investments will be needed to realise the potential of these technologies[88], particularly if a focus is placed on implementation in the community[89].

Quality antenatal care

The provision of good quality ANC is an evidence-based intervention that reduces maternal and neonatal mortality and morbidity, particularly in LMICs[90,91]. The quality of ANC is measured by three dimensions: number of visits, timing of initiation of care, and inclusion of all recommended components of care[90].

Number of antenatal care visits

Compared to a country's defined standard care, attending a reduced number of antenatal visits is associated with an increase in perinatal mortality[92]. Globally, only 64% of pregnant women receive the

Figure 1.1 Taking blood pressure in the primary health centre with an automated device

recommended minimum of four ANC visits in pregnancy[93]. A disproportionate number of these women reside in LMICs, such as rural Nigeria where only 39% of pregnant women were found to attend four or more ANC visits[94]. However, this pattern of fewer than recommended ANC visits has also been reported in inner city women in high-income countries[95].

KEY POINT

WHO recommends that the first ANC visit be within the first 4 months of pregnancy

Timing of initiation of care

Despite WHO recommendations to start ANC within the first 4 months of pregnancy, on a global scale, many women start ANC in the second or third trimester[96]. This is a particular issue in sub-Saharan Africa[96], such as in Tanzania where the median month of first visit for ANC was 5.5 months[97]. However, unsatisfactory patterns of care are also reported by other developing countries, such as Cambodia where the Cambodian Demographic Health Survey found that 30% of women who received ANC started that care in the second trimester[98].

Inclusion of all recommended components of care

The critical importance of inclusion of blood pressure in ANC is illustrated by the following quote:

> "Eclampsia doesn't happen frequently without pre-eclampsia and the way to know that, first, is the blood pressure"
>
> Focus Group Discussion participant from Society of Gynaecology & Obstetrics of Nigeria (SOGON)

Blood pressure measurement (and urine testing for proteinuria) is a key component of ANC that has as a primary aim, the detection of pre-eclampsia[90]. Although blood pressure measurement is one of the more commonly received components of ANC in LMICs[90,99,100], many women still do not have their blood pressure measured[91,100,101] and there is variability in rates of measurement from country to country. According to Demographic Health Survey publications, the proportion of women receiving ANC who have their blood pressure measured is >90% in Cambodia and Ghana, just over 85% in Nepal, Pakistan and Rwanda[90,98,102–104], but only 53% in Laos[105] and variable in many African countries (i.e., 75% in Malawi[78], 52.5% in Uganda[96] and 40% in Kenya[106]).

KEY POINT

Blood pressure measurement is one of the more commonly received components of ANC in LMICs, but estimates vary from country to country

Continued efforts are required to improve access to quality ANC. Predictors of women's attendance at four or more ANC visits and receipt of good quality ANC have been identified and are listed in Table 1.3[90,107]. Included among these characteristics are higher maternal education and higher household economic status. It follows from this information that interventions that aim to reduce maternal and perinatal morbidity and mortality from pre-eclampsia may focus in the short-term on targeting women at higher risk, such as those with lower levels of education and lower socioeconomic status. A sustainable longer-term intervention will require a multi-sectoral approach involving entire communities, including governments and policy-makers with the aim of improving access to education by girls and women and reducing economic inequalities[90]. However, to generate confidence in the health system and appropriate demand for services, women must be assured that each and every antenatal attendance will lead to provision of the essential components of care, such as blood pressure measurement using a correct technique and with functional equipment.

Health care worker staffing

The challenges of measuring blood pressure may be compounded by an inadequate number of health care workers and/or a lack of their training to measure blood pressure using appropriate technique. Inadequate staffing numbers can strain the ability of a facility to diagnose pre-eclampsia,

Table 1.3 Factors associated with better access to antenatal care (ANC)

	Attendance at ≥4 ANC visits	*Receipt of quality ANC*
Maternal characteristics		
Older age	✓	✓
Higher parity	✓	✓
Higher maternal education	✓	✓
Higher household economic status	✓	✓
Non-smokers	✓	
Women have a say in decision-making	✓	
Higher paternal education	✓	
Maternal occupation other than agriculture	✓	
Urban residence		✓
Exposure to general media		✓
Characteristics of ANC		
Receiving ANC from a skilled provider		✓
Receiving ANC in a hospital		✓

whether during ANC visits in an overcrowded health centre, or monitoring women in labour on a maternity ward. Although task-shifting to the community level and use of automated devices may address some service access gaps, the emphasis needs to be on functionality across the levels of the health system whether under government authority or other initiatives[77]. Interventions to improve health worker training and maintenance of competency for good maternity care are needed[99,101]. Appendix 1.1[108,109] contains an example of material used to train community health care workers to take blood pressure using the Microlife 3AS1-2 semi-automated blood pressure device (Figure 1.2).

Figure 1.2 Taking blood pressure in the community with the Microlife 3AS1-2 hand-held device

BEST PRACTICE POINTS

(Please see Appendix 1.2 for the evaluation of the strength of the recommendation and the quality of the evidence on which they are based.)

Diagnosis of hypertension

1. The diagnosis of hypertension should be confirmed by health facility blood pressure measurements.
2. Hypertension in pregnancy should be defined as a sBP ≥140 mmHg and/or dBP ≥90 mmHg, based on the average of at least two measurements, taken at least 15 minutes apart, using the same arm.
3. For the purposes of defining superimposed pre-eclampsia in women with pre-existing hypertension, 'resistant hypertension' should be defined as the need for three antihypertensive medications for blood pressure control at ≥20 weeks' gestation.
4. A 'transient' hypertensive effect should be defined a sBP ≥140 mmHg or a dBP ≥90 mmHg which is not confirmed on the same visit after the woman rests, or on subsequent visits.
5. A 'white coat' hypertensive effect refers to blood pressure that is elevated in a health facility (i.e., sBP ≥140 mmHg or dBP ≥90 mmHg) but by ABPM or HBPM, sBP is <135 mmHg and dBP is <85 mmHg.
6. 'Masked' hypertension refers to blood pressure that is normal in a health facility (i.e., sBP <140 mmHg and dBP <90 mmHg) but elevated by ABPM or HBPM (i.e., sBP of ≥135 mmHg or dBP ≥85 mmHg).
7. Severe hypertension should be defined as a sBP of ≥160 mmHg or a dBP of ≥110 mmHg based on the average of at least two measurements, taken at least 15 minutes apart, using the same arm. This finding should prompt urgent intervention to control the blood pressure.

Blood pressure measurement

1. Blood pressure should be measured using standardised technique, particularly with the woman seated and her arm at the level of the heart.
2. An appropriately sized cuff (i.e., length of 1.5 times the circumference of the arm) should be used.
3. Korotkoff phase V (marked as disappearance of Korotkoff sounds) should be used to designate dBP.
4. If blood pressure is consistently higher in one arm, the arm with the higher values should be used for all blood pressure measurements.
5. Blood pressure can be measured using a mercury sphygmomanometer, calibrated aneroid device, or an automated device that has been validated for use in pre-eclampsia.
6. Automated blood pressure machines that have not been validated for use in pre-eclampsia may under- or over-estimate blood pressure in those women, so those readings should be compared with those using mercury sphygmomanometry or a calibrated aneroid device.
7. In the health facility setting, when blood pressure elevation is non-severe and pre-eclampsia is not suspected, ABPM or HBPM is useful to confirm persistently elevated blood pressure.
8. When HBPM is used, maternity care providers should ensure that women have adequate training in measuring their blood pressure and interpreting the readings taken.
9. The accuracy of all blood pressure measurement devices used in health facilities should be checked regularly (e.g., annually) against a calibrated device.
10. The accuracy of all automated devices used for HBPM should be checked regularly against a calibrated device (e.g., at multiple ANC for an individual woman).

PRIORITIES FOR UNDER-RESOURCED SETTINGS

Table 1.4 outlines priorities for under-resourced settings. Unlike most diagnostic or therapeutic interventions in the area of hypertensive disorders of pregnancy, measurement of blood pressure and diagnosis of hypertension have more priorities at the community rather than the facility level. A sample policy brief that focuses on blood pressure measurement is contained in Appendix 1.3.

WHAT INTERNATIONAL GUIDELINES SAY (APPENDIX 1.4)

Abbreviations for Clinical Practice Guidelines are ACOG (American College of Obstetricians and Gynecologists)[110], AOM (Association of Ontario Midwives), NICE (National Institutes of Clinical Excellence)[111], NVOG (National Obstetrics and Gynaecology Society, Netherlands)[112], PRECOG (Pre-eclampsia Community Guideline)[119], PRECOG II (Pre-eclampsia Community Guideline II)[120], QLD (Queensland, Australia)[113,114], SOGC (Society of Obstetricians and Gynaecologists of Canada)[115], SOMANZ (Society of Obstetric Medicine of Australia and New Zealand)[116], WHO (World Health Organization)[117].

In a review of international clinical practice guidelines on the hypertensive disorders of pregnancy[118], nine guidelines stated that pregnancy hypertension was defined by both sBP and dBP together (≥140/90 mmHg) (QLD, NICE, NVOG, ACOG, SOGC, SOMANZ 2014), or dBP alone (≥90 mmHg) (PRECOG, PRECOG II, AOM); no definition is offered by the WHO guidelines. Eight of 10 guidelines define severe hypertension, seven as blood pressure ≥160/110 mmHg (NICE, QLD, NVOG, AOM, ACOG, SOGC, SOMANZ) and one as ≥170/110 mmHg (PRECOG II); one document specifies that severe hypertension requiring urgent treatment is ≥170/110 mmHg (SOMANZ 2014).

Table 1.4 Priorities for under-resourced settings

	Antepartum & postpartum	
	Initial priority	*Ultimate goal*
Community		
Primary health care centre (detect, stabilise and refer)	Availability of BP measurement devices Measurement of BP at each ANC and PNC visit	Availability of BP measurement devices Measurement of BP at each ANC and PNC visit Training and re-training of health workers with regards to appropriate BP measurement technique Training of community health care workers to take BP at home visits
Facility		
Secondary-level facility (detect, manage and refer if necessary)	Availability of BP measurement devices Measurement of BP at each ANC and PNC visit	Availability of BP measurement devices Measurement of BP at each ANC and PNC visit Training and re-training of health workers with regards to appropriate BP measurement technique
Tertiary-level (referral) facility (detect and manage definitively)	Availability of BP measurement devices Measurement of BP at each ANC and PNC visit	Availability of BP measurement devices Measurement of BP at each ANC and PNC visit Training and re-training of health workers with regards to appropriate BP measurement technique

ANC, antenatal care; BP, blood pressure; PNC, postnatal care

PRIORITIES FOR FUTURE RESEARCH

These cover care in well- and under-resourced settings, particularly as mercury sphygmomanometers have been removed from the vast majority of health facilities internationally, and their most common replacement, aneroid devices, are not as accurate and require regular calibration. An alternative to mercury manometry is needed. Low-cost, energy-efficient and robust automated blood pressure machines are needed for use in LMICs, in order that women have blood pressure measured (and accurately) as part of high-quality ANC. Also, further research is needed into the usefulness of HBPM in the ANC of all women, to detect and manage the hypertensive disorders of pregnancy. Implementation research on which cadres of health care workers, including community health workers, can accurately use the automated devices will enhance task sharing at facilities and in the community.

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2

Measurement of proteinuria

AM Côté, A Mallapur, G Katageri, U Ramadurg, S Bannale, L Wang, LA Magee, S Miller, W Stones

"I had every [indication] of pre-eclampsia except for proteinuria until 38 weeks. When I finally presented with +4 protein, my BP was 198/130 and I had gained 50 lbs of water in 6 weeks."

Jenn P

SYNOPSIS

In pregnancy, there is a focus on measurement of proteinuria as it has been regarded as critical to the diagnosis of pre-eclampsia, the most dangerous of the hypertensive disorders of pregnancy. However, it is increasingly recognised that proteinuria is not essential for the diagnosis of pre-eclampsia, which can be based on other end-organ complications (such as elevated liver enzymes). Although heavy proteinuria has been linked with an increased risk of stillbirth in a 'signs and symptoms only' model of maternal risk (i.e., miniPIERS), we lack the ability to identify a level of proteinuria above which maternal and/or perinatal risk is heightened. Therefore, at present, we rely on the detection of proteinuria that exceeds what is normally excreted by healthy pregnant women. Proteinuria detection methods are also a matter of keen debate, with all available methods having advantages and disadvantages.

PHYSIOLOGICAL CHANGES OF PROTEINURIA IN PREGNANCY

During normal pregnancy, proteinuria increases through the trimesters, from 0.15 g/d outside pregnancy to 0.3 g/d during pregnancy. This is attributable to the increase in renal plasma flow and glomerular filtration rate, as well as changes in protein handling in the nephron; these changes resolve after pregnancy[1].

The proteinuria of pregnancy consists of both glomerular and tubular proteins, although the proportion of each is still a matter of debate[2].The most abundant individual protein is from the renal tubules, Tamm-Horsfall protein. Other proteins include albumin, thyroxine-binding prealbumin, immunoglobulins, α1-antitrypsin, transferrin, β-lipoprotein and low-molecular weight proteins[1].

CAUSES OF PROTEINURIA

Proteinuria screening in pregnancy is focused on the detection of pre-eclampsia, the most common cause of proteinuria in pregnancy. Pre-eclampsia affects the glomeruli, and the lesion has been termed 'glomerular endotheliosis'. This terms describes glomerular endothelial swelling and loss of the integrity of the fenestrae (i.e., sieving apparatus), leading to leakage of protein into the renal tubules and associated occlusion of the capillary lumens[3].

Proteinuria may be transient in pregnancy, although when identified, repeat testing must be

done within days to ensure that pre-eclampsia is not missed and allowed to evolve unobserved. Transient causes are associated with normal renal function and no abnormalities of urinary sediment. Causes include orthostasis (i.e., upright posture), exercise, fever or sepsis, congestive cardiac disease, or central nervous system causes such as subarachnoid or intracerebral haemorrhage, or seizures. It should be noted that orthostatic proteinuria occurs in no more than 5% of adolescents and decreases in frequency with age, being less common in those 30 years of age or older[4].

When considering the causes of persistent proteinuria in pregnancy, a full differential diagnosis should be considered. How often new proteinuria is due to causes other than pre-eclampsia is unclear, especially in under-resourced settings. In the face of this uncertainty about the cause of the proteinuria, pre-eclampsia should be regarded as the working diagnosis given the maternal and fetal risks associated with this condition. Persistent proteinuria in pregnancy may be also caused by non-pre-eclampsia glomerular disease, tubular disease, or even non-renal disease (Table 2.1). Nephrotic-range proteinuria (≥3 g/d) is suggestive of glomerular renal disease. Abnormalities of the urinary sediment (e.g., micro- or macroscopic haematuria with IgA nephropathy) may or may not be seen with renal causes of proteinuria.

Table 2.1 Causes of proteinuria (modified from Côté and Sauve[67])

Transient causes
Orthostatic (i.e., related to upright posture)
Systemic (e.g., exercise, fever or sepsis, congestive cardiac disease)
Central nervous system (e.g., subarachnoic or intracerebral haemorrhage, seizures)
Contamination (e.g., from vaginal bleeding)
Persistent
Glomerular diseases
Pre-eclampsia
Pre-gestational diabetes type 1 or type 2
Immunoglobulin A (IgA) GN
Focal and segmental glomerulosclerosis (FSGS)
Lupus nephritis
Infection-related GN (e.g., HIV, hepatitis B and C, post-streptococcal, visceral abcess, endocarditis, other)
Drug-related GN
Other glomerular disease in young women: minimal change, membranous GN, membranoproliferative GN, other rare glomerular disease (e.g., amyloidosis), Fabry, Alport)
Non-glomerular (tubulointerstitial) disease
Structural (e.g., congenital anomalies, reflux nephropathy)
Polycystic kidney disease
Interstitial nephritis
Urinary tract infection

GN, glomerulonephritis

POLICY IMPLICATION

Detecting proteinuria

- Proteinuria screening must be available wherever antenatal or postnatal care is provided
- At minimum, proteinuria testing must be performed at the first of the four WHO-recommended antenatal visits and whenever hypertension is detected[5]
- Proteinuria testing must be performed at the 6-week postpartum visit in women who developed proteinuria in pregnancy[6]

(See Appendix 2.1)

SCREENING FOR PROTEINURIA IN ANTENATAL CARE

At minimum, all pregnant women should be assessed for proteinuria in early pregnancy, to detect pre-existing renal disease and to obtain a baseline measurement in women at increased risk of pre-eclampsia[7]. Thereafter, most assessment for proteinuria occurs in women suspected of having pre-eclampsia, such as when women present with hypertension or suggestive symptoms (such as headache). The frequency of such screening is uncertain. Ideally, countries should move toward universal screening at every visit as pre-eclampsia/eclampsia may first present with isolated proteinuria[8]. In the meantime, it would seem reasonable to retest for proteinuria in response to a rising blood pressure and/or maternal symptoms or maternal/fetal signs of

pre-eclampsia. It must be emphasised that proteinuria is but one diagnostic criterion for pre-eclampsia, and the end-organ complications of pre-eclampsia may occur in the absence of proteinuria. For example, in the latest eclampsia survey in the UK, 7.5% of women had only proteinuria (and 45% had neither hypertension nor proteinuria) in the week before their eclamptic seizure[9].

As per the WHO postnatal recommendations for the care of the mother and newborn[6], proteinuria should be re-tested in women who were identified as having had proteinuria in pregnancy, (see Chapter 11 for more information about postpartum management.)

MEASUREMENT OF PROTEINURIA FOR THE DIAGNOSIS OF PRE-ECLAMPSIA

There are many options for diagnosis of proteinuria, on either random (spot) samples (such as urinary dipstick testing, heat coagulation test, urinary protein : creatinine ratio (PrCr), or urinary albumin : creatinine ratio (ACR)) and various timed urine collections (usually 24-hour). Each has advantages and disadvantages and different results for diagnostic test accuracy (Appendix 2.2).

Urine tested for proteinuria should be as 'fresh' as possible. The longer the collection to testing interval, the more likely that bacterial contamination will skew the results. Without refrigeration, urine should be tested as soon as possible after collection, and definitely within 4 hours of collection. Urine collected over a 24-hour period must be refrigerated and brought to the laboratory on the day that collection finishes.

Point-of-care urine test strips come in opaque containers that specify expiry dates. They should not be used after that time. Once the container has been opened, the lid should be replaced between strip removal so that the unused strips are kept out of sunlight.

POLICY IMPLICATION

How to screen for proteinuria

Proteinuria screening should be performed using urinary dipsticks given their ease of use and low cost, until such time that another method proves to be superior

(See Appendix 2.1)

Urinary dipstick testing for proteinuria

There are many available types of urinary dipstick testing strips for visual and automated testing, and analysers for automated dipstick analysis. As it is unclear whether a particular method has an impact on test accuracy and pregnancy outcome, it may be prudent if possible, for the health care provider to use the same type of urinary dipsticks in the clinic and to send an individual patient to the same laboratory throughout her pregnancy so that differences in test results over time are more likely to be meaningful.

Visual interpretation of urinary dipstick

Urinary dipsticks may have up to 10 chemical pads for measuring different substances in urine, including protein and albumin, although strips that restrict measurement to proteinuria or albuminuria are available. The advantage of a strip with multiple pads is that it can reveal associated urinary abnormalities that are causes of low-level proteinuria, such as haematuria or either asymptomatic bacteriuria or symptomatic urinary tract infection (both of which should be treated with antibiotics) by showing leukocytes and nitrites. The disadvantages include multiple results that may result in confusion and inappropriate further investigation; for example, leukocytes may be a completely normal finding in pregnancy given contamination of the urine by vaginal discharge.

The urinary dipstick strip should be immersed completely in a well-mixed sample of urine for a short period of time, then extracted from the container and the excess urine removed by either supporting the edge of the strip over the mouth of the container, or drying the edges of the strip on absorbent paper (Figure 2.1). The strip is then left to stand for the time necessary for the reaction to occur (usually 60 seconds, as specified by the strip manufacturer). For visual analysis, the colour on the 'proteinuria' pad is compared with the chromatic scale specific to that strip and provided by the manufacturer. For automated analyses, the machine will read out the result. Results are reported as negative, trace, 1+, 2+, 3+, or 4+ based on the concentration of proteinuria detected. Although the concentration for a given '+' may vary from one manufacturer to another (particularly at the 4+ stage), 1+ proteinuria usually reflects 0.3 g/L of proteinuria. It follows that dehydration

Figure 2.1 Accredited social health associate (ASHA) worker, India, performing urinary dipstick testing

can increase proteinuria concentration and result in a 'positive' proteinuria dipstick result.

Urinary dipstick testing for proteinuria is inexpensive, easy and widely used. In a systematic review, 1+ proteinuria by visual dipstick testing showed low sensitivity (55%, 95% CI 37–72) and reasonable specificity (84%, 95% CI 57–95) for detection of 0.3 g/d of proteinuria[10]. A threshold of 2+ proteinuria by visual dipstick testing has reported sensitivity and specificity that varies from values of 58%[11] to values of ≥80%[12–14]. How should these results be interpreted for clinical practice? Given the <90% sensitivity of dipsticks using a threshold of 1+, a negative or trace value should not be ignored in a woman with new hypertension or symptoms or signs suggestive of pre-eclampsia. Given the reasonable specificity of dipsticks (at 1+ or 2+ levels), a result ≥1+ should prompt additional investigations even when the suspicion of pre-eclampsia is low. A urinary dipstick result of ≥2+ is suggestive of 0.3 g/d or more of proteinuria by 24-hour urine collection.

Automated testing of urinary dipstick

In theory, automation has the potential to reduce errors arising from subjective interpretation of dipstick readings.

Comparisons of automated with visual-read dipsticks have used thresholds of either 1+ or 2+. Two studies have compared the diagnostic test properties of automated dipsticks for proteinuria with visual read urinary test strips for proteinuria[13,15], using a threshold of 1+. Although one study compared test strips with 24-hour urinary protein excretion (g/d)[15] and the other study used 24-hour urinary protein concentration (g/L) as the comparator[13], both studies demonstrated superior diagnostic test properties of automated (versus visual) testing, using a threshold of 1+ for proteinuria. In contrast, a more recent study failed to show superiority of automated over visual testing[16]. When a threshold of 2+ proteinuria was used, automated testing also appeared to be superior to visual testing[13], with absolute values for sensitivity by automated testing as high as >80%[13,14] but as low as 23% in another study[17].

For detection of proteinuria by 24-hour urine collection or PrCr, published sensitivities for an automated dipstick threshold of 1+ or more (41%[17], 82%[15], 90%[13] and 100%[18]) and corresponding specificities (100%, 81%, 86% and 37%) have varied widely, even when the prevalence of proteinuria in the study populations was similar (i.e., 45%[15] and 48%[17]).

The diagnostic accuracy of automated testing may depend on the choice of test strip and/or analyser. It may be premature to recommend widespread adoption of automated urine proteinuria test strip readers, although one international guideline makes such a recommendation[19].

Urinary dipstick test strips are also available for detection of albuminuria (i.e., albumin concentration) specifically. However, we are not aware of studies that have compared albuminuria dipstick testing with proteinuria dipstick testing or other methods of proteinuria testing for detection of significant proteinuria in pregnancy. Of note, albuminuria dipsticks are more expensive than are proteinuria dipsticks.

HEAT COAGULATION TEST

The heat coagulation test may be used in under-resourced settings as an alternative to dipstick testing or other methods (discussed below) that are unavailable or too costly. A test tube is filled to two-thirds with urine. A few drops of dilute acetic acid are added to make the urine sample acidic. The upper part of the test tube containing urine is heated (but not boiled) over a burner.

The presence of protein is signified by the turbidity of the urine when the tube is placed in front of a typed sheet of paper according to a pre-specified chart (Figure 2.2)[20,21]. The lower part of the tube of urine acts as a control as that urine should remain clear (Figure 2.3).

The heat coagulation test may be less sensitive than visually interpreted urinary dipsticks (at ≥1+ level) for detecting 0.3 g/d or more of urinary

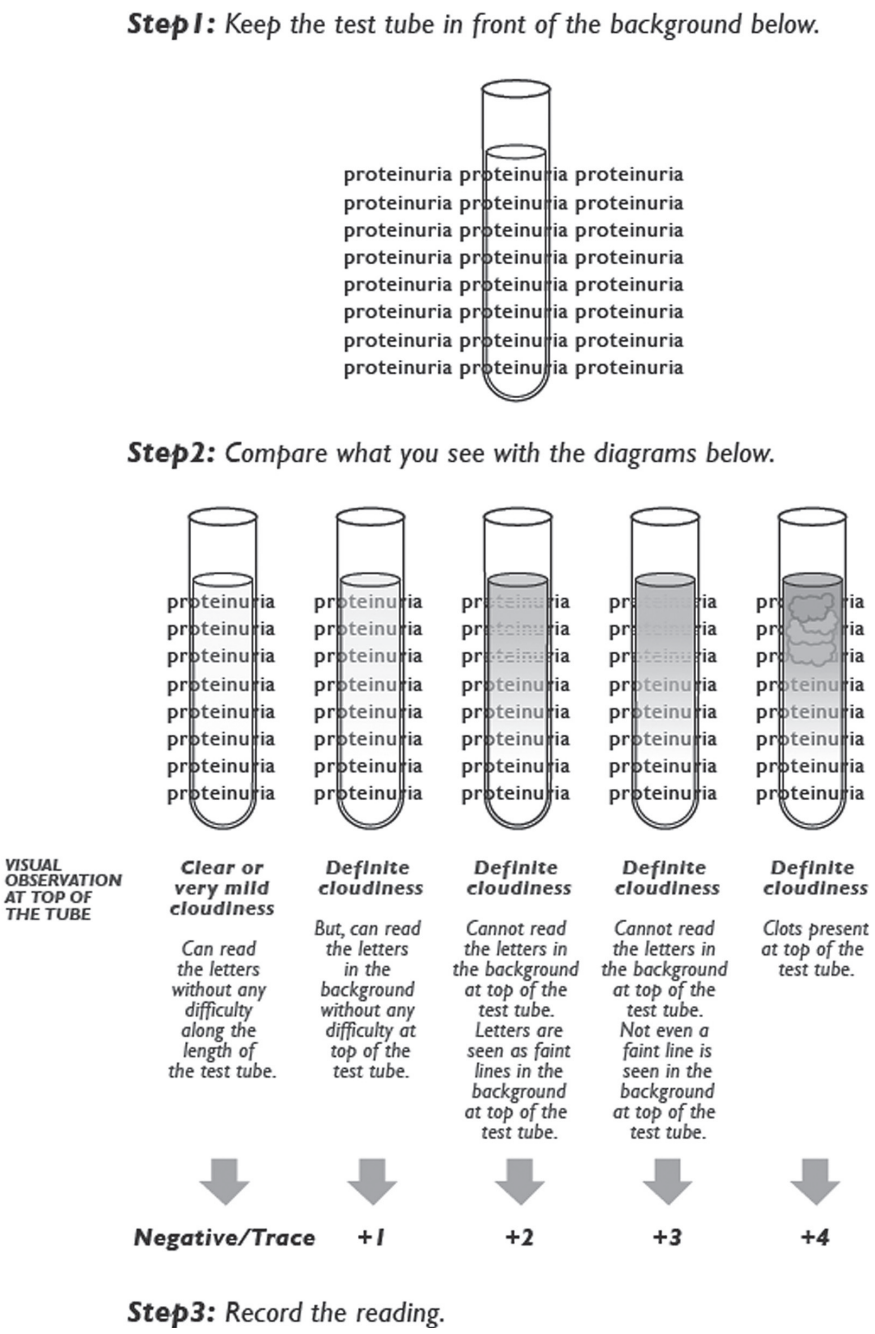

Figure 2.2 Performing the heat coagulation test and interpreting its results

protein, however, it has reported specificity that is more than 90%[20,21].

Sulfosalicylic acid testing

The sulfosalicylic acid (SSA) test is an alternative method of proteinuria testing for under-resourced settings. Ideally, the pH of urine is tested, and if >6, urine is acidified by adding one or two drops of 10% acetic acid. Then, 2 mL of 3% sulfosalicylic acid is added. After shaking the test tube, the turbidity is observed (Figure 2.4) and the tube is placed in front of a black line or bold printed fonts. The turbidity of the urine (as inferred by the ability

to see the black line or printed fonts) is used to infer the presence of proteinuria, as follows: (1) 'negative' when the black line or text is perfectly visible behind the first tube; (2) 'weakly positive' (protein concentration <0.3 g/L) when the black line or text is less visible; (3) 'positive' (protein concentration 0.3–1.0 g/L) when the black line or text is not quite visible; and (4) 'strongly positive' (protein concentration >1.0 g/L) when the black line or text is not visible at all[22].

Interest in using proteinuria testing by SSA as a screening test for proteinuria was based on the test's low cost, good specificity, feasibility and reliability.

Figure 2.3 Heat coagulation test tube showing proteinuria as turbidity at the top of the tube

In the 1980s, WHO recommended SSA testing for use in primary care centres, and two studies evaluated its test performance. Sensitivity and specificity of proteinuria testing in the field by SSA were 94.4% and 96.7% compared with dipstick testing (interpretation by laboratory staff presumed to be visual)[22], and 41.1% and 97.7%, respectively, compared with 24-hour urinary protein[23]. There are no published direct comparisons of the heat coagulation test and SSA. However, given that SSA testing is easier to perform and has similar diagnostic properties (when testing is compared with 24-hour urine testing), SSA testing would seem preferable.

Spot protein : creatinine ratio

Although point-of-care testing for spot PrCr is emerging and PrCr is easily collected by women, all PrCr ratio studies in pregnancy have had measurement of the protein and creatinine concentrations in a random urine sample performed then results calculated in the laboratory (Figure 2.5). There are many assays for proteinuria and creatinine; poor reporting of laboratory methods has prevented an analysis of the impact of various assays on PrCr results. Rapid interpretation has been further complicated by reporting of PrCr results in various units. Nevertheless, the urinary PrCr ratio has been accepted for diagnosis of proteinuria by the International, American, Australasian, Canadian and British pregnancy hypertension societies. In a systematic review, the reported cut-off varied from 17 to 57 mg/mmol (0.15–0.50 mg/mg) (median 24 mg/mmol) in nine studies (1003 hypertensive women). For a cut-off

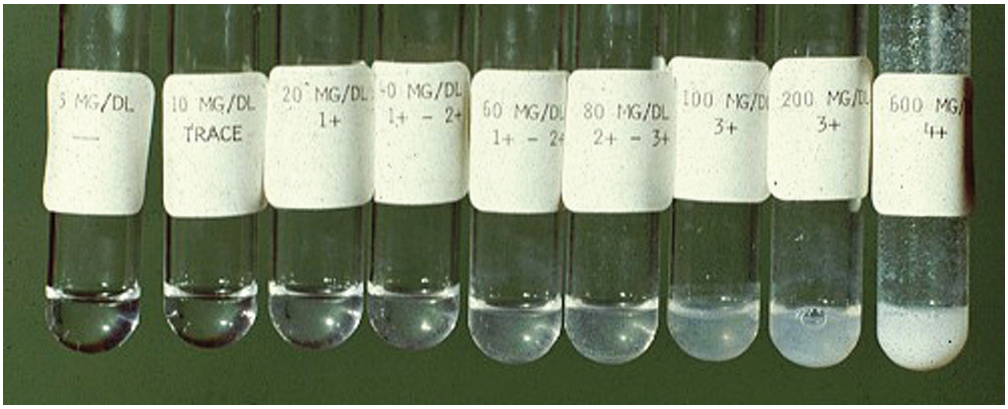

Figure 2.4 Turbidity of the urine after addition of acetic acid as part of sulfosalicylic acid (SSA) testing (from http://www.eclinpath.com/urinalysis/chemical-constituents/urine-protein-ssa/)

Figure 2.5 Woman in Nigeria preparing to collect her spot urine sample for protein : creatinine ration (PrCr) testing

of 30 mg of protein/mmol urinary creatinine, and among women with a hypertensive disorder of pregnancy specifically, the sensitivities and specificities were 83.6% (95% CI 77.5–89.7) and 76.3% (95% CI 72.6–80.0), respectively[24]. A more recent systematic review suggests that the optimum threshold for PrCr ratio to detect significant proteinuria may actually be slightly higher, at 34–40 mg/mmol (0.30–0.35 mg/mg) (summary sensitivity and specificity both >75% for 15 studies, 2790 women), although no threshold gave a sensitivity and specificity >80%[25]. A further meta-analysis of 24 studies (3186 women) endorsed a cut-off of 34 mg/mmol (0.30 mg/mg), with sensitivity and specificity >80%[26]. Four additional studies individually found sensitivity and specificities of at least 80% with optimal cut-offs of 27 mg/mmol (0.24 mg/mg)[27], 30 mg/mmol[28], 51 mg/mmol (0.45 mg/mg)[11], and 53 mg/mmol (0.47 mg/mg)[29], consistent with the previously reported range of 17–57 mg/mmol. One additional report was just outside this range (71 mg/mmol, 0.63 mg/mg)[30], and three others found that optimal cut-offs did not have both sensitivity and specificity ≥80%[31–33]. Taken together, we feel that continued use of the threshold of 30 mg/mmol is reasonable, but do recommend that proteinuria testing be viewed as only *one* aspect of the investigation of women with a hypertensive disorder of pregnancy and interpreted in the context of clinical symptoms, signs and other laboratory testing. A higher threshold may be more appropriate in twin pregnancy[34,35].

The best timing of spot urine sampling is debated. However, timing may not be critical in pregnancy[36–38] which is ideal for women with suspected pre-eclampsia who can be tested for proteinuria at the time of clinical presentation.

Spot albumin : creatinine ratio

Most clinical laboratories use immunoassays to measure urinary albumin, so there is less theoretical inter-laboratory variability for albuminuria than for proteinuria. (The remainder of labs use colourimetric methods that are less precise for low-level albuminuria.) However, there is no standardisation of method, and there are also multiple methods for measuring urinary creatinine, as stated for the PrCr. The impact of laboratory assays on albumin : creatinine ratio (ACR) results is not known.

Urinary ACR testing is available by a variety of point-of-care dipsticks. Three studies have evaluated performance in pregnancy. Two studies found the automated-read ACR dipstick to be insensitive: one used the ACR performed on a spot sample sent to the laboratory as the reference test using a cut-off of 3.4 mg/mmol (65 low risk and 43 high risk pregnancy cases)[39]. The second used 24-hour urinary protein as the reference test; reported sensitivity and specificity were 63% and 81%, respectively (163 hypertensive women)[40]. The third evaluated both visual and automated ACR dipstick performed at the bedside compared with 24-hour urinary protein (171 hypertensive women); automated ACR dipstick fared only slightly better than visual ACR dipstick with regards to sensitivity (i.e., 58% vs. 49%, respectively) and specificities were 83% for both approaches; neither ACR dipstick (visual or automated-read) in that study was better than visual *proteinuria* dipstick testing (which had a sensitivity of 51% and a specificity of 78%) for detection of 0.3 g/d or more of urinary protein in 24-hour collection[15].

Urinary ACR testing on spot urine samples is widely available in clinical laboratories in well-resourced settings. Most, but not all, studies have reported good test performance. The urinary ACR has performed well in: (1) detection of 24-hour urinary protein excretion in four prospective studies[18,41–43] (410 pregnant women), and (2) detection of 24-hour urinary albumin excretion in two other studies[44,45] (119 pregnant

women). An additional study reported that ACR correlated well with 24-hour albuminuria but not with 24-hour proteinuria[46] (31 women diagnosed with pre-eclampsia). Moreover, three different diagnostic cut-offs (of 2, 8 and 22.8 mg/mmol, equivalent to 18, 71 and 205 mg/g) have been reported for significant proteinuria[15,18].

In summary, there is insufficient information about use of ACR testing (by dipstick or through the laboratory) in pregnancy to recommend their use at the present time.

Timed urine collection

Quantification of urinary protein by 24-hour urine collection is considered to be the gold standard. However, 24-hour urine collection is time-consuming, inconvenient and often inaccurate due to inadequate 24-hour urine collection (as assessed by urinary creatinine collection of 13–18% of pre-pregnancy body weight as urinary creatinine (mmol/d))[47]. For diagnosis of proteinuria in non-pregnant populations, these logistical considerations have prompted the National Kidney Foundation and the International Society of Nephrology to abandon timed collections in favour of the spot urine samples[48,49]. However, if quantification of proteinuria is sought, then 24-hour urine collection for protein and creatinine should be used at high levels of proteinuria (i.e., spot PrCr >125 mg/mmol which is roughly equivalent to more than 1 g/d of proteinuria by 24-hour urine collection) as the spot PrCr is less reliable at high levels of proteinuria.

WHAT CONSTITUTES 'SIGNIFICANT' PROTEINURIA IN PREGNANCY?

Although 0.3 g/d of proteinuria represents the upper 95% confidence interval for proteinuria excretion in pregnancy, this threshold does not necessarily identify women at increased risk of adverse maternal and/or fetal outcomes. That threshold is not known.

A recent study reported that women who had ≥0.5 g/d were at higher risk of adverse outcomes than those with 0.3–0.5 g/d[50]. (This is discussed further in Chapter 3.)

In well-resourced settings where full maternal and fetal assessment is available, the magnitude of proteinuria once identified is not related to either short-term adverse maternal or perinatal outcomes, or long-term maternal renal prognosis. In the fullPIERS cohort, a prospective study of women admitted to hospital with pre-eclampsia, the magnitude of proteinuria (by 24-hour urine collection, visual dipstick testing, or spot PrCr) was not associated with adverse maternal or perinatal outcomes independent of routinely collected information on maternal symptoms, signs and basic blood work[51] (see Chapter 3). At least one observational study of women with pre-eclampsia failed to identify a definition of heavy proteinuria that was associated with adverse renal prognosis[52].

In contrast, in resource-poor settings where maternal symptoms and signs alone are used to guide treatment, proteinuria of ≥4+ is associated with an increased risk of stillbirth[53].

COST CONSIDERATIONS

Although visual dipstick proteinuria testing is the most widely used of the screening methods, there is no cost-effectiveness analysis of its use followed by confirmatory testing (with PrCr or 24-hour urine collection) for values ≥1+ or ≥2+.

The only health economic analyses identified were those conducted by the NICE Clinical Guideline Committee, for women with gestational hypertension who live in settings where all tests are available[54]. The Committee considered both the convenience of testing for health care providers and women, and the trade-off between the costs of a false positive test for proteinuria and the costs of missed adverse pregnancy outcomes. The analyses were highly influenced by the sensitivity of proteinuria testing methods. Assuming that sensitivity is high for both the automated dipstick and spot PrCr methods, spot PrCr may be more cost-effective than a strategy of automated dipstick testing *followed by* confirmation of ≥1+ proteinuria by either spot PrCr or 24-hour urine collection.

In low-resource referral hospital settings, limitations in central laboratory facilities will affect cost-benefit considerations.

BEST PRACTICE POINTS

(Please see Appendix 2.3 for the evaluation of the strength of the recommendation and the quality of the evidence on which they are based.)

1. All pregnant women should be assessed for proteinuria, at minimum, at their first antenatal visit.
2. Urinary dipstick testing (or SSA or heat coagulation testing if dipsticks are not available) may be used for screening for proteinuria when the suspicion of pre-eclampsia is low.
3. Significant proteinuria should be strongly suspected when urinary dipstick proteinuria is ≥2+.
4. Definitive testing for proteinuria (by urinary protein : creatinine ratio or 24-hour urine collection) is encouraged when there is a suspicion of pre-eclampsia.
5. Significant proteinuria is ≥0.3 g/d in a complete 24-hour urine collection or ≥30 mg/mmol (≥0.3 mg/mg) urinary creatinine in a random urine sample.
6. There is insufficient information to make a recommendation about the accuracy of the urinary albumin : creatinine ratio, although values <2 mg/mmol (<18 mg/g) are normal and all values ≥8 mg/mmol (≥71 mg/g) are elevated.
7. In well-resourced settings with sophisticated fetal monitoring, proteinuria testing does not need to be repeated once the significant proteinuria of pre-eclampsia has been confirmed.
8. In under-resourced settings, proteinuria testing should be repeated to detect 4+ dipstick proteinuria that is associated with an increased risk of stillbirth.

PRIORITIES FOR UNDER-RESOURCED SETTINGS

Proteinuria testing is recognised by WHO to be as a marker of high quality antenatal care[55]. In fact, proteinuria testing was recommended along with blood pressure monitoring as the original rationale for antenatal care. As such, implementation of proteinuria screening in low- and middle-income countries (LMICs) is a priority.

Demographic health survey data (2002–2008) indicate that few LMICs exceed a standard of urine testing in more than 80% of women attending antenatal care. The rate of urine testing at routine antenatal care visits is highly variable[56], particularly in sub-Saharan Africa and South/Southeast Asia where urine testing rates vary from testing in only 25% of women to testing in close to 100%. Urine testing occurs in at least 50% of women in North Africa/West Asia/Europe and at least 67% of women in Latin American/Caribbean countries. These data indicate a major failure of basic health system provision that inevitably results in avoidable large scale morbidity and mortality from hypertensive disease in pregnancy.

Table 2.2 outlines the priorities for implementation of proteinuria testing in LMICs, depending on the timing of testing (in pregnancy and postpartum) and the level of the health care system. In brief, the first priority is detection of women with pre-eclampsia (by testing for proteinuria at 20 weeks of pregnancy and beyond), followed by detection of women with underlying renal disease (by testing in the first or early second trimester, and at 6 weeks postpartum among women with proteinuria in pregnancy) who are at increased risk of pre-eclampsia.

Innovative proteinuria measurement devices are on the horizon for use in under-resourced settings and it is hoped that they will facilitate implementation of the priorities for testing outlined in Table 2.2. While the priority in high-income settings is towards laboratory-based analyses, the focus in LMICs is on point-of-care testing, particularly by community health care providers. Three active research tracks are as follows:

- *The proteinuria self-test for early detection of pre-eclampsia (the 'proteinuria pen')* was designed by graduate students at John Hopkins University,

Table 2.2 Prioritisation of urine testing for proteinuria by timing and level of health care system at which testing occurs

	Antepartum		*Postpartum*	
	Initial priority	*Ultimate goal*	*Initial priority*	*Ultimate goal*
Community				
Primary health care centre (detect and refer)	Urinary (clean-catch) dipstick testing at each visit after 20 weeks to detect pre-eclampsia	Urinary (clean-catch) dipstick testing at booking and at each visit after 20 weeks to detect both chronic renal disease and pre-eclampsia	Urinary (clean-catch) dipstick testing within 24 hours of delivery in hypertensive women to detect postpartum pre-eclampsia	Urinary (clean-catch) dipstick testing at 6 weeks after delivery for women with antenatal proteinuria to detect underlying renal disease and prompt referral
Facility				
Secondary-level facility (detect and manage/refer) Tertiary-level (referral) facility (detect and manage)	Urinary (clean-catch) dipstick testing at booking and at each visit after 20 weeks to detect both chronic renal disease and pre-eclampsia	Availability of confirmatory test for proteinuria in women with ≥1+ by urinary dipstick testing	Postpartum urinary (clean-catch) dipstick testing within 24 hours of delivery in hypertensive women to detect postpartum pre-eclampsia Postpartum urinary (clean-catch) dipstick testing at 6 weeks after delivery for women with antenatal proteinuria to detect underlying renal disease and prompt referral	

USA (http://www.appropedia.org/Proteinuria_Self-Test_Pen). Field testing is currently under the management of Jhpeigo. This felt-tip or ballpoint pen is filled with reagent that is used to mark a strip of paper. When a drop of urine is placed on the paper, if there is proteinuria, the reagent changes colour. The test is anticipated to cost <US$0.10 per use.

- *Point-of-care paper-based microfluidic diagnostic 'stamps'* have been developed by Diagnostics for All. Paper and an office printer are the equipment required to generate the postage stamp-sized paper testing tool, onto which a reagent and drop of urine are applied to indicate proteinuria (http://www.savinglivesatbirth.net/summaries/60). The test is anticipated to cost <US$0.10 per use).
- The urinary *Congo red dot test* uses a textile dye to detect elevated concentrations of misfolded urinary protein associated with pre-eclampsia[57] (http://www.usaid.gov/news-information/frontlines/open-development-development-defense/pinpointing-preeclampsia-simple-red). Testing requires the user to mix dye and urine together and put a drop on a piece of paper, where dye and any misfolded proteins in the urine combined to form a 'red dot'[57]. The test is anticipated to cost pennies per use.

WHAT INTERNATIONAL GUIDELINES SAY (APPENDIX 2.4)

Abbreviations for Clinical Practice Guidelines: ACOG (American College of Obstetricians and Gynecologists)[58], AOM (Association of Ontario Midwives), NICE (National Institutes of Clinical Excellence)[59], NVOG (National Obstetrics and Gynaecology Society, Netherlands)[60], PRECOG (Pre-eclampsia Community Guideline), PRECOG II (Pre-eclampsia Community Guideline II), QLD (Queensland, Australia)[61], SOGC (Society of Obstetricians and Gynaecologists of Canada)[62], SOMANZ (Society of Obstetric Medicine of Australia and New Zealand)[63], WHO (World Health Organization)[64].

Screening for proteinuria is advocated by five clinical practice guidelines for women with a hypertensive disorder of pregnancy (AOM[65], NICE, PRECOG[66], SOGC, SOMANZ); when performed,

testing methods should be by dipstick (visual) (PRECOG, AOM), automated (NICE), or either (SOGC), but NICE advocates using a random urine protein:creatinine ratio (PrCr) in a secondary care setting. Significant thresholds for proteinuria are: ≥1+ (PRECOG, SOGC) or ≥2+ (PRECOG II[68], QLD), with two guidelines specifying that a threshold of ≥1+ should be used only when there is associated hypertension (PRECOG II) or other manifestations of pre-eclampsia (AOM).

For quantification of proteinuria, criteria are: 'dipstick' ≥1+ (AOM), random urine PrCr ≥30 mg/mmol (PRECOG, PRECOG II, NICE, SOGC), and/or 24-hour urinary protein ≥0.3 g/d (PRECOG, PRECOG II, NICE, NVOG, ACOG SOGC) (with completeness of the urine collection emphasised by two CPGs (NICE, SOGC)).

PRIORITIES FOR FUTURE RESEARCH

- In low-resource country service settings, health systems research is needed on how to ensure consistent proteinuria screening in antenatal care, to the levels that are now being achieved for HIV testing.
- By current testing methods, what is the level of proteinuria that identifies a woman and/or fetus at increased risk of an adverse outcome?
- Are there better ways of measuring proteinuria? These should be cheaper and related to the risk of adverse pregnancy outcome. Three simple approaches, all point of care, show promise.

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3

Classification of the hypertensive disorders of pregnancy

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SYNOPSIS

During pregnancy, it is important to detect hypertension of any sort, as pregnancy hypertension is associated with increased maternal and perinatal risks. However, not all hypertensive disorders of pregnancy carry the same level of risk for women and their babies. Therefore, the classification of the hypertensive disorders of pregnancy into pre-existing (chronic) hypertension, gestational hypertension, pre-eclampsia, white coat hypertension and masked hypertension matters. Reducing the rates of false-positive and false-negative classification relative to current standard of care should help to better target health care spending and lower overall costs associated with the care of women with pre-eclampsia. Although classification of the hypertensive disorders of pregnancy is usually straightforward in higher income countries, this may not be the case in settings where late gestational age at booking is prevalent, and the final diagnosis may only be possible at 6 weeks postpartum. Also, as it is critical to identify women who require delivery, the only way to initiate the cure for pre-eclampsia, we endorse the Canadian approach of defining 'severe' pre-eclampsia according to the presence of severe complications that mandate delivery.

As pre-eclampsia is the most dangerous of the hypertensive disorders of pregnancy, tools have been developed in all settings to facilitate identification of women at highest risk of adverse outcomes: miniPIERS for under-resourced settings and fullPIERS for well-resourced settings; both models are optimised by pulse oximetry. There is a need to evaluate how new diagnostic and risk-stratifying biomarkers can be incorporated into existing protocols and to make these biomarkers available as point-of-care tests in all clinical settings.

INTRODUCTION

The purpose of classifying diseases is to facilitate communication among caregivers, and to create meaningful groups with different prognoses, considerations for surveillance, and/or outcomes[1]. As such, the hypertensive disorders of pregnancy are classified in Canada as pre-existing hypertension, gestational hypertension, pre-eclampsia, or 'other' (Table 3.1). A final diagnosis of the type of hypertensive disorder of pregnancy is retrospective, following the postpartum period. Pre-existing hypertension is often called chronic hypertension in other clinical practice guidelines (see "What international guidelines say" below).

The provision of antenatal care using the Scottish paradigm of accelerating frequency of visits towards term was developed, in large part, to facilitate the diagnosis of pre-eclampsia[2]. The full implementation

Table 3.1 Classification of the hypertensive disorders of pregnancy (reproduced with permission by the SOGC)[60]

	Comments
Pre-existing (chronic) hypertension	
	This is defined as hypertension that was present either pre-pregnancy or that develops at $<20^{+0}$ weeks gestation
With comorbid conditions(s)	Comorbid conditions (e.g., pre-gestational type I or II diabetes mellitus or kidney disease) warrant tighter BP control outside of pregnancy because of their association with heightened cardiovascular risk
With evidence of pre-eclampsia	This is also know as 'superimposed pre-eclampsia' and is defined by the development of one or more of the following at ≥20 weeks: • Resistant hypertension, *or* • New or worsening proteinuria, *or* • One/more adverse condition(s)¥ *or* • One/more severe complication(s)¥ Severe pre-eclampsia is defined as pre-eclampsia with one or more severe complication(s)
Gestational hypertension	
	This is defined as hypertension that develops for the first time at $\geq 20^{+0}$ weeks' gestation
With comorbid conditions(s)	Comorbid conditions (e.g., pregestational type I or II diabetes mellitus or kidney disease) warrant tighter BP control outside of pregnancy because of their association with heightened cardiovascular risk
With evidence of pre-eclampsia	Evidence of pre-eclampsia may appear weeks after the onset of gestational hypertension
Pre-eclampsia	
	Pre-eclampsia may arise *de novo*. It is defined by gestational hypertnesion and one or more of the following: • New proteinuria, *or* • One/more adverse condition(s)¥ *or* • One/more severe complication(s)¥ Severe pre-eclampsia is defined as pre-eclampsia with one or more severe complication(s)
*'Other hypertensive effects'**	
Transient hypertensive effect	Elevated BP may be due to environmental stimuli or the pain of labour, for example
White coat hypertensive effect	BP that is elevated in the office (sBP ≥140 mmHg or dBP ≥90 mmHg) but is consistently normal outside of the office (<135/85 mmHg) by ABPM or HBPM
Masked hypertensive effect	BP that is consistently normal in the office (sBP <140 mmHg or dBP <90 mmHg) but is elevated outside of the office (≥135/85 mmHg) by ABPM or repeated HBPM

ABPM, ambulatory BP monitoring; BP, blood pressure; dBP, diastolic BP; HBPM, home BP monitoring; sBP, systolic blood pressure after monitoring

* These may occur in women whose BP is elevated at $<20^{+0}$ or $\geq 20^{+0}$ weeks who are suspected at having pre-existing or gestational hypertension/pre-eclampsia, respectively

¥ Please see Table 3.2 for definitions of adverse conditions and severe complications of pre-eclampsia

of this paradigm was associated with reduced maternal mortality in the United Kingdom since the early 1900s and in Sri Lanka half a century later[2,3].

For pre-existing and gestational hypertension, there are two subgroups[2]: with comorbid conditions, because they constitute indications for tighter blood pressure control outside pregnancy, and evolution of disease can be more difficult to determine; and with pre-eclampsia, because it is associated with the greatest maternal and perinatal risks. Of women under 30 years of age, 1% are hypertensive, and approximately 1% of pregnancies

KEY POINT

In our opinion, the term 'pregnancy-induced hypertension,' or PIH, should no longer be used. In North America, PIH is used as a synonym for pre-eclampsia, whereas in the UK it means gestational hypertension *without* proteinuria. As such, the term has become debased, and may lead to confusion between clinicians

are complicated by pre-existing hypertension, 5–6% by gestational hypertension without proteinuria, and 1–2% by pre-eclampsia[4,5]. The incidence of the hypertensive disorders of pregnancy can be expected to increase in settings where there is a trend towards an older and more obese maternity population.

PRE-EXISTING (OR CHRONIC) HYPERTENSION

Pre-existing hypertension is defined as that which either pre-dates pregnancy or appears before 20^{+0} weeks of pregnancy. Pre-existing hypertension is associated with adverse outcomes for both mother and baby. For the mother, the following risks are heightened: superimposed pre-eclampsia (approximately 20%)[6–19], half of which develops at term[8,14,15,19,20], preterm delivery (about 33%)[6–8,10,12–19], and placental abruption (1.8%). Babies born to women with pre-existing hypertension are also at increased risk of acute or chronic hypoxia/acidosis. Approximately 15% of these babies are born small for gestational age (SGA)[8,10,11,13,14,16–19,21–27]. In a secondary analysis of women with singleton pregnancies and chronic hypertension diagnosed before 20 weeks in the National Institutes of Child Health and Development aspirin trial[28], the risks of adverse pregnancy outcomes increased with increasing blood pressure[29].

It is important to recognise that stillbirth risk reaches 0.1% by 36 weeks in pregnancies complicated by hypertension, similar to that reached at 41 weeks in low-risk pregnancies to justify labour induction[30]. Up to 50% of these newborns are admitted to high-level NICU care because of short-term complications, such as hypothermia, respiratory failure and feeding problems[15].

Women with comorbid conditions are highlighted because they may warrant special blood pressure treatment thresholds, particularly if the comorbid condition is type I or II (but not gestational) diabetes. Other comorbid conditions include major cardiovascular risk factors other than diabetes, renal parenchymal disease, vascular disease, or cerebrovascular disease. (For further discussion of antihypertensive therapy see Chapter 8.)

GESTATIONAL HYPERTENSION

Gestational hypertension is defined as hypertension that appears at $\geq 20^{+0}$ weeks, without the occurrence of proteinuria. However, using ambulatory blood pressure monitoring (ABPM), a 'white coat' effect is seen among about 30% of women diagnosed with hypertension at ≥20 weeks, and this rises to approximately 70% by the third trimester[31]. (For discussion of 'white coat' effect, see Chapter 1.)

Women with gestational hypertension have maternal and perinatal risks that are highly dependent on the gestational age at presentation and the progression to pre-eclampsia. When gestational hypertension appears before 34^{+0} weeks, approximately 35% of women develop pre-eclampsia with the associated heightened risks of maternal and perinatal complications[26,32–36]. Development of that pre-eclampsia takes an average of about 5 weeks[35,36].

For a discussion of the impact of comorbid conditions on recommendations for antihypertensive therapy see Chapter 8.

PRE-ECLAMPSIA

The term pre-eclampsia continues to be widely used internationally. It is widely recognised to be the hypertensive disorder of pregnancy associated with the greatest maternal and perinatal risks, particularly when it is severe in nature and/or presents before 34 weeks. In the latter case, a stillbirth rate of about 10% and a perinatal mortality rate of at least 5% have been reported[37]. The risk of small-for-gestational age (SGA) is also primarily concentrated in cases presenting at <34 weeks, while there is an increased number of large-for-gestational age (LGA) fetuses at term[37–39].

The origins of pre-eclampsia

As long ago as 1996, Ness and Roberts stated:

> "The cause of preeclampsia remains elusive in spite of many attempts to understand its biologic characteristics and to characterize its predictors. We suggest that there are distinct origins of preeclampsia, each with its own pathologic characteristics and natural history. One genesis is the result of reduced placental perfusion, which we will call placental, and another results from maternal disorders pre-existing (but sometimes not evident before) pregnancy. These pre-existing maternal disorders comprise predisposing factors for cardiovascular disease such as hypertension, renal disease, overweight, and diabetes."[40]

Over the past two decades, the amount of evidence to support this hypothesis has grown, leading more to pre-eclampsia being a pregnancy-specific inflammatory disorder of variable pathogenesis. We will share two examples of probable pathways to disease, summarised in Figure 3.1[41].

Angiogenic factor imbalance, with an excess of circulating anti-angiogenic factors (e.g., soluble fms-like tyrosine kinase (sFlt)-1 and soluble endoglin) and a reduction in pro-angiogenic factors (e.g., placental growth factor (PlGF)), has a clear role in identifying pregnancies complicated by placental underperfusion, be that manifested as pre-eclampsia or normotensive intrauterine growth restriction[42–45]. This angiogenic imbalance appears to be predictive of early-onset (at or before 34 weeks of pregnancy), primarily placental underperfusion-related, pre-eclampsia that is more dangerous to the individual woman with the condition, as demonstrated in both well- and under-resourced settings[41,46–48]. It may be of particular importance in identifying women with pre-existing medical conditions, especially renal disease, who have developed superimposed pre-eclampsia[49–51]. As yet, it is unclear why some women with angiogenic factor imbalance develop pre-eclampsia, while others remain normotensive, but the concentration of circulating placental debris may be an example of an important co-factor in stimulating the clinical syndrome of pre-eclampsia[52].

Data from the SCOPE (Screening for Pregnancy Endpoints) Consortium show that late-onset

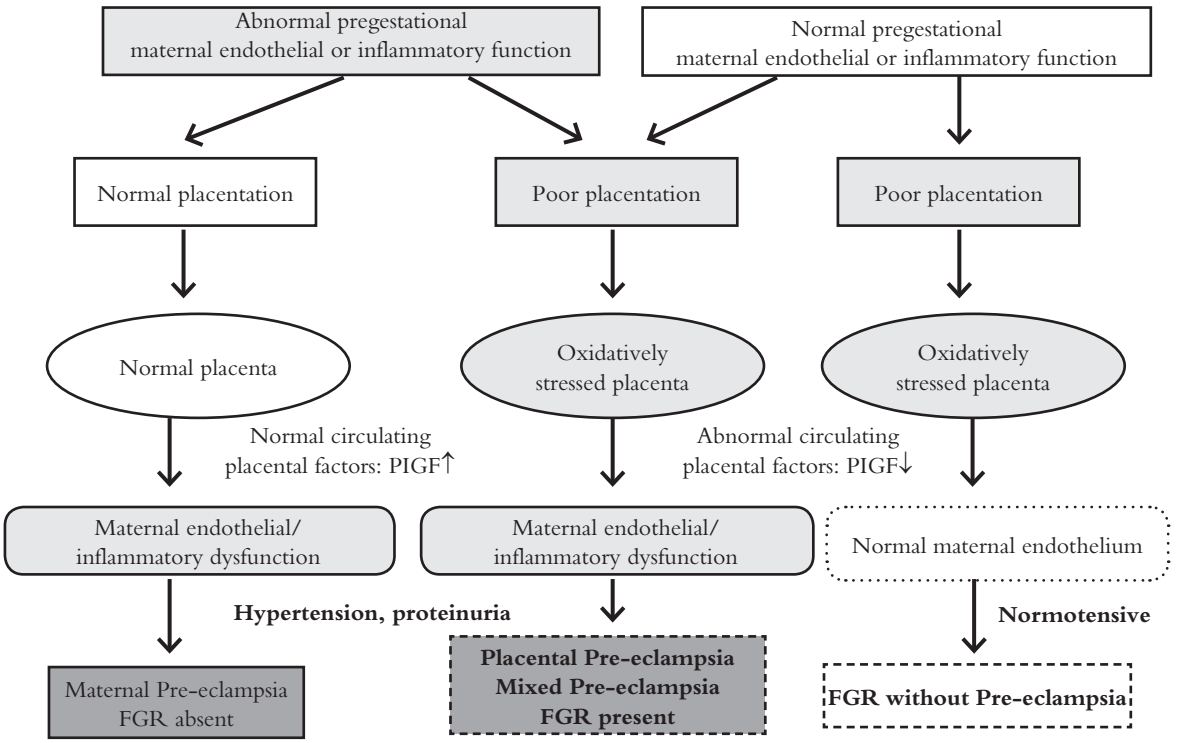

Figure 3.1 A model of pre-eclampsia (reproduced with permission from Staff AC *et al. Hypertension* 2013[41]). FGR, fetal growth restriction; PIGF, placental growth factor

pre-eclampsia is more closely related to factors that predict later cardiovascular disease through the metabolic syndrome[53,54], the so-called "maternal pre-eclampsia." Reflecting these findings, point-of-care assessment with glycosylated fibronectin, a strong marker of the risk of gestational diabetes and management, may provide a readily available method of confirming the diagnosis of "maternal" pre-eclampsia[55].

Clearly, in some women there is an overlap in precipitating factors. The combined aetiology may become increasingly important in lower-income countries in many of which pre-eclampsia of placental (versus maternal) origin currently predominates. This may be explained by the shorter time between first intercourse, coitarche and first pregnancy, thereby reducing the opportunity for exposure to paternal antigen through exposure to seminal fluid; this reduces the maternal immune adaptiveness that facilitates normal placental development[41,46]. However, pre-eclampsia of maternal origin may increase in prevalence as the obesity epidemic spreads across the globe. In addition, the maternal factors associated with the metabolic syndrome are associated with a pro-inflammatory state[53] that may be amplified by the burden of infectious diseases and chronic inflammation borne by women in less developed countries[56].

Defining pre-eclampsia

All hypertension societies consider pre-eclampsia to be a hypertensive disorder commonly defined by new-onset proteinuria, and possibly other adverse conditions (Table 3.2). A restrictive definition of pre-eclampsia is gestational hypertension with proteinuria, and this is often used by the research community and was endorsed for this purpose by the International Society for the Study of Hypertension in Pregnancy (ISSHP)[57]. The definition of pre-eclampsia as gestational hypertension with proteinuria or typical end-organ dysfunction is generally supported by other clinical practice guidelines (see "What international guidelines say" below)[58], and is likely to reduce maternal and perinatal risks[59].

'Resistant hypertension' is defined as hypertension that requires three concurrent antihypertensive medications for blood pressure control after 20 weeks' gestation. The 'adverse conditions' associated with pre-eclampsia consist of maternal symptoms and signs, abnormal maternal laboratory results, and abnormal fetal monitoring results that may herald the development of more severe complications. They are conditions to which we respond (e.g., low oxygen saturation) in order to avoid end-organ complications of pre-eclampsia (e.g., pulmonary oedema). The adverse conditions are discussed in detail below. This somewhat liberal definition of pre-eclampsia is intended to signal a need for heightened maternal and fetal surveillance, recognising that none of the adverse conditions are specific to pre-eclampsia.

Oedema and weight gain remain excluded from the definition of pre-eclampsia, as neither are significantly associated with perinatal mortality and morbidity[57,61]. Oedema, even facial oedema, is neither sensitive nor specific for pre-eclampsia[46,60,62].

Angiogenic imbalance is yet to be included in the definition. The diagnosis of hypertension and proteinuria are discussed in Chapters 1 and 2.

It should be remembered that pre-eclampsia can arise *de novo* postpartum, a condition that carries similar risks to antenatally detected pre-eclampsia that persists postpartum[63]. Women with *de novo* postpartum pre-eclampsia were included in the miniPIERS and fullPIERS (Pre-eclampsia Integrated Estimate of RISK) studies described in more detail, below[47,48]. (See 'Treatment postpartum' for further detail.)

'Severe' pre-eclampsia

What constitutes 'severe' pre-eclampsia is a matter of international controversy, although multi-organ involvement is the basis for the definition in guidelines from the UK (www.nice.org.uk/guidance)[64], Australasia (http://www.somanz.org/)[65], the United States[62], and the ISSHP[66] (see "What international guidelines say" below for more details)[58].

In Canada, the definition of 'severe' pre-eclampsia was modified to describe pre-eclampsia associated with one or more severe complications (including stillbirth). As such, women with severe pre-eclampsia as defined in Canada require delivery regardless of gestational age. Noticeable differences with other published definitions include the removal of heavy proteinuria as a criterion and the absence of the gestational age criterion present in the American and ISSHP guidelines.

Table 3.2 The adverse conditions that define pre-eclampsia and 'severe' pre-eclampsia according to the SOGC (reproduced with permission from SOGC)[60]

Organ system affected	*Adverse conditionals (that increase the risk of severe complications)*	*Severe complications (that warrant delivery)*
CNS	Headache/visual symptoms	Eclampsia PRES Cortical blindness or retinal detachment Glasgow coma scale <13 Stroke, TIA, or RIND
Cardiorespiratory	Chest pain/dyspnoea Oxygen saturation <97%[76]	Uncontrolled severe hypertension (over a period of 12 h despite use of three antihypertensive agents) Oxygen saturation <90%, need for ≥50% oxygen for >1 h, intubation (other than for Caesarean section), pulmonary oedema Positive inotopic support Myocardial ischaemia or infarction
Haematological	Elevated WBC count Elevated INR or aPTT[74] Low platelet count	Platelet count $<50 \times 10^9$/L Transfusion of any blood product
Renal	Elevated serum creatinine[47] Elevated serum uric acid	Acute kidney injury (creatinine >150 μM with no prior renal disease) New indication for dialysis
Hepatic	Nausea or vomiting RUQ or epigastric pain Elevated serum AST, ALT, LDH, or bilirubin Low plasma albumin[73]	Hepatic dysfunction (INR >2 in absence of DIC or warfarin/coumarin) Hepatic haematoma or rupture
Feto-placental	Non-reassurring FHR IUGR[37] Oligohydramnios Absent or reversed end-diastolic flow by Doppler velocimetry	Abruption with evidence of maternal or fetal compromise Reverse ductus venosus A wave[37] Stillbirth

AST, aspartate aminotransferase; ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation; FHR, fetal heart rate; INR, international normalised ratio; LDH, lactate dehydrogenase; PRES, posterior reversible leukoencephalopathy syndrome; RIND, reversible neurological deficit <48 h; RUQ, right upper quadrant; TIA, transient ischaemic attack

HELLP syndrome

While most guidelines identify HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome as a severity criterion, the 2014 Canadian guidelines do not. Why? As practitioners, when we are looking after women remote from term (e.g., <30 weeks' gestation), we offer expectant management to those women who accept this approach after counselling. Rather than wishing to avoid HELLP syndrome, or any of its component criteria, we aim to identify its development as early as possible and to respond to it to avoid more dangerous complications. We recognise that the HELLP syndrome adds risk to a pregnancy[67,68], and, by multivariable regression analysis, both platelet count and AST (aspartate aminotransferase) are independently informative components of the fullPIERS (Pre-eclampsia Integrated Estimate of RiSk) model (see below)[47]. The overlap between, and contrasting features of, HELLP syndrome and acute fatty liver of pregnancy should be considered[69]. Our practice is to include a random glucose in our laboratory assessment of women with suspected or confirmed pre-eclampsia to ensure that acute fatty liver of pregnancy does not go unrecognised[70,71].

The adverse conditions of pre-eclampsia
(Table 3.2)

In this classification system, we do not include those conditions that are serious end-organ complications of pre-eclampsia (e.g., eclampsia, abruption, pulmonary oedema, and stillbirth). These are complications that can have permanent sequelae and are life-threatening. Clinicians should seek to avoid these complications altogether, rather than await their development and then react with timely delivery. For this reason, reversed end-diastolic flow remains an adverse condition.

We have modified the remaining adverse conditions based on their associations with severe complications. Most of the informative data came from the univariable analyses in the fullPIERS model developed from a cohort of 2024 women admitted to hospital with pre-eclampsia[47,72–82]. As such, we have included in the adverse conditions maternal oxygen saturation, serum uric acid and serum albumin. Although headache and visual symptoms were not associated with severe complications in fullPIERS (*p* values of 0.30 and 0.96, respectively), we have retained them for face validity until the fullPIERS model can be externally validated.

We have noted but not added as adverse conditions other risk factors for severe complications among women with pre-eclampsia: young maternal age, maternal age ≥35 years in nullipara, immigrant status, nulliparity, extremes of maternal weight and, in the index pregnancy, multiple pregnancy and lower gestational age at presentation (so-called 'early' pre-eclampsia)[47,48,80–82].

In development of the fullPIERS model, oliguria was not examined as a predictor of adverse maternal (or perinatal) outcome. Oliguria is measurable in women who are hospitalised with pre-eclampsia (most accurately with an indwelling catheter) and is defined as <15 mL/h for 6 consecutive hours[83]. Oliguria is commonly observed in the hours following either vaginal or Caesarean delivery. Prolonged oliguria (for more than 12–24 hours) is more indicative of renal injury outside pregnancy[83], particularly when associated with a rising serum creatinine.

Each adverse condition is not associated with the same risk of severe complications. In the fullPIERS model, the following were *independently* associated with adverse maternal outcomes: preterm pre-eclampsia, chest pain or dyspnoea, or an abnormality of any of: oxygen saturation by pulse oximetry, platelet count, serum creatinine, or AST[47]. In fact, only pulse oximetry reaches an international standard of independent ability to personalise risk in women with pre-eclampsia as a solo test[76], and is retained in the fullPIERS model. Although other factors such as symptoms of headache and laboratory abnormalities may be predictive of adverse maternal events in univariable analyses[47,48,73–77,79,84–89], they were not independently predictive in the fullPIERS multivariable model[47].

Although an online calculator (www.cfri.ca/piers) is available for entry of continuous variables (like gestational age) into the fullPIERS model, the fullPIERS model must be externally validated before it can be recommended for routine clinical use, whether on admission or over the first 48 hours after admission[78]. Preliminary external validation suggests that the fullPIERS model has clinical utility, especially in women with more severe forms of pre-eclampsia[72].

It may be that factors such as uric acid would become important if the fullPIERS model were recalibrated to include women with the full spectrum of hypertensive disorders of pregnancy[84], another task currently underway. Evolving tests of platelet consumption, such as platelet distribution width may be informative of risk in women with pregnancy hypertension should initial findings be confirmed[90]. How more recently derived markers of platelet consumption (e.g., platelet distribution width) may interact with fullPIERS or have independent predictive ability is uncertain[90]. Definitive temporal and external validation studies of fullPIERS, and testing the interaction between fullPIERS and biomarkers being introduced into clinical practice (see below), are underway.

In a single site study of 46 women with either pre-eclampsia or eclampsia undergoing MRI, predictors specifically of posterior reversible leukoencephalopathy syndrome were younger age, higher systolic and diastolic blood pressures, eclampsia and lower platelets[91].

The associated miniPIERS model[48], which is solely based on demographics, symptoms and signs, is discussed in the "Priorities for under-resourced settings" section below, but may be informative for practitioners who are in well-resourced settings but who do not have immediate recourse to laboratory tests.

As all forms of pregnancy hypertension, especially pre-eclampsia, are risk factors for the development of peripartum cardiomyopathy, the routine use of pulse oximetry and judicious use of cardiac imaging will improve the detection of this life-threatening complication. Women of African and East Asian descent seem particularly prone to peripartum cardiomyopathy[92].

How *maternal* adverse conditions may predict adverse outcomes for the fetus or neonate among women with pre-eclampsia is unclear. The general perinatal literature identifies that abnormal fetal monitoring of various types may identify increased fetal risk. Table 3.2 reflects this literature as well as univariable analyses of the PIERS dataset for non-stress testing and maternal predictors of perinatal death or admission to NICU for >48 hours; other tests of fetal well-being were collected too infrequently to be considered. The biophysical profile is not listed because this test has not been demonstrated to be useful in women with hypertensive disorders of pregnancy or other high risk patients[37,93]; and, indeed may falsely reassure both practitioners and women when pregnancies are complicated by either early-onset IUGR[94] or pre-eclampsia[95]. Of fetal assessment modalities, umbilical artery Doppler studies are the best supported[37,96].

In 1153 women who participated in the Dutch Obstetric Consortium's HYPITAT trial at gestational ages $\geq 36^{+0}$ weeks[97], nulliparity, increasing body mass index (BMI), heavy dipstick proteinuria (≥3+), increasing serum uric acid and increasing serum creatinine were independent antenatal predictors of adverse neonatal outcomes of: 5-minute Apgar score <7, cord pH <7.05, or NICU admission[98].

The independent value, within a multivariable model, of various additional Doppler studies in assessing maternal and perinatal risks associated with a diagnosis of pre-eclampsia (not predicting that diagnosis) has yet to be assessed. Preliminary data suggest that uterine and ophthalmic artery Doppler may assist in risk stratification[99,100].

While conserved in the miniPIERS model (see below), proteinuria was not retained in the fullPIERS model developed in women with pre-eclampsia. However, like uric acid, proteinuria may be important to identify risk in women with the full spectrum of the hypertensive disorders of pregnancy, as women with 0.3 g/d of proteinuria had complication rates above those of women managed as outpatients (gestational hypertension and pre-existing hypertension), meriting closer surveillance and endorsing 0.3 g/d as an appropriate threshold for determining in-patient management[101], confirming previous studies[102]. Adverse perinatal outcomes were higher still in women with 0.5 g/d proteinuria, as observed in miniPIERS, below[47,101].

OTHER

In Canada, in 2014, a new category of 'other' was added to the classification system, to raise awareness that blood pressure that is not consistently elevated in the office setting and at home is associated with maternal and perinatal risks that appear to be intermediate between those of women with normal blood pressure and those with hypertension in the office and ambulatory or home settings.

'White coat' effect

'White coat' hypertension is seen when blood pressure is elevated in the office, but normal by ambulatory blood pressure monitoring (ABPM) or at home. (See Chapter 1 for numerical values.)

White coat effect in early pregnancy is common (approximately 30%), similar to estimates outside of pregnancy[103]. The limited literature suggests that there is a heightened risk of adverse maternal outcomes compared with normotensive pregnancy, but the risks are probably smaller than with pre-existing hypertension[104]. Of these women, 40% progress to gestational hypertension and 8% to pre-eclampsia.

ABPM has identified that approximately 30% of women with gestational hypertension demonstrate a white coat effect on their blood pressure, although estimates have been as high as 70% in the third trimester[31]. There is wide variability in the rates of associated maternal and perinatal complications, but many studies have identified risk that is intermediate between that of normotensive women and that of women with gestational hypertension[31].

Masked hypertension

'Masked' hypertension refers to blood pressure that is normal in the office but elevated by ABPM or at home. (See Chapter 1 for numerical values.)

Masked hypertension may be present in about 30% of women with pre-existing hypertension[103].

However, the associated perinatal risks are unknown. Outside pregnancy, cardiovascular risk associated with masked hypertension is similar to that associated with sustained hypertension.

Masked gestational hypertension was seen in 4–15% of women in prospective cohort studies; pregnancy outcomes were similar to those of women with sustained gestational hypertension[105,106]. This diagnosis could be considered (and ABPM or home blood pressure monitoring performed) if there are unexplained maternal or perinatal complications that are associated with the hypertensive disorder of pregnancy, but the usefulness of this approach has not been studied.

INVESTIGATIONS TO CLASSIFY THE HYPERTENSIVE DISORDERS OF PREGNANCY

Pre-existing hypertension

Women with pre-existing hypertension are most likely (>95%) to have essential hypertension, but secondary causes should be considered. A basic work-up has been suggested for women for whom suspicion of a secondary cause is low (see the annually updated Canadian Hypertension Education Program document for a more extensive discussion (https://www.hypertension.ca/en/chep)).

Conditions such as obesity, associated non-alcoholic steatohepatitis, or immune thrombocytopoenia may make interpretation of blood work for pre-eclampsia end-organ dysfunction difficult later in pregnancy. Consequently, it may be appropriate to conduct additional baseline testing in women with these conditions early in pregnancy.

Women with a strong clinical risk marker for pre-eclampsia should be considered for baseline proteinuria quantification (by spot protein : creatinine ratio or 24 h urine collection) given the insensitivity of dipstick proteinuria testing. A fasting blood glucose ≥7 mmol/l prior to pregnancy or ≥5.3 mmol/l in pregnancy should prompt appropriate investigation and subspecialty referral[107].

An abnormal P wave in lead V1 by electrocardiogram may increase the risk for gestational hypertension or pre-eclampsia[108].

In terms of imaging, echocardiography may be useful in selected women, such as those with known or suspected left ventricular dysfunction or heart failure (https://www.hypertension.ca/en/chep). Plasma lipids should not be measured routinely because both cholesterol and triglycerides increase physiologically during pregnancy and are not considered when making treatment decisions.

When pre-eclampsia is suspected

Pre-eclampsia may be a disease in evolution, with clinical manifestations unfolding in a serial fashion. When there is ongoing suspicion of pre-eclampsia, the nature and frequency of serial surveillance are unclear, but a change in clinical status for mother or fetus would be a reasonable indication for repeat testing. Pre-eclampsia imitators share manifestations with pre-eclampsia, but require different treatments (Table 3.3).

Maternal investigations

In addition to measurement of blood pressure, women with suspected pre-eclampsia should undergo blood and urine testing as outlined in Table 3.3[70]. This testing is designed to (1) detect end-organ involvement that increases the risk of adverse maternal and/or perinatal outcomes (e.g., elevated serum uric acid), (2) detect one of those adverse outcomes (e.g., acute renal failure), (3) evaluate the seriousness of the adverse outcome (e.g., haemoglobin in setting of placental abruption) (Table 3.2), or (4) explore important differential diagnoses (e.g., acute fatty liver of pregnancy or primary renal disease).

The maternal testing in Table 3.3 (alone or in combination) is of prognostic value once pre-eclampsia has been diagnosed, but its value for the purposes of diagnosis is based on expert opinion. Most abnormalities are not specific to pre-eclampsia, so the usefulness of the testing relies more on multiple (rather than single) abnormalities. In addition, as differentiating pre-eclampsia from gestational hypertension can be difficult, it is possible that maternal venous Doppler studies, particularly renal interlobar vein impedance index (RIVI), will assist in this regard, but initial findings require further validation[109,110]. Innovative methods such as brain mapping with electroencephalography and advanced retinal imaging have not been fully evaluated, but may assist in targeting magnesium sulphate therapy towards those women who would most benefit from it[111,112].

Table 3.3 Investigations to diagnose and monitor women with a hypertensive disorder of pregnancy (reproduced with permission from the SOGC)[60]

Investigations for diagnosis	*Description in women with pre-eclampsia*	*Description in women with other conditions*
Maternal testing		
Uterine testing		
Urinalysis (routine and microscopy with/without additional tests for proteinuria)	Proteinuria (as discussed under *Proteinuria*) without RBCs or casts	Haemoglobinuria (dipstick 'haematuria' without RBCs): haemolytic anaemia RBCs alone: renal stones, renal cortical necrosis (also associated with back pain and oliguria/anuria) RBCs and/or casts are associated with other glomerular disease and scleroderma renal crisis and (about half of) TTP-HUS Bacteria: UTI or asymptomatic bacteriuria Proteinuria is usually absent in secondary causes of hypertension such as phenochromocytoma, hyperaldosteronism, thyrotoxicosis, coarctation of the aorta, and withdrawal syndromes
Oxygen saturation		
Pulse oximetry	SpO_2 <97% associated with a heightened risk of severe complications (including non-respiratory)	May be decreased in any cardiorespiratory complication (e.g., pulmonary embolism)
CBC and blood film		
Haemoglobin	↑ due to intravascular volume depletion ↓ if microangiopathic haemolysis (with HELLP)	↑ due to volume depletion from any cause (e.g., vomiting ↓ if microangiopathic haemolysis from other cause ↓ with any chronic anaemia (nutritional or myelodysplasia) ↓ with acute bleeding of any cause
WBC and differential	↔	↑ due to neutrophilia of normal pregnancy ↑ with inflammation/infection ↑ with corticosteroids
Platelet count	↓ associated with adverse maternal outcome	↓ with gestational, immune (ITP), or thrombotic thrombocytopoenia (TTP), APS, AFLP, myelodysplasia
Blood film	RBC fragmentation	Microangiopathy due to mechanical causes (e.g., cardiac valvopathy, cavernous haemangioma), DIC or other disorders of endothelial function (e.g., APS, TTP-HUS, vasculitis, malignant hypertension)
Tests of coagulation		
INR and aPTT	↑ with DIC which is usually associated with placental abruption ↑ is associated with adverse maternal outcome	May be ↑ in APS, DIC from other causes including sepsis, amniotic fluid embolism, stillbirth, massive haemorrhage, haemangiomas, shock ↑ is prominent in AFLP
Fibrinogen	↔	↓ with all causes of DIC including massive haemorrhage, genetic disorders ↓ more profound with AFLP than with HELLP Usually normal in TTP-HUS (ADAMTS13 vWF cleaving protein may be moderately decreased in HELLP[106] but ADAMTS13 antibody should be absent

continued

Table 3.3 *continued*

Investigations for diagnosis	*Description in women with pre-eclampsia*	*Description in women with other conditions*
Serum chemistry		
Serum creatinine	↑ due to haemoconcentration and/or renal failure ↑ associated with adverse maternal outcome	↑ with other acute or chronic kidney disease Renal failure prominent in malignant hypertension, TTP-HUS (along with thrombocytopoenia), AFLP (along with liver dysfunction)
Serum uric acid	↑ associated wtih adverse maternal and perinatal outcomes	↑ with dehydration, medication (e.g., HCTZ), genetic causes
Glucose	↔	↓ with AFLP, insulin therapy
AST or ALT	↑ associated with adverse maternal outcome	↑ with AFLP and other 'PET imitators'† but to a lesser degree, and usually normal in TTP-HUS May be increased in other pregnancy-related conditions (e.g., intrahpatic cholestasis of pregnancy) or conditions not associated with pregnancy (e.g., viral hepatitis or cholecystitis)
LDH	↑ which may be prominent ↑ the is associated with adverse maternal outcome	↑ with AFLP, intravascular haemolysis ↑ LDH/AST ratio (>22) with TTP-HUS[107]
Bilirubin	↑ unconjugated from haemolysis or conjugated from liver dysfunction	(early) ↑ in AFLP, ↑ with haemolytic anaemia, other liver disease with dysfunction, genetic diseases
Albumin	↓ associated with adverse maternal and perinatal outcomes	↓ as negative actue phase reactant with acute severe illness, malnutrition, nephrotic syndrome, crystalloid infusion
Fetal testing	Abnormalities are not specific to the cause of poor placentation and/or placental dysfunction	
Uterine artery Doppler velocimetry	Unilateral/bilateral notching, or elevated pulsatility index or resistance index may support a diagnosis of placental insufficiency including pre-eclampsia	

AFLP, acute fatty liver of pregnancy; APS, antiphospholipid syndrome; CBC, complete blood count; DIC, disseminated intravascular coagulation; HCTZ, hydrochlorthiazide; HUS, haemolytic-uraemic syndrome; ITP, immune thrombocytopoenic purpura; PET, pre-eclampsia; SpO_2, oxygen saturation by pule oximetry; RBC, red blood cell; TTP, thrombotic thrombocytopoenic purpura

The pre-eclampsia imitators are conditions with numerous manifestations shared by pre-eclampsia (Table 3.3)[46,113]. To greater or lesser degrees, all of these conditions share the clinical features of hypertension, central nervous system symptoms and abdominal pain, and the laboratory features of proteinuria, anaemia, thrombocytopoenia, micro-angiopathic haemolysis and elevated lactate dehydrogenase (LDH). However, acute fatty liver of pregnancy tends to have prominent vomiting, liver dysfunction (with jaundice and diabetes insipidus) and renal failure[114].

Thromboses and skin involvement suggest catastrophic antiphospholipid antibody syndrome[115]. Thrombotic thrombocytopaenic purpura-haemolytic uraemic syndrome (TTP-HUS) has prominent neurological manifestations (termed TTP), vomiting and renal manifestations (termed HUS); laboratory evidence of disseminated intravascular coagulation and elevated liver enzymes would be unusual[116]. Scleroderma renal crisis and malignant hypertension show predominant renal manifestations[117,118].

Phaeochromocytoma may mimic pre-eclampsia in both well-resourced and resource-limited settings[119,120], presenting as episodic headaches, anxiety (resembling a panic attack), altered skin sensation, seizures, flank pain, pallor, diaphoresis, tachycardia, paroxysmal hypertension with paradoxical orthostatic/postural hypotension (a fall in systolic blood pressure >20 mmHg or in diastolic blood pressure >10 mmHg upon standing), and

hyperglycaemia. Elevated plasma metanephrins, urinary catecholamines and imaging will secure the diagnosis.

The importance of determining whether or not pre-eclampsia (particularly in those exceptional cases with onset before 20 weeks or more than 3 days postpartum) may actually be another disorder is that subspecialty referral is warranted for specific therapy (beyond supportive care). Such specific therapies include immunosuppression and heparin for catastrophic antiphospholipid syndrome, plasma exchange and steroids for TTP-HUS, angiotensin converting enzyme (ACE) inhibitors for scleroderma renal crisis and alpha-agonists for phaeochromocytoma. Of course, women with acute fatty liver of pregnancy (AFLP) should be delivered immediately regardless of gestational age.

Biomarkers

Taking into account the points made above, in a minority of women with pre-eclampsia, clinical uncertainty around the diagnosis arises. It is in this context that translational biomarkers may improve diagnostic accuracy and clinical performance. Such women could be those who appear to have pre-eclampsia superimposed on pre-existing hypertension and/or renal disease[49–51], are highly symptomatic but normotensive and/or non-proteinuric, or present with either gestational hypertension or gestational proteinuria in isolation. These women with "atypical" pre-eclampsia bear the same risks as others with classically clinically defined disease[121]. Indeed, such women may bear increased risks as responses to their symptoms and signs may be delayed as they do not fulfil diagnostic criteria that can be strictly applied by clinicians unaware of the atypical presentation of pre-eclampsia in a significant subset of women.

As we approach the definition of varying phenotypes of pre-eclampsia (e.g., severe versus non-severe, early- versus late-onset) by clinical and biochemical criteria, adherence to standardised biomedical research protocols will hasten our understanding of the causes of pre-eclampsia and development of targeted treatment strategies. To assist in that process, the PRE-EMPT Global Pregnancy Collaboration (http://pre-empt.cfri.ca/colaboratory) has presented what they consider to be the minimum requirements for a data set in a study of pre-eclampsia that will facilitate comparisons[122]. In addition, they have presented a comprehensive or "optimal" data set for in-depth investigation of pathophysiology[122].

As intimated above, within the past decade, an imbalance between pro- and anti-angiogenic factors has been proposed to underlie many features of the maternal syndrome of pre-eclampsia[42,123–127]. While such an imbalance appears to be observed quite consistently in women with early-onset pre-eclampsia[41,43], it is shared with pregnancies complicated by placentally mediated fetal growth restriction[44]. Therefore, while angiogenic imbalance may reflect the presence of the underlying placental dysfunction particularly important with early-onset pre-eclampsia, it is unlikely to be a singular aetiological pathway but will be shared with risks of intrauterine growth retardation and fetal death[128,129].

In the near future, those biomarkers with the greatest potential to be introduced into day-to-day clinical care to individualise maternal and perinatal risk are PlGF and sFlt-1, either a single analyte (i.e., PlGF) or as a ratio between anti- and pro-angiogenic factors (e.g., sFlt-1/PlGF ratio)[41–43,45,123–127,130,131]. We are aware of two such platforms that are being licensed and brought to the international market.

The recently published PELICAN prospective multicentre study evaluated the diagnostic accuracy of low plasma PlGF concentration (<5th centile for gestation) in women presenting with suspected pre-eclampsia between 20^{+0} and 34^{+6} weeks' gestation (and up to 41 weeks' gestation as a secondary analysis)[45]. The outcome was delivery for confirmed pre-eclampsia within 14 days. Of 625 women, 346 (55%) developed confirmed pre-eclampsia. In 287 women enrolled $<35^{+0}$ weeks' gestation, PlGF <5th centile had high sensitivity (0.96; 95% confidence interval, 0.89–0.99) and negative predictive value (0.98; 0.93–0.995) for delivery for pre-eclampsia within 14 days; specificity was lower (0.55; 0.48–0.61). Area under the receiver-operating characteristic curve for low PlGF (0.87, standard error 0.03) for predicting delivery for pre-eclampsia within 14 days among women presenting with suspected pre-eclampsia was greater than all other commonly used tests, singly or in combination (range, 0.58–0.76; $p < 0.001$ for all comparisons). The authors concluded that PlGF is better than other currently used tests and presents an innovative

adjunct to management of such women. This is consistent with studies using the sFlt-1/PlGF ratio[125,126].

Adding Doppler studies may further improve the maternal and fetal risk stratification capacity of angiogenic imbalance in women with established pre-eclampsia[126,127].

Other time-of-disease potential biomarkers of both the presence of pre-eclampsia and its severity include neutrophil gelatinase-associated lipocalin (NGAL)[132–134], the marker of central nervous system injury S100B[135], leptin[136], interferon-γ[136] and glycosylated fibronectin[55].

Urinary tests of interest for the differentiation of pre-eclampsia from other hypertensive disorders of pregnancy are the Congo red test, podocyturia and kidney injury molecule-1[137–139]. (See Chapter 2 for further detail about the Congo red test.)

Fetal monitoring

Fetal testing is also listed in Table 3.3. Uterine artery Doppler velocimetry may be useful in hypertensive pregnant women to support a placental origin for the hypertension, proteinuria, and/or adverse conditions[140]; obstetric consultation would then be warranted.

Oligohydramnios, absent or reversed end-diastolic flow in the umbilical artery, or a deep, absent or reversed A wave in the ductus venosus would be more consistent with placental dysfunction than with decreased biological growth potential, uncertain dates, or aneuploidy as a cause of IUGR and may also be useful to inform timing of delivery[37,141–144]. Reduced maternal plasma PlGF implies IUGR of placental origin, rather than constitutionally small fetal size[44].

It is very important to note that the addition of biophysical profile to a schedule of fetal surveillance has not been shown to improve outcomes in high risk pregnancies[93]. Indeed, it appears that the biophysical profile tends to falsely reassure practitioners and lead to worse outcomes when pregnancies are complicated by either pre-eclampsia or IUGR[94,95].

THE PATIENT PERSPECTIVE

We support incorporating the patient perspective into care. Engaged patient advocacy organisations are the Preeclampsia Foundation (www.preeclampsia.org/), Action on Pre-eclampsia (APEC) (www.apec.org.uk/), Australian Action on Pre-eclampsia (AAPEC; www.aapec.org.au), New Zealand Action on Pre-eclampsia (NZ APEC) (www.nzapec.com/) and Association de Prevention et d'Actions contre la Pre-Eclampsie (APAPE) (www.eclampsie.moonfruit.fr/)[145].

The Preeclampsia Foundation advocates for better patient (and health care provider) education about the antenatal, early postnatal and long-term maternal implications of pre-eclampsia; an emphasis on early maternal signs and symptoms of pre-eclampsia; better doctor–patient communication about pre-eclampsia; and evidence-based guidelines for pre-eclampsia screening, detection; and management[145]. This is an approach that would seem to have global appeal, as illustrated by the following quote.

> ". . . they also have pre-eclampsia in the developed countries, but they don't die the way our own patients are dying, not because we do not know how to manage them but [because] they don't come early and by the time they come, it is so late".
>
> Focus Group Discussant, Society of Obstetricians and Gynaecologists of Nigeria, 03 Nov 2012

Post-traumatic stress

There is growing evidence that women may experience post-traumatic stress disorder up to 7 years postpartum[146–156], the prevalence of symptoms being highly variable, ranging from the minority to the majority of women, and higher after maternal hospitalisation for more than 1 week, preterm hypertensive disorder of pregnancy onset or delivery, NICU admission, adverse neonatal outcomes, or uncertainty about the child's long-term health[151]. Symptoms are not specific to the hypertensive disorders of pregnancy, and follow preterm delivery for other indications[155]. Although post-traumatic stress symptoms do not have an impact on infant cognitive or psychomotor development at 1 year of age, maternal symptoms are amenable to clinical psychological therapy, and earlier referral may abbreviate treatment[152].

Women and their maternity care providers seem to view experiences of pre-eclampsia differently. For health care professionals, pre-eclampsia represented the care that must be delivered, primarily responding to the biology of

pre-eclampsia. For women, generally lacking knowledge and understanding about pre-eclampsia, pre-eclampsia represents fear and risk[157].

Patient education and engagement

In a survey of women who had experienced pre-eclampsia, eclampsia and/or HELLP, pre-eclampsia was viewed as very important to all, and traumatic to many, respondents including women, their partners, close relatives, or friends. The provision of information and support was valued prior to, and at the time of, diagnosis as well as being revisited during ongoing care[157].

Even in well-resourced settings, women are not knowledgeable about the hypertensive disorders of pregnancy, even those with pre-existing hypertension. They have a poor understanding of pre-eclampsia[158,159], and hypertensive disorders of pregnancy, even those with pre-existing hypertension, and are not satisfied with the medical information they receive. This suggests that clinicians should both place more value on informing women about either their condition or its potential course, and check that women have understood the information[160,161]. Although limited health literacy may complicate risk, communication tools have been developed for such purposes[160,161].

Current ANC practice guidelines offer little information on educating patients about pre-eclampsia. However, when women receive and understand education about pre-eclampsia, they are more likely to promptly report symptoms[159]. Formal study is required to see whether this will indeed lead to early diagnosis and management, and improved maternal and perinatal outcomes, as hoped[158,159].

Women enjoy participating in aspects of their care, be it receiving information as study participants[162], or participating in management of their blood pressure[163]. Women have expressed a preference for home or day care[164] and self (rather than 24-h ambulatory) blood pressure monitoring[165]. They do not object to being randomised[166].

BEST PRACTICE POINTS

(Please see Appendix 3.1 for the evaluation of the strength of the recommendation and the quality of the evidence on which they are based.)

1. Hypertensive disorders of pregnancy should be classified as pre-existing hypertension or gestational hypertension with or without pre-eclampsia, or 'other' hypertension on the basis of different diagnostic and therapeutic considerations.
2. The presence or absence of pre-eclampsia must be ascertained, given its clear association with more adverse maternal and perinatal outcomes.
3. In women with pre-existing hypertension, pre-eclampsia should be defined as resistant hypertension, new *or* worsening proteinuria, one or more adverse conditions, or one or more severe complications.
4. In women with gestational hypertension, pre-eclampsia should be defined as new-onset proteinuria, one or more adverse conditions, or one or more severe complications.
5. The assessment of maternal angiogenic factor balance appears to inform the diagnosis of pre-eclampsia, and other placental complications of pregnancy, where uncertainty exists, especially when 'superimposed pre-eclampsia' is suspected.
6. Severe pre-eclampsia should be defined as pre-eclampsia complicated by one or more severe complications.
7. For women with pre-existing hypertension, serum creatinine, fasting blood glucose, serum potassium and urinalysis should be performed in early pregnancy if not previously documented.
8. Among women with pre-existing hypertension or those with a strong clinical risk marker for pre-eclampsia, additional baseline laboratory testing may be based on other considerations deemed important by health care providers.
9. Women with suspected pre-eclampsia should undergo laboratory maternal testing and a schedule of pertinent fetal testing described in Table 3.3.

10. Doppler velocimetry-based assessment of the fetal circulation may be useful to support a placental origin for hypertension, proteinuria, and/or adverse conditions (including IUGR), and for timing of delivery.
11. The biophysical profile is not recommended as part of a schedule of fetal testing in women with a hypertensive disorder of pregnancy.
12. If initial testing is reassuring, maternal and fetal testing should be repeated if there is ongoing concern about pre-eclampsia (e.g., change in maternal and/or fetal condition).
13. In resource-constrained settings, the miniPIERS model can provide personalised risk estimation for women with any hypertensive disorder of pregnancy. In many of these women, the ultimate diagnosis cannot be confirmed until at least 3 months after delivery.
14. Health care providers should be alert to symptoms of post-traumatic stress following a hypertensive disorder of pregnancy; and refer women for appropriate evaluation and treatment.
15. Health care providers should inform their patients, antepartum and postpartum, about pre-eclampsia, its signs and symptoms, and the importance of timely reporting of symptoms to health care providers.
16. Information should be re-emphasised at subsequent visits.

PRIORITIES FOR UNDER-RESOURCED SETTINGS

Hypertensive disorders of pregnancy diagnosis and severity

Identifying women with pregnancy hypertension before it becomes life-threatening is particularly important for colleagues in resource-constrained settings. For example, in a single-site retrospective analysis of demographic and clinical data of 1027 patients with eclampsia over a 10-year period, Adamu *et al*. observed a maternal case fatality rate of 17.9%, which was particularly high among women who had received no antenatal care (18.7%), compared with those who had received such care (5.9%)[167]. In this series, the perinatal mortality rate was 38%, of which 81% were stillbirths.

For many colleagues in the global maternal care community, access to laboratory facilities and modalities for outpatient blood pressure monitoring is limited or even absent. Therefore, it has been imperative to determine how best to classify pregnancy hypertension in resource-constrained settings. Clarifying the diagnosis of pre-eclampsia is a clinical priority as the WHO Multicountry Survey on Maternal and Newborn Health has determined that maternal near-miss cases were eight times more frequent in women with pre-eclampsia, and up to 60 times more frequent in women with eclampsia, when compared with women with other hypertensive disorders of pregnancy[168].

It is imperative that all women everywhere have access to accurate blood pressure measurements and dipstick proteinuria assessment as a global priority. In the UK, which had maternal mortality data a century ago that were similar to those of many less-developed countries today, over 90% of the observed reduction in maternal mortality occurred prior to the provision of either effective antihypertensives or magnesium sulphate (Figure 3.2). As stated above, the provision of antenatal care including blood pressure and proteinuria assessment, with appropriate referral pathways, has been associated with markedly reduced maternal mortality in Sri Lanka, even during the period when care was complicated by the presence of civil war[3] (Figure 3.3). (See Chapters 1 and 2 for priority recommendations for further detail about accurate and cost-effective semi-automated blood pressure devices and costs of proteinuria detection, as well as advocacy tools for colleagues to use to elicit appropriate funding for these key resources for pregnant women wherever they reside[169,170]).

In many less-developed countries, women do not present for maternity care until at least 20 weeks' gestation[171–182]. As a result, the firm classification of a hypertensive disorder of pregnancy may not be achievable until after the woman has delivered. In response to this reality, we have developed and validated the miniPIERS model to personalise the risk for severe complications experienced by women with any hypertensive disorder of pregnancy who present in under-resourced settings[48]. Data were collected

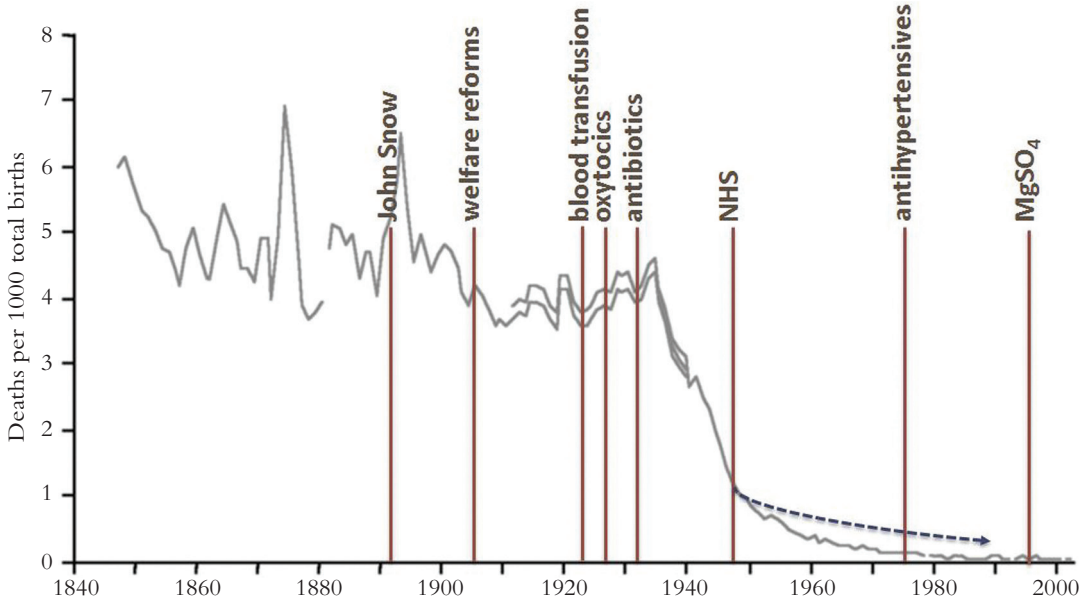

Figure 3.2 The rate of maternal deaths in the UK compared with sentinel events in maternity care and public health. The dotted line represents the projected rate of fall without the introduction of universal pregnancy and postpartum care through the National Health Service

prospectively on 2081 women with any hypertensive disorder of pregnancy admitted to a participating centre in Brazil, Fiji, Pakistan, South Africa, or Uganda. The final miniPIERS model includes parity (nulliparous versus multiparous); gestational age on admission (as best ascertained at the time of the encounter), headache/visual disturbances, chest pain/dyspnoea, vaginal bleeding with abdominal pain, systolic blood pressure, and dipstick proteinuria. In the miniPIERS cohort, up to 40% of the women were unbooked at the time that their hypertension was first diagnosed. However, best estimation of gestational age at that encounter led to gestational age being a powerful and independent identifier of maternal risk in the miniPIERS cohort.

An online calculator (cfri.ca/piers) is available for entry of continuous variables (such as gestational age) into the miniPIERS model to provide real-time personalised risks to all women whose caregivers have access to the internet. An mHealth app is in development and will be made available through the PRE-EMPT website (pre-empt.cfri.ca).

Once women in less-resourced settings are diagnosed with pre-eclampsia every effort should be made to give them access to oximetry and appropriately targeted laboratory testing[47].

Over 90% of women who suffer hepatic haematoma and/or rupture will have preceding HELLP syndrome[183].

Defining a woman with 'severe' pre-eclampsia as one with a miniPIERS predicted probability >25% classifies women with 85.5% accuracy; this accuracy is greater if pulse oximetry is added to the model[184]. We believe that miniPIERS could be used in resource-constrained settings to identify women who would benefit most from interventions such as magnesium sulphate, antihypertensives, or transportation to a higher level of care, especially if supported by a usability-tested mobile health (mHealth) application such as PIERS on the Move[185,186].

Facility versus community

In our view, maternity care providers should be able to screen women for pre-eclampsia and the other hypertensive disorders of pregnancy irrespective of where that woman is encountered. In addition, should hypertension be detected, then personalised risk assessment should be universal through the strengths and flexibility of mHealth. In the community, the determination of an individual woman's hypertensive disorder of pregnancy will

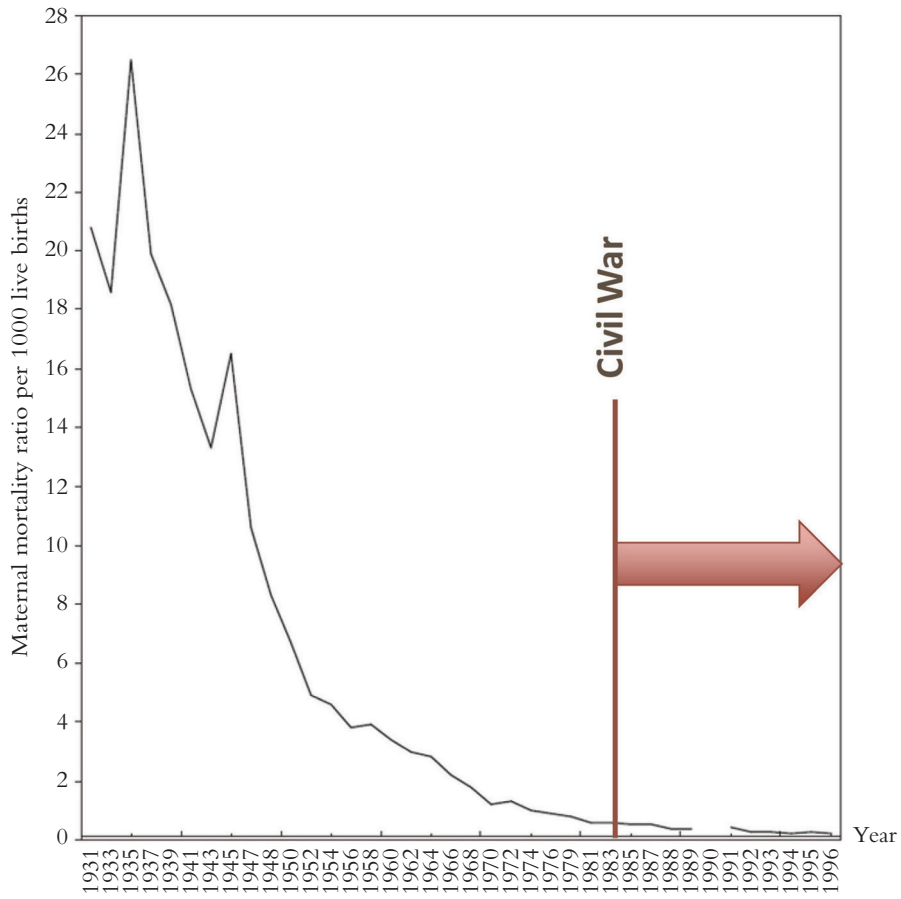

Figure 3.3 The trend of the maternal mortality ratio in Sri Lanka, 1931–1996 (modified from Fernando *et al.*[3])

be driven largely by the presence or absence of proteinuria and knowledge of any prior diagnosis of hypertension.

With the miniPIERS model and app, especially supplemented by oximetry, maternity care providers can assess and triage risk for hypertensive women wherever they are, whether that is in a hut in sub-Saharan Africa or in a private practice on Harley Street[48,184–186]. The outpatient use of a point-of-care assessment of angiogenic factor imbalance and GlyFn may aid in decision-making about the necessity for, and timing of, admission[45,55,126].

Where resources are limited, miniPIERS-based maternal assessment may remain the cornerstone of care either out-of-hospital/heath centre or in facilities where laboratory support is not readily accessible. However, the certainty of discriminating between pre-eclampsia and other hypertensive disorders of pregnancy is increased by access to laboratory results and ancillary clinical investigations, so practitioners who have the advantage of working in well-resourced settings should use evidence-based assessment of risk that takes into account maternal demographics, symptoms, signs, fetal assessment, and laboratory tests. Using the fullPIERS model limits the scope, and cost, of that testing for maternal risk assessment[47].

Finally, there is a need to strengthen pre-eclampsia knowledge among women and their communities, as illustrated by the following quote and discussed above.

> "We arrange community based meetings to educate the women, their family members and traditional birth attendants. We try to share knowledge with them about pregnancy, and complications during pregnancy, so much so, that we can prevent women from dying."
>
> Lady Health Supervisor, Matiari, Pakistan, 19 Mar 2012

WHAT INTERNATIONAL GUIDELINES SAY

We have compared the recent international guidelines in English, French, Dutch and German[58]. Included in this review were the guidelines developed in: Canada (Society of Obstetricians and Gynaecologists of Canada (SOGC) (2014), Association of Ontario Midwives (AOM))[60,187,188]; the United Kingdom (National Institute for Health and Clinical Excellence (NICE), Pre-eclampsia Community Guideline (PRECOG), PRECOG II)[59,189,190]; the United States of America (American College of Obstetricians and Gynecologists (ACOG), American Society of Hypertension (ASH))[62,191] and New Zealand (Society of Obstetric Medicine of Australia and New Zealand (SOMANZ))[192]; Australia (Queensland Maternity and Neonatal Clinical Guidelines Program (QLD))[193,194]; The Netherlands (Nederlandse Vereniging voor Obstetrie en Gynaecologie (NVOG))[195]; and Germany (Deutschen Gesellschaft fur Gynakologie und Geburtshilfe (DGGG))[196]. Most clinical practice guidelines (CPGs) were national (8/13), but three were multinational, from Australasia (Society of Obstetric Medicine of Australia and New Zealand (SOMANZ))[197], the World Health Organization (WHO)[198,199], and the European guideline for cardiovascular diseases (ESC)[200].

We determined that there is between-guideline consistency with regards to the definitions of chronic (pre-existing) and gestational hypertension (Appendix 3.2). Chronic hypertension pre-dates pregnancy or is documented before 20 weeks. One guideline specifies that this must be essential (i.e., without known cause (QLD)) and three list either secondary causes and/or comorbid conditions that would influence decisions about blood pressure control (AOM, QLD, SOGC).

By general consensus, gestational hypertension is new hypertension that develops at or after 20 weeks; although implied by all guidelines, some specify that there must be neither proteinuria (QLD) nor other features of pre-eclampsia (N = 2) (ACOG, NICE). Three guidelines specify that blood pressure must return to normal postpartum, at 12 weeks (N = 2) (QLD, NVOG) or at an unspecified time (ACOG).

All guidelines define pre-eclampsia as gestational hypertension with proteinuria. More often than not, this is a mandatory criterion (N = 5) (PRECOG, PRECOG II, WHO, NICE, NVOG) (compared with not mandatory (N = 4) (AOM, QLD ACOG, SOGC)) (Appendix 3.3). Two CPGs specify that the proteinuria must resolve after delivery (PRECOG, PRECOG II). Although four also include gestational hypertension with one/more systemic feature of pre-eclampsia, there is no consistency with regards to those features that include fetoplacental abnormalities and/or maternal symptoms, signs and abnormal laboratory findings (ACOG, AOM, QLD, SOGC). The most common maternal manifestations listed are headache/visual symptoms (N = 4 CPGs), right upper quadrant/epigastric abdominal pain (N = 3), severe hypertension (N = 2), eclampsia (N = 2), pulmonary oedema (N = 3), low platelets (N = 4), elevated serum creatinine (N = 4), and elevated liver enzymes (N = 4); only one CPG specifies hyperreflexia. Fetal manifestations of pre-eclampsia are specified by three CPGs, all of which list IUGR (not defined) (N = 3) and abruption without evidence of fetal compromise (N = 3); one specifies stillbirth.

'Superimposed' pre-eclampsia is not clearly defined. Three CPGs do not address this at all, and six define it variably as worsening hypertension (N = 3) (AOM, ACOG, SOGC), new/worsening proteinuria (N = 3) (AOM, ACOG, SOGC) or one/more other systemic features (N = 4) (NVOG, AOM, ACOG, SOGC). 'Worsening' hypertension is defined clearly by two CPGs as either: (1) a sudden increase in blood pressure or the need to increase antihypertensive dose (ACOG), or (2) the need for three antihypertensive medications for blood pressure control at ≥20 weeks (SOGC). Proteinuria is a mandatory criterion according to ACOG (Appendix 3.3).

'Severe' pre-eclampsia is defined by most (7/9) CPGs, but there is little consistency. Heavy proteinuria is included by some (N = 3) (WHO, NVOG, AOM), but specifically excluded by others (N = 2) (ACOG, SOGC). Five CPGs define end-organ complications of severe pre-eclampsia; the most common maternal are: headache/visual symptoms (N = 5 CPGs), right upper quadrant/epigastric abdominal pain (N = 4), severe hypertension (N = 5), eclampsia (N = 2), pulmonary oedema (N = 3), low platelets (N = 4), renal insufficiency (N = 3), and elevated liver enzymes (N = 3); these mirror the diagnostic criteria used in

some guidelines. Fetal manifestations of pre-eclampsia are specified by three CPGs, all of which list stillbirth and none of which specify abruption without evidence of fetal compromise; IUGR is included by WHO and SOGC, but specifically excluded by ACOG. The SOGC 'severity' criteria are indications for delivery, and include some features that are in other CPGs: (1) define pre-eclampsia but not severe pre-eclampsia (e.g., stroke), (2) define both pre-eclampsia and severe pre-eclampsia (e.g., eclampsia, pulmonary oedema, platelet count $<100\times10^9$/L, and acute kidney injury), or (3) define neither pre-eclampsia nor severe pre-eclampsia but are widely regarded as indications for delivery (e.g., uncontrolled severe hypertension).

In the three CPGs that specify that proteinuria is mandatory to define pre-eclampsia (WHO, NICE, NVOG), severe pre-eclampsia is the development of: (1) pre-eclampsia at <34 weeks (WHO), or (2) one/more features of end-organ dysfunction that is either not defined (WHO, NICE) or listed as "symptoms" (NVOG), heavy proteinuria (NVOG, WHO), or severe hypertension (NVOG, WHO) (Appendix 3.3).

In the four CPGs that do not include proteinuria as mandatory to define pre-eclampsia (AOM, QLD ACOG, SOGC), severe pre-eclampsia is the development of: (1) pre-eclampsia at 34 weeks (AOM), (2) proteinuria plus one/more features that alone would signify pre-eclampsia (cerebral/visual disturbances, pulmonary oedema, platelet count, 100×10^9/L, renal insufficiency, or elevated liver enzymes) (ACOG), or (3) one/more features of end-organ dysfunction described as: heavy proteinuria (AOM), one/more features of HELLP (QLD), new persistent and otherwise unexplained right upper quadrant/epigastric abdominal pain (ACOG), severe hypertension (AOM, ACOG), or those dysfunctions requiring delivery (SOGC) (Appendix 3.3).

Eclampsia is consistently defined by new onset and otherwise unexplained seizures in the setting of pre-eclampsia (N = 5 CPGs) (NICE, QLD, WHO, ACOG, SOGC). No guideline defines the widely used term, 'imminent eclampsia.'

PRIORITIES FOR FUTURE RESEARCH

All future research activities should be compliant with new international, consensus-derived minimal standards for pre-eclampsia research[122]. Through the PRE-EMPT Global Pregnancy Collaboration, investigators will be able to gain access to data management platforms by the end of 2016 (https://pre-empt.cfri.ca/colaboratory). It is a global imperative that representative biobanks are developed that have whole blood, plasma, serum, placental tissue to inform our understanding of pathways to healthy and complicated pregnancies, and the design of tailored interventions, for the most vulnerable women in less developed countries.

Biomarkers and biology

In our opinion, a singular priority is to better determine the biomarkers that are either specific to pre-eclampsia or more general to placental disease and are relevant to women in specific global regions. How these variations in the pathways towards, and responses to, disease modify the performance of current, translational and future diagnostic and classification tests is largely unknown.

Through better understanding of the biology of pre-eclampsia and the other hypertensive disorders of pregnancy, we will be enabled to better define and sub-classify the forms of hypertensive disorders of pregnancy that complicate pregnancies globally[41]. It is almost certain that the pathways to gestational hypertension and pre-eclampsia vary between women in well-resourced, more socially liberal countries, and those from less-resourced and more socially conservative countries. While the clinical manifestations of the disease appear to be common between communities of women, we need to determine whether the pathways to disease are shared. Differential origins of disease may arise due to variability in the social, environmental, infectious, and inflammatory determinants of maternal health and vulnerability.

The interaction between genes, the epigenome, commensal and pathological organisms, and the wider environment must vary between and within clusters of women. Indeed, biomarkers passed over in more-developed countries may become important time-of-disease risk identifiers in less-developed countries where the burden of severe disease with multiple end-organ complications is far greater. Such a biomarker is S100B[135].

Obtaining robust socio-demographic, clinical and biomarker data from before pregnancy, during

pregnancy (normal and complicated), and at time of disease is an urgent priority, especially for women in less-developed countries who bear a disproportionate burden of risk in terms of the development of pre-eclampsia, from dying from it, or losing their baby to it.

Precision medicine

For better assessment of personalised risks borne by women with a hypertensive disorder of pregnancy, we need to strengthen the miniPIERS model with pulse oximetry[48,184] and/or point-of-care assessment of angiogenic factor balance and GlyFn[42,43,45,55], should they be shown to improve the performance of the miniPIERS model. This may place advanced diagnostic capability in the hands of minimally trained, mHealth app-supported health workers in women's homes.

The incremental value of supplementing and/or recalibrating the fullPIERS model with angiogenic factors (e.g., PlGF) and/or GlyFn needs to be assessed. In addition, expanding the scope of fullPIERS to include women with all hypertensive disorders of pregnancy would improve its clinical utility. Recalibration of the model may well be required.

Similar parallel models to miniPIERS and fullPIERS are required to assess fetal risks and to optimise the timing of delivery and long-term outcomes for the fetuses of pregnancies complicated by pregnancy hypertension. Initially, this research is likely to be focused on well-resourced settings and, subsequently, on less-resourced settings. However, it must be remembered that there are many highly resourced centres providing care in less-developed countries. Partnering with such institutions will accelerate discovery that is pertinent to the global maternal population.

Markers of maternal cardiorespiratory health

A priority for research is the better assessment of the cardiorespiratory status of pregnant women, especially those with pre-eclampsia.

A prospective population-based study with nested case–control analysis used the UK Obstetric Surveillance System to identify all 25 women in the UK over a 6 year period with myocardial infarction (MI) in pregnancy, compared with a control group of 1360 women. Following mutivariable logistic regression, hypertension and pre-eclampsia were independently associated with MI in pregnancy as well as maternal age, smoking and twin pregnancy[201]. This may stem from global diastolic dysfunction, left ventricular remodelling, interstitial pulmonary fluid and increased brain natriuretic peptide (BNP) that may represent an adaptive response to maintain myocardial contractility with pre-eclampsia, at least at term in less- and more-developed settings[202–205]. These preliminary findings are consistent with what has been observed in the miniPIERS and fullPIERS studies with respect to pulse oximetry[47,76,184].

These findings need to be confirmed and expanded across the clinical spectrum of disease (early- and late-onset pre-eclampsia) as well as the geographical and socio-economic spectra in which pregnant women find themselves.

The impact of classification

Finally, implementation research observing the impact on maternal and perinatal outcomes and health services costs (direct and indirect) of introducing new classification paradigms is important, so that health decision-makers can make evidence-informed choices about defining national classification systems. Such implementation research might usefully include a stepped wedge design through a series of jurisdictions.

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4

Epidemiology of the hypertensive disorders of pregnancy

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SYNOPSIS

This chapter provides a review of the literature on incidence and prevalence of the hypertensive disorders of pregnancy including chronic hypertension, gestational hypertension, pre-eclampsia and HELLP syndrome. Estimates are provided for both high-income and low- or middle-income country settings published within the past 10 years. Where possible, we have emphasised population-based data derived from national or regional data sets. Overall, the hypertensive disorders of pregnancy occur in 5–10% of pregnancies worldwide, with limited data suggesting an upward trend in incidence. The most common are gestational hypertension and pre-eclampsia, with pre-eclampsia being the most dangerous as it is associated with the highest prevalence of maternal and perinatal complications. There are many individual disease risk factors for the hypertensive disorders of pregnancy related to demographic, familial, personal medical/obstetric history, or to the current pregnancy; these are discussed in detail in Chapters 5 and 6 as these risk factors are used to identify women at increased risk who warrant enhanced antenatal surveillance and preventative therapy[1].

SEARCH STRATEGY

For this review, two literature searches were performed using the search strategies provided in Appendix 4.1. Publications were included in the review if they were published in English in the past 10 years. For incidence and prevalence estimates, publications were reviewed if they included either a population-based or cross-sectional hospital cohort reporting incidence or prevalence of all combined hypertensive disorders of pregnancy or any one of pre-eclamspia, gestational or chronic hypertension or haemolysis elevated liver enzymes and low platelets (HELLP) syndrome. For morbidity and mortality estimates publications that reported prevalence of any major adverse event known to be associated with a hypertensive disorder of pregnancy (as described in Chapter 3) within a population-based or cross-sectional hospital-based cohort of women with confirmed diagnosis of any hypertensive disorder of pregnancy were reviewed.

THE BURDEN

Combined hypertensive disorders of pregnancy estimates

Determining the true incidence of the hypertensive disorders of pregnancy is complicated by variations in the reported classification of the disorders (as

KEY POINT

The most commonly cited and accepted estimate of hypertensive disorder of pregnancy occurrence is 5–10%[1]

described in Chapter 3) and study design, with few reliable estimates provided by population-based cohorts and inflated estimates of prevalence reported by hospital-based studies. As such, incidence and prevalence estimates vary significantly based on country of origin and quality of available data. Although the definitions of chronic hypertension and gestational hypertension are reasonably standard (i.e., hypertension before or at/after 20 weeks of pregnancy, respectively), the definition of pre-eclampsia is not, and this may contribute to further variation.

In low- and middle-income countries (LMICs), incidence estimates are restricted to hospital-based cross-sectional surveys. Therefore, these are likely to be overestimates owing to the high proportion of births (and disproportionately, normal births) occurring in the home in most LMICs. In the WHO Multicountry Survey on maternal and newborn health, 313,030 women were included who were admitted to 357 health facilities in 29 countries across Africa, Asia, Latin America and the Middle East (2010–2012)[2]. In all 2.7% of the total number of women included in the study were reported to have suffered from chronic hypertension, pre-eclampsia, or eclampsia; gestational hypertension was not included in this estimate. This prevalence estimate ranged between 1.8% in the Middle East and 4.5% in the Americas region. In contrast, smaller single hospital-based surveys have reported higher hypertensive disorder of pregnancy rates, ranging from 4.0% to 12.3%[4–7]; however, even with large numbers, such as the 164,250 women in a single hospital-based cohort study in southern India (1996–2010), estimates must be viewed as potentially inflated owing to selection bias. The mobile health-supported community surveillance activities of the Community-Level Interventions for Pre-eclampsia (CLIP) trials in Mozambique, Pakistan and India will provide accurate population estimates of hypertensive disorders of pregnancy prevalence in these countries (http://www.thelancet.com/protocol-reviews/13PRT-9313)

A hypertensive disorder of pregnancy incidence of 5–10% is supported in high-income countries (HICs) in several large national cohorts that have reported rates of 4.6–9.2% based on publications since 1995[8–11].

Chronic hypertension and gestational hypertension appear to be much less common than pre-eclampsia, although limited population-level estimates exist.

Chronic hypertension (≈1%)

Reliable estimates for LMIC settings for chronic hypertension can be based solely on the WHO multicountry survey described above (of hospital-based cross-sectional data) which found a prevalence of 0.29% in the total cohort ranging between 0.21% in the African region and 0.32% in the Western Pacific region[2].

More reliable estimates are available for HICs. In a national cohort of all hospital deliveries in Canada in all provinces except Quebec (2003–2010), the incidence of chronic hypertension was 0.4%[11]. These data are consistent with 0.6% reported in the Alberta Perinatal Health Registry of all births in the province of Alberta, Canada (2000–2009)[12]. In the American National Inpatient Sample data set, chronic hypertension complicated 1.5% of births (2007–2008)[13], and 0.83–0.85% of births in New York State, USA (1995–2004)[14]. A similar rate of 1.3% was reported in the UK (1996–2010)[15].

Gestational hypertension (≈3%)

We found very limited data on prevalence of gestational hypertension for LMICs and no data giving a reliable estimate of incidence. In a hospital-based cohort of 193,554 births registered in two provinces of Southern China (1993–1996), gestational hypertension occurred at a rate of 9.5%[16]; this was a secondary analysis of data from a study evaluating the impact of folic acid supplementation on the incidence of neural tube defects and there is likely to be selection bias.

Gestational hypertension rates in HICs differ substantially from those described above. In a national cohort of all hospital deliveries in Canada in all provinces except Quebec (2003–2010), the incidence of gestational hypertension was 1.1%[11]. In New York State, USA (1995–2004), gestational hypertension complicated 1.4–2.5% of births (2007–2008)[13].

Pre-eclampsia (≈2–4%)

In the largest hospital-based cohort to report prevalence of pre-eclampsia in LMICs, the WHO Multicountry Survey reported an overall prevalence of 2.2% ranging from 1.4% in the Middle East region

to 3.9% in the African region[2]. Other cohorts reviewed since 1995 reported prevalence estimates ranging from 1.2% to 8.4%[16–19]. In a WHO systematic review of 129 studies covering approximately 39 million women from 40 countries (2002–2010), the crude incidence of pre-eclampsia was 2.3% (4.6% using a model-based estimate to account for lack of data sets from certain regions causing under-representation of countries believed to have higher rates of pre-eclampsia), ranging from 1.2% in the Middle East to 4.2% in the Western Pacific[3]. However, there was substantial regional variation, from 0.7% reported in a small study from Morocco to 15.6% reported in a Turkish data set. If estimates are restricted to those from national cohorts, data were available from seven countries that collectively reported pre-eclampsia rates of 1.4–4.0%[3].

This range has been supported by other reported national population-level cohorts, primarily from HICs. For example, in the Norwegian National Birth Registry (1967–2008), the incidence of pre-eclampsia was 2.8%[20] and 2.2% in another national data set from South Korea (2007–2010)[21]. Regional population-level data sets from Canada, the USA and Australia report incidence estimates between 1.3 and 3.4%[11,12,14,20,22–24].

Early-onset (vs. late-onset) disease Late-onset pre-eclampsia is more common than early-onset disease, the latter usually being defined as onset or delivery prior to 34 weeks. Estimates vary, but early-onset disease appears to represent no more than one-third of pre-eclampsia. In the National Birth Registry of Denmark covering all singleton births (1993–2007), the incidence of early-onset pre-eclampsia was 1.0% and late onset 1.9%[15]. In Washington State, USA among all singleton births (2000–2008), early-onset disease pre-eclampsia incidence was 0.3% and late-onset 2.7%[22,23].

HELLP syndrome (<1% of all births, <50% of women with pre-eclampsia) There are few epidemiological data about the prevalence of HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome, a severe manifestation of pre-eclampsia. No population-based estimates of incidence were identified in the literature. A 2009 review of management of HELLP syndrome quotes a prevalence of 0.5–0.9% of all pregnancies, based on small case series and retrospective hospital- and USA-based cohort studies published in the early 1990s[25]. A more recent, but small, retrospective hospital-based cohort included 5155 women admitted to a tertiary academic centre in Turkey (1997–2004) and found an incidence of HELLP of 0.5%[26]. Other LMIC- and HIC-based cohort studies suggest a higher prevalence of HELLP syndrome ranging from 2.5% to 50%[27–30]. However, some of these studies are tertiary facility-based with cohorts of women selected based on complicated pre-eclampsia. In addition, in settings where expectant management of early-onset pre-eclampsia is not the norm, the opportunity for pre-eclampsia to evolve into HELLP syndrome is abbreviated. Therefore, variability in estimates of HELLP syndrome incidence is likely to have been magnified by differences in study inclusion criteria, study settings and patterns of clinical management, and are not reliable.

Temporal trends in the hypertensive disorders of pregnancy

Data related to temporal trends are limited, but suggest an increase in incidence of all hypertensive disorders of pregnancy and specific disorders over time.

In a prospective cohort from a single hospital in India, the incidence of hypertensive disorders of pregnancy has increased from 10.3% of all births (1996–2004) to 11.8% (2005–2010)[4]. This study did not provide an analysis of significance relating to the temporal trend.

Similar increasing trends in chronic hypertension have been observed in HICs. In the US National Inpatient Sample data set, an increase in chronic hypertension was reported from 0.9% (1995–1996) to 1.5% of births (2007–2008) as discussed above[13]. The rising incidence of chronic hypertension in HIC settings is thought to reflect changing demographics, as pregnant women are tending to be both older and more frequently either overweight or obese.

The incidence of pre-eclampsia appears to be rising in HICs, including the USA (1980–2010)[23] and Norway (1967–2008)[31]. For example, in Washington State, USA, hypertensive disorders of pregnancy complicated 2.9% of all singleton live births in 2000 and increased significantly ($p<0.001$) to 3.1% in 2008[22]. When considering all births in the USA, the rates increased significantly ($p<0.001$) from 2.4% (1987–1988) to 2.9% (2003–2004)[32].

One exception to this trend was reported in a regional dataset from New South Wales in Australia where the hypertensive disorders of pregnancy *decreased significantly* ($p<0.001$) in incidence from 4.6% of all births (2000) to 2.4% (2008)[24]; the authors of this study suggested that earlier intervention and increased use of induction of labour or elective Caesarean delivery at earlier gestational ages for chronic or gestational hypertension were reducing the diagnosis of pre-eclampsia, although this should not have altered the overall rate of hypertension in the population.

Other trends in pre-eclampsia

The risk of having a pregnancy complicated by pre-eclampsia is thought to vary across climates and regions. Higher rates have been associated with rainy seasons in studies from several countries[8,9,33–36]. In addition, pre-eclampsia appears to complicate more commonly the pregnancies of immigrant women, compared with women born in the respective country. According to several large national datasets from HICs in Europe and Canada, women of African, Caribbean, and South and East Asian descent endure higher rates of pre-eclampsia compared with women of European descent[37–40].

RISK FACTORS FOR HYPERTENSIVE DISORDERS OF PREGNANCY OCCURRENCE OR RECURRENCE

Risk factors for pre-eclampsia include a wide array of conditions that reflect the complexity of the disease process[41]. These can be categorised as demographic, familial factors, past medical/obstetric history, current pregnancy history and paternal factors. These factors are used to identify women at increased risk of a hypertensive disorder of pregnancy who warrant enhanced surveillance and/or preventative therapy. As such, these risk factors are discussed in detail in Chapters 5 and 6. As risk markers for recurrence of pre-eclampsia are used in the same way, they too are discussed in Chapter 5.

MORTALITY AND MORBIDITY ASSOCIATED WITH THE DISORDERS OF PREGNANCY

Hypertensive disorder of pregnancy-related mortality and morbidity are to a large extent, but not entirely, owing to pre-eclampsia. A more detailed discussion of complications by type of hypertensive disorder of pregnancy can be found in Chapter 3.

> "I was told upon arriving at the hospital that they had managed to regain a pulse after 25 minutes but that my wife had most likely suffered severe brain damage from the lack of oxygen . . . She never regained consciousness and on August 6, three days after being removed from support, she passed into the arms of her loving Lord. The silence, since then, has been deafening."
>
> Widower of a woman with pre-eclampsia, courtesy of the Preeclampsia Foundation, USA

Maternal mortality

The hypertensive disorders of pregnancy, and particularly pre-eclampsia and eclampsia, are significant contributors to the global burden of maternal and perinatal mortality[42–46], being responsible for an estimated 10.0% of maternal deaths, annually[46]. Pre-eclampsia remains one of the top four causes of maternal mortality (and morbidity) in high-, middle- and low-income countries. Using data from 29 LMICs participating in the WHO Multicountry Survey on maternal and neonatal health, the odds of maternal death associated with the diagnosis of pre-eclampsia (compared with no pre-eclampsia) was 3.73 (95% CI 2.15–6.47) and with eclampsia (vs. no eclampsia) (OR 42.4, 95% CI 25.1–71.4)[2]. Similar results to the pre-eclampsia-related risk were illustrated by data from the UK Obstetric Surveillance System that reported an increased odds of maternal death of 2.4 (95% CI 1.3–4.5) associated with a hypertensive disorder of pregnancy (compared with no hypertensive disorder of pregnancy)[50].

A vastly disproportionate burden of maternal deaths related to the hypertensive disorders of pregnancy is borne by women in LMICs[51–53]; estimated to be >99% of all hypertensive disorder

KEY POINT

The majority of deaths associated with hypertensive disorders of pregnancy occur in LMICs in the absence of a trained health professional

of pregnancy-related maternal deaths. This is believed to be owing primarily to delays in triage (identification through basic blood pressure and urine screening of who is, or may become, severely ill and should seek a higher level of care), transport (getting women to appropriate care), and treatment (provision of appropriate treatment such as magnesium sulphate, antihypertensive therapy and timed delivery)[57,58]. A major contributing factor to the morbidity and mortality associated with pre-eclampsia is the shortage of health workers adequately trained in the detection and triage of suspected cases[60]. The consequences of delayed management are illustrated by Figure 4.1 of an 18-year-old mother brought to hospital after 14 hours of status eclampticus in Dhaka, Bangladesh; she suffered a stillbirth and remained comatose for the 3 days until her death shortly after this image was taken. Her family asked us to use this photograph to emphasise the importance of, and potential tragedy resulting from, pre-eclampsia and eclampsia.

Figure 4.1 This photo was taken in the Eclampsia Ward, Dhaka Medical College Hospital, Dhaka, Bangladesh. The 18-year-old woman lying supine had been admitted 14 hours after the onset of her first seizure in status eclampticus 3 days earlier. She had been delivered of a stillborn infant by Caesarean delivery soon after admission and had remained unresponsive since admission, and remained so until her death. Bed sharing with her is another woman post-eclampsia who had had an unremarkable recovery from her seizures. The 18-year old's hand is being held by her mother with her grandmother in the background. They asked that this image be shared to emphasise the importance of, and tragedy associated with, pre-eclampsia and eclampsia

According to global estimations, there has been a downward trend in hypertensive disorder of pregnancy-related maternal mortality, suggesting an improvement in our ability to care for women with pre-eclampsia. In the 2013 report on maternal deaths from the Global Burden of Disease Study, the absolute number of maternal deaths attributed to the hypertensive disorders of pregnancy was 29,275; this compared favourably with 47,100 deaths in the 2010 report and 69,800 in the 1990 one[46]. This trend towards a reduction in total number of maternal deaths associated with the hypertensive disorders of pregnancy has also been shown by the WHO[43].

Maternal morbidity

For every maternal death, it has been estimated that an additional 20 or 30 women suffer significant morbidity. In the same manner as maternal death, the burden of maternal morbidity is estimated to be highest in LMICs. The term, 'morbidity', covers a wide range of problems of varying severity. WHO has defined 'near-miss morbidity' as the near-death of a woman who has survived a complication (occurring during pregnancy or childbirth, or within 42 days of the termination of pregnancy). 'Severe' pre-eclampsia is a near-miss according to the WHO[61]. Although the definition of 'severe' pre-eclampsia varies by organisation as does the definition of 'pre-eclampsia' itself (as discussed in Chapter 3), the unifying principle is that pre-eclampsia is always potentially life-threatening. As there are women (such as those with hypertension, headache and visual symptoms) who are defined as having pre-eclampsia by some organisations, but gestational hypertension by others, it should not be surprising that 'gestational hypertension' is not a benign condition according to published literature[62–66]. The progression to pre-eclampsia occurs in 15–56% of women who initially present with gestational hypertension[62,65,67], as discussed in detail in Chapter 3.

Several large cohort studies have estimated the contribution of the hypertensive disorders of pregnancy to 'near-miss morbidity' as defined by the WHO[61]. The proportion attributable to the hypertensive disorders of pregnancy appears to be higher in LMICs than in well-resourced settings. In a Brazilian study of 16,243 deliveries in two large obstetric facilities (2011–2012), the hypertensive

disorders of pregnancy were responsible for 1102 (67.5%) near-misses[68]. In a similar study from Abu Dhabi of 122,702 deliveries in all major maternity units across a single province (2000–2006), 553 (59.5%) of all near-miss cases were attributed to the hypertensive disorders of pregnancy[69]. These estimates are in contrast to a large hospital-based cohort study in the USA of 115,502 deliveries (2008–2011) that found that 68 (20.5%) of near-miss cases were attributable to the hypertensive disorders of pregnancy[70]. It is probable that women in Abu Dhabi presented later in the course of their disease compared with women with greater antenatal surveillance and earlier diagnosis in the USA where expectant management of early-onset pre-eclampsia is not a uniform standard of care.

Maternal morbidities associated with the hypertensive disorders of pregnancy are thought to be a result of excessive inflammation and endothelial damage[71] and include virtually all end-organ complications. Estimates of complications that are most feared (such as hepatic haematoma/rupture or central nervous system complications of eclampsia, stroke, retinal detachment and blindness), most common (such as HELLP syndrome, pulmonary oedema, or placental abruption), or most easily recognised (such as acute renal failure)[64–73] come mainly from hospital-based studies, with the exception of eclampsia.

As observed with incidence estimates for the hypertensive disorders of pregnancy, most studies of morbidity rates are based on either cross-sectional or prospective cohorts collected in hospital after a diagnosis of pre-eclampsia has been made and may not be representative of the hypertensive disorder of pregnancy population as a whole. Rates of hypertensive disorder of pregnancy-related morbidity reported in LMICs tend to be higher (10–20%)[68,69,72–80] than those reported in HICs (5–9%)[22,30,50,70,81]. In addition, higher morbidity rates are reported in association with 'severe' pre-eclampsia, however defined[82–85].

KEY POINT

Rates of hypertensive disorder of pregnancy-related morbidity reported in LMICs tend to be higher (10–20%) than those reported in HICs (5–9%). Higher rates are also reported in association with 'severe' pre-eclampsia, however defined

The two large, multicountry, but facility-based, PIERS (Pre-eclampsia Integrated Estimate of RiSk) studies highlight the disparity in maternal outcomes between high- and low-resourced settings that probably reflect differences in health care resource access and underlying social determinants of health. The PIERS research programme has published a list of relevant maternal morbidities associated with the hypertensive disorders of pregnancy (see Chapter 3). This list was developed by an International Delphi consensus group[30] consisting of experts in obstetrics, paediatrics, anaesthesia, neonatology, medicine, global health and epidemiology from 19 high-, middle- and low-resourced countries. Two cohorts of women were collected as part of the PIERS project. The fullPIERS cohort included data from 2023 women admitted with a diagnosis of pre-eclampsia in a participating hospital in Canada, the UK, Australia or New Zealand; maternal morbidity, as defined by the Delphi group was 5.0% within 48 hours of admission and 13.0% at any time after admission. This is in contrast to the miniPIERS cohort that included data from 2081 women admitted with any hypertensive disorder of pregnancy to one of seven participating hospitals in Brazil, Uganda, South Africa, Pakistan or Fiji; maternal morbidity was 12.5% within 48 hours of admission and 19.3% at any time after admission.

Eclampsia

Estimates of eclampsia incidence have been refined by efforts to reduce the global burden of disease using magnesium sulphate, an agent that is effective for eclampsia prophylaxis and treatment. According to the WHO Multicountry Survey, eclampsia occurs in 1.0–2.0% of pregnancies[2]. The incidence is lower in HICs, with published estimates from population-level data below 1% (ranging from 2–8.6/10,000 live births)[24,38,86–91].

Stroke

In the USA, hypertensive disorder of pregnancy-related stroke, particularly postpartum, appears to be on the rise, with a reported 5-fold increase in incidence from 1994 to 2011[92]. Severe systolic hypertension (i.e., ≥160 mmHg) appears to be a particular risk factor for hypertensive disorder of pregnancy-related stroke[93,94].

Perinatal mortality and morbidity

Adverse outcomes for both mother and fetus tend to cluster around the diagnosis of pre-eclampsia whether defined traditionally (as gestational hypertension and proteinuria) or broadly (as gestational hypertension with end-organ dysfunction)[95].

Adverse perinatal outcomes associated with the hypertensive disorders of pregnancy include stillbirth, neonatal death, oligohydramnios, bronchopulmonary dysplasia and fetal growth restriction[71,96,97].

Of perinatal deaths (i.e., stillbirth or neonatal death), an estimated 9–20% are reported to be directly related to the hypertensive disorders of pregnancy in several large multi-country cohort studies[98–100]. In the WHO Multicountry Survey study, women with pre-eclampsia or eclampsia had an odds ratio of perinatal death of 3.0 (95% CI 2.7–3.3) and 4.9 (95% CI 4.1–5.9), respectively, compared with women without a hypertensive disorder of pregnancy[2]. In the Nationwide Inpatient Sample study of all deliveries reported in the USA, 7.5% of all stillbirths were in association with pre-eclampsia[101].

Adverse perinatal outcomes, including stillbirth, are modified by gestational age. The risk of stillbirth is higher at earlier gestational ages. In the Norwegian Medical Birth Registry (1999–2008), the RR of fetal death among women with pre-eclampsia was 86 (95% CI 46–142) at 26 weeks' gestation, 7.3 (95% CI 3.3–11.0) at 34 weeks, and 3.0 (95% CI 1.7–4.1) at 38 weeks[102]. Pre-eclampsia is recognised as a significant contributor to iatrogenic preterm birth and associated neonatal morbidity[103–108]. A secondary analysis of data from the WHO Global Survey data set, including 172,461 deliveries from 145 facilities across 22 low-resourced countries, determined that pre-eclampsia was associated with 8 times the odds of provider-initiated preterm birth[109].

Although most studies reporting complications focus on a diagnosis of pre-eclampsia, chronic hypertension (compared with normal blood pressure) has been associated with an increased risk of preterm birth[110,111] (RR 2.7, 95% CI 1.9–3.8)[112] and perinatal death (RR 4.2, 95% CI 2.7–6.5)[112], as well as congenital malformations (whether women were treated with antihypertensive therapy (OR 1.3, 95% CI 1.2–1.5) or not 1.2 (95% CI 1.1–1.3))[113].

> "I would not wish the days that followed on anyone. Leaving the hospital with a teddy bear and an urn instead of a sweet little baby is unthinkable. Having your daughter's milk come in without the baby grandson for whom it was intended was heart-wrenching."
>
> Rita C, courtesy of the Preeclampsia Foundation, USA

PRIORITIES FOR FUTURE RESEARCH

With regards to the epidemiology of pre-eclampsia, the main priorities for future research include development of consistent definitions of hypertensive disorder of pregnancy types, and robust population-level surveillance systems incorporating across multiple country settings. Particularly in LMICs where the burden, and health consequences, of these disorders is thought to be greatest, population-level surveillance is required in order to properly ascertain the effectiveness of interventions and public health programmes aimed at improving maternal health. These improved surveillance systems should include information related to risk factors that would improve our knowledge of how risk factors may vary based on classification of the disorder and other subgroups of pregnant women.

As populations of pregnant women continue to experience demographic shifts worldwide, other priorities will be to understand the contribution of these changes to disease burden and complication rates.

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5

Risk factors and predictors of pre-eclampsia

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"I value screening so that I can appropriately contextualise my risk and plan accordingly. Not for anything, but with other children at home, knowing at 12 weeks that I am higher risk for complications would give me much better lead time to look finding a childcare provider and to budget for it even if I wound up not ultimately needing more advanced care."

Pre-eclampsia survivor

SYNOPSIS

This chapter, reviews the risk factors for pre-eclampsia, but focuses more on the predictors of pre-eclampsia and, to a lesser extent, other placental complications of pregnancy, especially gestational hypertension and intrauterine growth restriction (IUGR). Early prediction of pre-eclampsia will aid in identifying women at highest risk, allow for preventative interventions such as low-dose aspirin, and guide surveillance to avoid severe complications. The strongest risk factors for pre-eclampsia include previous pre-eclampsia, antiphospholipid antibody syndrome, pre-existing medical conditions and multiple pregnancy. Currently, there is no single predictor of pre-eclampsia among women at either low or increased risk of pre-eclampsia that is ready for introduction into clinical practice, but the most promising predictors are the angiogenic factors and uterine artery Doppler velocimetry combined with other biochemical factors using multivariate models.

However, it should be stated that very few of the informative data have been derived from populations of women who bear the greatest burden of experiencing complications of pre-eclampsia, namely women in less-developed countries.

WHAT TO PREDICT

In our opinion, this area of research and clinical practice has been confused by a number of factors, of which we emphasise three.

First, and of particular relevance for colleagues in less-resourced settings, is the need to identify women who are at increased risk for any placenta-derived antenatal complication, whether pre-eclampsia, gestational hypertension, or intrauterine growth restriction (IUGR). Clinically, what matters is to identify those women who would most benefit from careful surveillance during their pregnancy, ideally using the model of accelerating antenatal visits (every 4 weeks until 27 weeks, every 2 weeks between 28 and 35 weeks, and weekly from 36 weeks) that has largely become the standard of care throughout more-developed communities, and, potentially, prophylaxis against later disease (e.g., low-dose aspirin and calcium supplementation (see Chapter 6)). It should be remembered that this

pattern of antenatal surveillance was developed in Edinburgh largely to identify women with pre-eclampsia, so that they could be delivered before complications arose. Once effective screening methods have been identified, societies need to determine what false-positive rate they will accept, with what sensitivity, to identify an enriched cohort of pregnant women who will most benefit from increased surveillance. Therefore, what may really matter is the ability to exclude women who will go on to have uncomplicated pregnancies. For these women, the risks of pregnancy then focus around the time of birth and the early puerperium. Such risks are those of the other leading causes of maternal mortality, obstetric haemorrhage, sepsis and prolonged labour. Such women may benefit from the WHO four-visit model of antenatal care, which failed to show benefit when subjected to a randomised controlled trial[1]. By design, the WHO four-visit model misses the increased maternal and perinatal risks that derive from the majority of cases of pre-eclampsia that have their first clinical manifestations between 36 weeks' gestational and delivery.

Second, has been the conflation of all forms of pre-eclampsia (whether of primarily placental (early-onset) or maternal (late-onset) origin) into a single diagnosis; we now recognise that, other than the commonality of the presence of a placenta, the pathways to disease vary widely between placental and maternal disease[2]. The same issue arises for so-called IUGR. Many, even most, pregnancies in which either the fetal abdominal circumference or estimated fetal weight drops below the 10th centile by ultrasound are not complicated (other than by resulting investigations and interventions) – rather, the fetus is constitutionally small[3].

Third, how can we be certain that the pathways to pre-eclampsia are shared by women in more-developed countries (who usually have a prolonged coitarche-to-pregnancy interval, often using non-barrier contraception, and are increasingly often over 30 years-old at first ongoing pregnancy and overweight or obese) and women in less-developed countries (who are often young and anaemic, bear a burden of chronic infection, and conceive within months of first intercourse)? It may be that screening biomarkers that are shown to be effective in more-developed countries in ongoing research will fail women in less-developed settings – this is a research priority mentioned below. Conversely, reverse innovation of screening biomarkers that are effective in less-developed settings may not have clinical utility in more-developed country populations.

In the following sections, the risk factors and predictors of pre-eclampsia are discussed in detail.

RISK FACTORS

Risk factors are any attributes or exposures that increase the chances for an individual to develop a disease[4]. Risk factors for pre-eclampsia include a wide array of conditions that reflect the complexity of the disease process and their strengths of association are quantified using risk ratios or odds ratios[5]. These can be categorised based on familial factors, demographic factors, past medical or obstetric history, pregnancy-associated factors, paternal factors and miscellaneous factors. The following risk factors are summarised in Table 5.1.

Familial factors

Pre-eclampsia is a complex disorder, which is seen to be inherited in a familial pattern[6]. The placenta plays a central role in the pathogenesis of pre-eclampsia, thus implying that both maternally and paternally derived fetal genes may play a role in the development of the disease[6]. Pre-eclampsia complicating any of a given woman's pregnancies is a significant risk factor for pre-eclampsia complicating her daughters' pregnancies[7]. Chesley and Cooper reported that for those women who experienced pre-eclampsia, the rate of disease was higher in sisters (37%), daughters (26%) and grand-daughters (16%) when compared with daughters-in-law (6%)[8]. A recent review suggested that those with a family history of pre-eclampsia are at an increased risk for this disease (RR 2.90, 95% CI 1.70–4.93)[9]. A large population-based study reported a significantly higher risk of pre-eclampsia in sisters diagnosed with pre-eclampsia (RR 2.6, 95% CI 1.8–3.6)[10]. This risk increased further with the severity of disease (i.e., 2+ proteinuria) (RR 3.7, 95% CI 2.5–5.5)[10].

Further, a large Danish study reported that a history of early- or intermediate-onset pre-eclampsia in the mother or sister increased the risk of the similar form of pre-eclampsia by at least 150% compared with an absence of such family histories. For those women with a history of late-onset pre-eclampsia, this risk only increased by 73%[11].

Table 5.1 Summary of risk markers for pre-eclampsia (modified from PRECOG-I and -II[139])

Maternal				
		Current pregnancy		
Demographics and family history	*Past medical or obstetric history*	*First trimester*	*Second or third trimester*	*Paternal*
	Previous pre-eclampsia	**Multiple pregnancy**		
	Antiphospholipid antibody syndrome			
	Pre-existing medical condition(s)			
	• Pre-existing hypertension or booking dBP ≥90 mmHg			
	• Pre-existing renal disease or booking proteinuria			
	• Pre-existing diabetes mellitus			
Afro-Caribbean or South Asian race	Lower maternal birth weight and/or preterm delivery	Short maternal stature ≤164 cm/5'5"	Excessive weight gain in pregnancy	Paternal age ≥45 years
Maternal age ≥35–40 years	Thrombophilias	Overweight/obesity		
Family history of pre-eclampsia (grandmother, mother or sister)	Increased pre-pregnancy triglycerides, total cholesterol and/or non-HDL-cholesterol	Reduced physical activity		Mother had pre-eclampsia
Family history of early-onset cardiovascular disease	Non-smoking	First ongoing pregnancy		Fathered pregnancy complicated by pre-eclampsia with another partner
Rural location (LMICs)	Cocaine and/or methamphetamine use	New partner		
	Previous miscarriage at ≤10 weeks with same partner	Short duration of, or reduced, exposure to sperm of current partner		
	Previous pregnancy complicated by IUGR	Reproductive technologies		
	Maternal uterine anomaly	Inter-pregnancy interval ≥4 years		
	Increased stress	Mental health (depression and/or anxiety)		
		Booking sBP ≥130 mmHg	Elevated BP (gestational hypertension)	

continued

Table 5.1 *continued*

Maternal				
		Current pregnancy		
Demographics and family history	*Past medical or obstetric history*	*First trimester*	*Second or third trimester*	*Paternal*
Rural location (LMICs)	(Recurrent miscarriage)	Booking dBP ≥80 mmHg	Gestational proteinuria	
		Vaginal bleeding in early pregnancy		
		Gestational trophoblast disease		
		Anaemia with low vit C and E intake (LMICs)		
		Severe anaemia (Hb <7.0 g/L)		
		Abnormal serum screening analytes	Abnormal serum screening analytes	
		Investigational laboratory markers	Investigational laboratory markers	
		Reduced 25(OH)-vit D	Abnormal uterine artery Doppler	
		Female fetus (early-onset)	Infection during pregnancy (e.g., UTI, periodontal disease)	
		Male fetus (late-onset)		
		Congenital fetal anomalies		

BP, blood pressure; dBP, diastolic blood pressure; HDL, high-density lipoprotein; LMICs, low- and middle-income countries; sBP, systolic blood pressure; UTI, urinary tract infection; vit, vitamin

In addition, a paternal familial component has been suggested; the partners of men who were the product of a pregnancy complicated by pre-eclampsia were, themselves, more likely to develop pre-eclampsia than women whose partners were born of normotensive pregnancies[12].

Women with a maternal and/or paternal history of hypertension or diabetes mellitus had a statistically significant increased risk to develop pre-eclampsia[13,14].

Demographic factors

Age

Extremes of maternal age have been associated with risk of pre-eclampsia/eclampsia[2]. Maternal age ≥40 years has been associated with an increased risk (OR 1.49, 95% CI 1.22–1.82)[15]. The WHO Multicountry Survey of Maternal and Newborn Health reported that women ≥35 years were at high risk of pre-eclampsia, though not eclampsia. However, women ≤19 years of age were at high risk for eclampsia, but not a diagnosis of pre-eclampsia – probably related to underdiagnosis of pre-eclampsia in populations of women without full antenatal surveillance[16].

Ethnicity

Women belonging to Afro-Caribbean or South Asian ethnicity have been shown to be at higher risk when compared with Caucasians[15,17]. African-American women with severe pre-eclampsia demonstrate higher blood pressures and require more antihypertensive treatment, while Caucasian women have a higher incidence of HELLP (haemolysis, elevated liver enzymes and low platelet) syndrome[18].

Past medical or obstetric history

Maternal birth weight

Women with low birth weight (<2500 g) have been shown to have double the risk of experiencing pre-eclampsia (OR 2.3, 95% CI 1.0–5.3) when compared with women who weighed 2500–2999 g at birth[15]. Further, the risk increased four-fold for those women who weighed <2500 g at birth and were overweight as adults[19]. A Danish cohort study reported that there was an increased frequency of pre-eclampsia in women who were born prematurely and were small-for-gestational age[20].

Stature and pre-pregnancy body mass index

A large population-based study reported that short stature of women (≤164 cm/5'5") predisposed them to an increased risk of severe pre-eclampsia[21]. Women who are overweight or obese are known to be at increased risk for pre-eclampsia[22]. A recent meta-analysis concluded that overweight/obesity as well as maternal adiposity is associated with an increased risk of pre-eclampsia[23]. Increased BMI is an important risk factor for pre-eclampsia and severe pre-eclampsia with an attributable risk of 64%[24]. This risk[25] may be increased two- to three-fold as BMI increases from 21 kg/m^2 to 30 kg/m^2.

Pre-existing medical conditions

Pre-gestational diabetes (type 1 and type 2) is associated with two- to four-fold increased risk of pre-eclampsia[10,26,27]. In addition, pre-gestational diabetes may be a significant contributor to new-onset late-postpartum pre-eclampsia[28].

Lecarpentier *et al.* reported that 23% of women with chronic hypertension were at risk of superimposed pre-eclampsia. Mean arterial pressure (MAP) ≥95 mmHg was a good predictor of this risk[29]. A recent systematic review by Bramham *et al.* reported that the relative risk of superimposed pre-eclampsia in women with chronic hypertension was nearly eight-fold higher than was pre-eclampsia in the general pregnancy population[30]. Adverse neonatal outcomes such as preterm delivery (<37 weeks of gestation), low birth weight and perinatal death in this group of women were three-to-four times as likely[30].

Women with both chronic hypertension and pre-gestational diabetes are eight times more likely to be diagnosed with pre-eclampsia when compared with women without either condition[31].

Pre-eclampsia may occur frequently in pregnant women with chronic kidney disease, lupus nephropathy, as well as diabetic nephropathy[32]. For women with diabetes, proteinuria of either 190–499 mg/day or ≥+2 on urine dipstick at booking[33,34] is associated with a significantly higher risk of pre-eclampsia.

A meta-analysis of 74 studies evaluating hyperlipidaemia and risk of pre-eclampsia reported that elevated levels of total cholesterol, non-high density lipoprotein (HDL)-C and triglycerides are observed during all trimesters of pregnancy, while lower levels of HDL-C are seen during the third trimester[35].

Thrombophilias

Special mention should be made of testing for inherited thrombophilias (such as factor V Leiden mutation, prothrombin gene mutation, protein C or S deficiency, or antithrombin III deficiency) or acquired thrombophilia (such antiphospholipid antibodies). Among the genetic thrombophilias, a recent meta-analysis of 31 case–control studies concluded that factor V Leiden single nucleotide polymorphism (SNP) is associated with an increased risk of pre-eclampsia. No association was found between methylene tetrahydrofolate reductase (MTHFR) SNP and prothrombin SNP and risk of pre-eclampsia[36].

The antiphospholipid syndrome (APS) is a systemic autoimmune disorder with raised titres of antiphospholipid antibodies and is characterised by arterial and venous thrombosis, and adverse pregnancy outcomes[37]. A meta-analysis of 28 studies reported that the risk of pre-eclampsia was two times higher in women who tested positive for lupus anticoagulant and anticardiolipin antibodies (OR 2.34, CI 1.18–4.64 and OR 1.52, CI 1.05–2.20, respectively)[38]. However, this association was only reported in case–control, and not in cohort, studies[38].

While we recognise that this is a very controversial area, in our opinion, thrombophilia screening is not recommended specifically for investigation of previous pre-eclampsia or other placental complications, with the exception of testing for antiphospholipid antibodies if the woman meets the clinical criteria for the diagnosis[39,40].

Parity

Pre-eclampsia is recognised to more commonly complicate a woman's first pregnancy[6]. A large population-based study reported that nulliparous women were at increased risk of pre-eclampsia compared with parous women (OR 3.6, 95% CI 2.6–5.0)[41]. A recent population-based cohort study reported that nulliparity significantly increased the risk of late-onset pre-eclampsia when compared with early-onset disease[42].

Interval between pregnancies

The risk of pre-eclampsia is generally lower in the second pregnancy if conceived with the same partner. After adjustment for the presence or absence of a change of partner and maternal age, the odds for pre-eclampsia for each 1-year increase in the birth interval were increased (OR 1.12, 95% CI 1.11–1.13)[43]. In a large cohort study, a birth interval of more than 4 years increased the risk of pre-eclampsia in women who had no prior history (OR 1.4, 95% CI 1.2–1.6)[44].

Previous miscarriages

Analysis of data obtained from the Norwegian Mother and Child Cohort Study suggested that there may be an increased risk of pre-eclampsia for women with recurrent miscarriages (adjusted OR 1.51, 95% CI 0.80–2.83), although this was not statistically significant[45]. Similar findings were reported from a Canadian study where history of prior abortion had no effect on risk of pre-eclampsia[46]. However, for women who had recurrent spontaneous abortions and infertility treatment, a three-fold increased risk of pre-eclampsia was seen compared with controls[45].

Previous pre-eclampsia

Women with a history of pre-eclampsia in a previous pregnancy had an increased risk of pre-eclampsia in the current pregnancy compared with parous women with no previous pre-eclampsia (OR 21.5, 95% CI 9.8–47.2). This association was particularly strong for early-onset, moderate and severe disease[41]. In women with prior pre-eclampsia, greater risk is associated with earlier gestational age at delivery. The risk of recurrent pre-eclampsia was 12% for those who previously delivered at term and increased to 40% for those who delivered before 28 weeks of gestation[44]. Although multiple gestation, change of partner, long inter-pregnancy interval, and high BMI are considered risk markers for the *occurrence* of pre-eclampsia, neither multiple gestation or a different partner in the previous pregnancy with pre-eclampsia[47–49], nor long inter-pregnancy interval[50,51] have been demonstrated to further increase the risk of *recurrent* pre-eclampsia. In contrast, higher BMI in a previous pre-eclampsia pregnancy does further increase the risk of recurrence in a subsequent pregnancy[44]; this is important to emphasise as BMI is a modifiable antenatal risk factor.

Previous pregnancy with gestational hypertension

Pre-eclampsia in a previous pregnancy may 'recur' in a subsequent pregnancy as gestational hypertension, just as gestational hypertension in a previous pregnancy may recur as pre-eclampsia in a subsequent pregnancy. Women with a history of pre-eclampsia have similar rates of either pre-eclampsia (median 15%) or gestational hypertension (median 22%) in a subsequent pregnancy. In contrast, most women with a history of gestational hypertension who experience a subsequent hypertensive pregnancy will experience gestational hypertension again (median of 21%, range 8–47%); far fewer will experience their recurrence as pre-eclampsia (median of 4%, range 1–6%) (4 studies, 1311 women)[52–55]. The gestational age at which gestational hypertension developed in the previous pregnancy does not seem to affect whether the hypertensive disorder of pregnancy in the next pregnancy is gestational hypertension or pre-eclampsia.

Pregnancy-associated factors

Multiple pregnancy

Multiple gestations are a risk factor for pre-eclampsia[56,57]. A multicentre study by Sibai *et al.* reported that women with twin pregnancy had higher rates of gestational hypertension (RR 2.04, 95% CI 1.60–2.59) and pre-eclampsia (RR 2.62, 95% CI 2.03–3.38)[58]. Increased placental mass during a twin gestation may lead to increased circulating levels of soluble fms-like tyrosine kinase-1 (sFlt1), which is a circulating antiangiogenic marker of placental origin, and may play an

important role in pathophysiology of, especially early-onset, pre-eclampsia[59].

Fetal gender

A Norwegian cohort study reported that pre-eclampsia occurred more often in the male fetus for those who delivered at 40 weeks or later. For preterm births (gestational weeks 25–36), the proportion of female offspring in pregnancies complicated by pre-eclampsia was considerably higher than that of males[60]. Despite the preponderance of male fetuses in women with pre-eclampsia, no fetal sex-related differences were found in perinatal outcomes (stillbirth, perinatal or neonatal mortality) in such women[61].

Use of assisted reproductive technology

A recent systematic review reported that assisted reproductive technology (ART) (especially *in vitro* fertilization) was associated with higher risk of gestational hypertension and pre-eclampsia when compared with non-ART pregnancies[62]. Results from the CoNARTaS cohort study reported that hypertensive disorders occurred in 5.9% of singleton and 12.6% of twin ART pregnancies compared with 4.7% of singleton and 10.4% of twin pregnancies in spontaneously conceived pregnancies[63].

Infections

A nested case–control study from the UK reported that antibiotic prescriptions (included as a proxy for acute infection) (OR 1.28, 95% CI 1.14–1.44) and urinary tract infection (UTI) (OR 1.22, 95% CI 1.03–1.45) in pregnancy were associated with an increased risk of pre-eclampsia after controlling for confounders such as maternal age, pre-existing renal disease, diabetes and multiple gestation[64]. A meta-analysis of 40 studies reported that women with a UTI and those with periodontal disease were more likely to develop pre-eclampsia than women without these infections. There was no association between the other maternal infections such as chlamydia, malaria, treated or untreated HIV and group B streptococcal colonisation and risk of pre-eclampsia[65,66].

Congenital malformations

A large retrospective study from the Perinatal Information System database in Uruguay reported that fetal malformation was associated with an increased risk of pre-eclampsia (RR 1.26, 95% CI 1.16–1.37)[67]. Congenital anomalies have also been reported to be more strongly associated with early-onset pre-eclampsia rather than late-onset disease (adjusted OR 2.59, 95% CI 1.66–4.02)[42].

Paternal factors

Paternal age

Epidemiological studies suggest that the risk for pre-eclampsia doubles if the woman has a partner aged >45 years[68,69], perhaps as a result of spermatozoa being damaged owing to genetic mutations that occur with ageing or to environmental factors such as exposure to radiation and heat[22].

Primipaternity and sperm exposure

A landmark study by Robillard *et al.* in 1994 showed that conception within the first 4 months of sexual cohabitation of the couple presented a major risk (40–50% incidence) for hypertension to complicate a pregnancy[70]. However, this risk declined significantly for women after at least 1 year of sexual cohabitation before conception[70]. More recent work by Olayemi *et al.* reported that there was a 4% decrease in the risk of developing hypertension for every month increase in cohabitation[71]. This risk was not statistically significant for pre-eclampsia[71]. Repeated intercourse with the same partner leads to maternal mucosal tolerance to paternal antigens, which may be mediated by seminal vesicle-derived transforming growth factor β (TGFβ)[68].

Paternal medical history

The data for paternal history of cardiovascular disease and risk of pre-eclampsia have been conflicting. In a case–control study, Rigo *et al.* reported that early-onset chronic hypertension and early-onset myocardial infarction in the father was associated with a three-fold increased risk of pre-eclampsia after controlling for other confounders[72]. However, the population-based HUNT study reported that there was no association between the hypertensive disorders of pregnancy and paternal cardiovascular risk factors such as BMI, blood pressure and lipid profile[73].

Miscellaneous factors

Smoking

Cigarette smoking is known to have adverse effects on all organ systems. However, a systematic review of 48 epidemiological studies reported that smoking during pregnancy approximately halves the risk of pre-eclampsia[74]. This protective effect was consistently seen irrespective of parity and severity of disease[74]. The pathophysiology of this relationship is not well established. However, it is proposed that smoking might have effects on angiogenic factors, endothelial function and the immune system, which may contribute to the lowered risk of pre-eclampsia[74]. In an attempt to establish causality between smoking and pre-eclampsia, data from the National Swedish Birth Register showed that smoking in two pregnancies again halves the risk of pre-eclampsia, compared with the risk borne by women who did not smoke in either pregnancy[75].

No significant associations have been observed between smokeless tobacco use and pregnancy-associated hypertension in various studies[76,77]. Therefore, it is proposed that combustion products from cigarette smoke other than nicotine may be responsible for the decreased pre-eclampsia risk seen amongst smokers[76].

Physical activity

Exercise and physical activity is recommended during pregnancy to improve maternal health. In their systematic review, Kasavara *et al.* reported that physical activity had a protective effect on the development of pre-eclampsia (OR 0.77, 95% CI 0.64–0.91), while this effect was not seen in cohort studies (OR 0.99, 95% CI 0.93–1.05)[78]. However, a recent meta-analysis conducted by Aune *et al.* reported that those women who engaged in high levels of physical activity pre-pregnancy and continued to do so during early pregnancy, were less likely (by 35% and 21%, respectively) to develop pre-eclampsia, compared with those who participated in low levels of physical activity[79].

Micronutrient deficiencies

Vitamin D deficiency is commonly reported in women and has been investigated to assess its link with pre-eclampsia. There have been conflicting results regarding the serum concentrations of 25-hydroxy vitamin D and the subsequent risk of developing pre-eclampsia[80,81], mainly owing to small sample size of these studies. A recent large case–control study has reported that maternal vitamin D deficiency, defined as 25-hydroxy vitamin D <30 nmol/L, was associated with double the risk of pre-eclampsia when compared with concentrations >50 nmol/L[82].

The Vitamins in Preeclampsia (VIP) Trial reported that vitamin C (1000 mg) and vitamin E (400 IU) supplements given prophylactically from the second trimester of pregnancy have no effect on reduction in the rate of pre-eclampsia in women at risk[83]. Similar findings have been reported by the WHO multicountry vitamin supplementation survey from India, South Africa and Vietnam[84].

Mental health

Depression and anxiety in the first trimester of pregnancy are known to increase the risk of pre-eclampsia by two- to three-fold[85]. In addition, lifetime stress and perceived stress during pregnancy may double the risk of developing pre-eclampsia; an interaction that may be mediated by the neuropsychoimmunological pathway[86].

Socioeconomic status

In developing countries, rural dwellers were twice as likely to develop pre-eclampsia compared with those living in urban areas. Furthermore, women with concurrent anaemia and poor intake of fruits and vegetables were at higher risk of pre-eclampsia[87]. Severe anaemia (haemoglobin <70 g/L) was associated with a three-fold greater risk of pre-eclampsia in women living in less-developed countries[88]. A lack of antenatal care and less than secondary-level education were pertinent risk factors for risk of pre-eclampsia in these regions[88].

PREDICTION (APPENDICES 5.1–5.3)

At present, maternal characteristics which include well-established risk factors discussed above such as maternal age, nulliparity, pre-existing medical conditions and history of pre-eclampsia, are mostly used to screen for pre-eclampsia by clinicians during antenatal visits[56,57,89]. However, these risk factors are not sufficient as only approximately 30% of women who subsequently develop pre-eclampsia are identified by their use[90]. Pre-eclampsia research is now tailored towards development of a predictive model utilising the risk factors mentioned above

along with measurable clinical and laboratory biomarkers to predict the onset of pre-eclampsia.

In the context of this chapter, we are talking about the prediction of a diagnosis of pre-eclampsia (or other placental complications) occurring at some point in the future, not the prediction of complications (prognosis), or risk stratification, in either individual or populations of women whose pregnancies have been complicated by the clinical syndrome of pre-eclampsia (the focus of much of the Chapter 3). According to WHO, a prediction test should be simple, non-invasive, inexpensive, rapid, easy to carry out early in gestation, impose minimal discomfort or risk on the woman, be a widely available technology, and the test results must be valid, reliable and reproducible[91,92].

The performance of predictive tests is generally summarised in the text and tables as being poorly associated, moderately associated and strongly associated when the positive likelihood ratio (LR+) is <5, 5–9.9 and ≥10, respectively (Appendix 5.1). Similarly, for tests that poorly, moderately or strongly exclude risk, their performance is summarised as negative likelihood ratios (LR-) of >0.2, 0.11–0.2 and ≤0.1, respectively. Other summary statistics used in this chapter are the sensitivity ("true positive rate", the proportion of positives that are correctly identified as such, e.g., the percentage of women who will develop the complication who are correctly identified) and specificity ("true negative rate", the proportion of negatives who are correctly identified as such, e.g., the percentage of women who are correctly identified as not developing the condition) of the test to predict the outcome, namely pre-eclampsia, as well as the area under the receiver-operator characteristic curve (AUC ROC)[93–95].

It should be remembered that nearly all the studies referred to in this section relate to women in more-developed countries. Their relevance to women in less-developed countries is uncertain. It is women in less-developed countries who carry the greatest burden of risk for the complications of pre-eclampsia.

PREDICTORS (UNIVARIABLE ANALYSES)

Clinical examination

Blood pressure

Blood pressure, which forms the basis of diagnosis for pre-eclampsia in all international guidelines, is routinely measured during pregnancy[89]. The Society of Obstetrics and Gynaecologists of Canada (SOGC) recommends measurement of blood pressure using a mercury sphygmomanometer, a validated automated blood pressure device or a calibrated aneroid device[56,57]. As high blood pressure is an indication of the increased vascular resistance observed in pre-eclampsia, there have been studies examining the value of blood pressure measurements using systolic blood pressure, diastolic blood pressure, or MAP indices for the prediction of pre-eclampsia[96–99].

A systematic review and meta-analysis by Cnossen *et al.* evaluated the predictive accuracy of using blood pressure measurements in the second trimester for pre-eclampsia. This review included 34 studies reporting the use of blood pressure measurements (systolic blood pressure, diastolic blood pressure and MAP) in predicting pre-eclampsia for women at low risk[96]. The pooled LRs were weakly associated with developing pre-eclampsia. The authors concluded that no index of blood pressure measurement predicted pre-eclampsia well enough to be clinically useful.

Urine

Proteinuria

Proteinuria is routinely measured during pregnancy, especially in women with new-onset hypertension occurring after 20 weeks' gestation to establish the diagnosis of pre-eclampsia[56,57] (see Chapter 2). Underlying renal disease is a recognised clinical risk factor for pre-eclampsia and as such, documentation of proteinuria early in pregnancy is associated with an increased risk of pre-eclampsia (see Pre-existing medical conditions, above). Recently, significant attention has been devoted to the role of albuminuria, and more specifically for lower levels of albuminuria (or 'microalbuminuria') for the prediction of pre-eclampsia. In a review of the published studies retrieved from a structured literature search (1980 to mid-March 2008), a total of seven studies were performed in early pregnancy (defined as <20 weeks) and 13 studies in late pregnancy (≥20 weeks)[100]. Overall, the negative predictive value of 'microalbuminuria' was high but the test performance was not good enough for clinical use, which is consistent with most other individual prediction tests described in this section. The largest study (N = 2486 women) performed at

11^{+0}–13^{+6} weeks demonstrated an increased albumin : creatinine ratio in women who later developed pre-eclampsia compared with those who did not; however, the combined prediction models incorporating the albumin : creatinine ratio results did not yield to significantly improved AUCs over maternal variables alone[101]. Prediction of pre-eclampsia in early pregnancy (17–20 weeks) by estimating the albumin : creatinine ratio was also performed using high-performance liquid chromatography (HPLC)[102]. In this cohort of 265 women with singleton pregnancy, six developed pre-eclampsia; the AUC to predict pre-eclampsia was 0.753. Although the interpretation is of a good predictive test, this study has not been replicated and, in addition, the impact is limited by accessibility to HPLC in clinical practice, especially in less-resourced settings.

Podocyturia (podocyte : creatinine ratio)

Glomerular epithelial cells (podocytes) are involved in the maintenance of the function and structure of the filtration barrier in the kidney[103]. As a consequence of endothelial dysfunction and disruption of the selective filtration barrier in the kidney associated with pre-eclampsia, these podocytes proteins which include podocin, nephrin, synaptopodin and podocalyxin, lose their functional ability and are shed in urine (i.e., podocyturia)[104,105]. Podocyturia is expressed as podocytes : creatinine ratio and has been shown to be associated with manifestation of renal dysfunction in women with pre-eclampsia[103].

A case–control study by Kelder *et al.* analysed maternal urine mRNA levels of three markers of podocytes (VEGF, nephrin and podocin) using quantitative polymerase chain reaction (qPCR-based analysis)[103]. The urine measurements were collected in the early third trimester. None of the three podocyte markers were strong predictors of pre-eclampsia independently, but a combination of all the markers showed a moderate performance in predicting the occurrence of pre-eclampsia.

Craici *et al.* examined the predictive accuracy of podocyturia in the second trimester using only podocin as a marker in a prospective cohort study[105]. In contrast to the study by Kelder *et al.*, this study reported 100% sensitivity (95% CI 78–100) and 100% specificity (95% CI 92–100) in predicting pre-eclampsia, using podocin staining of blood and urine samples. In addition, this study reported a strong LR+ for predicting the occurrence of any hypertensive disorder of pregnancy.

Another prospective study carried out by Jim *et al.* examined the predictive accuracy of podocyturia (using podocin), nephrinuria and albuminuria in the second and third trimesters from urine samples using cytospin technique[104]. Only albuminuria in this study showed a moderate LR+ for the prediction of pre-eclampsia.

The differences in the predictive accuracy for podocin and nephrin in the three studies above may be owing to different analytic techniques, prevalence of pre-eclampsia, and population (e.g. high-risk women versus unspecified). The study designs and gestational age also differed in the studies. Except in the study by Craici *et al.*, none of the urine markers attained the required predictive LR values for clinical use. Further research is needed to make conclusive statements on the use of podocyturia as a screening test for pre-eclampsia.

Calcium (calcium : creatinine ratio)

As a result of renal dysfunction (decreasing glomerular filtration rate) which occurs in pre-eclampsia, there is an increase in serum creatinine and decrease in calcium, thus a decrease in calcium : creatinine ratio has been reported in some studies[106]. Vahdat *et al.* studied the predictive accuracy of urine calcium : creatinine ratio of 150 women during late second trimester. Using a cut-off value of 0.071 in this study, calcium : creatinine ratio was a poor predictor for pre-eclampsia.

Inositol phosphoglycan-P (IPG : creatinine ratio)

Inositol phosphoglycan-P type (IPG-P) which belongs to the insulin mediator family has been reported to be high in urine in pre-eclampsia[107]. A prospective longitudinal study investigated the use of IPG-P : creatinine ratio as a predictive screening test for pre-eclampsia 2 weeks prior to its onset in 416 women. IPG-P : creatinine ratio had moderate LR- and LR+ and may become a useful screening test for pre-eclampsia up to 2 weeks before diagnosis.

Ultrasound markers

Uterine artery Doppler ultrasonography

Doppler ultrasound is a non-invasive technique, and, in this setting, is used to study the uteroplacental

circulation and changes in blood flow resistance[108]. The flow change can be measured as pulsatility index (PI) or resistance index (RI)[108,109].

As an uncomplicated pregnancy progresses, blood flow resistance in the uterine arteries decreases with gestation owing to invasion of the spiral arteries by the trophoblasts[109–111]. The corollary is that increased impedance to blood flow in the uterine arteries has been observed in pregnancies complicated by impaired trophoblast invasion of the spiral arteries, as occurs with placental pre-eclampsia and IUGR of placental origin[111].

The change in uterine artery blood flow between the first and second trimesters has been examined by screening studies to identify pregnancies at risk of pre-eclampsia and fetal growth restriction[109]. The increase in impedance in the uterine arteries is more reflective of preterm pregnancy complications than those at term, as poor placentation is more associated with early-onset pre-eclampsia[110,111].

Abnormal uterine artery Doppler velocimetry may be defined as bilateral notching with or no notching with mean resistance index (RI) >0.70 (>95th centile), mean RI >0.55 (i.e., >50th centile), or unilateral notching with mean RI >0.65 (>90th centile), at 22–24 weeks[56,57].

A few studies have examined abnormal uterine artery resistance during the first and second trimesters for prediction of pre-eclampsia[108,112]. Using a case–control design, Bolin *et al.* measured uterine artery PI in the first and second trimesters as part of routine antenatal screening[109]. Uterine artery PI was expressed in multiples of median (MoM) values and the predictive accuracy for preterm pre-eclampsia was assessed. The uterine artery PI had a poor predictive ability for identifying women at risk of preterm pre-eclampsia.

However, a retrospective observational study by Napolitano *et al.* evaluated uterine artery Doppler PI as a predictor of early-onset and preterm pre-eclampsia in the first and second trimesters[112]. The uterine artery PI was adjusted for gestational age and the PI MoM ratio between the second and first trimesters (uterine artery ratio) was compared with the PI MoM mean difference between the second and the first trimesters (uterine artery difference). For the prediction of early-onset pre-eclampsia, the AUC ROC values were 0.786 (95% CI 0.703–0.869) for the uterine artery ratio and 0.851 (95% CI 0.753–0.950) for the mean uterine artery difference. For the prediction of preterm pre-eclampsia, the AUC ROC of the uterine artery ratio and mean uterine artery difference were 0.701 (95% CI 0.626–0.776) and 0.705 (95% CI 0.599–0.812), respectively. The study concluded that the mean uterine artery difference was the best index for predicting pre-eclampsia and a better predictor of early-onset pre-eclampsia.

Two reviews examining Doppler studies as an individual predictor of pre-eclampsia were found. The review by Papageorghiou *et al.* investigated the use of uterine artery Doppler measurement in the second trimester for the prediction of pre-eclampsia using findings from 15 studies[108]. The sensitivities reported in these studies ranged from 26 to 89% and the specificities ranged from 86 to 96%. The pooled LR+ and LR- were 5.9 and 0.55, respectively, suggesting that second trimester Doppler measurement had a moderate predictive value for pre-eclampsia. However, the studies included in this review differed in Doppler techniques, definition of abnormal flow velocity and pre-eclampsia, populations and disease incidence.

The latter review by Cnossen *et al.* evaluated the accuracy of uterine artery Doppler for predicting pre-eclampsia in low- and high-risk women[96]. Seventy-four studies that reported uterine artery Doppler data in the first and/or second trimesters were included in the review. The review concluded that uterine artery Doppler velocimetry was more accurate in second trimester for prediction than in the first trimester and PI with notching had the best predictive accuracy for pre-eclampsia in both high- and low-risk women. Again, the review was limited by the different Doppler indices used by the included studies.

In conclusion, uterine artery Doppler PI may be a moderate predictor of pre-eclampsia and may be used to 'rule in' pre-eclampsia risk in the second trimester. However, owing to inconsistencies reported in the studies, further studies are required.

Laboratory markers

The markers of pre-eclampsia risk that become available in the second and third trimesters are based on the pathophysiological changes that characterise pre-eclampsia and precede clinical disease. Many have been evaluated, and they

include measures of the following: placental perfusion and vascular resistance (e.g., mean second trimester blood pressure, 24-hour ambulatory blood pressure monitoring, Doppler ultrasound); cardiac output and systemic vascular resistance; fetoplacental unit endocrinology (e.g., pregnancy-associated plasma protein-A (PAPP-A) and placental growth factor (PlGF) in the first trimester, and alpha fetoprotein, hCG and inhibin A in the early second trimester); renal function (e.g., serum uric acid or microalbuminuria); endothelial function and endothelial–platelet interaction (e.g., platelet count, antiphospholipid antibodies, or homocysteine); oxidative stress (e.g., serum lipids); and circulating pro- and anti-angiogenic factors[113,114].

There have been many systematic reviews of primary studies evaluating clinically available biomarkers as well as Doppler ultrasound interrogation of the uterine and umbilical arteries[115–117]. Tests have been chosen for study based on their association with adverse pregnancy outcomes, including pre-eclampsia. Notable examples are serum analytes involved in maternal serum screening for trisomy 21 (4 studies, 427,751 women)[118], serum uric acid measured before 25 weeks (5 studies, 572 women)[119], and Doppler ultrasonographic interrogation of the uterine artery (74 studies, ~80,000 women)[96]. The methodological quality of the primary studies is very variable, related to women enrolled, gestational age at testing, test performance (such as different Doppler sampling techniques or definitions of abnormal flow velocity waveform), and criteria for the diagnosis of pre-eclampsia.

As markers of the fetoplacental unit are commonly used for trisomy 21 screening, it has been proposed that these markers be used for pre-eclampsia risk estimation, in combination with clinical markers. It will be necessary to evaluate whether maternal serum screening for the sole purpose of pre-eclampsia screening, in combination with clinical markers and possibly uterine artery Doppler, leads to improved outcomes. For the moment, further studies are needed before widespread clinical use of serum screening for pre-eclampsia can be advocated, either in high- or low-risk populations. In addition, it must be acknowledged that with the development of non-invasive prenatal testing[120], the use of maternal serum screening might soon become obsolete.

Endothelial dysfunction tests/placental proteins

High-sensitivity C-reactive protein (hs-CRP)

hs-CRP is a systemic inflammatory marker which is produced by the placenta and released into the maternal circulation[121]. This marker can be found in fetal urine and amniotic fluid, and is sensitive to inflammation and tissue damage. Studies have reported an observed increase in maternal hs-CRP level in pre-eclampsia and other adverse pregnancy outcomes. Kashanian *et al.* conducted a prospective cohort study of 394 women evaluating the predictive accuracy of serum hs-CRP for pre-eclampsia in the first trimester[121]. The result from this study show poor LRs of hs-CRP for the prediction of pre-eclampsia.

Fibronectin

Fibronectin, which is released by the placenta, is associated with endothelial damage and inflammation in pre-eclampsia. Higher plasma levels of fibronectin have been reported in women with pre-eclampsia compared to uncomplicated pregnancies leading to research on its predictive ability for pre-eclampsia. A systematic review by Leeflang *et al.* evaluated the predictive ability of fibronectin in five studies[122]. These studies measured total and/or cellular fibronectin in the first or second trimesters. Fibronectin had a pooled moderate LR+ and, therefore, may be a useful test for predicting pre-eclampsia.

Angiogenic factors

Placental growth factor

PlGF, which is a member of the vascular endothelial growth factor (VEGF) family, is a pro-angiogenic factor produced by the syncytiotrophoblast[123,124]. PlGF is at lower maternal circulating concentrations at time of disease with pre-eclampsia, compared with normal pregnancy[123–125]. PIGF assessment point-of-care platforms currently are available[3,126,127].

Ghosh *et al.* evaluated maternal serum PlGF as a predictive test in the second trimester for predicting early-onset pre-eclampsia in a prospective cohort of 722 women[123]. In this study, PlGF was poorly associated with pre-eclampsia as a predictive test. Another study by Ghosh *et al.* compared serum PlGF measurements in the first trimester with measurements in the second trimester for predicting

early-onset pre-eclampsia[128]. Although PlGF performed better in the second trimester compared with the first trimester measurements, both performances were poor for the prediction of pre-eclampsia, as confirmed in an independent cohort of high-risk women in their second trimester to predict early-onset pre-eclampsia[128,129].

In all the aforementioned studies by Ghosh *et al.*, PlGF concentrations were measured by enzyme linked immunosorbent assay (ELISA) technique using the DRG PlGF Enzyme Immunoassay Kit and early-onset pre-eclampsia was defined as pre-eclampsia diagnosed by 32 weeks' gestation[123,128,129].

Chappell *et al.* assessed PlGF in 625 women in their second and third trimester for the prediction of pre-eclampsia with delivery within 14 days[125]. In this prospective cohort multicentre study, plasma PlGF concentration was measured using the Alere Triage® assay. Using a cut-off of PlGF below the 5th centile, PlGF was strongly associated with a negative likelihood of pre-eclampsia with delivery within 14 days of diagnosis.

There are notable differences in the predictive performance and quantification methods of PlGF and in the incidence of pre-eclampsia among these studies investigating PlGF as an independent predictor of pre-eclampsia.

Soluble fms-like tyrosine kinase 1 (sFlt-1 : PlGF ratio)

sFlt-1 is an anti-angiogenic factor produced by the placenta. It antagonises the activities of VEGF and PlGF by binding to them[90,124]. This results in reduction of the free circulating levels of VEGF and PlGF, as observed in women with pre-eclampsia. Some studies have reported that the sFlt-1 : PlGF ratio can be used to identify patients at risk of pre-eclampsia[90,130].

One of these studies was conducted by Engels *et al.* and measured serum samples of sFlt1 : PlGF ratio using automated Elecsys system and assessed its utility in the second and third trimester for predicting pre-eclampsia and HELLP syndrome[130]. Compared with PlGF alone or sFlt1 alone, sFlt1 : PlGF ratio gave the best predictive accuracy for pre-eclampsia and was strongly associated with a positive likelihood of developing pre-eclampsia.

Teixeira *et al.* investigated the predictive value of PLGF, sFlt-1 and sFlt-1 : PLGF ratio in a prospective longitudinal study[131]. Maternal plasma concentrations were measured in 71 high-risk women using a commercial kits (R&D Systems) in their second trimester. In this study, the sFlt-1 : PLGF ratio had a better discriminative ability (AUC ROC 0.95) for the prediction of pre-eclampsia compared with only PlGF (AUC ROC of 0.90) or sFlt-1 (AUC ROC 0.78).

Another prospective study evaluated serum sFlt-1 : PlGF ratio as a predictor of pre-eclampsia in high-risk women[132]. Blood samples were measured in the second and third trimester using electrochemiluminescence technology (Roche). The third trimester sFlt-1 : PlGF ratio performed better than second trimester and was a moderately associated with a negative likelihood for pre-eclampsia.

A nested case–control study by Forest *et al.* evaluated the serum sFlt-1 : PlGF ratio in the second and early third trimesters[133]. sFlt-1 was measured by ELISA using the Quantikine Human Immunoassay (R&D Systems) and PlGF was measured using an automated immunoassay analyzer (DELFIA System, PerkinElmer). The sFlt-1 : PlGF ratio was moderately well associated with later early-onset pre-eclampsia. This contrasts with a similar nested case–control study evaluating serum sFlt-1 : PlGF ratio measured in the late second trimester using the R&D Systems assay and which reported strong associations for predicting early-onset pre-eclampsia in high risk women[134].

Except for a study by McElrath *et al.*[124], all other included studies in this chapter support growing evidence that sFlt1 : PlGF ratio has good potential as a predictive test for pre-eclampsia in the third trimester, especially in high risk women. The study by McElrath *et al.* quantified plasma sFlt-1 and PlGF concentrations measured in the second trimester using the Abbott Diagnostics' platform and showed poor association for the prediction of pre-eclampsia[124]. The contradicting results from this study may have been owing to the use of a different measurement platform and the use of PlGF : sFlt-1, in contrast to the sFlt1 : PlGF ratio used in other studies.

PREDICTING PRE-ECLAMPSIA (MULTIVARIABLE ANALYSES)

No single clinical, blood or ultrasonographic test reaches the ideal of ≥90% sensitivity and specificity for the prediction of pre-eclampsia. Only Doppler ultrasound (i.e., any or unilateral notching and/or

elevated RI) has a sensitivity >60%, particularly when testing is performed in women at increased risk (vs. low risk) of developing pre-eclampsia, in the second (vs. the first) trimester, and for predicting severe and early-onset pre-eclampsia (rather than milder forms of the disease).

Therefore, as there is no single test that predicts pre-eclampsia with sufficient accuracy to be useful clinically[91], interest has grown in the development of multivariable models that include both clinical and laboratory predictors, available at booking and thereafter in pregnancy[135].

The largest relevant studies have been performed by investigators at King's College, London, UK[101]. For example, at 11–14 weeks, a combination of MAP, uterine artery PI, PAPP-A and PlGF was able to identify 93% of early-onset pre-eclampsia, 36% of late-onset pre-eclampsia, and 18% of gestational hypertension such that 20% of women identified as being screen positive developed a hypertensive disorder of pregnancy; this is consistent with other studies[136].

In specialised clinics, women at increased risk of pre-eclampsia may benefit from this type of risk stratification followed by specific preventative intervention(s); however, this is yet to be proven. Similarly, screening of nulliparous or otherwise low risk women is not yet recommended. Prospective longitudinal studies are needed to assess the validity of published observations in other patient populations where some models have performed differently[137]. Future studies should also distinguish the ability of screening approaches to predict pre-eclampsia that is more severe or that which occurs early (vs. at term). Clinicians are encouraged to support clinics investigating predictive models.

In the SCOPE (Screening for Pregnancy Endpoints) Consortium cohort[138], nine clinical predictors of (almost exclusively, late-onset) pre-eclampsia (many of which were identified by PRECOG[139] and NICE 2008[140]) were identified among nulliparous women carrying singleton pregnancies: one protective (miscarriage at ≤10 weeks' gestation with the same partner) and eight associated with increased risk (younger maternal age, higher mean arterial blood pressure, higher BMI, family history of pre-eclampsia, family history of coronary heart disease, woman with lower birth weight, vaginal bleeding during early pregnancy and short duration of sexual relationship). Of note, the performance of this model was not enhanced by knowledge of uterine artery Doppler results. Using the model, which remains to be validated, the probability of pre-eclampsia would increase from 5 to 10% and half of women who go on to develop pre-eclampsia would be detected.

Clinical history/maternal characteristics

The most common clinical risk factors associated with pre-eclampsia include first pregnancy/primigravidity, maternal age, diabetes, history of pre-eclampsia and other hypertensive disorders of pregnancy, family history of pre-eclampsia, and long inter-pregnancy interval[56,57,89,90]. Women with a history of pre-eclampsia are at increased risk (16–65%) of developing pre-eclampsia in a subsequent pregnancy depending on the onset or severity of the disease in the previous pregnancy[140]. The risk of recurrence for women who had pre-eclampsia is approximately 25% for women who also had HELLP syndrome, about 55% for those who had preterm delivery (<28 weeks)[140] and approximately 65% for women who had early-onset pre-eclampsia[141]. In addition, the increased risk for developing pre-eclampsia for women with a history of gestational hypertension ranges from 2 to 9%[140,141] and the reported RR of pre-eclampsia for a woman with a history of chronic or gestational hypertension is RR 8.9, CI 5.7–13.8 and RR 9.8, CI 4.9–19.1, respectively[141].

However, only a few studies have reported the predictive abilities of the clinical factors for pre-eclampsia, most often in combination with other potential predictive markers as clinical risk factors are not very useful predictors individually[90].

Maternal characteristics with biomarkers (placental protein 13, PAPP-A and free beta subunit of hCG)

Placental protein (PP)-13, PAPP-A and free beta subunit of hCG (β-hCG) are produced and secreted by the syncytiotrophoblast and are involved in implantation, trophoblast invasion and remodelling of the spiral arteries[97,142,143]. In healthy pregnancies, there is an increase in PP-13 and free β-hCG from the first trimester which decreases with gestation, whereas in pre-eclampsia, PP-13 and free β-hCG are reportedly lower in the first trimester, but

significantly higher in the second and third trimesters. Low concentration of PAPP-A in the first semester has also been reported to be associated with pregnancy complications[97,142]. The potential role of these placental proteins as a predictor of pre-eclampsia was assessed in a prospective cohort by Schneuer *et al.*[142]. Serum samples in the first trimester in combination with maternal characteristics (previous hypertension, parity, weight and age) and other biomarkers (β-hCG, PAPP-A) using multivariate models showed a moderate LR+ association for the prediction of early-onset pre-eclampsia.

Maternal characteristics with MAP

In a prospective screening study of 17,383 cases, Gallo *et al.* combined maternal characteristics (gestational age at screening, maternal weight and height, Afro-Caribbean racial origin, family history of pre-eclampsia, prior personal history of pre-eclampsia, cigarette smoking and chronic hypertension) with MAP measured in the first and second trimesters[98]. The model predicted pre-eclampsia with moderate test performance.

Maternal characteristics with biomarkers (serum PIGF and free β-hCG)

First trimester maternal serum PIGF, free β-hCG and maternal history were evaluated for the prediction of pre-eclampsia in a prospective cohort study of 2118 women[144]. Serum blood concentrations of PlGF and free β-hCG were quantified by DELFIA Xpress (Perkin Elmer) and adjusted for gestational age and maternal BMI. The multivariate model with serum PlGF, free β-hCG and chronic hypertension had a moderate LR+ for predicting early-onset pre-eclampsia.

Maternal characteristics with MAP and biomarkers (hyperglycosylated human chorionic gonadotrophin and PAPP-A)

A nested case–control study developed a regression model combining parity, MAP and first trimester hyperglycosylated hCG (hCG-h) and PAPP-A for the prediction of early-onset pre-eclampsia[145]. The study reported a moderate performance of the model for predicting the development of early-onset pre-eclampsia.

Maternal characteristics with MAP and biomarkers (taurine, PAPP-A, ADAM12 and PlGF)

Kuc *et al.* studied the utility of taurine, an amino acid which is involved in trophoblast invasion, the levels of which are altered at the time of disease with pre-eclampsia, in combination with MAP, maternal characteristics (parity, weight) and other biomarkers (PAPP-A, ADAM12 and PlGF) using a multiple logistic regression model[97]. Maternal serum samples were collected in the first trimester in 667 women in the nested case–control study. Early-onset pre-eclampsia with small-for-gestational age (SGA) was predicted moderately with the multivariate model with a strong LR-. A second model developed by in another case–control study showed moderate performance for the prediction of only early-onset pre-eclampsia[143].

Maternal characteristics with uterine artery PI

A review by Kleinrouweler *et al.* evaluated the value of adding second trimester uterine artery Doppler to patient characteristics in identification of nulliparous women at high risk for pre-eclampsia[111]. A logistic regression model combining blood pressure, uterine artery and bilateral uterine artery notching showed a good discriminatory predictive performance with an AUC of 0.85 (95% CI 0.67–1.00) in the study.

In another study, combining uterine artery PI expressed as $\log^{10}$ MoM and maternal characteristics (weight, height, race, parity and chronic hypertension) used in the early third trimester showed moderate association for predicting late-onset pre-eclampsia[146].

Maternal characteristics with blood pressure and uterine artery PI

Prediction of early onset pre-eclampsia in a prospective multicentre cohort study in 627 women was evaluated using demographic, clinical and ultrasound data in the first trimester[99]. The multivariate model included age, weight, systolic blood pressure, diastolic blood pressure and MAP at enrolment, parity, history of pre-eclampsia or hypertension, diabetes mellitus, log (uterine artery PI) and a history of preterm labour. The model

strongly predicted the development of early-onset pre-eclampsia in the development study. The performance of the model was moderate on external validation by Oliveira *et al.* in a prospective, observational study of 2669 women recruited in their first trimester[147].

Maternal characteristics with uterine artery Doppler and biomarkers (ADAM12 and PAPP-A)

In a prospective cohort study, Goetzinger *et al.* assessed the accuracy of a multivariate model combining first trimester bilateral uterine artery notching and PAPP-A, and maternal characteristics (chronic hypertension, history of pre-eclampsia, pre-gestational diabetes, obesity) for the prediction of pre-eclampsia[148]. The model was developed in one-half of a prospective cohort of 1200 patients in first trimester and validated in the second-half. The validated model had a moderate predictive accuracy for pre-eclampsia. It is worth mentioning that the split-half method of validation used has been reported to have some major drawbacks in prediction modelling.

Maternal characteristics with MAP and biomarkers (PlGF)

PlGF combined with MAP and maternal characteristics (a sister with a history of pre-eclampsia and a history of previous fertility treatment) were assessed for predictive accuracy for preterm pre-eclampsia in low-risk nulliparous women[149]. In the prospective multicentre cohort study, plasma PlGF was measured in second trimester using the triage assay. The model predicted pre-eclampsia with moderate performance.

Maternal characteristics with uterine artery PI and biomarkers (PlGF)

Serum concentrations of PlGF collected during the first, second and third trimesters of pregnancy and quantified using R&D were assessed in a case–control study of 541 women for the prediction of pre-eclampsia[150]. In a logistic regression model combining relative difference of PlGF from the first to the second trimester with BMI, second trimester uterine artery PI was a moderate predictor of pre-eclampsia.

Other multivariate studies

Circulating proteins and angiogenic factors

In a prospective study by Katsipi *et al.*, second trimester measurements of pulse wave velocity (PWV), which is a measure of aortic stiffness, was combined with serum levels of sFlt-1 in a regression model[151]. The model was a strong predictor of pre-eclampsia in high-risk pregnant women.

Park *et al.* assessed the predictive accuracy of the sFlt-1 : PlGF ratio (measured in the second and third trimesters (Roche Elecsys)) in combination with PAPP-A for late-onset pre-eclampsia in low risk women[90]. In this study, the third trimester sFlt-1 : PlGF ratio had a better predictive accuracy than the second trimester ratio and was a strong predictor of developing late-onset pre-eclampsia in low-risk women[90].

Myatt *et al.* combined first-trimester measurements of biomarkers (using Luminex assays[152]) with risk factors in an observational study in 2434 nulliparous women at low risk[137]. The best multivariable model included African-American race, systolic blood pressure, BMI, education level, ADAM-12, PAPP-A and PlGF, but performed poorly in predicting pre-eclampsia.

In a prospective cohort of 235 women, second-trimester uterine artery Doppler, serum biomarkers and lipid-related markers were evaluated for the prediction of pre-eclampsia[152]. The final model included maternal age, nulliparity, bilateral uterine artery notch, PlGF, sFlt-1, leptin and triglycerides, and was a poor predictor of pre-eclampsia in the high-risk cohort.

Histidine-rich glycoprotein (HRG), a multi-domain protein which has both pro- and anti-angiogenic properties, was studied as a predictor for preterm pre-eclampsia in combination with uterine artery pulsatility index (expressed as MoM) in a case–control study of 175 women[109]. The multivariate model showed a moderate LR- for predicting preterm pre-eclampsia.

In conclusion, most of the multivariate models combining maternal characteristics or biomarkers with other variables were either poor predictors of pre-eclampsia or did not give sufficient information to confirm the predictive ability of the test. Only a few seemed promising, especially those combining angiogenic factors with some other markers[151,155].

BEST PRACTICE POINTS

(Please see Appendix 5.5 for the evaluation of the strength of evidence.)

1. Women should be screened for clinical risk markers of pre-eclampsia from early pregnancy.
2. Consultation with an obstetrician or an obstetric internist/physician should be offered to women with a history of previous pre-eclampsia or another strong clinical marker of increased pre-eclampsia risk, particularly multiple pregnancy, antiphospholipid antibody syndrome, significant proteinuria at booking, or a pre-existing condition of hypertension, diabetes mellitus, or renal disease.
3. Screening for non-clinical risk markers cannot be recommended routinely at present for women at low or increased risk of pre-eclampsia until such screening has been shown to improve pregnancy outcome.

WHAT INTERNATIONAL GUIDELINES SAY (APPENDIX 5.4)

Abbreviations for Clinical Practice Guidelines are as follows ACOG (American College of Obstetricians and Gynecologists)[155], NICE (National Institutes of Clinical Excellence)[140], SOGC (Society of Obstetricians and Gynaecologists of Canada)[56,57], AOM (Association of Ontario Midwives)[156].

In a systematic review of international clinical practice guidelines on the hypertensive disorders of pregnancy[89], only three (ACOG, AOM, SOGC) out of 13 guidelines gave recommendations for the screening or prediction of pre-eclampsia or other hypertensive disorders of pregnancy. Well-established clinical risk markers such as medical history were the only recommended markers for screening. None of the guidelines recommended the use of ultrasonography or biomarkers; however, two guidelines (NICE, SOGC) suggested that a combination of these tests with clinical risk markers may be useful but require further studies to make sufficient conclusions.

SUMMARY

The ability to predict pre-eclampsia will facilitate early recognition of the disease, risk stratification and better management of these women to prevent associated severe complications, whilst making optimum use of limited resources[93,94]. In addition, predicting pre-eclampsia may provide more clarification of the pathogenesis and mechanisms involved in pre-eclampsia and might result in strategies for developing better prophylactic interventions and treatment[92]. There is need for large studies to validate the clinical value of these predictors and models before they can be applicable in clinical care for the prediction of pre-eclampsia.

PRIORITIES FOR FUTURE RESEARCH

Key priorities when conducting research on predicting pre-eclampsia include:

- Large prospective studies with adequate sample sizes as many of the studies reviewed in this chapter had small sample sizes with very low rates of pre-eclampsia.
- Studies reporting predictive accuracy according to disease onset and population risk will be beneficial in risk assessment and screening so as to allocate interventions to women who need them most. More focus should be targeted at predicting pre-eclampsia in the first trimester so that prophylactic interventions can be commenced.
- Standardisation of definitions and analytical methods will be useful for comparison and meta-analysis of results from prediction studies.
- Multivariate models need to be validated externally before they can be used in clinical practice. Only two studies among all the studies with multivariate models mentioned external validation[99,148]. Research has shown that the performance of a model can be overoptimistic when assessed in the same population used for building the model owing to overfitting[157,158]. Assessing the validity of these models in other population needs to be carried out to assure validity and reliability of predictive performance.
- There is a large knowledge deficit related to risk prediction for women in less-developed countries. An urgent priority is to diminish this deficit.

PRIORITIES IN UNDER-RESOURCED SETTINGS (TABLE 5.2)

Delays in disease identification and treatment are major contributing factors to the increased burden

Table 5.2 Priorities for prediction of hypertensive disorder of pregnancy in under-resourced settings

Antepartum and postpartum	
Initial priority	*Ultimate goal*
Early screening for pregnant women using risk factors and readily available predictive tests	Identification of high-risk women and initiation of preventative therapies
Cost-effectiveness studies for potential predictors	Use of cheap, point-of-care tests for early prediction
Recognition of recurrence risk factors based on prior pregnancy	Monitor and early treatment in future pregnancy

of the hypertensive disorders of pregnancy in LMICs[159]. Pre-eclampsia is a heterogeneous condition with different phenotypes. Future research is required to identify the risk factors and disease presentation for pre-eclampsia in low-income settings, which may differ from that in high-resourced settings, to allow for early interventions. Also, there might be need for earlier screening and initiation of preventative treatments in LMICs owing to the severity of outcomes in these settings.

A shortage of well-trained health professional and financial costs remain a significant risk burden for women in LMICs[160]. Therefore, for any predictive test to be beneficial in such settings, it should be a cheap, easy-to-use, point-of-care test that requires minimal training. Potential predictive tests that quickly measure angiogenic imbalance and glycosylated fibronectin during pregnancy are now available; however, further research is required to ascertain their use as a predictive tool.

Cost-effectiveness studies of these potential predictors are important especially for the LMICs which suffer most of the burden from pre-eclampsia[93]. An economic analysis of screening for pre-eclampsia using placenta markers (PP-13 and PlGF) and uterine artery Doppler compared with standard care has shown that screening for pre-eclampsia may be cost-effective[161]. Though the feasibility of uptake of this screening in a LMIC setting has not been studied, it represents a possible area of future research[162–169].

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6

Preventing pre-eclampsia and its complications

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SYNOPSIS

There is a considerable literature devoted to the prevention of pre-eclampsia in order to avoid the associated maternal and perinatal complications. However, pre-eclampsia, at least in its non-severe form, may serve some adaptive function in terms of improved neonatal outcomes in the neonatal intensive care unit[1] or neurodevelopmental outcome[2]. Therefore, we have based our preventative recommendations on the prevention of pre-eclampsia and/or the prevention of its associated complications where literature permits.

Preventative interventions may be best started before 16 weeks' gestation when most of the physiologic transformation of uterine spiral arteries occurs, or even before pregnancy. Such early intervention has the greatest potential to decrease the early forms of pre-eclampsia that are associated with incomplete transformation of uterine spiral arteries[3].

Pregnant women have been classified as being at 'low' or 'increased' risk of pre-eclampsia most commonly by the presence or absence of one or more of the risk markers (see Chapter 5, Table 5.1). Although the strength of evidence around various interventions to prevent pre-eclampsia varies, there is strong evidence that low-risk women who have low dietary intake of calcium (<600 mg/d) may benefit from calcium supplementation (of at least 1 g/d, orally) to prevent pre-eclampsia. High-risk women are recommended to take calcium supplementation (of at least 1 g/d) if calcium intake is low, and are also recommended to initiate low-dose aspirin (75–100 mg/d) at bedtime before 16 weeks of gestation. Widespread implementation of these interventions is recommended to help prevent pre-eclampsia and its complications.

WOMEN AT 'LOW RISK'

Women at 'low risk' of pre-eclampsia are most commonly those from unselected obstetric populations and may be nulliparous or multiparous. (Please see Appendix 6.1 for details of individual randomised controlled trials or systematic reviews of randomised controlled trials that reported on the outcomes of pre-eclampsia, gestational hypertension, maternal morbidity, small-for-gestational-age (SGA) infants, or neonatal morbidity such as neonatal intensive care stay.)

Abstention from alcohol

There are no trials studying the effect of alcohol abstention on the incidence of hypertensive disorders of pregnancy. Reduced consumption is recommended to reduce blood pressure in non-pregnant individuals[4], but in pregnancy,

abstention is recommended as there is no proven safe level of alcohol intake in pregnancy[5].

Aspirin (low dose)

There is weak evidence that low-dose aspirin can prevent pre-eclampsia in moderate-risk women (RR 0.86, 95% CI 0.79–0.95; 25 trials, 28,469 women)[6]. However, no trials have evaluated the effect of low-dose aspirin started in the first trimester, something that may be more effective among women at increased risk (see Women at increased risk below).

Calcium

At a population level, there is an inverse relationship between dietary calcium intake and both blood pressure among non-pregnant individuals and the incidence of pre-eclampsia[7]. Dietary calcium intake may mediate this effect by inhibiting parathyroid activity thereby decreasing intracellular calcium and causing vasodilatation[8].

Although one trial found no decrease in pre-clampsia with 1.5 g/d oral calcium supplementation (RR 0.91, 95% CI 0.69–1.19; 357 women)[9], other reviews found that oral calcium supplementation (of at least 1 g/d) decreased the incidence of pre-eclampsia in low-risk women (8 trials, 15,143 women; RR 0.45, 95% CI 0.41–0.83), gestational hypertension (RR 0.71, 95% CI 0.57–0.89; 8 trials, 15,143 women)[7] and preterm birth (RR 0.76, 95% CI 0.60–0.97; 10 trials, 15,275 women)[10]. Maternal death or serious morbidity (which included severe hypertension) is also reduced (RR 0.80, 95% CI 0.65–0.97; 2 trials, 9732 women) which more than offsets the increase in HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome (RR 2.67, 95% CI 1.05–6.82; 2 trials, 12,901 women) reported in the calcium supplementation arms of the two trials that reported HELLP syndrome[10]; it is possible that the blood pressure lowering effect of calcium supplementation permitted more time for pre-eclampsia to progress to HELLP syndrome.

Oral calcium supplementation of <1 g/d has been trialed in mixed populations of women at low and high risk (e.g. pregnant teenage girls, women with previous pre-eclampsia or women with positive roll over test); see Women at increased risk below.

The benefits of calcium supplementation in women at low risk of pre-eclampsia are most likely restricted to women with low calcium intake; potential harms in this population have not been ruled out and in a supplementation trial of 1.5 g/d in The Gambia, calcium treatment was associated with lower bone mineral content throughout lactation[11]. An alternative to supplementation may be to increase dietary calcium intake, by 3–4 dairy servings per day (as one serving corresponds to 250–300 mg of calcium).

Dietary changes

A variety of dietary and lifestyle interventions can reduce the risk of pre-eclampsia (overall RR 0.81, 95% CI 0.69–0.94; 18 trials, 8712 women): by dietary change (RR 0.67, 95% CI 0.53–0.85; 6 trials, 2695 women), not but by essential fatty acid supplementation alone (RR 0.92, 95% CI 0.71–1.18; 6 trials, 4579 women) or by mixed interventions of diet, physical activity and lifestyle (RR 0.93, 95% CI 0.66–1.32; 6 trials, 1438 women)[12].

Dietary salt restriction (with confirmed compliance) does not affect the incidence of gestational hypertension (RR 0.98, 95% CI 0.49–1.94; 2 trials, 242 women) or pre-eclampsia specifically (RR 1.11, 95% CI 0.46–2.66; 2 trials, 603 women[13]). No trials were identified of a heart-healthy diet that was associated with a lower risk of pre-eclampsia in a single case–control study[14]. However, there is a strong belief in many jurisdictions that decreasing dietary salt is a prudent action to take, as illustrated by the following quote:

> "We advise her to eat less salt and not to eat oily food, pickles."
>
> Auxiliary Nurse Midwife/Nurse, Belgaum, India (from CLIP Feasibility Study)

Nutritional education counselling was associated with a reduction in preterm birth (RR 0.46, 95% CI 0.21–0.98; 2 trials, 449 women), and a reduction in low birth weight babies (RR 0.04, 95% CI 0.01–0.14; 1 trial, 300 women)[15]. Specifically within undernourished women, nutritional advice was found to increase birth weight (mean difference 489.76, 95% CI 427.93–551.59; 2 trials, 320 women). Balanced protein/energy supplementation in pregnancy did not affect pre-eclampsia incidence (RR 1.48, 95% CI 0.82–2.66; 2 trials, 463 women), but both stillbirth (RR 0.60, 95% CI 0.39–0.94; 5 trials, 3408 women) and SGA babies (RR 0.79,

95% CI 0.69–0.90; 7 trials, 4408 women) were reduced in incidence[15]. High-protein supplementation may have been associated with harm by increasing the risk of SGA babies (RR 1.58, 95% CI 1.03–2.41; 1 trial, 505 women), although weight at 1 year of age did not differ between the high- and low/no supplementation groups[15]. Isocaloric protein supplementation was found to be unlikely to benefit pregnant women or their infants; it did not affect birth weight (mean difference 108.25 g, 95% CI 220.89–437.40, $I^2 = 84\%$) or weekly gestational weight gain (mean difference 110.45 g/week, 95% CI –82.87–303.76, $I^2 = 85\%$; 2 trials, 184 women)[15]. Theoretical concerns about the effect of starvation ketosis on fetal neurodevelopment have led to recommendations that women should not pursue weight-loss dieting in pregnancy[16].

No trials of probiotics were identified, but the consumption of milk-based probiotics was associated with a lower risk of pre-eclampsia in a Norwegian population-based cohort study of 33,399 primiparous women; the decrease was marked for severe pre-eclampsia (aOR 0.79, 95% CI 0.66–0.96; 32,158 women)[17].

A preventative strategy with considerable potential appeal to women is administration of flavanoids, antioxidants found in citrus fruits, dark chocolates and tea. The idea is based on the inverse relationship between higher chocolate intake and lower blood pressure in pregnancy in a prospective cohort study of 2291 women[18]. Two small trials have found conflicting effects of flavanol-rich chocolate on blood pressure in pregnancy; one trial (90 women) found that blood pressure was lower when high-cocoa-content chocolate was ingested from 11 to 13 weeks' gestation[19], whereas another trial (44 women) found that blood pressure (and endothelial function) were unchanged among normotensive women at baseline[20]. Another trial (160 women) has finished recruiting but the impact of the intervention on endothelial function has not yet been reported[21]. We await adequately powered trials that examine the impact of flavonoids on pre-eclampsia or maternal or perinatal morbidity.

Folate-containing multivitamins

It is accepted that women should take a folate-containing multivitamin when planning pregnancy and into early pregnancy for primary prevention of neural tube and, possibly, other congenital anomalies[22]. However, periconceptional and ongoing regular use of multivitamins has also been associated with prevention of gestational hypertension (1 trial, 138 women)[23] and pre-eclampsia in women with a body mass index (BMI) $<25\,kg/m^2$ (prospective cohort, 1835 women)[24]. The international Folic Acid Clinical Trial (FACT) is focused on women at increased risk of pre-eclampsia, and is discussed below[25].

Lifestyle changes

Low- to moderate-intensity regular exercise is beneficial for general health reasons to maintain or improve physical fitness (11 trials, 472 women)[26], and observational studies have associated exercise with a reduced risk of pre-eclampsia in a 'dose-dependent' fashion[27–34]. Overweight women who exercised from early pregnancy had improved exercise capacity (1 trial, 132 women)[35], but we were unable to identify trials of exercise for pre-eclampsia prevention among women at low risk.

Greater workload[31,36] and stress have been associated with pre-eclampsia[37], although the quality of studies is not high[38]. We were unable to identify randomised trials of workload reduction to prevent pre-eclampsia, despite this being a common obstetric intervention.

Micronutrients other than calcium

Micronutrient deficiencies (other than calcium) are common in pregnancy when one takes a global perspective. Deficiencies of magnesium, zinc and pyridoxine have been associated with an increase in hypertensive disorders of pregnancy and/or their complications[39–41].

Magnesium supplementation (various preparations), primarily in women at low risk, did not affect the incidence of pre-eclampsia (RR 0.87, 95% CI 0.58–1.32; 3 trials, 1042 women), preterm birth <37 weeks' gestational age (RR 0.89, 95% CI 0.69–1.14; 7 trials, 5981 women), low birth weight <2500 g (RR 0.95, 95% CI 0.83–1.09; 5 trials, 5577 women) or SGA infants (RR 0.76, 95% CI 0.54–1.07; 3 trials, 1291 women)[40]. A subsequent trial also found that magnesium supplementation (of 300 mg/d from 25 weeks) prevented an increase in diastolic blood pressure during the last weeks of pregnancy (1 trial, 59 women)[42].

Zinc supplementation (20–90 mg elemental zinc), primarily in women of low income, did not affect the hypertensive disorder of pregnancy incidence, although preterm delivery was decreased (RR 0.86, 95% CI 0.76–0.97; 16 trials, 7637 women)[43].

One trial found that antioxidant/phytonutrient supplementation (from plant foods) in the first trimester did not decrease rates of pre-eclampsia in low-risk women (RR 1.22, CI 0.40–3.77)[44].

Prostaglandin precursors

Diets rich in marine oils are associated with a reduced risk of pre-eclampsia[45]. These marine oils are rich in prostaglandin precursors and may be beneficial by reducing inflammation and vasoconstriction. A systematic review reported that in mixed populations that included both low- and high-risk women, prostaglandin precursors (which included other oils such as evening primrose oil) did not decrease the risk of pre-eclampsia (RR 0.86, 95% CI 0.59–1.27; 6 trials, 2783 women), but they did decrease birth before 34 weeks (RR 0.69, 95% CI 0.49–0.99; 2 trials, 860 women)[45]. A randomised controlled trial assessing the effect of fish oil supplementation in the second half of pregnancy also found no reduction in pre-eclampsia (RR 0.87, 95% CI 0.60–1.25; 2399 women)[46]. It should be noted that given concerns about contaminants such as mercury, increased dietary intake of fish for the purpose of fish oil consumption is not recommended[47].

Smoking cessation

While it is true that smoking is associated with a reduced risk of pre-eclampsia in observational studies[48–50], smoking also increases the risk of impaired fetal growth and preterm birth[51–53].

Smoking cessation has been shown to decrease the incidence of low birth weight babies (RR 0.82, 95% CI 0.71–0.94; 14 trials, 8562 women) and preterm birth (RR 0.82, 95% CI 0.70–0.96; 14 women, 7852 women)[54]. Although various smoking cessation approaches have been tried, a randomised controlled trial evaluating the effectiveness and safety of nicotine replacement therapy in pregnancy did not show a difference in either pregnancy outcomes or long-term quit rates in pregnancy[55].

Thiazide diuretics

Thiazide diuretics did not decrease pre-eclampsia (RR 0.68, 95% CI 0.45–1.03; 4 trials, 1391 women) or adverse outcomes, but they did increase maternal side-effects (vs. placebo) in women at low risk of pre-eclampsia (RR 5.81, 95% CI 1.04–32.46; 2 trials, 1217 women)[56].

Vitamins C and E

Pre-eclampsia is associated with oxidative stress. However, among women at low risk given vitamins C (1000 mg/d) and E (400 international units/day) therapy from either the first or early second trimester, vitamins C and E did not decrease the incidence of pre-eclampsia (RR 0.85, 95% CI 0.48–1.51; 4 trials, 2441 women). In fact, vitamins C and E increased use of any antihypertensive (RR 1.77, 95% CI 1.22–2.57; 2 trials, 4272 moderate- and high-risk women) and antenatal hospital admission for hypertension (RR 1.54, 95% CI 1.00–2.39; 1 trial, 1877 moderate- and high-risk women)[57].

Subsequent trials have confirmed this lack of benefit. A total of 10,514 nulliparous women at low risk for pre-eclampsia were randomly assigned to daily 1000 mg of vitamin C and 400 IU of vitamin E or matching placebo from 9 to 16 weeks until delivery. Intervention was not associated with prevention of severe hypertension (RR 1.07, 95% CI 0.91–1.25) or pre-eclampsia (RR 1.07, 95% CI 0.93–1.24)[58]. Similarly, no significant effect on gestational hypertension (RR 0.99, 95% CI 0.78–1.26) or pre-eclampsia (RR 1.04, 95% CI 0.75–1.44) was observed among 2647 pregnant women randomised to vitamin C and E or placebo[59]. One randomised controlled trial with 299 women evaluating vitamin E therapy (N = 151) versus placebo (N = 148) from early second trimester until delivery found no statistically significant difference in gestational hypertension, but there was a tendency towards a lower incidence of hypertension in the treatment arm (RR 0.36, 95% CI 0.12–1.09)[60]. Another randomised controlled trial with 932 women evaluated 100 mg vitamin C supplementation alone versus placebo from 12 to 22 weeks of gestation and found no difference in the incidence of pre-eclampsia (RR 0.77, 95% CI 0.37–1.56), severe pre-eclampsia (RR 1.25, 95% CI 0.34–4.56), gestational hypertension (RR 0.67, 95% CI 0.43–1.03),

preterm delivery (RR 0.92, 95% CI 0.63–1.34) or low birth weight (RR 1.07, 95% CI 0.72–1.59)[61].

Vitamin D

Vitamin D may play a protective role against pre-eclampsia through beneficial effects on immune modulation and vascular function[62–64]. A significant relationship between vitamin D deficiency and increased risk of pre-eclampsia has been shown by systematic reviews and meta-analyses of observational studies[65,66]. This represents an area where further studies are required.

Other interventions for which no recommendation can be made

Interest in supplementation with iron and/or folate (beyond 10 weeks' gestation) stems from the importance of anaemia in developing countries and further progressive anaemia associated with pregnancy[67]. There is insufficient evidence on the effect on pre-eclampsia of either routine (vs. no routine) iron supplementation (usually 60–100 mg elemental iron/day) (1 trial, 47 women) or routine iron with/without folic acid supplementation (1 trial, 48 women)[68].

Pyridoxine has many roles, including neurological development and function. Although in a systematic review, pyridoxine supplementation did not decrease the risk of pre-eclampsia, the trials were of poor quality with poor reporting of substantive outcomes, making it impossible to draw conclusions (oral pyridoxine RR 1.71, 95% CI 0.85–3.45; 2 trials, 1197 women) (pyridoxine lozenges RR 1.43, 95% CI 0.64–3.22; 1 trial, 944 women)[69].

Garlic may lower blood pressure[70], reduce oxidative stress[71] and inhibit platelet aggregation[72], but a systematic review found no clear effect on pre-eclampsia (RR 0.78, 95% CI 0.31–1.93). As only one trial with 100 women was included, further trials are needed to draw any reliable conclusions about garlic and its effect on pre-eclampsia[73].

We were unable to identify trials administering the following agents for primary prevention of pre-eclampsia: vitamin A, selenium, copper and iodine.

It must be noted that in some regions, there is strong interest in traditional medicines for pre-eclampsia prevention. Evidence is lacking to support or refute these practices.

> "About snails, we use the fluid from a snail to prepare traditional medicine to treat patients with high blood pressure . . . we use the snail's fluid to prepare a traditional medicine for them . . . and they would use a teaspoon to take the medicine . . . those that always have high blood pressure . . . people whose blood pressure is always high . . . people like that . . . within 3 months or so . . . they would be lying on a sick bed . . . they would rolling on the floor in pains . . . and be doing all sorts of things . . . so we treat them so that the high blood pressure wouldn't cause complications for them".
>
> Head Traditional Birth Attendant, Yewa South, Nigeria (from CLIP Feasibility Study)

WOMEN AT INCREASED RISK

Women identified as being at 'increased risk' of pre-eclampsia have been most commonly those with a personal or family history of a hypertensive disorder of pregnancy, chronic medical disease (including hypertension), and/or an abnormal uterine artery Doppler velocimetry before 24 weeks. However, there was variability between studies in inclusion criteria (including use of the roll-over test reflecting increased sensitivity to angiotensin-II) and other characteristics of the population, including ethnicity, parity, socioeconomic status and access to prenatal care. No study identified used only the roll-over test to enroll women.

A growing literature suggests that combining clinical, biochemical and/or ultrasonographic risk markers may better identify women at increased risk of pre-eclampsia (as as discussed in Chapter 5); however, to date no intervention trial has used such an approach to evaluate a preventative therapy[74–76]. The ASPRE trial is doing so for aspirin (150 mg/d at bedtime), as discussed below[77]. (Please see Appendix 6.2 for details of individual randomised controlled trials or systematic reviews of randomised controlled trials that reported on the outcomes of pre-eclampsia, gestational hypertension, maternal morbidity, SGA infants, or neonatal morbidity such as neonatal intensive care stay.)

Antihypertensive therapy

Antihypertensive therapy does not prevent pre-eclampsia (RR 0.93, 95% CI 0.80–1.08; 23 trials, 2851 women) or the associated adverse perinatal outcomes, but it decreases by half the

incidence of development of severe hypertension (RR 0.49, 95% CI 0.40–0.60; 2 trials, 2558 women)[78]. Antihypertensive therapy cannot be recommended for pre-eclampsia prevention until it can be demonstrated that the decrease in maternal blood pressure is not outweighed by a negative impact on perinatal outcomes[79,80]. (Antihypertensive therapy for treatment of elevated blood pressure is discussed in Chapter 8)

Aspirin (low dose)

In women identified as at increased risk of pre-eclampsia based on clinical characteristics, low-dose aspirin results in a small decrease in pre-eclampsia (RR 0.75, 95% CI 0.66–0.85; 18 trials; 4121 women for this outcome), preterm delivery <37 weeks' gestation (RR 0.89, 95% CI 0.81–0.97; I^2 32%; 10 trials, 3252 women for this outcome), perinatal death (RR 0.69, 95% CI 0.53–0.9; 17 trials, 4443 women for this outcome) (40 trials, 33,098 women overall)[6], and intrauterine growth restriction (RR 0.80, 95% CI 0.65–0.99; I^2 36.9%, 13 trials, 12,504 women for this outcome)[81]. There is low level evidence that low-dose aspirin may help to prevent pre-eclampsia (RR 0.67, 95% CI 0.48–0.94; 5 trials, 898 women) in multiple gestations[82]. The ASPRE trial is doing so for aspirin (150 mg/d at bedtime) started in the first-trimester in women identified as being at increased risk[77].

Aspirin does not increase or decrease miscarriage risk[83]. There is no evidence of short- or long-term adverse effects on the mother or newborn.

Who should receive aspirin, in what dose, and when are unclear. Subgroup analyses in meta-analyses suggest a number of important considerations. First, *aspirin is more effective in decreasing pre-eclampsia among women at high risk* (NNT 19, 95% CI 13–34) compared with those at moderate risk (NNT 119, 95% CI 73–333), though a recent meta-analysis did not show any effect of preconceptionally started aspirin in reducing hypertensive pregnancy complications in IVF women[84]. Second, *aspirin may be more effective at decreasing the following outcomes when it is initiated before 16 weeks' gestation: severe pre-eclampsia*[85], preterm pre-eclampsia, preterm delivery, perinatal death and SGA infants[81,86–90]. Preconception-initiated low-dose aspirin was associated with the outcome of higher live birth rates in women with a single documented loss at less than 20 weeks' gestation during the previous year[91]. However, a recent secondary analysis showed that 60 mg of aspirin daily, initiated before or after 16 weeks' gestation was not effective for the prevention of pre-eclampsia[92]. Therefore, *aspirin may be more effective when used at a higher dose*[6,93]. Approximately one-third of pregnant women are both resistant to the effects of 75–80 mg of aspirin and at increased risk of adverse pregnancy outcomes[94,95]. A retrospective controlled study (270 women) suggested that adjusting aspirin dosage based on platelet function testing may improve the effectiveness of aspirin without a demonstrated increase in adverse neonatal outcomes[96]. Furthermore, two randomised controlled trials found that *taking aspirin at bedtime (instead of the morning) resulted in lower blood pressure and fewer adverse pregnancy outcomes* such as pre-eclampsia, SGA babies and preterm birth[97,98]. Finally, *aspirin may be continued until delivery* as was prescribed in most trials; however, some care providers of women in these trials stopped aspirin prior to delivery and the benefits of continuing aspirin throughout the third trimester have also been questioned[99] (see Chapters 8 and 10).

Calcium

Oral calcium supplementation (of at least 1 g/d) in high-risk women (e.g. teenagers or women older than 40 years, women with previous pre-eclampsia, women with increased sensitivity to angiotensin II, women with pre-existing hypertension) was found to decrease the incidence of pre-eclampsia (RR 0.22, 95% CI 0.12–0.42; 5 trials, 587 women), gestational hypertension (RR 0.47, 95% CI 0.22–0.97; 4 trials, 327 women) and preterm delivery (RR 0.45, 95% CI 0.24–0.83; 4 trials, 583 women)[7]. Three of the five relevant trials were conducted in low calcium intake populations. No trial included women with previous pre-eclampsia. There were no documented adverse effects of calcium supplementation, but none of these trials of women at high risk of pre-eclampsia reported the outcome of HELLP syndrome. An alternative to supplementation may be an increase in dietary calcium intake, by 3–4 dairy servings per day (as one serving corresponds to 250–300 mg of calcium).

Oral calcium supplementation of <1 g/d is also effective in mixed populations of women at low and increased risk of pre-eclampsia, but the effect

within each of these populations is not known. The Calcium and Pre-eclampsia (CAP) Study is an ongoing randomised trial of low-dose calcium supplementation among women at high risk of pre-eclampsia)[100].

Aspirin (low-dose) combined with calcium

Two small trials (91 women) have looked at the combined effect of low-dose aspirin and calcium supplementation (one <1 g/d[101] and one more than 1 g/d[102]). The combined therapy from 20 to 27 weeks' gestation was associated with a non-significant decrease in pre-eclampsia (52.5% vs. 73.1%, $p = 0.11$) and IUGR (25.0% vs. 4.8%, $p = 0.07$) that may warrant further study, particularly as both therapies are currently recommended individually[102]. In particular, it is not known what the effect would be of supplementation before 16–20 weeks of gestation, and bioavailability studies are required to determine how much aspirin and calcium are actually being absorbed by study participants[102]. The other trial of aspirin and low-dose calcium found that combined therapy was associated with significant improvement in pro-inflammatory factors of highly sensitive C-reactive protein (hs-CRP), plasma total antioxidant capacity (TAC) and total glutathione (GSH)[101].

Dietary changes

We were unable to identify trials of dietary salt restriction on the incidence of pre-eclampsia among women at increased risk. Women with pre-existing hypertension who are already following a dietary approached to stop hypertension (DASH) diet may continue this diet during pregnancy, but there is no evidence to support this practice.

We were unable to identify trials of a heart-healthy diet for pre-eclampsia prevention.

Obesity is both a major public health problem and a risk marker for pre-eclampsia. No effect on gestational hypertension (or pre-eclampsia specifically) has been demonstrated when overweight women have received dietary counselling during pregnancy to curb the rate of weight gain (3 trials, 384 women)[15]. No trials have addressed the impact of pre-pregnancy or early pregnancy weight reduction on pre-eclampsia; there are theoretical concerns about the impact of starvation ketosis on fetal neurodevelopment[16].

Garlic may decrease lipid peroxidation and platelet aggregation. One small trial of 100 women at increased risk of pre-eclampsia based on a positive roll-over test found that garlic supplementation in the third trimester of pregnancy reduced the occurrence of gestational hypertension (18% vs. 36%, $p = 0.04$), but not of pre-eclampsia (14% vs. 18%, $p = 0.80$)[103]. Another small trial (N = 235) found that coenzyme Q10 supplementation from 20 weeks until delivery (compared to placebo) reduces the risk of developing pre-eclampsia (14.4% vs. 25%, $p = 0.035$, RR 0.56, 95% CI 0.33–0.96)[104].

Folate-containing multivitamin

Periconceptional and ongoing regular use of multivitamins was associated with higher birth weight centiles in a secondary analysis of the Vitamins in Pre-eclampsia (VIP) (vitamin C and E trial) in the UK[105]. Periconceptional use of a folate-containing multivitamin is recommended for all women of child-bearing age for prevention of neural tube and, possibly, other birth defects. The Canadian FACT trial of folic acid 0–1.1 mg versus 4–5.1 mg (4.0 mg folic acid as the intervention) from 10 to 14 weeks for the prevention of pre-eclampsia has recently completed recruitment and the results are anticipated[106].

Heparin

Heparin may improve placentally mediated outcomes through anticoagulant and/or potentially non-anticoagulant actions, such as endothelium-dependent vasodilation[107] and/or reversal of the anti-angiogenic actions of explanted placental villi on cultured endothelial cells[108].

A number of small randomised controlled trials have studied prophylactic doses of heparin (mostly low molecular weight heparin (LMWH)) for women with a history of various placental complications in previous pregnancies. The 2013 Cochrane review (9 trials, 979 women) found that prophylactic doses of heparin (of any type) compared with no treatment, decreased perinatal mortality (2.9% vs. 8.6%; RR 0.40, 95% CI 0.20–0.78), preterm delivery before 34 weeks (8.9% vs. 19.4%; RR 0.46, 95% CI 0.29–0.73), and SGA infants (7.6% vs. 19.0%; RR 0.41, 95% CI 0.27–0.61) in women at high risk of placentally mediated complications[109]. In another review focused on only LMWH (6 trials, 848 women),

LMWH, compared with no treatment, reduced the risk of 'severe' or early-onset pre-eclampsia (1.7% vs. 13.4%; RR 0.16, 95% CI 0.07–0.36), preterm delivery before 37 weeks (32.1% vs. 47.7%; RR 0.77, 95% CI 0.62–0.96), and SGA infants (10.1% vs. 29.4%; RR 0.42, 95% CI 0.29–0.59), without a significant effect on perinatal mortality (pregnancy loss >20 weeks 1.9% vs. 5.3%; RR 0.41, 95% CI 0.17–1.02)[110]. In both analyses, a significant decrease in any pre-eclampsia was seen, but there was more between-trial difference in pre-eclampsia incidence than could be expected by chance alone, as was the case in the LMWH analysis for a composite of placentally mediated pregnancy complications (i.e., pre-eclampsia, placenta abruption, SGA infants, or fetal loss after 12 weeks) (18.7% vs. 42.9%; RR 0.52, 95% CI 0.32–0.86). However, a recent trial with 292 women observed no impact of antepartum prophylactic dose dalteparin (5000 IU once daily up to 20 weeks' gestation and twice daily thereafter until at least 37 weeks' gestation) on a composite outcome of severe or early onset pre-eclampsia, SGA infants, pregnancy loss, or venous thromboembolism in women with thrombophilia at high risk of complications (venous thromboembolism, pregnancy loss, or placentally mediated pregnancy complications) in both an intention-to-treat analysis (17.1%, 95% CI 11.4–24.2% vs. 18.9%, 95% CI 12.8–26.3%; risk difference −1.8%, 95% CI −10.6–7.1%) and an on-treatment analysis (19.6% vs. 17.0%; risk difference +2.6%, 95% CI −6.4–11.6%), but there was an increased risk of minor bleeding associated with LMWH (19.6% vs. 9.2%; risk difference 10.4%, 95% CI 2.3–18.4; $p = 0.01$)[111].

Pending the results of larger trials powered for perinatal mortality or severe maternal morbidity, or individual patient data meta-analysis of greater numbers of smaller trials, LMWH for pre-eclampsia prevention should be used cautiously. The independent role of concomitant treatment with aspirin also remains to be elucidated.

LMWH in prophylactic subcutaneous doses is associated with minimal risks for the mother and, theoretically, none for the fetus as it does not cross the placenta. In a meta-analysis of 64 studies (2777 women), major allergic reactions were uncommon (1.2%) and no woman developed heparin-induced thrombocytopaenia. LMWH in prophylactic doses was associated with very low risks of antenatal bleeding (0.42%), intrapartum bleeding (0.92%) and wound haematoma after either Caesarean or vaginal delivery (0.65%)[112]. In the randomised controlled trial cited above, LMWH was associated with an increase in minor bleeding compared with no treatment[111]. LMWH to prevent recurrent early-onset pre-eclampsia and/or IUGR could be stopped at 34–36 weeks' gestation, so the potential side-effects of LMWH intrapartum and postpartum are not as relevant. However, a recent international audit on maternal and fetal safety of tinzaparin (at therapeutic and prophylactic doses), the adjudication committee considered that serious bleeding events (before, during and after delivery) were *probably related* to tinzaparin therapy in 2.3% of pregnancies, and *possibly related* to tinzaparin in 7.7% (1256 pregnancies in 1109 women)[113]. There was no reported spinal haematoma; 10.4% of the women received tinzaparin within 24 hours of epidural or spinal anaesthesia with a median tinzaparin injection to delivery interval of 12.9 hours (range 0–23.5). Osteoporotic fractures occurred in 0.2% of women, although all had other risk factors for osteoporosis. Neonatal haemorrhage did not occur. Major allergic reactions were uncommon (1.8%). No women developed heparin-induced thrombocytopaenia.

L-arginine

Supplements containing L-arginine and 'antioxidant vitamins' have been shown to reduce diastolic blood pressure[114] or both systolic and diastolic blood pressure, and the incidence of pre-eclampsia in a population at high risk of the condition (2 trials, 672 women)[115,116]. Another systematic review supported that L-arginine supplements reduced the incidence of pre-eclampsia in high-risk women (RR 0.34, 95% CI 0.21–0.55), as well as risk of preterm birth (RR 0.48, 95% CI 0.28–0.81). The protective effect was greater in women with established hypertensive disease (RR 0.21, 95% CI 0.05–0.98)[117]. Data from several small randomised trials suggests that L-arginine given to women with already diagnosed gestational hypertension (with or without proteinuria) or with IUGR can lead to improvement of maternal blood pressure and uteroplacental circulation[118–123].Optimal dosage needs to be defined and large randomised trials are required.

Lifestyle changes

There are robust epidemiological data that weight gain between pregnancies (even in non-obese

women) is associated with significantly more pre-eclampsia and other pregnancy complications, such as Caesarean delivery and gestational diabetes[124].

Physical activity is associated with a reduced incidence of pre-eclampsia[125,126]. In women at increased risk of pre-eclampsia, it is not known whether exercise (to improve or maintain fitness) is of greater benefit than risk. No impact of exercise was seen on gestational hypertension or pre-eclampsia (2 trials, 45 women), although the trials were small and the confidence intervals were wide[126,127]. Similar results were seen in another small trial of 79 sedentary women with previous pre-eclampsia, among whom walking exercise vs. stretching exercise during pregnancy did not decrease the incidence of pre-eclampsia[128].

Physically demanding work is associated with a higher risk of gestational hypertension and pre-eclampsia (OR 1.60, 95% CI 1.30–1.96; 4 observational studies, 5837 women)[36]. Although workload reduction is a common obstetric intervention, we were unable to identify randomised studies of workload or stress reduction on the incidence of pre-eclampsia. These are unlikely to be forthcoming given the nature of the interventions.

Increased rest at home (varying from 30 minutes to 6 hours/day) in the third trimester of pregnancy decreased the incidence of pre-eclampsia (RR 0.05, 95% CI 0.00–0.83; 1 trial, 32 women for increased rest alone; RR 0.13, 95% CI 0.03–0.51 for rest plus a nutrient supplement; 1 trial, 74 women)[129]. Other substantive outcomes (such as adverse effects of rest and women's views) were not reported. There is a lack of clarity about the definition of bed rest and uncertainty about whether women comply with activity restriction[130].

Metformin

One trial (N = 105 women) observed that women with polycystic ovarian syndrome (PCOS) randomised to receive metformin (vs. placebo) from the first-trimester of pregnancy showed significant improvement of the uterine artery Doppler pulsatility index to a similar extent as that observed with low-dose aspirin[131]. This trial did not have the power to observe a significant difference in the rate of pre-eclampsia (5.7% with metformin, 5.7% with aspirin, and 11.4% in the placebo group, $p = 0.58$). However, in a secondary analysis of another trial of 400 obese non-diabetic women (BMI >35 kg/m^2) randomised to metformin (1–3 g daily, gradually titrated over 4 weeks) or placebo, metformin was associated with a significant decrease in pre-eclampsia (2.0% vs. 8.2%, $p = 0.005$)[132]. Further studies are warranted.

Micronutrients other than calcium

Magnesium supplementation (various preparations) administered to a mixed population of women at low and high risk in (7 trials, 2689 women) did not decrease the risk of pre-eclampsia, but decreases were seen in preterm birth (RR 0.73, 95% CI 0.57–0.94), low birth weight (RR 0.67, 95% CI 0.46–0.96) and incidence of SGA infants (RR 0.70, 95% CI 0.53–0.93)[40]. However, no conclusions can be drawn because only one included trial was of high quality.

In one trial (100 women), selenium supplementation in the third trimester was reported to decrease gestational hypertension, but this was not defined[133]. Another small trial (166 women) found no significant decrease in the rate of pre-eclampsia[134].

One study found that daily ingestion of a phytonutrient supplement did not decrease rates of pre-eclampsia in high-risk women[135].

We did not identify trials of zinc, pyridoxine, iron (with/without folic acid), zinc, multivitamins with/without micronutrients, vitamin A, iodine, or copper for pre-eclampsia prevention in women at increased risk.

Prostaglandin precursors

According to the most recent Cochrane systematic review, prostaglandin precursors did not decrease the risk of pre-eclampsia in mixed populations of women at low and high risk (RR 0.87, 95% CI 0.59–1.28; 5 trials, 1683 women)[45]. Birth before 34 weeks was marginally decreased (RR 0.69, 95% CI 0.49–0.99). However, a recent trial including pregnant women with previous pregnancy complications showed that fish oil supplementation was associated with a more advanced gestational age at delivery in low and middle (but not high) fish consumers[136].

Vitamins C and E

In five trials (3005 women) of women at increased risk of pre-eclampsia for various reasons,

antioxidants (usually combined therapy with vitamins C 1000 mg/d and E 400 international units/day) did not decrease the risk of pre-eclampsia (RR 0.56, 95% CI 0.29–1.11)[56]. These findings were supported by subsequent trials[137,138]. Vitamins C and E have been associated with adverse outcomes, including increased use of intravenous antihypertensive therapy (RR 1.94, 95% CI 1.07–3.53)[139], low birth weight babies (28% (N = 387) vs. 24% (N = 335), RR 1.15, 95% CI 1.02–1.30; 2395 women)[131], fetal loss or perinatal death (RR 2.20, 95% CI 1.02–4.73; 2536 women), preterm prelabour rupture of membranes (RR 1.97, 95% CI 1.31–2.98; 2363 women)[140].

Nitric oxide donors

Nitric oxide (NO) donors like pentaerithrityl-tetranitrate (PETN) have protective effects on the endothelium. One trial found no decrease in pre-eclampsia from NO-donor PETN, but a decrease in IUGR and/or perinatal death (adjusted RR 0.41, 95% CI 0.18–0.91) and for IUGR (adjusted RR 0.44, 95% CI 0.20–0.97), and preterm birth before 32 weeks' gestational age (adjusted RR 0.20, 95% CI 0.05–0.80)[141].

Other

Treatment of periodontal disease is not associated with a reduced risk of pre-eclampsia (4 trials)[142,143]. However, it is possible that the type of treatment (scaling vs. chlorexidine mouthwash) could influence its impact, as it has been seen for prevention of preterm birth[144].

RESOURCE-CONSTRAINED SETTINGS

Pre-eclampsia is ". . . considerably more prevalent in LMICs [low- and middle-income countries] than in affluent communities"[145]. Furthermore, over 99% of pre-eclampsia and eclampsia-related mortality occurs in LMICs, particularly in sub-Sahara Africa and on the Indian subcontinent[146].

Factors that determine the potential impact of an intervention on prevention of pre-eclampsia include its availability, acceptability and cost-effectiveness, as well as the strength of the infrastructure of a health care system. The latter is where LMICs face the greatest challenge. Their unique challenges to intervention implementation include:

- Low rates of antenatal visits and low levels of education in the population, which could be addressed by community engagement and educational activities[146,147].
- Poverty and weak public infrastructure (such as paved roads and available transportation) which prevent access to health care[148]. Addressing these issues will require engagement of government and policy makers.
- A shortage of trained health care workers[146,149]. Major efforts have been directed towards 'task shifting', training and employing community health care workers to play a fundamental role within the health care system in LMICs. In this way, it is hoped that women with hypertensive disorders of pregnancy will receive timely care. This strategy recognises that the majority of pre-eclampsia related deaths in LMICs occur in the community[146].
- A lack of high quality guidance material such as protocols and guidelines[150], something that this book aims to address for the hypertensive disorders of pregnancy.

What follows here are implications relevant to resource-constrained settings for the given recommendations to help prevent pre-eclampsia.

Aspirin (low dose)

A decision analytic model comparing aspirin prophylaxis (vs. no prophylaxis) in a theoretical cohort of 100,000 pregnant women concluded that it was a more cost-effective strategy than no prophylaxis. Lower costs ($18,720 vs. $18,804) and marginal difference in quality-adjusted life years (26.7417 vs. 26.7422) favours aspirin prophylaxis – a better choice than no prophylaxis[151].

Calcium supplementation

The impact of calcium in reducing pre-eclampsia is dependent on the baseline calcium intake of the population and pre-existing risk factors[152,153]. Global trends of dietary calcium intake typically show lower intake in LMICs (ranging from 300 to 600 mg/day) compared with high-income countries (e.g., 969 mg for France)[154]. Although these data suggest that calcium supplementation is particularly important for women in developing countries, suboptimal global implementation of this intervention remains. In a study of women

receiving antenatal care in Brazilian public hospitals, over 90% of women consumed less than 1 g of calcium per day, yet less than 6% of women received a prescription for calcium supplements[155]. Similar results were observed in a teaching public hospital in Argentina[156].

Implementation of the recommended high-dose calcium supplementation (1 g calcium/day or more) in settings of low-dietary calcium is problematic to policy-makers and programme managers in LMICs for a number of reasons[157]. Lack of infrastructure challenges the procurement of the preparation, transportation of the heavy tablets, storage, quality control and compliance assurance[158]. The cost implications of the recommended calcium supplementation dose may be a financial barrier; for example, chewable calcium carbonate tablets cost US $3–6/pregnancy[159]. A cost–benefit ratio must be considered by ministries of health in decisions to scale up this intervention[149]. Also, there are potential risks of calcium supplementation, particularly in excess, associated with supplementation in pregnancy, such as HELLP syndrome[7] and rebound postnatal bone demineralisation following supplementation in pregnancy[160].

Potential solutions to the problems discussed include a recently developed micronutrient powder designed to optimise absorption of all its contents (calcium, iron and folic acid)[161] and low-dose calcium supplementation for which there are limited data suggesting effectiveness in reducing pre-eclampsia risk[7]. Until these findings are confirmed by larger, sufficiently powered randomised trials[100,162], lower-dose supplements (500–600 mg/day) may be considered in preference to no supplementation in settings of low dietary calcium where high-dose supplementation is not feasible[7,152].

Cost-effectiveness analyses of increasing calcium intake should consider increasing dietary intake versus calcium supplementation, with consideration that many countries do not have sufficient availability of dairy products to meet dietary needs[163].

Folate-containing multivitamin

An average of 20–30% of pregnant women have a vitamin deficiency of some kind. Without supplementation, approximately 75% of these women would show a deficit of at least one vitamin. In India, for example, about 25% of pregnant women are folate deficient[164].

Global periconceptional folic acid supplement use is low, taken by fewer than 50% of women in many countries[165]. A study of American women found that 29.7% used periconceptional folic acid supplement[166]. A study of 21,889 women in Tanzania in a geographical area with a high prevalence of anaemia found a prenatal intake of folic acid of 17.2%; notably, women were less likely to take folic acid supplements if they had pre-eclampsia/eclampsia during pregnancy (OR 0.48, 0.38–0.61)[167].

Factors associated with lower preconceptional use of folic acid are younger age, lower levels of maternal formal education, single marital status and unplanned pregnancy. In Canada, folic acid supplementation has been shown to vary according to maternal country of origin. In comparison with Canadian born women, immigrants from Northern African, Middle Eastern, Caribbean, Latin American, a South Pacific country or from China were significantly less likely to use supplements[168]. It may be that certain groups of immigrant women engage in less family planning and have more unintended pregnancies, lack knowledge regarding the benefit of folic acid supplementation, or cannot afford tablet supplements[165]. Policy makers and health practitioners can be aware of risk factors for low use and help increase folic acid supplementation in these populations.

Exercise

Literature suggests that physical activity declines during pregnancy[169,170]. Barriers to activity during pregnancy reported by women include pregnancy symptoms, lack of time, access to child care and concerns about their safety and that of their unborn baby[171–175] and lack of advice from health professionals[176]. Conversely, significant enablers included positive psychological feelings, family influence and receiving advice from health professionals[177].

A lack of information by certain populations may contribute to low levels of exercise in pregnancy. A very recent study in a developing country found that only 36.6% of women thought that regular exercise was not harmful during pregnancy[178]. Low-income African American women report several factors that prevent them

from exercising, including a lack of information about safe types, frequency and duration of exercise. Cultural myths also exist about certain types of movements that are believed to potentially cause problems with pregnancy. For example, placing arms over their heads raised concerns that the umbilical cord would wrap around and strangulate the baby's neck[179]. This population also reports both a lack of motivation to exercise in pregnancy and a decreased level of physical activity in pregnancy[180]. Health care providers can be aware that cultural myths that may decrease exercise, and can pose questions to understand the beliefs of their patients regarding physical activity in pregnancy. It may be beneficial to provide information to help dispel misperceptions and ensure women understand the role of exercise in contributing to health pregnancy outcomes.

Low molecular weight heparin

If LMWH were effective for prevention of placental complications, a dalteparin study (116 women) found that the incremental cost of preventing one case of severe pre-eclampsia or a SGA infant was $54.00[181]. Further research is needed to clarify whether LMWH can be considered a cost-effective intervention in resource-constrained settings.

Lifestyle changes

Although no randomised trials exist on stress reduction on the incidence of pre-eclampsia, studies do suggest possible benefits for women at increased risk. Proximity to city parks has been shown to be associated with a beneficial impact on blood pressure during the first trimester of pregnancy[182]. Further research is needed to elucidate the mechanism accounting for this benefit and to determine whether the recommendation of visiting a green area is an effective and cost-effective intervention.

Yoga is a method associated with stress reduction. High-risk pregnant women in a controlled trial that were randomised into a yoga versus control group showed a significant reduction in pre-eclampsia ($p = 0.042$). Further research is needed to determine whether this is a cost-effective intervention for women[183].

BEST PRACTICE POINTS

(Please see Appendix 6.3 for the evaulation of the strength of recommendations and the quality of the evidence on which they are based.)

Prevention of pre-eclampsia in women at low risk

1. Calcium supplementation (of at least 1 g/d, orally) is recommended for women with low dietary intake of calcium (<600 mg/d, corresponding to less than two dairy servings per day).
2. The following are recommended for other established beneficial effects in pregnancy: abstention from alcohol for prevention of fetal alcohol effects, exercise for maintenance of fitness, periconceptional use of a folate-containing multivitamin for prevention of neural tube defects and smoking cessation for prevention of low birth weight and preterm birth.
3. The following may be useful: periconceptional and ongoing use of a folate-containing multivitamin or exercise.
4. The following are *not* recommended for pre-eclampsia prevention, but may be useful for prevention of other pregnancy complications: prostaglandin precursor or supplementation with magnesium or zinc.
5. The following are *not* recommended: dietary salt restriction during pregnancy, calorie restriction during pregnancy for overweight women, low-dose aspirin, vitamins C and E or thiazide diuretics.
6. There is insufficient evidence to make a recommendation about the following: a heart-healthy diet, workload or stress reduction, supplementation with iron with/without folate, pyridoxine, or food rich in flavanoids.

Prevention of pre-eclampsia in women at increased risk

1. The following are recommended for prevention of pre-eclampsia: low-dose aspirin and calcium supplementation (of at least 1 g/d) for women with low calcium intake.
2. Low-dose aspirin (75–100 mg/d) should be administered at bedtime and initiated after diagnosis of pregnancy but before 16 weeks' gestation and may be continued until delivery.
3. Prophylactic doses of LMWH may be considered in women with previous placental complications (including pre-eclampsia) to prevent the recurrence of 'severe' or early-onset pre-eclampsia, preterm delivery, and/or SGA infants.
4. The following may be useful: L-arginine, metformin in PCOS and/or overweight women, increased rest at home in the third trimester and reduction of workload or stress.
5. The following may be useful for prevention of other pregnancy complications: prostaglandin precursors, magnesium supplementation and heparin thromboprophylaxis.
6. The following are recommended for other established beneficial effects in pregnancy (as discussed for women at low risk of pre-eclampsia): abstention from alcohol, periconceptional use of a folate-containing multivitamin and smoking cessation.
7. The following are *not* recommended: calorie restriction in overweight women during pregnancy, weight maintenance in obese women during pregnancy, antihypertensive therapy specifically to prevent pre-eclampsia, vitamins C and E.
8. There is insufficient evidence to make a recommendation about the usefulness of the following: the heart-healthy diet, exercise, selenium, garlic, zinc, pyridoxine, iron (with or without folate), or multivitamins with/without micronutrients all.

WHAT INTERNATIONAL GUIDELINES SAY

A systematic review of 13 international clinical practice guidelines (CPGs) on hypertensive disorders of pregnancy[184] summarises international consensus regarding definitions for women at low and at increased risk of pre-eclampsia.

Women at low risk are recommended NOT to restrict dietary salt or take vitamins C and/or E by four guidelines[185–188] and NOT to take diuretics by three guidelines[186–188]. Only two guidelines recommend calcium supplementation (1–2 g/day)[187,188]. Only one guideline (SOGC, Society of Obstetricians and Gynaecologists of Canada) mentioned low-dose aspirin as an intervention that was NOT recommended[187]. One guideline (SOGC) reported several interventions with insufficient evidence to make a recommendation, including a heart-healthy diet, workload or stress reduction, iron supplementation with/without folate, vitamin D, pyridoxine and food rich in flavonoids[187].

Women at increased risk of pre-eclampsia are recommended to take calcium supplementation (1–2.5 g/d) if they have low calcium intake by three guidelines[187–189]. Five guidelines recommended low-dose aspirin (60–162 mg/d)[185–189] with initiation in early pregnancy[185–189], and three guidelines recommend that it continue until delivery[186,187,189]. Women at increased risk are recommended NOT to restrict dietary salt by three guidelines[185,186,188] or to take vitamins C and/or E by four guidelines[185–188].

SUMMARY

Pre-eclampsia and its complications represent an important cause of maternal and perinatal morbidity and mortality. Optimising primary prevention efforts in the periconceptional and antenatal period are essential to reduce this burden. This chapter summarises the most current evidence-based recommendations regarding lifestyle changes and drugs that have been shown to help prevent pre-eclampsia and its complications. Health care providers should promote these recommendations to help minimise the deleterious effects of pre-eclampsia and its complications. Considerations unique to LMIC and to marginalised populations that may affect implementation of recommended interventions are also presented. Reducing the impact of pre-eclampsia in LMIC countries and marginalised populations will require health systems capacity building, strengthening of infrastructure, and implementation of interventions appropriate to low-resource settings.

PRIORITIES FOR FUTURE RESEARCH

This chapter identifies gaps in knowledge regarding the prevention of pre-eclampsia. The effectiveness of prevention efforts relies on the dissemination of knowledge among health care providers and women with subsequent uptake of given recommendations. To help identify barriers and help achieve these objectives, there is a need for further implementation research.

Further research is also needed to elucidate the effects of the following in preventing pre-eclampsia in low-risk women: a heart-healthy diet; workload or stress reduction; supplementation with iron without or without folate; and pyridoxine or food rich in flavonoids. In women at increased risk, further investigation is required regarding the effects of the heart-healthy diet; exercise; selenium; garlic; zinc; pyridoxine; iron (with or without folate); and multivitamins with/without micronutrients.

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7

Diet, lifestyle and place of care

LA Magee, S Mundle, JM Moutquin, S Sharma, P von Dadelszen

SYNOPSIS

Non-pharmacological management of women with the hypertensive disorders of pregnancy involves consideration of dietary interventions, lifestyle and place of care. There is scant literature on the role of dietary interventions or lifestyle change (including bed rest and stress reduction) for women with established hypertensive disorders of pregnancy; the limited literature has focused on these practices as preventative measures against pre-eclampsia (discussed in Chapter 5). As such, the bulk of this chapter focuses on place of care, including transport from community to facility. There is enormous potential benefit of addressing delays in transport to facility in LMICs, where more than 99% of hypertensive disorders of pregnancy-related maternal deaths occur. Communities have a critical role to play in ensuring that women and their families are prepared for birth and hypertensive disorder of pregnancy-related or any other emergencies that may arise.

DIET

Hydration

It is recognised that in LMICs, women may intentionally dehydrate themselves during the work day when toileting facilities are not readily available. There is some concern that this may lead to erroneous proteinuria. There is no relevant literature in pregnancy, although there is some supporting evidence from high-performance athletics. This exercise literature has associated dehydration with an increase in proteinuria in proportion to the intensity of that exercise[1,2].

Dietary change

There are no specific guidelines for diet during pregnancy for women with pre-eclampsia.

Dietary modifications that effectively lower blood pressure among non-pregnant individuals are weight loss, reduced salt intake, increased potassium intake, moderation of alcohol consumption and an overall healthy dietary pattern[3]. Many of these interventions have been evaluated as preventative therapy among women at increased risk for pre-eclampsia, and this approach is discussed in Chapter 6.

Calorie restriction among overweight or obese hypertensive women

Dietary interventions have been studied to curb weight gain in pregnancy, primarily among overweight and obese women[4,5]. (Table 7.1 shows the 2009 Institute of Medicine guidelines that recommend a total weight gain of 15–25 lb (6.8–11.3 kg) for overweight women and 11–20 lb (5.0–9.1 kg) for obese women[6].) The dietary interventions studied reduced maternal weight gain and the incidence of pre-eclampsia. However, the objective was to *prevent* pre-eclampsia or other pregnancy complications rather than treat women

Table 7.1 Recommendations for total and rate of weight gain during pregnancy, by pre-pregnancy BMI[6]

Pre-pregnancy BMI	*BMI (kg/m²) (WHO)*	*Total weight gain range (lbs)*	*Rate of weight gain in 2nd and 3rd trimesters (mean range in lbs/week)*
Underweight	<18.5	28–40	1 (1–1.3)
Normal weight	18.5–24.9	25–35	1 (0.8–01)
Overweight	25.0–29.9	15–25	0.6 (0.5–0.7)
Obese	≥30.0	11–20	0.5 (0.4–0.6)

who had a hypertensive disorder of pregnancy. We were unable to identify randomised controlled trials of weight loss among overweight or obese pregnant women who were already hypertensive and they are the focus of this chapter. A Cochrane systematic review for search of randomised controlled trials, quasi randomised trials and cluster randomised trials was unable to identify relevant trials in any overweight or obese pregnant women[7]. Actual weight loss is not recommended during pregnancy because of the potential adverse effects of catabolism and ketosis on fetal brain development.

Salt intake

Salt in the diet comes from added table salt, as well as that added to foods as a preservative. The recommended level of salt intake is 140 mmol/d (~3200 mg/day), equivalent to just under one and a half teaspoons of table salt per day from any source. In a trial of sodium reduction and the DASH diet (i.e., Dietary Approaches to Stop Hypertension), both were shown to decrease blood pressure[8]. The DASH diet was a modification of the North American diet, and involved a reduction in red meat and sugar, and an increase in whole grains, low-fat dairy products, fruits, vegetables, fish, nuts and poultry. The levels of salt intake studied were high (~150 mmol/d, consistent with a usual North American diet), intermediate (~100 mmol/d), or low (~50 mmol/d). Among non-pregnant subjects of whom 59% were women, the DASH diet lowered blood pressure in all subjects, particularly those who were already hypertensive, and the blood pressure reduction occurred regardless of pre-trial salt intake (that was high, intermediate, or low). Reducing the sodium intake from the high to the intermediate level reduced the sBP by 2.1 mmHg ($p < 0.001$) during the control diet and by 1.3 mmHg ($p = 0.03$) during the DASH diet. Reducing the sodium intake from the intermediate to the low level caused additional reductions of 4.6 mmHg during the control diet ($p < 0.001$) and 1.7 mmHg during the DASH diet ($p < 0.01$). A reduction in salt intake and the DASH diet were independently effective in lowering blood pressure, and the effects of both were greater than the effects of either intervention alone.

We were unable to identify trials of salt restriction or dietary change among already hypertensive pregnant women. This was true of ongoing salt restriction among women with chronic hypertension and new, severe salt restriction among women with any hypertensive disorder of pregnancy.

LIFESTYLE

Physical activity

We were unable to identify studies of the impact of exercise on outcomes in any hypertensive disorder of pregnancy. However, pre-eclampsia is considered by some authorities to be a contraindication to vigorous exercise[9].

It is common practice to recommend workload reduction or cessation, or stress management (e.g meditation) when non-severe elevations in blood pressure are found in association with chronic or gestational hypertension, or pre-eclampsia and outpatient care is continued. There are no randomised controlled trial data to support this practice, although it may be practical, facilitating maternal and fetal monitoring. Outside pregnancy, stress management by relaxation techniques may be useful to improve blood pressure control if stress appears to be exacerbating hypertension[10]. Although blood pressure may be improved by workload reduction/cessation or stress management in women with any hypertensive disorder of pregnancy, there is currently no evidence that these lifestyle changes improve pregnancy outcomes.

Since its introduction in 1952[11], bed rest has become standard therapy for women with a hypertensive disorder of pregnancy, as either primary or adjunctive therapy[12]. How bed rest is defined has varied widely, and compliance with recommendations has been questioned. However, bed rest should be determined to be clearly beneficial before it can be recommended, in hospital or at home, because it may have harmful physical, psychosocial and financial effects[13]. There is limited randomised controlled trial evidence to consider.

For women with gestational hypertension (without evidence of pre-eclampsia), routine activity at home (compared with at least some bed rest in hospital) is associated with more severe hypertension (RR 1.72, 95% CI 1.12–2.63) and preterm birth (RR 1.89, 95% CI 1.01–3.45; 2 trials, 304 women). It is unclear whether the beneficial effect of bed rest in hospital is derived from the bed rest or the hospitalisation. It is clear, however, that women prefer routine activity at home[14,15].

We found no studies on the cost-effectiveness of dietary and lifestyle changes for the treatment of any hypertensive disorder of pregnancy.

PLACE OF CARE

Organising out-of-hospital care for women with pre-eclampsia must follow a full assessment of maternal and fetal well-being. Ideally, this assessment would be performed in hospital. Women eligible for out-of-hospital care must not have severe disease, as classified by the Canadian HDP Working Group (see Chapter 3). Of note, published outpatient studies have excluded women with severe hypertension or severe pre-eclampsia (by multiple definitions that are less serious than the Canadian definition) from evaluation of alternatives to inpatient care.

Options for outpatient care include obstetric day units and antepartum home care that is delivered through structured antepartum home care programmes. A woman's eligibility is dependent on the proximity of the hospital to her residence, a home environment that allows the home care team to provide the necessary maternal and fetal surveillance, a woman's likelihood of compliance, the lability of a woman's blood pressure, the absence of comorbid conditions, and no evidence of active progression of pre-eclampsia.

Hospital day units

Many women are not eligible for care in day units. Eligibility has varied from 30% to 60% of women assessed[16,17]. The target group in these studies has been women with gestational hypertension, and care in hospital day units has been compared with inpatient care (2 trials, 449 women)[17,18]. The likelihood of re-admission to hospital and actual days in hospital were reduced by care in day units and maternal and perinatal outcomes were similar, but so were costs[19,20]. However, women preferred out-of-hospital care when asked in the context of trials[17] or in previous observational studies[21].

Home care

Most women are not eligible for formal home care programmes. Although eligibility criteria have varied, published estimates suggest that no more than 25% of women assessed can be cared for in this way[22]. Women can accurately measure blood pressure at home using an automated device[23]. Although blood pressure at home is not consistently different from that in hospital, values for individual women vary widely, particularly for those on antihypertensive therapy[24].

In observational studies, the definition of home care has varied with regards to prescriptions for bed rest; proportion of assessments that are done by the women versus those done by a nurse or midwife; and communication in person, by telephone, or electronically[25,26]. However, all involved some component of daily contact with the woman and, in most cases, a weekly outpatient visit to the hospital or office[22,25,26].

In observational studies of antepartum home care compared with care in hospital, hospital admission[26] and re-admission rates[22] were quite high (i.e., 25% and 44%, respectively). However, home care resulted in similar maternal and perinatal outcomes among women with mild pre-eclampsia (321 women)[22] or gestational hypertension (592 women)[27] and at lower cost[26]. Women were satisfied with home care[28].

No randomised controlled trials have compared care at home through formal antepartum home care programme with care in hospital. All of these programmes include some component of bed rest. The potential beneficial effect of bed rest associated with hospitalisation, and uncertainty about which component is important, are discussed above.

Community-based care

In under-resourced settings, particularly LMICs, maternal and newborn care services have been increasingly delivered through community-based packages delivered by outreach workers – residents trained to provide basic maternal and newborn health services. A 2015 Cochrane review of 26 cluster-randomised and quasi-randomised trials provided encouraging evidence that these community-based interventions may improve outcomes for mothers and babies[29]. Packages of community care had a possible decrease in maternal mortality (RR 0.80, 95% CI 0.64–1.00; 11 studies, 167,311 women), and a definite decrease in maternal morbidity overall (RR 0.75, 95% CI 0.61–0.92; 4 studies, 138,290 women); the reduction was driven by decreases in some morbidities (such as postpartum haemorrhage, RR 0.63, 95% CI 0.52–0.76; 1 study, 19,525 women) but not others (such as puerperal sepsis, RR 0.84, 95% CI 0.65–1.08; 1 study, 19,525 women). The interventions were not focused on hypertensive pregnancy, but there was no reduction in eclampsia (RR 0.74, 95% CI 0.43–1.27; 1 study, 19,525 women). Community-based packages of care reduced perinatal mortality overall and stillbirth and neonatal death specifically, although all pooled estimates showed more between-study difference than could be expected by chance alone. The authors concluded that there is sufficient evidence to scale up community-based care through packages that are delivered by community-based workers.

Drugs and therapeutics that could be used at the community-level for management of hypertension or other hypertensive disorder of pregnancy-related complications are discussed in Chapter 8.

TRANSPORT TO FACILITY

Care in the community is predicated on the assumption that ill women and babies can be transported to facility in a timely and safe manner.

In well-resourced settings, eligibility for antepartum home care programmes is based on an individualised assessment of transport plans and their safety. Formal guidelines are published to guide transport from community facilities to higher-level care[30].

In under-resourced settings, women and their families spend a considerable time waiting for transportation and travelling to the health facility, and this contributes to maternal and perinatal death and illness; this delay in transport has been described in a 'three-delay model' along with delays in triage and treatment[31]. As such, reliable, suitable and affordable transport has the potential to play a key role in enabling expectant mothers and newborn children to receive necessary care at local health centres, district hospitals, or regional referral centres.

> "Those places are too remote for them to say they want to quickly rush the pregnant woman to a hospital . . . even if the health care worker writes a referral note for the pregnant woman . . . how would they transport the pregnant woman? . . . maybe there's no road network . . . or maybe there's no vehicle or even a motorcycle . . . the pregnant woman might die while they are scrambling around".
>
> Community Director, Ogun, Nigeria (from the CLIP Feasibility Study)[32]

Barriers to timely transportation are mediated by several factors, such as permission to seek transport, access, risk perceptions and choice, financial costs, excessive travel time and distance, adequate road infrastructure and inadequate neonatal care in the transport system[31,33]. Barriers vary in their importance depending on the individual settings. For example, access to road infrastructure is poorest in Sub-Saharan Africa where, overall, only 30% of the rural population has adequate access to transport[33]. Ultimately, the impact that these barriers may have on outcome depends on a woman's individual circumstances. For example, it has been estimated that the time interval from the onset of antepartum haemorrhage to death can be 12 hours, while the interval from postpartum haemorrhage to death can be as short as 2 hours[34].

Many of these barriers must be addressed by the health care system (e.g., ambulance services) or government (e.g., road infrastructure) in order to improve outcomes. In rural Niger, prior to the introduction of the ambulance, the only way for a woman with obstructed labour to reach the hospital was to walk 75 km or go by camel[35], but after introduction of the radio-ambulance system, the number of emergency transports from the periphery or health centre to the district hospital increased by 20-fold[35] and in 14% of cases, the obstetric or medical problems could be dealt with by the ambulance team without evacuating the patient to the district hospital. This highlights the importance

of integrating communication channels along with transport services.

The woman and her community can address some of the barriers to transport and care-seeking.

Community engagement

Community engagement involves the collective action of individuals, families, religious leaders, policy makers, health care providers and community members toward the creation of meaningful and sustainable change. Studies indicate that successful health behaviour change occurs when interventions create positive social, individual and environmental conditions. Community-based interventions that include women's and men's support groups, education, counselling, home visits, emergency transport initiatives and fundraising activities, have shown significant improvements in maternal and perinatal morbidity and mortality[36–40].

Within the hypertensive disorders of pregnancy specifically, the CLIP (Community Level Interventions in Pre-eclampsia) trial (ClinicalTrials.gov Identifier: NCT01911494) is evaluating a package of care of which community engagement is a critical component. The strategy involves participation of local stakeholders and community members in ways that are culturally and contextually appropriate, meaningful and sustainable. The latter is a key aspect of the strategy; for example, in CLIP, communities are being encouraged and supported to raise their own funds for transport (and facility health care), as providing financial aid is only ever a temporary measure.

In the CLIP trial, mapping was undertaken of both (1) past and current activities related to community engagement around maternal health, and (2) the available maternal health facilities from primary health centre to tertiary care facilities[33]. Table 7.2 provides the tool used for community engagement mapping, as an example of how this may be done. Then, a community-specific engagement strategy was developed, with direct input from community members, for the purpose of creating awareness and action around pre-eclampsia/eclampsia and the prevention of the associated maternal and perinatal morbidity and mortality. Topics of key importance to be covered were chosen, as follows:

1. *Warning symptoms and signs of pregnancy complications, particularly pre-eclampsia and eclampsia,* with specific focus on:
   a. Relating the association of danger symptoms/signs with the occurrence of pre-eclampsia/eclampsia, using the warning symptoms of pre-eclampsia and eclampsia pictograms;

Table 7.2 Tool for current community engagement mapping

	Do current activities exist targeting this objective? (yes/no)			
Activities related to	*No*	*Yes → describe**	*Contact person*	*Source of information*
Pregnancy-related complications				
General maternal health				
Household decision-making around pregnancy and childbirth (e.g. husband's and mother in-law's permission to go to hospital when necessary)				
Transportation initiatives				
Fundraising, insurance schemes or other initiatives related to reducing the barrier of cost of transport and treatment				
Other activities at the individual, household or community level related to maternal health				

*What type of activities, for whom, how often, where and who leads them

   b. Identifying the need for referral when danger symptoms/signs associated with pre-eclampsia/eclampsia occur; and
   c. Considering discussion of PPH, a 'visible' cause of maternal death, as a segue into discussion of pre-eclampsia/eclampsia as a 'silent' killer of pregnant and postpartum women.
2. *Permission for women to seek care*
   a. Recognising the need for decision-making power and/or prior permissions in the event of obstetric emergencies; and
   b. Discussion of how women can obtain prior permission to seek that care
3. Identification of a *skilled birth attendant*
4. Identification of a *facility for delivery*
5. Identification of *transport and treatment funds*
   a. Recognising the need to develop plans for financial resources when required in emergency conditions associated with pre-eclampsia/eclampsia. Funds may be personal or from the community. The community engager should facilitate the individual communities to form their own plan for raising transport and treatment funds for women in their communities;
   b. Encouraging the identification of existing community resources (if applicable) and the development of community funds for seeking emergency care. In CLIP, the community is told that the trial will *supplement* any existing funds, but fundraising activities must build on those funds to make this sustainable; and
   c. Identifying available and appropriate modes of transport, their associated costs, and the means by which these modes can be accessed in emergencies.
6. *Feedback mechanisms about adverse outcomes and 'great saves'*
   a. In CLIP, the team requests that families of sufferers share their experiences with the community.

The CLIP trial will complete recruitment in 2017, and findings should be available in 2018.

BEST PRACTICE POINTS

(Please see Appendix 7.1 for the evaluation of the strength of the recommendation and the quality of the evidence on which they are based.)

1. There is insufficient evidence to make a recommendation about the usefulness of the following: ongoing salt restriction among women with pre-existing hypertension, new severe dietary salt restriction for women with any hypertensive disorder of pregnancy, and a heart-healthy diet or calorie restriction for obese women specifically.
2. There is insufficient evidence to make a recommendation about the usefulness of exercise, workload reduction, or stress reduction.
3. For women with gestational hypertension (without pre-eclampsia), some bed rest in hospital (compared with unrestricted activity at home) may be useful to decrease severe hypertension and preterm birth.
4. For women with pre-eclampsia who are hospitalised, strict bed rest is not recommended.
5. For all other women with hypertensive disorders of pregnancy, the evidence is insufficient to make a recommendation about the usefulness of some bed rest, which may nevertheless, be advised based on practical considerations.
6. Inpatient care should be provided for women with severe hypertension or severe pre-eclampsia, however, defined.
7. A component of care through hospital day units or home care can be considered for women with non-severe pre-eclampsia or non-severe (pre-existing or gestational) hypertension.
8. In under-resourced settings, transport from community to facility must be considered a responsibility of women, their families, their communities, civil society and their care providers.

PRIORITIES FOR UNDER-RESOURCED SETTINGS

Table 7.3 outlines priorities for care for women in under-resourced settings. Key issues relate to place of care given the high proportion of women who deliver at home without a skilled birth attendant or plans for transport to facility should complications arise.

Communities should play a key role in birth preparedness and complication-readiness, including how to arrange for transport to the primary health centre or higher-level facility; obtaining prior permission for transport should an emergency arise between antenatal visits; saving money for obstetric care; identifying a skilled birth attendant; and identifying a facility for delivery.

Those facilitating community engagement should consider covering broader issues in maternity care, including appropriate timing of pregnancy in order to avoid hypertensive disorder of pregnancy-related (and other) pregnancy complications. Avoidance of teen pregnancy (discussed in Chapter 5) and food security for adolescent girls (related to malnutrition, a risk factor for pregnancy complications in general) must be addressed by communities as culturally appropriate priorities.

WHAT INTERNATIONAL GUIDELINES SAY (APPENDIX 7.2)[41]

Abbreviations for Clinical Practice Guidelines: ACOG (American College of Obstetricians and Gynecologists)[42], NICE (National Institutes of Clinical Excellence)[43], PRECOG (Pre-eclampsia Community Guideline)[44], QLD (Queensland, Australia)[45,46], SOGC (Society of Obstetricians and Gynaecologists of Canada)[47], SOMANZ (Society of Obstetric Medicine of Australia and New Zealand)[48], WHO (World Health Organization)[49].

There is little agreement, and a lack of detail, about diet, lifestyle change and place of care in international guidelines. In a review of guidelines that cited recommendations that were either based on high-quality evidence leading to a strong recommendation, or were cited by at least included

Table 7.3 Priorities for non-pharmacological management of women with a hypertensive disorder of pregnancy (HDP) by level of health care system at which care is delivered

	Antepartum & postpartum	
	Initial priority	*Ultimate goal*
Community		
Primary health care centre (detect, stabilise and refer)	Clear communication with referral unit regarding transport to appropriate place of care	Clear communication with referral unit regarding transport to appropriate place of care
	Clear transport plan to secondary or tertiary-level facilities	Clear transport service to secondary or tertiary-level facilities
		Community engagement about maternal health*
Facility		
Secondary-level facility (detect, manage and refer if necessary)	Clear transport service to tertiary-level facility	Clear transport service to tertiary-level facility
	Hospitalisation of women with severe hypertension or severe pre-eclampsia†	Hospitalisation of women with severe hypertension or severe pre-eclampsia†
Tertiary-level (referral) facility (detect and manage definitively)	Hospitalisation of women with severe hypertension or severe pre-eclampsia†	Hospitalisation of women with severe hypertension or severe pre-eclampsia†
		Outreach to communities for women with HDP managed in the outpatient setting

* Community engagement should cover topics about timing of pregnancy, prior permissions to seek care, birth preparedness and transport to facility

† 'Severe' pre-eclampsia is defined according to the definition by the Canadian HDP Working Group – pre-eclampsia with one/more serious complications. For details, see the Chapter 3

guidelines (of 13 included), only bed rest and indications for hospital admission were discussed.

Recommendations against bed rest were made by four guidelines, although no high-quality or consistent recommendations were made (NICE, WHO, ACOG, SOGC). Two exceptions were made by type of hypertensive disorder of pregnancy: (1) women with gestational hypertension may benefit from bed rest in hospital (SOGC), and (2) women with severe pre-eclampsia were excluded from the ACOG bed rest recommendations.

For place of care, the only indication for hospital admission that was consistently recommended was severe hypertension (QLD, NICE, PRECOG, SOGC, SOMANZ).

PRIORITIES FOR FUTURE RESEARCH

In well-resourced settings, research must address the role, if any, of bed rest for women who are at home with hypertensive disorders of pregnancy and those who are in hospital, as well as the safety of antepartum home care for women with hypertensive disorders of pregnancy.

In under-resourced settings, where more than 99% of women with hypertensive disorders of pregnancy die, lives lost from pre-eclampsia and eclampsia result from delays in triage, transport and treatment. Previous research in the field of hypertensive disorders of pregnancy has focused on institutional-level interventions, such as $MgSO_4$ for eclampsia prevention and treatment, or antihypertensive therapy for severe hypertension. However, if we are to address the tragedies of women dying prior to reaching facility or arriving there moribund, or women being irreversibly affected by pre-eclampsia by suffering complications prior to arriving at facility, we need to address care in the community and transportation issues.

There is now sufficient evidence of the effectiveness of community-based care packages in maternal and newborn care that research is required specifically for the hypertensive disorders of pregnancy. The CLIP trial is a singular step towards addressing the excess maternal and perinatal mortality that derive from the failure to identify and rapidly manage pre-eclampsia and eclampsia at the community level in LMICs. The intervention is a combination of community engagement and community-based triage, transport and treatment by community-based workers.

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8

Fluids, drugs and transfusion

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SYNOPSIS

The management of the hypertensive disorders of pregnancy encompasses far more than use of antihypertensive therapy. Women with pre-existing or gestational hypertension are at risk of it evolving into pre-eclampsia, a multisystem disorder of endothelial dysfunction. As such, attention must be paid to judicious fluid management, antihypertensive therapy of severe and non-severe hypertension with oral or parenteral agents, magnesium sulphate ($MgSO_4$) for eclampsia prevention and treatment as well as fetal neuroprotection with birth at <34 weeks, antenatal corticosteroids for acceleration of fetal pulmonary maturity, and various therapies for HELLP (haemolysis, elevated liver enzyme, low platelet) syndrome, including transfusion of blood products and, possibly, corticosteroids. The WHO Model List of Essential Medicines includes all of the aforementioned interventions other than fluid therapy for pregnant women. It is our responsibility to ensure that we advocate the use of effective interventions whether we practice in well- or under-resourced settings.

INTRODUCTION

At present, timed delivery of the placenta is the only cure for the hypertensive disorders of pregnancy. Care aims to optimise outcome for the fetus and reduce maternal risk related to end-organ complications (Table 8.1).

Fluid management

Plasma volume expansion

Plasma volume expansion is not recommended for women with pre-eclampsia. The rationale for this practice was that women with pre-eclampsia are intravascularly volume contracted and sympathetic tone is high. Observational studies suggested that plasma volume expansion (with crystalloid or colloid) improved maternal haemodynamics, umbilical blood flow velocities, fetal growth and perinatal mortality. However, trials (of colloid solution) demonstrated no improvement in maternal or perinatal outcomes (4 trials, 277 women)[2,3]. In the largest trial (216 women), plasma volume expansion was associated with harm – namely more Caesarean deliveries, a (non-significantly) shorter pregnancy prolongation, and a (non-significant) increase in pulmonary oedema[3]. Also, there was no evidence of benefit as measured by an increase in fetal middle cerebral or umbilical artery blood flow velocity[4], a decrease in sympathetic tone[5], or an improvement in neurodevelopmental outcomes at the age of 1 year[6].

KEY POINT

Use fluids judiciously in the hypertensive disorders of pregnancy, particularly pre-eclampsia

Table 8.1 Management of pre-eclampsia. (Adapted from Mol *et al.*, *Lancet* 2015 Sep 2. pii: S0140-6736(15)00070-7[1] with permission)

Antepartum (regardless of gestational age) and postpartum (unless otherwise specified)	
Place of care	**Inpatient** care when there is severe hypertension or maternal symptoms, signs, or abnormal laboratory tests
	Outpatient care can be considered, recognising that many women are not eligible and hospital re-admission rates are high following home care
Consultation	**Obstetrics** to ensure that pre-eclampsia risk is recognised and appropriate maternal and fetal surveillance is put in place
	Anaesthesia to plan maternal monitoring and plan neuraxial analgesia/anaesthesia in labour to assist with blood pressure control and facilitate Caesarean delivery (should it be necessary)
Fluid management	**Restrict** to a maximum of 80 mL/h when an IV is in place
Antihypertensive therapy	**Severe hypertension (blood pressure ≥160/110 mmHg):** Consider oral or parenteral agents that can be repeated in 30 min if blood pressure remains at ≥160 mmHg systolic or ≥110 mmHg diastolic: • Nifedpine capsule (10 mg orally without biting to a maximum of 30 mg) • Nifedipine tablet (10 mg orally to a maximum of 30 mg) • Hydralazine (5 mg IV bolus then if needed, 5–10 mg IV to a maximum of 45 mg) • Labetalol (20 mg IV then if needed, 40 mg then 80 mg to a maximum of 300 mg) Consider alternative oral agents that can be repeated in 1 h (supported by less evidence in pregnancy): • Labetalol (200 mg orally) • Clonidine (0.1–0.2 mg orally)*† • *Only postpartum* – Captopril (6.25–12.5 mg orally)*
	Non-severe hypertension • Methyldopa (500–2000 mg/d in 3 or 4 divided doses) • Labetalol (300–2400 mg/d in 3 or 4 divided doses) • Nifedipine (20–120 mg/d once daily)
$MgSO_4$	**Eclampsia *treatment*** • 4 g IV (over 5 min) then 1 g/h IV • If already on $MgSO_4$, administer another 2–4 g IV (over 5 min) and increase infusion to 2 g/h IV
	Eclampsia *prevention* among women with pre-eclampsia • 4 g IV (over 5 min) then 1 g/h IV
	Fetal neuroprotection 4 g IV (with/without 1 g/h until delivery or 24 h maximum) for women with imminent delivery at $<34^{+0}$ weeks who do not otherwise quality for eclampsia prevention or treatment
Corticosteroids	Antenatally only, for **fetal pulmonary maturity** when delivery is anticipated within the next 7 days and at $<34^{0-6}$ weeks
	HELLP syndrome (10 mg dexamethasone IV every 12 h for 48 h) if improvement in laboratory parameters alone will change management, such as eligibility for neuroaxial anaesthesia/analgesia or platelet transfusion
Platelet transfusion for HELLP syndrome	Recommended for counts: $<20 \times 10^9$/L, $20–49 \times 10^9$/L prior to Caesarean, or $\geq 50 \times 10^9$/L (± packed red blood cells) with excessive active bleeding, platelet dysfunction, a rapidly falling platelet count, or coagulopathy[2]

* Captopril (25 mg) and clonidine (0.1 mg) are being compared in a postpartum randomised controlled trial (NCT01761916) based on the effectiveness of these medications for severe hypertension treatment outside pregnancy

† Clonidine therapy is not recommended during breastfeeding (http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm)

Fluid restriction

Women with pre-eclampsia who are on delivery suite, for stabilisation or delivery, require IV access. In an international benchmarking study, restricting IV fluids was associated with lower rates of pulmonary oedema without an increase in acute renal failure[7]. As such, IV fluid of no more than 80 mL/h is recommended[8].

Oliguria (<15 mL of urine/h for 6 consecutive hours) is common in pre-eclampsia, particularly postpartum. Reasons include oxytocin administration and high levels of antidiuretic hormone following surgery. In the absence of pre-existing renal disease or a rising creatinine that mandate fluid challenge to rule out a component of pre-renal failure as a cause of renal dysfunction, oliguria should be tolerated and observed, at least over hours because fluid administration can precipitate pulmonary oedema in a dose-dependent fashion[3,7]. Furosemide should not be administered unless there is pulmonary oedema or the woman has oliguric renal failure (in which case increasing urine output simplifies management but does not improve prognosis in renal failure). 'Renal-dose' dopamine is not recommended; although it appears to increase postpartum urine output in women with pre-eclampsia; this is of uncertain clinical importance (1 trial, 40 women)[9].

Antihypertensive treatment of severe hypertension (blood pressure of ≥160 mmHg systolic or ≥110 mmHg diastolic)

The following discussion applies to women with either pre-existing or gestational hypertension, with or without evidence of pre-eclampsia.

In the WHO Prevention and Treatment of Pre-eclampsia and Eclampsia recommendations, antihypertensive treatment of severe hypertension during pregnancy was *strongly* recommended[10]. This seems very reasonable despite the fact that the quality of evidence on which the recommendation was based was graded as 'very low'. First, there are no relevant placebo-controlled randomised controlled trials that prove that women randomised to antihypertensive therapy more frequently have their blood pressure lowered compared with those randomised to placebo; however, such randomised controlled trials would be unethical and will never be done. Second, severe systolic hypertension is a independent risk marker for stroke in pregnancy[11]. Third, an individual short-acting antihypertensive agent is successful at lowering maternal blood pressure in at least 80% of women, based on randomised controlled trials of one antihypertensive drug versus another (as discussed below). Finally, a recent report of the Confidential Enquiries into Maternal Deaths in the UK that covered the hypertensive disorders of pregnancy (2005–2008) identified the failure to treat the severe (particularly systolic) hypertension of pre-eclampsia as the single most serious failing in the clinical care of the women who died[12,13]. It is of note that concerted efforts in the UK to address treatment of severe hypertension have been associated with a fall in the contribution of the hypertensive disorders of pregnancy to maternal mortality, based on 2009–2012 data[14]. Similarly, in South Africa that has a legislated Confidential Enquiries into Maternal Deaths process, maternal deaths owing to complications of hypertension have featured prominently, and recommendations for antihypertensive therapy have been associated with a reduction of deaths in this category[15].

In deciding on the need for treatment and the urgency with which blood pressure should be lowered, both the absolute level of blood pressure (i.e., severe or non-severe) and the rate with which it has risen should be considered. Experimental evidence from cats suggests that an abrupt (versus step-wise) increase in blood pressure is associated with more permeability of the cerebral vessels, taken as a measure of vascular injury[16]. Presumably, abrupt increases in intraluminal pressure may result in mechanical distension of the cerebral vessel wall which may adapt better to gradual or step-wise increases.

Women with a hypertensive 'urgency' (i.e., acute rise in blood pressure that is not associated with end-organ dysfunction) may be treated with oral antihypertensive agents that have peak drug effects in 1–2 hours (e.g., oral labetalol), recognising that gastric emptying may be delayed or unreliable among women in active labour. Choice of agents is discussed below.

In contrast to a hypertensive 'urgency', a hypertensive 'emergency' is associated with end-organ complications, such as eclampsia, pulmonary oedema and renal failure. Whether headache and visual symptoms should be considered

end-organ complications of a hypertensive 'emergency' is not known. They are non-specific and common, being documented in about 30% of women who are hospitalised with pre-eclampsia[17].

There is a general appreciation that the goal of antihypertensive therapy for severe hypertension is not normalisation of blood pressure, but rather, lowering of blood pressure to a non-severe level of hypertension that decreases the risk of stroke[18]. Also, there is recognition that lowering of blood pressure, even to levels that remain outside the hypertensive range has the potential to precipitate fetal distress and fetal heart rate monitoring (FHR) monitoring is advised[8,18].

Based on extrapolation of the approach outside pregnancy, hypertensive emergencies should be treated with short-acting antihypertensive agents and an arterial line when possible aimed at lowering mean arterial blood pressure by no more than 25% over minutes to hours; this is equivalent to taking a blood pressure of 220/130 mmHg to 165/98 over 1–2 hours, and then further lowering blood pressure below 160/100 mmHg over the next 2 hours.

Outside pregnancy, American[19], British[20] and European guidelines[21] all recommend that antihypertensive therapy be initiated with two oral agents when blood pressure is ≥20 mmHg systolic or ≥10 mmHg diastolic above target. The American (JNC VII) guidelines stress that initial therapy of severe hypertension should be with two oral agents. This recommendation is based on the multifactorial nature of the blood pressure elevation and the limited (but variable) average blood pressure reduction of 9.1 mmHg systolic and 5.5 mmHg diastolic achieved after treatment with any one agent, given compensatory mechanisms in response to any single agent of a given class[22]. However, these recommendations are based on treatment in the setting of chronic hypertension, outside pregnancy, and following long-term therapy[19]. In pregnancy, initiating antihypertensive therapy with one agent may be more appropriate given the intravascular volume depletion associated with both severe hypertension and pre-eclampsia, and the potential for fetal compromise if blood pressure is acutely lowered too much.

KEY POINTS

- Women with severe hypertension in pregnancy (or postpartum) should be treated with antihypertensive therapy
- The antihypertensive agents used most commonly are oral nifedipine (capsules or tablets) or IV labetalol or hydralazine (see Table 8.1 and Appendix 8.1, Figures S8.1 and S8.2)

Choice of antihypertensive agent

Table 8.2 presents the antihypertensive agents used most commonly for hypertensive urgencies in pregnancy, as well as alternatives that have a different pharmacology. Only hydralazine is on the WHO Model List of Essential Medicines (2015) for treatment of severe hypertension, although nifedipine capsules (10 mg) are listed as a tocolytic[23].

The treatment approach recommended here is cautious, in an attempt to lower blood pressure progressively, over hours and to minimise the risk of maternal hypotension and/or fetal distress. First, although nifedipine capsules have been recommended in doses of 20 mg by the American College of Obstetricians and Gynecologists if a 10 mg dose fails[18], this dosing approach is not recommended here because few of the relevant trials have administered nifedipine in this way[24,25]. Second, none of the agents recommended here are to be repeated prior to 30 min unless there is a hypertensive emergency, although some societies recommend more frequent administration (i.e., every 10 min for labetalol and every 20 min for either hydralazine or nifedipine)[18].

Recommendations about antihypertensive therapy for severe hypertension in pregnancy come from 47 trials (4322 women) that have compared one short-acting antihypertensive with another[26–28]. Just over half of these trials (i.e., 28/47) involved comparisons between parenteral hydralazine (usually 5 mg), parenteral labetalol (usually 20 mg) and calcium channel blockers (usually oral nifedipine 10 mg capsules). Each of these three agents is a reasonable choice for treatment of severe hypertension (in doses listed in Table 8.2). Some antihypertensive agents may be more or less appropriate for some women based on associated medical conditions (such as asthma) or therapies (such as current treatment with full doses of labetalol as an outpatient). Hydralazine may be associated with more adverse effects for the mother and labetalol with neonatal bradycardia, as discussed below.

Most published trials have compared parenteral hydralazine (usually 5 mg IV) with either calcium channel blockers (N = 11 trials, 699 women, usually nifedipine 10 mg capsules orally)[26,27,29] or parenteral labetalol (N = 8 trials, 384 women, usually 20 mg IV)[26,27], with repeat doses administered every 15–20 minutes to achieve blood pressure control in at least 80% of women; in nine other trials, hydralazine was compared with drugs used regionally or infrequently: mini-dose diazoxide (1 trial, 124 women)[30], ketanserin (4 trials, 210 women)[26], urapidil (3 trials, 101 women)[27,31] and prostacyclin (1 trial, 47 women)[26].

Compared with calcium channel blockers (usually nifedipine), hydralazine may be a *less* effective antihypertensive and also associated with more maternal side-effects (11 trials of which 9 studied oral nifedipine 10 mg, one nifedipine 5 mg, and one parenteral isradipine[26,27,32]. There is no published review of all relevant trials, so one summary statistic is not available.

Compared with labetalol, hydralazine may be a *more* effective antihypertensive but also associated with more maternal hypotension and maternal side-effects (8 trials, 384 women)[26,27]. Most of the published hydralazine trials were included in a 2003 meta-analysis that compared hydralazine with any other short-acting antihypertensive agent; hydralazine was found to be associated with more adverse effects, including maternal hypotension, Caesarean delivery and adverse FHR effects[26]. It should be noted that in two hydralazine versus labetalol trials, parenteral labetalol was associated with more neonatal bradycardia (which required intervention in one of six affected babies in one trial[26,33,34].

Compared with labetalol, oral nifedipine (N = 7 trials, 363 women)[28,35–39] appears to be similarly effective for blood pressure control (RR 0.42, 95% CI 0.18–0.96), as does parenteral nicardipine (60 women)[40], although there is only one such trial.

In the trials discussed above, labetalol was administered parenterally; however, it has been given orally for hypertensive urgencies. In a dose of 200 mg, oral labetalol has been used with good effect as part of a regional pre-eclampsia protocol[41]. In a clinical trial of preterm severe hypertension, 100 mg of oral labetalol every 6 hours achieved the stated blood pressure goal (of about 140/90 mmHg) in 47% of women[42]. We believe that these data are insufficient to support the NICE 2010 recommendation to use oral labetalol as initial therapy for severe hypertension in pregnancy[43]; however, if severe hypertension is detected in the office setting, an oral dose of labetalol or another antihypertensive may be useful to administer while the woman is being transported to hospital for further evaluation and treatment[44]. Other than oral nifedipine (discussed above), methyldopa may be suitable although probably starting with a 750 mg dose rather than the 250 mg used in the one relevant randomised controlled trial[42]; IV methyldopa is manufactured for women who are unable to take the medication by mouth. Prazosin may be associated with an increase in stillbirth and is not recommended[45].

The nifedipine preparations that are appropriate for treatment of severe hypertension are the capsule and the PA tablet[29,46]. The PA tablets have been withdrawn from some markets. Most authors of randomised trials did not specify whether nifedipine capsules were bitten (prior to swallowing), which may have a greater effect on blood pressure. The 10 mg tablet may be associated with less maternal hypotension than the 10 mg capsule when bitten/punctured (2 trials, 87 women)[29,46]. Theoretically, the 5 mg (instead of the 10 mg) capsule may reduce the risk of a precipitous fall in blood pressure, although there are only two published reports comparing nifedipine 5 mg with hydralazine 5 mg IV (250 women)[34,47].

Nifedipine or other calcium channel blockers can be used together with $MgSO_4$. The risk of neuromuscular blockade with contemporaneous use of nifedipine and $MgSO_4$ is <1%, based on a single-centre, controlled study and a complete data synthesis from the literature[48,49]. Blockade is reversed with 10 g of IV calcium gluconate.

$MgSO_4$ is not an antihypertensive agent[50]. However, transient decreases in blood pressure may be seen. Observational literature describes no decrease[51] or a transient decrease in blood pressure[52–55] 30 minutes after 2–5 g of IV $MgSO_4$ (with or without ongoing infusion), usually in patients with pre-eclampsia. In randomised controlled trials of $MgSO_4$ for fetal neuroprotection, an excess of hypotension was seen (i.e., 9.7% with $MgSO_4$ versus 6.5% with placebo, RR 1.51, 95% CI 1.09–2.09)[56]. When $MgSO_4$ was compared directly with parental nimodipine, $MgSO_4$ was less effective in lowering blood pressure (2 trials, 1683 women)[27] or parenteral labetalol (1 trial, 177 women)[57]. Therefore, although a sustained

Table 8.2 Agents used most commonly for treatment of a blood pressure ≥160/110 mmHg

			*Pharmacokinetics**			
Agent	*Mechanism of action*	*Dosage*	*Onset*	*Peak*	*Duration*	*Comments*
Most commonly recommended						
Labetalol	†Peripheral alpha-1 and (non-selective) beta-1 and 2 receptor antagonist	Intermittent dosing Start with 20 mg IV over 2 min Repeat with 40 mg then 80 mg IV (each over 2 min) q 30 min Continuous infusion 1–2 mg/min (max dosage 300 mg)	5 min	30 min	4 h	Best avoided in women with asthma or heart failure Neonatology should be informed if the woman is in labour, as parenteral labetalol may cause neonatal bradycardia Parenteral therapy should be followed by ongoing oral therapy to maintain BP
Nifedipine	Calcium channel blocker (vasodilator)	Capsule 5–10 mg to swallow without biting Repeat every 30 min	5–10 min	30 min	6 h	There are three types of nifedipine preparations with which all staff must be familiar: capsules, intermediate-release tablets (PA, SR or retard tablet) and slow-release tablets (XL, MR or LA) Nifedipine may be given at the same time as $MgSO_4$
		PA, SR or retard tablet 10 mg to swallow Repeat every 30 min (max dosage 30 mg)	30 min	240 min	6 h	
Hydralazine	Direct-acting vasodilator	Intermittent dosing 5 mg IV Repeat 5–10 mg IV every 30 min (may be given IM but unusual) Continuous infusion 0.5–10 mg/h IV (max dosage 45 mg)	5 min	30 min	3–8 h	May increase the risk of maternal hypotension

Labetalol	†Peripheral alpha-1 and (non-selective) beta-1 and -2 receptor antagonist	200 mg orally Repeat in 4 h (max dosage 2400 mg/day in 4 divided doses‡)	20–120 min	1–4 h	8–12 h	Duration is dose-dependent
Methyldopa	Centrally acting alpha-2 receptor agonist	750 mg orally Repeat in 6 h (max dosage 2000 mg/day in 4 divided doses‡)	Not known	4–6 h	24–48 h	Less effective than oral nifedipine
Clonidine¶	Centrally acting alpha-2 receptor agonist	0.1–0.2 mg orally Repeat in 1 h (max dosage 0.8 mg‡)	30–60 min	2–4 h	6–10 h	Clonidine therapy is not recommended during breastfeeding§
Captopril¶ *only postpartum*	Angiotensin-converting enzyme inhibitor	6.25–12.5 mg orally Repeat in 1 h (max dosage 75 mg)	30 min	60–90 min	≥8 h	Captopril must NOT be administered before delivery, but it is acceptable for use during breastfeeding§ Duration is dose-dependent
Nitroglycerin infusion	Direct vasodilators that has its affects veins more than arterioles	5 μg/min, increased every 5 min (max rate 100 μg/min)	2–5 min	5 min	5–10 min	Main side-effects are headache (due to direct vasodilation) and tachycardia (from reflect sympathetic activation) Methaemoglobinaemia has been reported after 24 h of treatment

BP, blood pressure; IM, intramuscular; IV, intravenous; $MgSO_4$, magnesium sulphate

* General reference www.drugs.com

† Beta-blockade is 3–7 times more than alpha-blockade, especially at lower doses

‡ Dosing of this drug may continue after the severe hypertension has resolved, as it is used for chronic treatment of non-severe hypertension

¶ Captopril (25 mg) and clonidine (0.1 mg) are being compared in a postpartum randomised controlled trial (NCT01761916) based on the effectiveness of these medications for severe hypertension treatment outside pregnancy

§ http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm

lowering of blood pressure cannot be anticipated following a loading dose of $MgSO_4$, the potential for a transient lowering of blood pressure 30 minutes after administration should be considered when antihypertensives are co-administered.

Nitrogylcerin (by infusion) compared favourably with oral nifedipine in one small trial (32 women)[58] and no adverse clinical effects were demonstrated in other small studies[58.60].

Mini-dose diazoxide (i.e., 15 mg IV every 3 minutes) was associated with less persistent severe hypertension compared with parenteral hydralazine (5 mg) in another small trial (124 women)[30].

For refractory hypertension in an intensive care setting, consideration can be given to using sodium nitroprusside or higher dose diazoxide. The theoretical concerns about nitroprusside are well known: light-sensitivity, the need for careful monitoring and the potential to cause fetal cyanide toxicity. A published review of case reports (22 women, 24 fetuses) documented stillbirths among five of 18 women (27.8%) treated antenatally with nitroprusside, although the authors could not attribute these deaths to fetal cyanide toxicity[61]. High dose diazoxide (i.e., 75 mg IV every 30 min) was associated in one trial (90 women) with an excess of maternal hypotension (17.8%) compared with IV labetalol (0%)[62].

Observational literature illustrates that hypotension may result with any short-acting antihypertensive agent administered to women with pre-eclampsia, because they are intravascularly volume depleted. Therefore, it is prudent to continuously monitor FHR until blood pressure has stabilised.

Postpartum, hydralazine, labetalol, nifedipine and methyldopa are appropriate for use during breastfeeding, although only two trials have compared hydralazine with either labetalol[63] or nifedipine[64] for treatment of severe hypertension. Nitroglycerine and diazoxide have not been studied in breastfeeding, although treatment with one of these agents would be expected to be very brief. Nitroprusside is not advised in breastfeeding because of the potential for toxic metabolites (thiocyanate and cyanide) to cross into breast milk[65]. Captopril could also be administered orally for severe hypertension based on its effectiveness for this indication outside pregnancy[66] and its acceptability during breastfeeding[65]. Although neonatologists may express concerns about this in babies born preterm or of low birth weight, no reports of adverse effects were identified. Oral clonidine which is effective for severe hypertension outside pregnancy is not advocated for use in breastfeeding because of high serum levels in breastfed infants[65].

No relevant economic analyses were identified.

Antihypertensive treatment of non-severe hypertension (blood pressure of 140–159/90–109 mmHg)

Management of a pregnant woman with a blood pressure of 140–159/90–109 mmHg is much debated. Any antihypertensive therapy will, compared with placebo or no therapy, decrease the risk of transient, severe hypertension (RR 0.49, 95% CI 0.40–0.60; 20 trials, 2558 women; NNT 10, 95% CI 8–13) without a clear difference in other maternal or perinatal outcomes, such as stroke, perinatal death, or preterm delivery (29 trials, 3350 women)[67]. The results of a small pilot randomised controlled trial (132 women)[68] and a meta-regression of randomised controlled trials (42 trials, 3892 women[69,70]) raised concerns that antihypertensive therapy may be harmful. The meta-regression of randomised controlled trials found a significant relationship between the antihypertensive-induced fall in mean arterial pressure and the risk of SGA infants or lower birth weight. On the other hand, a small trial of 125 women with mild essential or gestational hypertension found that 'very tight' (goal blood pressure <130/80 mmHg) versus 'tight' control (goal blood pressure 130–139/80–89 mmHg) was associated with fewer antenatal hospitalisations and a later gestational age at delivery[71].

The results of a large definitive trial, CHIPS (Control of Hypertension In Pregnancy Study), has provided evidence that non-severe hypertension in pregnancy should be treated with antihypertensive therapy[72]. 'Tight' blood pressure control (target diastolic 85 mmHg) (versus 'less tight' control, target diastolic 100 mmHg) achieved a lower blood pressure by 5.8/4.6 mmHg ($p < 0.001$). 'Tight' (versus 'less tight') control resulted in similar rates of adverse perinatal outcome: the primary outcome of perinatal death or high level neonatal care for >48 hours (30.7% versus 31.4%; aOR 0.98, 95% CI 0.74–1.30) and birth weight <10th percentile for gestational age and gender (19.7% versus 16.1%; aOR 1.28, 95% CI 0.93–1.79). However, 'tight' (versus 'less tight') control resulted in fewer adverse

maternal outcomes: a significant decrease in severe maternal hypertension (27.5% versus 40.6%; aOR 0.56, 95% CI 0.42–0.75) but similar rates of serious maternal complications (2.0% versus 3.7%; aOR 0.57, 95% CI 0.26–1.27).

Although there is ongoing debate about whether blood pressure should be lowered below a diastolic blood pressure of 80 mmHg in the setting of proteinuria (compared with non-proteinuric) patients, a goal of <130/80 mmHg is specified only for patients with diabetes mellitus in order to decrease the risk of long-term cardiovascular disease and diabetic nephropathy[73].

As blood pressure is lowest at about 20 weeks', women may be able to discontinue antihypertensives in early pregnancy. Medication should be restarted as blood pressure rises again later in pregnancy.

There is no evidence that blood pressure should be managed differently in women with pre-eclampsia compared with those with pre-existing or isolated gestational hypertension. It should be noted that 47.3% of women developed pre-eclampsia in the CHIPS trial, and the diastolic blood pressure goal to which women were randomised continued to be applied until delivery[72].

Guidance on treatment of secondary causes of hypertension is available from general hypertension sources[73].

When a decision is made to lower blood pressure, antihypertensive therapy is warranted. Relaxation techniques (such as guided imagery) were not successful in lowering blood pressure in one trial (69 women)[74].

Therapy is usually initiated with one antihypertensive agent, although this will not be sufficient if blood pressure is more than 20/10 above the target[19]. It is important to be familiar with a number of antihypertensive options. Outside pregnancy, only 30–50% of patients respond to a particular antihypertensive drug. Also, women may have another medical problem that is a contraindication to a specific medication (such as severe asthma and beta-blockers) or a characteristic that makes one type of agent more likely to be effective (such as Black race and calcium channel blockers).

Choice of antihypertensive agent

Table 8.3 presents the most commonly used antihypertensive agents for non-severe pregnancy hypertension.

There is little to guide the choice of antihypertensive agent, including effects on FHR and pattern, maternal and perinatal outcomes, and long-term paediatric neurodevelopment. Methyldopa, labetalol and nifedipine are the most commonly recommended antihypertensives in international practice guidelines, although oral labetalol is not widely available in LMICs[75]. Only methyldopa is on the WHO Model List of Essential Medicines (2015) for non-severe pregnancy hypertension[23], and it appears to be a reasonable antihypertensive choice; in the CHIPS trial, women treated with methyldopa (versus labetalol) may have had better outcomes, although this comparison was non-randomised and subject to the possibility of residual confounding[76]. Angiotensin converting enzyme inhibitors and receptor blockers should not be used later in pregnancy, and prazosin and atenolol may be best avoided, as discussed below.

KEY POINTS

- Antihypertensive therapy for non-severe pregnancy hypertension does not affect outcomes for the baby, but does decrease severe hypertension and therefore, risk, for the mother
- Oral methyldopa and oral labetalol are used most frequently for treatment of non-severe hypertension, but there are a wide variety of agents that can be used
- ACE inhibitors and ARBs should NOT be used in pregnancy

Whether pre-eclampsia haemodynamics (either high cardiac output or peripheral vascular resistance) should be used to guide therapy is unclear; although haemodynamics may interact with the pharmacodynamics of antihypertensives to influence development of fetal growth restriction or pre-eclampsia[77], it is unknown if individualised therapy would improve outcomes and be cost-effective.

FHR and pattern

Oral antihypertensives do not appear to change FHR or pattern, but the quality of the data is poor[78]. A prudent approach would be to regard changes in FHR or pattern to evolution of the

Table 8.3 Agents used most commonly for a blood pressure of 140–159/90–109 mmHg

Agent	*Mechanism of action*	*Dosage*	*Comments*
Methyldopa	Centrally acting alpha-2 receptor agonist → decreased sympathetic outflow → decreased peripheral vascular resistance	250–500 mg PO BID-QID (max dosage 2000 mg/day)	There is no evidence to support a loading dose of methyldopa Psychological side-effects (e.g., drowsiness or depression) may occur but women do not change drugs more frequently than with other medication Within first 6 weeks of therapy, <10% may develop hepatitis or cholestasis that can be detected by laboratory testing; abnormalities should reverse with discontinuation, but liver failure is rare After 6 months of therapy, 10–20% develop a positive direct Coombs test, but it does not interfere with typing or cross matching and associated haemolytic anaemia is rare
Labetalol	*Peripheral alpha-1 and (non-selective) beta-1 and 2 receptor antagonist → decreased peripheral vascular resistance with no reflex increase in heart rate	100–400 mg PO BID-QID (max 2400 mg/day)	Some experts recommend a starting dose of 100 mg PO TID because the half-life of labetalol is shorter in pregnancy May be associated with postural hypotension, especially at higher doses
Nifedipine	Calcium channel blocker → vascular smooth muscle relaxation → decrease peripheral vascular resistance	PA, SR or retard tablets 10–20 mg PO BID-TID (max 180 mg/day) XL, MR or LA preparation 20–60 mg PO OD-BID (max 120 mg/day)	Peripheral oedema as a side-effect may be more common at doses of 120 mg/day or more

BID, twice/day; PO, per os; QID, four times/day; TID, three times/day)
* Beta-blockade is 3–7 times more than alpha-blockade, especially at lower doses

underlying hypertensive disorder of pregnancy, and not to the antihypertensive agent that the woman is taking.

Maternal and perinatal outcomes

In randomised controlled trials, usually of women without comorbidities, a wide variety of antihypertensive agents (started after the first trimester of pregnancy) have been compared with placebo or no therapy and shown to decrease the risk of severe hypertension (as discussed above): methyldopa, labetalol, other pure beta-blockers (acebutolol, mepindolol, metoprolol, pindolol and propranolol), calcium channel blockers (isradipine, nicardipine, nifedipine and verapamil), hydralazine, prazosin and ketanserin (29 trials, 3350 women)[67].

In comparative trials of one antihypertensive agent versus another, meta-analysis has revealed no clear differences in maternal and perinatal outcomes (22 trials, 1723 women)[67], and small trials published subsequently have been consistent with these conclusions (2 trials, 163 women)[79,80]. Most trials have compared beta-blockers with methyldopa. Although alternative drugs may be more effective at reducing the risk of severe hypertension than methyldopa (RR 0.54, 95% CI 0.30–0.95; 11 trials, 638 women), and beta-blockers and calcium channel blockers considered together may decrease the risk of proteinuria (as a surrogate for pre-eclampsia) (RR 0.73, 95% CI 0.54–0.99; 11 trials, 997 women), the significance of these findings is unclear. The effects on both severe hypertension and proteinuria are not seen in individual drug comparisons.

Thiazide diuretics can be considered for use in hypertensive women, but they are used mainly in specific circumstances identified before pregnancy, such as medullary sponge kidney for which a decrease in renal calcium excretion is advantageous.

Despite concerns that they may inhibit the normal plasma volume expansion of pregnancy, thiazides used after the first trimester in randomised controlled trials for pre-eclampsia prevention did not (negatively or positively) affect maternal or perinatal outcomes, including pre-eclampsia (5 trials, 1836 women)[81].

ACE inhibitors and angiotensin receptor blockers (ARBs) should not be used in pregnancy as they are fetotoxic. The hypertensive disorders of pregnancy guidelines in the UK have identified advising women about these risks as a key priority for implementation[43]. If used prior to pregnancy for renoprotection among women with diabetes mellitus and pre-pregnancy microalbuminuria, there is no reasonable alternative available in pregnancy. However, most renoprotection is afforded by good control of blood pressure. Some ACE inhibitors are acceptable during breastfeeding and, as such, can be restarted after delivery[65].

There are a number of drugs that may be best not to use in pregnancy. It is not clear why atenolol (in contrast to other beta-blockers, even cardioselective) may be associated with adverse effects on fetal growth[81–86], an effect that has not been consistently observed[87]. Until further data are available on the risks of atenolol in pregnancy, other agents may be preferable to use. More stillbirths were reported in the prazosin arm of one trial of early severe pre-eclampsia (150 women)[45]. Oral hydralazine is not recommended because of maternal side-effects when used alone[88].

For women with pre-existing hypertension, antihypertensive choice for pregnancy is best made pre-pregnancy. However, 50% of pregnancies are unplanned. Relative to the baseline risk of major malformations (1–5%), most antihypertensives are not teratogenic but the quality of the evidence is only fair and controversies remain. As blood pressure falls in early pregnancy (reaching its nadir at 20 weeks), many women may be able to discontinue their antihypertensive therapy and maintain normotension, thereby avoiding first trimester exposure of the fetus to antihypertensive agents. If this is not possible, it should be noted that methyldopa, labetalol and nifedipine are used commonly in early pregnancy. Although clinical practice guidelines from the UK state that thiazides are teratogenic, no specific reference was provided[43]. There is even controversy over whether ACE inhibitors increase the risk of major malformations following first trimester exposure. A high-impact study that found ACE inhibitors were teratogenic[89], but the study was criticised because of potential residual confounding of the drug–outcome relationship. A subsequent prospective cohort study did not find ACE inhibitors (or ARBs) to be teratogenic following first trimester exposure, but they were associated with an increase in miscarriage[90]. A meta-analysis of controlled cohort studies found that any antihypertensive therapy (and not just treatment with ACE inhibitors or ARBs) was associated with heightened teratogenic risk, although the quality of the evidence was not high (five cohort studies involving 786 infants exposed to ACE inhibitors or ARBs, 1723 exposed to other antihypertensives, and 1,091,472 unexposed)[91]. Whether to replace ACE inhibitors, ARBs, atenolol, or less commonly used antihypertensives before or in early pregnancy, and if so with what, is uncertain. Conception may take up to 12 months, but women over 30 years suffer more subfertility.

Long-term paediatric neurodevelopment

There is very little published research on the potential long-term developmental effects of antihypertensive therapy and the hypertensive disorders of pregnancy for which they are prescribed. Unfortunately, different studies have focused on either the hypertensive disorders of pregnancy or the antihypertensive treatment, each type of study focusing on different confounders. Most studies are observational cohort studies and cannot address effectively both known and unknown confounders of the relationship between outcomes and either the hypertensive disorder of pregnancy or its antihypertensive therapy. Also, few existing studies have been published over a 35-year period, making it difficult to synthesise them owing to major changes in methods of treatment for hypertensive disorders of pregnancy, paediatric follow-up and neurodevelopmental testing methods.

What can be said is that follow-up data from placebo-controlled randomised controlled trials have not revealed clear adverse effects on health or neurodevelopment of nifedipine at 1 year of age (110 children)[92], atenolol at 18 months of age (190 children)[93], or methyldopa at 7.5 years (242 children)[94]. Data from a controlled observational study were reassuring for labetalol (N = 32

pregnancies), but compared with women exposed to medications without known neurodevelopmental effects (N = 42), women who took methyldopa in pregnancy (N = 25) had children with lower scores on measures of Full-Scale IQ (105.2 ± 12.5 vs. 111.9 ± 11.4, $p = 0.04$) and Performance IQ (98.8 ± 16.2 vs. 110.2 ± 12.9, $p = 0.002$); although the mean scores were within the normal range, the duration of treatment with methyldopa was an independent predictor of children's Performance IQ[95].

What is important to note is that the hypertensive disorders of pregnacy do appear to be associated with some effects on neurodevelopment, independent of any antihypertensive therapy. We were unable to identify literature on the impact on child development of pre-existing hypertension itself (compared with normotensive pregnancy). However, the children of women with gestational hypertension or pre-eclampsia appear to have a relatively modest, inconsistent increase in neurodevelopmental problems, such as inattention and externalising behaviours (e.g., aggressiveness), fine or gross motor function, or verbal ability[96–99]. These studies are presented in detail elsewhere[8].

The reader should also be aware of a growing literature describing adverse effects of pre-eclampsia on offspring health, particularly cardiovascular[100], reproductive[101] and even cognitive at advanced age[102].

No relevant analyses were found about the cost-effectiveness of antihypertensive therapy (or not) for non-severe hypertension in pregnancy, although an economic analysis of the CHIPS trial (see above) is anticipated for publication in 2016[103]. No economic analyses were identified for comparisons of different antihypertensive agents.

Magnesium sulphate therapy for eclampsia prevention and treatment, and fetal neuroprotection

Magnesium sulphate ($MgSO_4$) is listed on the WHO Model List of Essential Medicines (2015) for treatment of eclampsia and severe pre-eclampsia[23]. Benzodiazepines are listed as anticonvulsants, but not specifically for eclampsia.

For eclampsia treatment

$MgSO_4$ is effective for eclampsia treatment, more than halving the risk of recurrent seizures compared with phenytoin (7 trials, 972 women)[104], diazepam (7 trials, 1396 women)[105], or a lytic cocktail (usually chlorpromazine, promethazine and pethidine) (3 trials, 397 women)[106]. Also, $MgSO_4$ was associated with a reduction in some other adverse maternal outcomes, such as death (compared with diazepam or a lytic cocktail) or pneumonia and ventilatory support (compared with phenytoin or a lytic cocktail). Of note, the protocol for women in the $MgSO_4$ arm of the largest of these trials, the Collaborative Eclampsia Trial, did not include administration of benzodiazepines for seizure termination. The initial intravenous treatment protocol was $MgSO_4$ 4 g IV (or 5 g in South Africa) over 5 minutes, followed by an infusion of 1 g/h; a recurrent seizure was treated with another 2–4 g IV over 5 minutes. Serum magnesium levels were not measured, but women were followed clinically for adverse magnesium-related effects. Algorithms have been published to improve eclampsia care.

We were unable to identify a cost-effectiveness analysis of $MgSO_4$ for eclampsia treatment.

For pre-eclampsia (eclampsia prevention)

$MgSO_4$ is more effective than placebo/no therapy for eclampsia prevention among women with pre-eclampsia, more than halving the occurrence of seizures (RR 0.41, 95% CI 0.29–0.58; 6 trials, 11,444 women)[107]. In the Magpie Trial, the largest of the prevention trials, pre-eclampsia was defined as hypertension and ≥1+ proteinuria[108]. The initial treatment protocol was $MgSO_4$ 4 g IV over 10–15 minutes, followed by an infusion of 1 g/h. The number needed to treat (NNT) (95% CI) to prevent one seizure among women with severe pre-eclampsia was 50 (34–100) and for non-severe pre-eclampsia 100 (100–500). (Severe pre-eclampsia was defined as severe hypertension (systolic blood pressure ≥170 mmHg or diastolic ≥110 mmHg, measured twice) and proteinuria ≥3+ by dipstick, or more moderate hypertension (systolic blood pressure ≥150 mmHg or diastolic ≥100 mmHg, measured twice) and proteinuria (≥2+), as well as TWO or more symptoms/signs of 'imminent eclampsia' (unspecified).) $MgSO_4$ also decreased the risk of abruption (RR 0.64, 95% CI 0.50–0.83; NNT of 100 (50–1000)) but increased the risk of Caesarean delivery (50% vs. 47%; RR 1.05, 95% CI 1.01–1.10). $MgSO_4$ was more frequently associated with side-effects (24% vs. 5%; RR 5.26, 95% CI 4.59–6.03).

$MgSO_4$ is more effective than other agents for eclampsia prevention among women with pre-eclampsia (9 trials, 6301 women). $MgSO_4$ compared with phenytoin reduced eclampsia (RR 0.08, 95% CI 0.01–0.60) but increased Caesarean delivery (RR 1.21, 95% CI 1.05–1.41; 4 trials, 2343 women)[107]. $MgSO_4$ compared with nimodipine reduced eclampsia, but there were more maternal respiratory problems (1.3% vs. 0.4%; RR 3.61, 95% CI 1.01–12.91) and the need for additional antihypertensive therapy (54% vs. 46%; RR 1.19, 95% CI 1.08–1.31; 1 trial, 1650 women)[109]. Other trials comparing $MgSO_4$ with other agents (diazepam in 2 trials, 2241 women; methyldopa in 1 trial, 31 women; and nitrates in 1 trial, 36 women) were too small for conclusions to be drawn[107].

Although $MgSO_4$ is effective for eclampsia prevention in women with pre-eclampsia, the challenge remains how to use $MgSO_4$ cost-effectively for this purpose. $MgSO_4$ for eclampsia prevention is costly[110]. In high income countries, the number of women who need to receive $MgSO_4$ to prevent one case of eclampsia is 324 (95% CI 122–∞), compared with 43 (95% CI 30–68) in low-income countries[110]. The incremental cost of preventing each case of eclampsia in 2001 US$ was $21,202 in high-income and $456 in low-income countries, driven by the costs of maternal surveillance in high-income settings and by the drug cost in low-income ones. If only women with severe pre-eclampsia were to be treated with $MgSO_4$, the incremental cost would be US$12,942 in high- and $263 in low-income countries.

The high costs of $MgSO_4$ for eclampsia prevention has generated controversy about whether women with non-severe pre-eclampsia should receive $MgSO_4$, particularly as $MgSO_4$ is associated with more Caesarean deliveries and maternal adverse effects[110]. Potential solutions to this challenge include restricting treatment to 'severe' pre-eclampsia and lowering the $MgSO_4$ dose and/or duration of therapy.

Restricting therapy to 'severe' pre-eclampsia only

There are a number of concerns about this approach. First, in a comprehensive review of eclampsia (21,149 women with eclampsia from 26 countries contributing to at least one variable of interest), a significant proportion lacked evidence of 'severe pre-eclampsia' based on severe hypertension (32% of 3443 women), headache (66% of 2163 women), visual disturbances (27% of 2163 women), or epigastric pain (25% of 2053 women); 25% (of 3443 women) were actually normotensive and 25% (of 1092 women) asymptomatic[111]. Second, in a large American centre that changed its policy from universal prophylaxis of all women with gestational hypertension to a selective approach for only women with severe gestational hypertension, there was more eclampsia and, in those women, more general anaesthesia and adverse neonatal outcomes, although absolute rates of these complications were very low[112]. Finally, whether we could successfully target at least 80% of women with severe pre-eclampsia if we tried is questionable; only 62% of women who were hospitalised with pre-eclampsia and also suffered an adverse maternal outcome were treated with $MgSO_4$ in an international prospective cohort study[17]. Also, if we chose this approach, cost-savings would be offset by the need to administer $MgSO_4$ for fetal neuroprotection when women with non-severe pre-eclampsia deliver at <32 weeks (see below)[113].

Lowering the dose or duration of $MgSO_4$ therapy

Interest in $MgSO_4$ dose reduction has been fuelled by fear of serious maternal side-effects and the perception that women must have serum magnesium levels, as illustrated by the following quote:

> "We know that the gold standard is magnesium sulphate, but you know the problem associated with that, monitoring level and so on and so forth. But then the diazepam that can be used without much monitoring."
>
> Society of Obstetricians and Gynaecologists of Nigeria, Nigeria

However, in a comprehensive review of 143 publications (including 21 randomised controlled trials, total of 23,916 women), appropriate administration of $MgSO_4$ was not associated with an increase in maternal death or cardiorespiratory arrest, and estimates from non-randomised studies largely supported those from randomised controlled trials[114]. In a review specifically of 24 studies (9556 women) conducted in LMICs, serious side-effects

were infrequent (i.e., one maternal death associated with a serum magnesium level of 24 mEq/L; 1.3% respiratory arrest; cardiac arrest not reported) and when concerns arose (e.g., absent patellar reflex, 1.6%), a delay in repeat administration (3.6%) was generally sufficient to mitigate the effect; calcium gluconate was administered to <0.2% of treated women[115].

Dose reduction is of particular interest in LMICs, where women tend to have lower body weight and the cost of $MgSO_4$ itself drives the cost of treatment; 22/25 published studies of $MgSO_4$ administration in LMICs used a modified dosing regimen that decreased overall dose and was associated with a median eclampsia rate of 3.0%, even when studies of eclampsia treatment were included[116]. However, an important consideration is that global obesity rates are rising and women with a BMI >30 kg/m^2 may need *higher* than standard doses of $MgSO_4$[117].

Modified regimens for eclampsia *treatment* have been studied in six trials (899 women). Two trials (481 women) compared a $MgSO_4$ loading dose with loading dose plus maintenance therapy for 24 hours; there were no clear between-group differences in recurrent seizures or other outcomes but the 95% CIs were wide[118,119]. Four trials (359 women) compared low dose $MgSO_4$ with standard dosing over 24 hours; the studies were small but at least one found that lower doses were associated with a higher risk of recurrent seizures[120–123]. One trial (98 women) evaluated a postpartum course of $MgSO_4$ shortened to two intramuscular doses given 4 hours apart; there was no difference in outcomes[124].

Modified regimens for eclampsia *prevention* among women with pre-eclampsia have been evaluated in six trials (685 women)[125–127]; an additional trial (60 women) that compared 1 g/h versus 2 g/h maintenance dosing antenatally (and found no difference in outcomes) was not considered to have studied a reduced dosing regimen[128]. One trial (17 women) compared an IV with an IM maintenance regimen for 24 hours; no reliable conclusions could be drawn[129]. Five trials (668 women) evaluated shortened maintenance regimens of postpartum $MgSO_4$, compared with continuing the $MgSO_4$ for 24 hours after the birth; eclampsia was not more common in the abbreviated treatment groups but the trials were too small for reliable conclusions to be drawn[125,130–132]. Given a rate of 0.75% of eclampsia in the $MgSO_4$ arm of women in eclampsia prevention trials, a sample size of 3285/group would be required to rule out a doubling of the eclampsia rate (from 0.75% to 1.5%) with a modified $MgSO_4$ therapy regimen (assuming an alpha of 0.05 and power of 80%). Therefore, there are insufficient data to evaluate the effectiveness of a modified (reduced dose) regimen of $MgSO_4$ for eclampsia prevention.

All $MgSO_4$ data presented thus far relate to administration in facilities. In-community administration of $MgSO_4$ for eclampsia decreased recurrence in one randomised controlled trial (265 women)[133], and administration for pre-eclampsia is being studied in a cluster randomised controlled trial in four LMICs[134] (pre-empt.cfri.ca).

KEY POINTS

$MgSO_4$ for eclampsia treatment and prevention

- *IV only*: 4 g $MgSO_4$ IV (over 5 min), then maintenance dose of 1 g/h
- *IV & IM*: 4 g $MgSO_4$ IV (over 5 min) + 5 g IM into each buttock (total 10 g IM), then 5 g IM every 4 h
- Administer an additional 2–4 g IV (over 5 min) if there is a seizure while on $MgSO_4$
- There are insufficient data to evaluate the effectiveness of a modified (reduced dose) regimen of $MgSO_4$ for eclampsia prevention

Fetal neuroprotection

- 4 g $MgSO_4$ IV (with/without 1 g/h until delivery or 24 h maximum) for women with imminent delivery at <34 weeks who do not otherwise quality for eclampsia prevention or treatment

For fetal neuroprotection

At <32 weeks, $MgSO_4$ decreased the risk of cerebral palsy (RR 0.68, 95% CI 0.52–0.91) or 'death or cerebral palsy' (RR 0.86, 95% CI 0.74–1.00) (3 trials, 3981 infants). As such, $MgSO_4$ is recommended for fetal neuroprotection in the setting of imminent preterm birth (i.e., within the next 24 hours) at gestational ages up to 31^{+6} weeks[56].

Women with pre-existing or gestational hypertension who are at risk of imminent preterm birth at up to 33^{+6} weeks would be candidates to

receive $MgSO_4$ for fetal neuroprotection. $MgSO_4$ for fetal neuroprotection (compared with no treatment) is cost-effective. $MgSO_4$ leads to better outcomes for the baby (56.684 vs. 56.678 quality-adjusted life years) and costs less (US$1739 vs. US$1917) when administered to women at high risk of preterm birth before 31^{+6} weeks owing to preterm labour or preterm premature rupture of membranes[135,136].

Therapies for HELLP syndrome

Platelet count may decrease rapidly in HELLP, mandating frequent serial measurement of platelet count within hours. After delivery, most women have a further decrease in their platelet count and/or rise in their liver enzymes until day 2 postpartum. By day 4 after delivery, some improvement in laboratory parameters should be apparent such that by day 6 (or within 3 days of the platelet nadir), the platelet count should be at least 100×10^9/L[137].

Transfusion

Blood and blood components (including coagulation factors) are listed on the WHO Model List of Essential Medicines (2015)[23]. WHO recognises that, ". . . self-sufficiency, unless special circumstances preclude it, in the supply of safe blood components based on voluntary, non-remunerated blood donation, and the security of that supply are important national goals to prevent blood shortages and meet the transfusion requirements of the patient population. All preparations should comply with the WHO requirements." The reality is very different in LMICs, as illustrated by the following quote:

> "Blood problem is the main problem, blood is not available in government hospitals, sometimes drug addicts or hepatitis patient blood is transfused"
>
> Male decision-maker, Pakistan, CLIP Feasibility Study 2012

Platelet transfusion (with/without other blood products) is indicated based on platelet count, mode of delivery, presence of active bleeding, and coagulopathy, as shown in Table 8.4. There is general agreement that perioperative, prophylactic transfusion of platelets is not necessary above a count of 50×10^9/L[138] in the absence of clinical bleeding or platelet dysfunction[139]. At platelet counts <10–20×10^9/L, prophylactic pre-delivery transfusion of platelets may be considered as the risk of profound haemorrhage is increased even with non-operative delivery[140]. Platelets must be

KEY POINTS

- The laboratory abnormalities of pre-eclampsia that describe HELLP syndrome may worsen for up to 5 days after delivery
- Platelet count is not a sensitive indicator of coagulopathy in pre-eclampsia
- Corticosteroids should be administered only if more rapid resolution of laboratory abnormalities will change management

Table 8.4 Recommendations about transfusion of platelets related to mode of delivery (and packed red blood cells, cryoprecipitate and fresh frozen plasma if necessary) in HELLP[8] (from SOGC 2014 guidelines, with permission)

	Mode of delivery	
Platelet count	*Caesarean delivery*	*Vaginal delivery*
<20×10^9/L	✔	✔
20–49×10^9/L	✔	Consider in presence of: • Excessive active bleeding • Known platelet dysfunction • Platelet count falling rapidly • Coagulopathy
≥50×10^9/L	Consider in presence of: • Excessive active bleeding • Known platelet dysfunction • Platelet count falling rapidly • Coagulopathy	Consider in presence of: • Excessive active bleeding • Known platelet dysfunction • Platelet count falling rapidly • Coagulopathy
Regardless of the platelet count	X No platelets should be transfused if there is a strong suspicion of HIT or TTP-HUS	

HIT, heparin-induced thrombocytopaenia; TTP-HUS, thrombotic thrombocytopaenic purpura – haemolytic uraemic syndrome

thawed prior to administration, and a standard unit of apheresis platelets can be expected to raise the platelet count by at least 5×10^9/L, with a peak at 10–60 minutes post-transfusion. Four units of platelets can contain as much as 2 mL of RBCs to which women who are anti-D(Rho)-negative may become sensitised. Therefore, women who are anti-D negative and receive a platelet transfusion should receive a 300 μg dose of anti-D immune globulin, a dose sufficient to prevent sensitisation following transfusion of up to 30 units of platelets[140].

Although a platelet count $<150 \times 10^9$/L is associated with a heightened risk of abnormal coagulation, platelet count is not a sensitive indicator of coagulopathy. Coagulation should be assessed independently of platelet count in pre-eclampsia prior to neuraxial analgesia/anaesthesia or surgery[141].

Corticosteroids

Dexamethasone is listed on the WHO Model List of Essential Medicines (2015) for maternal administration to benefit the neonate[23], based on evidence that the drug accelerates fetal pulmonary maturation when indicated at <34 weeks[142].

When given specifically for HELLP syndrome, corticosteroids (particularly dexamethasone) more rapidly improve platelet count and other haematological and biochemical indices of the HELLP syndrome (ALT, AST, LDH), especially when the treatment is initiated before delivery (11 trials, 550 women)[143]; however, no significant impact was seen on major maternal (death or severe morbidity) or perinatal (death or severe morbidity) outcomes, and transfusion requirements and rates of regional anaesthesia were not reported. In a small retrospective study of 37 women, regional anaesthesia was more often achieved (in 42% of women vs. 0%) when steroids were given to women with platelet counts $<90 \times 10^9$/L[144]. When dexamethasone for HELLP was incorporated into the local treatment protocol (along with $MgSO_4$ and antihypertensive therapy), one centre noted a reduction in severe maternal morbidity and a low rate of disease progression[145]. However, these data are not sufficient to guide practice. The COHELLP trial (NCT00711841) will determine whether postpartum dexamethasone decreases the key clinical outcome – severe maternal morbidity[146].

Other

HELLP syndrome must be differentiated from other 'imitators', as discussed in Chapter 3. Women with progressive HELLP syndrome, particularly postpartum, have been described in observational studies to improve with plasma therapies that are effective for thrombotic thrombocytopaenic purpura (TTP), a HELLP mimicker[147]. No randomised controlled trials were identified.

Thromboprophylaxis

Unfractionated heparin (sodium) is listed on the WHO Model List of Essential Medicines (2015)[23].

Thromboprophylaxis (with unfractionated or low molecular weight heparin) should be considered when thromboembolic risk is at least 1%. This risk level is reached antenatally, when pre-eclampsia is associated with two or more other risk markers, and postnatally, when either pre-eclampsia is associated with at least one other risk marker (e.g., obesity or maternal age >35 years) or women with any hypertensive disorder of pregnancy were on antenatal bedrest for at least 7 days (regardless of mode of delivery)[148,149]. Whether emergency Caesarean delivery warrants thromboprophylaxis in all women is not consistent between guidelines. It must be noted that guidelines are based largely on observational data. Although the influential Royal College of Obstetricians and Gynaecologists Guidelines[149] have been associated with a decline in thromboembolism-related maternal deaths in the UK, there are insufficient data from randomised controlled trials on which to base guideline recommendations[150].

Novel therapies for pre-eclampsia

Novel therapies for pre-eclampsia target various aspects of pre-eclampsia pathogenesis and are in development[151]. Most of these therapies ultimately target increased nitric oxide (NO) production and vasodilatation. There is insufficient information to evaluate their effects, and their use in clinical practice is not yet recommended.

Agents under active investigation and that show promise include pravastatin, L-arginine, S-nitrosoglutathione (GSNO), sildenafil, esomeprazole[152] and antithrombin.

Pravastatin is being evaluated in a randomised controlled trial for prevention of severe

complications in women with early 'severe' pre-eclampsia[153] (STaMP, EudraCT Number: 2009-012968-13). The rationale is that statins reduce antiangiogenic factors and increase NO production (Figure 8.1). With an ageing obstetric population, these medications will be used more frequently for cardiovascular disease prevention; although questioned as being teratogenic, particularly with regards to central nervous system and limb anomalies, a recent large retrospective cohort study failed to find that statins are teratogenic[154].

In multiple small randomised controlled trials, women with gestational hypertension or pre-eclampsia were administered L-arginine, a NO precursor, as it is an amino acid required for the body's production of NO. L-arginine is available as a powder, tablet, or intravenous infusion. L-arginine increased the time to delivery (mean difference 11.5 days, 95% CI 5.2–17.9; 2 trials, 135 women) and reduced blood pressure, diastolic (mean difference 4.9 mmHg, 95% CI 4.2–5.5; 4 trials, 204 women) more than systolic (mean difference 3.2 mmHg, 95% CI -1.5–7.9; 4 trials, 204 women) (7 trials in total, 916 women)[155].

S-nitrosoglutathione (GSNO) is a NO donor that causes vascular relaxation. When given to women with severe pre-eclampsia, GSNO improved blood pressure, platelet count and uterine artery Doppler resistance. This, in addition to the fact that it does not appear to induce tolerance, makes it an interesting drug for future study[151].

Sildenafil is a phosphodiesterase type-5 inihbitor that increases concentrations of cGMP, resulting in relaxation of vascular smooth muscle (Figure 8.1). It has been marketed extensively for treatment of erectile dysfunction in men. Sildenafil is currently being studied in four randomised controlled trials

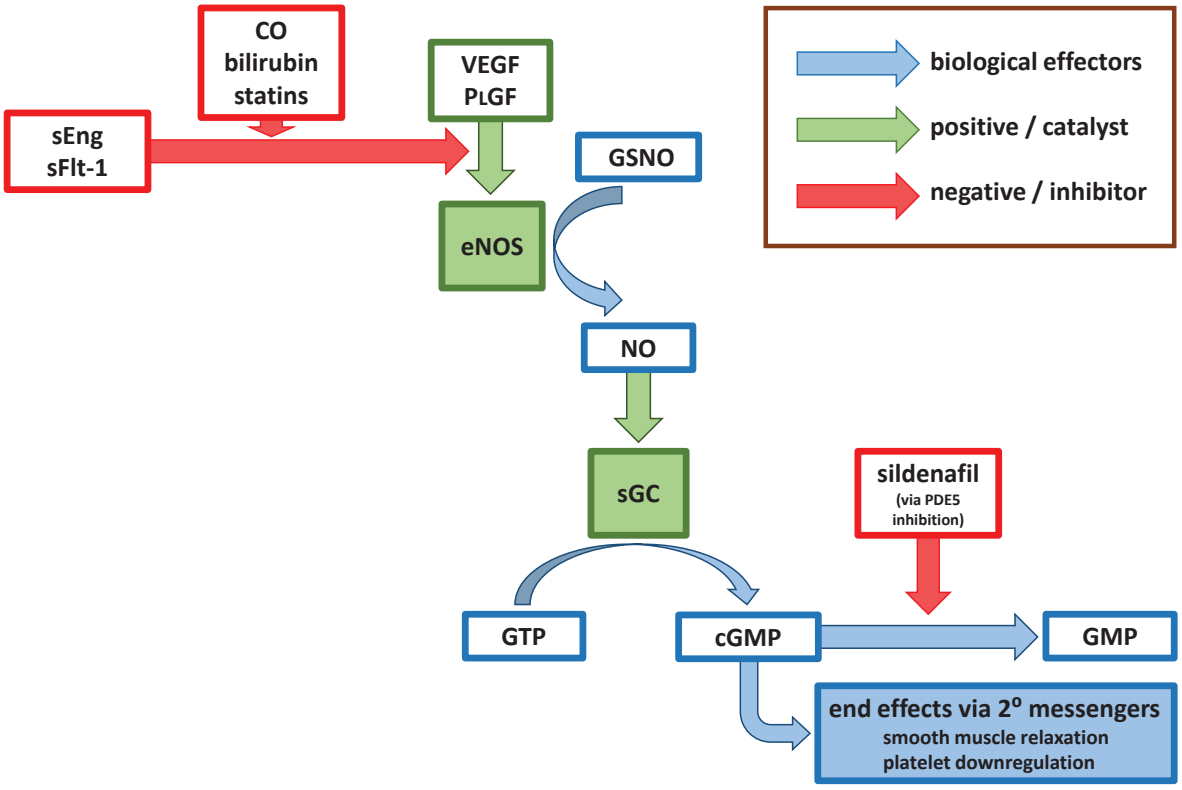

Figure 8.1 Overview of the mechanisms of action of various novel therapies for pre-eclampsia (modified from Everett *et al. J Matern Fetal Neonatal Med* 2012;25(1):50–52). 2°, secondary; cGMP, cyclic guanosine monophosphate; CO, carbon monoxide; GMP, guanosine monophosphate; GSNO, S-nitrosoglutathione; GTP, guanosine triphosphate; PDE5, phosphodiesterase-5; PlGF, placental growth factor; sEng, soluble endoglin; sFlt-1, soluble fms-like tyrosine kinase; sGC, soluble guanylyl cyclase; VEGF, vascular endothelial growth factor

for treatment of severe, early-onset IUGR[156]. The randomised controlled trial of sildenafil for pre-eclampsia did not improve maternal or perinatal outcomes, but the pre-eclampsia was of late-onset, the type less likely to have the abnormal placentation that sildenafil aims to target (see Chapter 3).

Esomeprazole is a proton pump inhibitor used to treat gastric reflux. Preclinical laboratory studies have demonstrated that esomeprazole decreases sFlt-1, soluble endoglin, and measures of oxidative stress[157].

Recombinant antithrombin (ATryn®) is being studied for the treatment of preterm pre-eclampsia at $<31^{+0}$ weeks[158].

Remote literature describes potentially beneficial effects of abdominal decompression, by application of intermittent negative pressure over the abdomen for 30 minutes, once to three times daily (3 trials, 367 women)[159]. Each trial was potentially biased, and only one enrolled women with pre-eclampsia or pre-existing hypertension. However, abdominal decompression was associated with beneficial effects: a reduction in pre-eclampsia or worsening pre-eclampsia (RR 0.36, 95% CI 0.18–0.72; 1 trial, 80 women), low birth weight babies (RR 0.50, 95% CI 0.40–0.63; 2 trials, 304 women), and perinatal mortality (RR 0.39, 95% CI 0.22–0.71; 3 trials, 367 women).

Sleep-disordered breathing has been linked with gestational hypertension. Treatment of that sleep-disordered breathing did not improve blood pressure, but the one relevant trial (24 women) treated women for only one night, so it is impossible to draw conclusions[160].

Also, immediate postpartum curettage, usually under ultrasound guidance, was associated with lower blood pressure, higher platelet count and higher urine output, but differences in harder clinical outcomes (such as hospitalisation or need for transfusion) were not demonstrated (3 trials, 497 women)[161–163]. Uterine perforation was not documented to have occurred.

Agents that have shown disappointing results in studies to date include Digibind and recombinant activated protein C.

Digibind (anti-digoxin antibody) was studied in a randomised controlled trial (NCT00158743) of postpartum women with severe pre-eclampsia. The rationale was that binding of endogenous digitalis-like factors would lead to vasodilatation. Deterioration in creatinine clearance was blunted in the Digibind group, but there was no difference in hard clinical outcomes, including blood pressure[164].

Activated protein C (APC) is a serine protease that was studied as a disease-modifying treatment for critically ill subjects. Despite its anti-inflammatory, antithrombotic and fibrinolytic properties, APC did not improve mortality in sepsis and it was withdrawn from the market. In a controlled series of nine women with antenatal, severe pre-eclampsia, APC increased urine output (consistent with initiation of disease resolution), but did not improve other clinical outcomes[165].

Evidence-based care in under-resourced settings

The hypertensive disorders of pregnancy rate among the four top causes of maternal mortality and morbidity worldwide, but more than 99% of hypertensive disorder of pregnancy-related maternal deaths occur in under-resourced settings, particularly sub-Saharan Africa and South Asia[166]. There, efforts to improve outcomes by promoting evidence-based care in facility have taken many approaches, including practice audit and development of practice guidance and tools[15]. Care in the community, including task-shifting to community health workers is complementing this approach. These approaches are discussed in detail below, but it should be noted that their application in well-resourced settings could improve care there as well.

Audit of practice and outcomes

Introducing quality of care indicators for pre-eclampsia/eclampsia appears to be acceptable to hospital-based practitioners (South Thailand)[167]. Practice audit according to those indicators can identify case management problems; however, the quality of the analysis, clarity of recommendations for improvement, and follow-up to confirm implementation of solutions are related to their effectiveness (Benin, West Africa)[168]. When done properly, criteria-based audit at university teaching hospitals has improved pregnancy outcomes, including maternal mortality (Tanzania)[169].

Whether high-quality practice audit works equally well at all levels of the health care system has been questioned. After a multifaceted intervention, adherence with practice indicators

increased, but variably, being substantially lower at district (for approximately 70% of indicators) than at referral hospitals (>90%) (South Thailand)[167]. Similar results were seen in a cluster randomised controlled trial (Senagal and Mali); the intervention of maternal death reviews combined with best practice implementation for emergency obstetric care, was supported by regular visits by trained facilitators. Hospital-based maternal mortality was decreased (OR 0.85, 95% CI 0.73–0.98), but only at first-level referral hospitals and not at regional referral hospitals[170].

Various audit data collection sheets have been published, although they have been designed to comply with either local guidelines[171] or national guidelines[43]. As such, they may be less applicable at other sites or in other countries, especially as many criteria are not based on high-quality evidence but rather, on what is achievable in that particular setting.

Emergency drills (also known as 'fire drills') provide a simulated experience for participants to practice problem-solving and decision-making skills in the management of an obstetric or newborn emergency, with emphasis on thinking quickly, reacting (intervening) rapidly, and working as a team. Also, they provide opportunities to both revise essential skills and develop confidence in dealing with emergencies that do not occur frequently. Formal programmes have been developed, such as the Essential Steps in Managing Obstetric Emergencies (ESMOE) – Emergency Obstetric Simulation Training (EOST) and then adapted for use in countries such as South Africa. This programme's drills for eclampsia and pre-eclampsia (N = 2) have been provided in Appendix 8.2.

Standardising care in facility

The lack of easy to use protocols and monitoring charts in the management of pre-eclampsia/eclampsia are felt to contribute to substandard care of women in resource-poor settings, particularly when care is provided by those with less experience. Even when the necessary drugs and supplies are available for high-quality pre-eclampsia/eclampsia management, there is a lack of provider knowledge and experience (Afghanistan)[172].

Although developing guidance is hampered by the lack of high-quality evidence in some areas of care, a variety of tools have been studied to improve evidence-based hypertensive disorder of pregnancy care, including monitoring and treatment guides and emergency medical kits, building on the popularity of the 'eclampsia box' in the Collaborative Eclampsia Trial. A tool that provided a visual record of monitoring and treatment, as well as treatment guidance of women with severe pre-eclampsia/eclampsia, was viewed as potentially useful in clinical care by the majority of skilled birth attendants surveyed and an implementation study has been planned (sub-Saharan Africa)[173]. Single-use obstetric emergency medical kits made available for in-hospital care were used frequently for care of women with pre-eclampsia/eclampsia (in 52/192 cases of kit use), and there was an associated (non-significant) 30% decrease in all-cause maternal mortality (Kenya)[174]. Lack of IV pumps for administration of $MgSO_4$ maintenance therapy was addressed by a single trial (300 women); women allocated to IV $MgSO_4$ using a mechanical, flow-controlled pump (Springfusor®) experienced less pain and fewer other side-effects than women allocated to IV and IM $MgSO_4$ loading with IM maintenance[175]. More than 90% of women in both groups completed their full course of therapy.

The NICE guidelines published detailed algorithms for care in well-resourced settings. These were based on the 2010 NICE guidelines, UK, but the algorithms could be adapted for local use[43].

Initiating treatment in the community

At the primary health centre level, fewer than half of centres initiated treatment for pre-eclampsia (40.0%) or eclampsia (28.0%) prior to transfer to facility (rural Nigeria)[176]. Taken in the context of the 'three delays' model of maternal mortality, this represents a lost opportunity for improving maternal outcome.

The nine manuals of the Perinatal Education Programme (PEP) in South Africa have been produced and distributed by the Perinatal Education Trust, a non-profit organisation that aims to improve outcomes for pregnant women and their babies, especially in poor, rural communities (pepcourse.co.za). PEP is self-help training for health professionals who are responsible for their own education. The course is cheap and does not require a teacher. Material is presented in a series of

manuals that learners can either download for free or purchase from suppliers of medical books. Learners usually study in groups of 5–10 to foster co-operative learning. The group studies the chapters independently, usually meeting every 2–3 weeks to allow for discussion of the units or demonstration of specific skills. Since the inception of PEP in 1988, approximately 50,000 manuals have been distributed and an estimated 80,000 health care providers have used PEP course work. Course evaluation takes the form of self-assessed multiple choice tests before and after each chapter, and a final multiple-choice examination by the Perinatal Education Trust for each manual. By 2014, over 20,000 PEP certificates had been awarded to more than 10,000 participants in South Africa.

The Community-Level Interventions for Pre-eclampsia (CLIP) Trial is a cluster randomised controlled trial that is evaluating a community-based package of triage, treatment and transport for women identified with hypertensive pregnancy (2013–2017) in four LMICs (India, Nigeria, Mozambique and Pakistan)[134] (pre-empt.cfri.ca). Community health workers are being instructed to administer oral methyldopa for severe hypertension and $MgSO_4$ IM for eclampsia prevention and treatment (Appendix 8.1).

BEST PRACTICE POINTS

(Please see Appendix 8.3 for the evaluation of the strength of the recommendation and the quality of the evidence on which they are based.)

Fluid

1. Plasma volume expansion is not recommended for women with pre-eclampsia.
2. IV fluid intake should be minimised to 80 mL/h in women with pre-eclampsia to avoid pulmonary oedema.
3. Fluid should not be routinely administered to treat oliguria (<15 mL/h for 6 consecutive hours) for the sole purpose of increasing urine output.
4. For treatment of persistent oliguria, neither dopamine nor furosemide is recommended.

Antihypertensive therapy for severe hypertension

1. Blood pressure should be lowered to <160 mmHg systolic and <110 mmHg diastolic.
2. Initial antihypertensive therapy in the hospital setting should be with nifedipine short-acting (capsules), parenteral hydralazine, or parenteral labetalol.
3. Alternative antihypertensive medications include oral methyldopa, oral labetalol, oral clonidine, oral captopril (only postpartum), or a nitroglycerin infusion (for doses, see Table 8.2).
4. Refractory hypertension may be treated with sodium nitroprusside.
5. Nifedipine and $MgSO_4$ can be used contemporaneously.
6. $MgSO_4$ is not recommended solely as an antihypertensive agent.
7. Continuous FHR monitoring is advised until blood pressure is stable.

Antihypertensive therapy for non-severe hypertension

1. Antihypertensive drug therapy should aim for a diastolic blood pressure of 85 mmHg.
2. The choice of antihypertensive agent for initial treatment should be based on characteristics of the patient, contraindications to a particular drug, and physician and patient preference.

3. Initial therapy in pregnancy can be with one of a variety of antihypertensive agents methyldopa, labetalol, other beta-blockers (acebutolol, metoprolol, pindolol, and propranolol) and calcium channel blockers (nifedipine).
4. ACE inhibitors and ARBs should not be used during pregnancy.
5. Atenolol and prazosin are not recommended prior to delivery.
6. Captopril, enalapril, or quinapril may be used postpartum, even during breastfeeding.
7. There is no compelling evidence that antihypertensive treatment of hypertension (with labetalol, nifedipine, and probably methyldopa) is associated with adverse effects on child development.
8. Gestational hypertension and pre-eclampsia may each be associated with an increase in adverse paediatric neurodevelopmental effects, such as inattention and externalising behaviours.

$MgSO_4$

1. $MgSO_4$ is recommended for first-line treatment of eclampsia.
2. $MgSO_4$ is recommended for eclampsia prevention in women with *severe* pre-eclampsia.
3. $MgSO_4$ may be considered for eclampsia prevention in women with *non-severe* pre-eclampsia based on cost considerations.
4. $MgSO_4$ should be used in standard dosing, usually 4 g IV loading dose followed by 1 g/h.
5. Routine monitoring of serum magnesium levels is not recommended.
6. Phenytoin and benzodiazepines should not be used for eclampsia prophylaxis or treatment, unless there is a contraindication to $MgSO_4$ or it is ineffective.
7. In women with pre-existing or gestational hypertension, $MgSO_4$ should be considered for fetal neuroprotection in the setting of imminent preterm birth within the next 24 hours at $\leq 33^{+6}$ weeks.

Therapies for HELLP syndrome

Recommendations

1. Every obstetrical centre should be aware of the local delay between ordering and receiving platelets units.
2. For a platelet count $<20 \times 10^9$/L, platelet transfusion is recommended, regardless of mode of delivery.
3. For a platelet count $20–49 \times 10^9$/L platelet transfusion is recommended prior to Caesarean delivery.
4. For a platelet count $20–49 \times 10^9$/L, platelet transfusion should be considered prior to vaginal delivery if there is excessive active bleeding, known platelet dysfunction, a rapidly falling platelet count, or coagulopathy).
5. For a platelet count of $\geq 50 \times 10^9$/L, platelet transfusion should be considered prior to either Caesarean or vaginal delivery if there is excessive active bleeding, known platelet dysfunction, a rapidly falling platelet count, or coagulopathy.
6. We do not recommend corticosteroids for treatment of HELLP until they have been proven to decrease maternal morbidity.
7. We recommend against plasma exchange or plasmapheresis for HELLP, particularly within the first 4 days postpartum.

Other therapies for treatment of pre-eclampsia

1. Women with pre-eclampsia before 34 weeks' gestation should receive antenatal corticosteroids for acceleration of fetal pulmonary maturity.
2. Thromboprophylaxis may be considered antenatally among women with pre-eclampsia who have two or more additional thromboembolic risk markers, postnatally among women with pre-eclampsia who have at least one additional thromboembolic risk marker, or postnataly among women any hypertensive disorder of pregnancy who were on antenatal bed rest for at least 7 days.

PRIORITIES FOR UNDER-RESOURCED SETTINGS

Table 8.5 outlines priorities for care in the community (to prevent eclampsia and hypertension-related stroke prior to referral to facility[177]) and in facilities (to prevent and treat severe acute maternal morbidity and decrease maternal and perinatal mortality, particularly for the periviable fetus)[178–180].

All of the interventions relevant specifically to the hypertensive disorders of pregnancy and recognised by the WHO as essential medicines are included here: antihypertensive therapy for severe or non-severe hypertension, $MgSO_4$ for eclampsia prevention or treatment, blood products, and

Table 8.5 Priorities for management of women with a hypertensive disorder of pregnancy (HDP) by level of health care system at which care is delivered

	Antepartum & postpartum	
	Initial priority	*Ultimate goal*
Community		
Primary health care centre (detect, stabilise and refer)	Antihypertensives for severe hypertension	Antihypertensives for severe or non-severe hypertension
	$MgSO_4$ administered before referral in order to prevent or treat eclampsia	$MgSO_4$ administered before referral in order to prevent or treat eclampsia
	Clear communication with referral unit regarding transport and medication	Clear communication with referral unit regarding transport and medication (including individualisation of antenatal corticosteroid therapy)
Facility		
Secondary-level facility (detect, manage and refer if necessary)	In women with a HDP, appropriate use of antihypertensive therapy, $MgSO_4$	In women with a HDP, appropriate use of antihypertensive therapy, $MgSO_4$, fluids (restricted), and corticosteroids
	Appropriate triage of women for referral to tertiary-level care (including those eligible for expectant care* and those at high risk of or with severe maternal morbidity)	Appropriate triage of women for referral to tertiary-level care (including those eligible for expectant care and those with or at high risk of severe maternal morbidity)
	Availability of pRBCs	Availability of pRBCs, platelets, and clotting factors
Tertiary-level (referral) facility (detect and manage definitively)	Appropriate use of antihypertensive therapy, $MgSO_4$, fluids (restricted) and corticosteroids in women with a HDP	Appropriate use of antihypertensive therapy, $MgSO_4$, fluids (restricted), and corticosteroids in women with a HDP
	Appropriate triage and care of women eligible for expectant care* and those at high risk of or with severe maternal morbidity	Appropriate triage and care of women eligible for expectant care and those at high risk of or with severe maternal morbidity
	Availability of pRBCs, platelets, and clotting factors	Availability of pRBCs, platelets, and clotting factors
	Management of the periviable neonate	Management of the periviable fetus and neonate
		Advanced management options including the establishment of Obstetric Critical Care Units in close proximity to labour wards to provide advanced monitoring (e.g., intra-arterial BP measurement) and treatment (e.g., ventilatory support) of complicated cases

pRBCs, packed red blood cells; BP, blood pressure

* For a discussion about timing of delivery, see Chapter 9

antenatal corticosteroids for acceleration of fetal pulmonary maturity. Sample policy statements for antihypertensive therapy and $MgSO_4$ are provided for local adaptation (Appendix 8.4).

An initial focus should be on the early administration of antihypertensive agents and $MgSO_4$ in the community prior to transfer to facility, or in secondary-level facilities prior to transfer to tertiary-level facility. Reluctance to care for these women prior to their arrival at tertiary-level facilities is illustrated by the following quote:

> "Many doctors also don't like to treat eclampsia. If the lady has eclampsia, or imminent eclampsia or severe pre-eclampsia because of the risk with the morbidity and the mortality to both the baby and the mother they try to shift the patient to the higher centres"
>
> Obstetrician, CLIP Feasibility Study, Bagalkot, India

WHAT INTERNATIONAL GUIDELINES SAY (APPENDIX 8.5)

Abbreviations for Clinical Practice Guidelines: ACOG (American College of Obstetricians and Gynecologists)[181], AOM (Association of Ontario Midwives), NICE (National Institute for Health and Clinical Excellence)[43], NVOG (National Obstetrics and Gynaecology Society, The Netherlands)[182,] PRECOG II (Pre-eclampsia Community Guideline) and PRECOG II (Pre-eclampsia Community Guideline II), QLD (Queensland, Australia)[183,184], SOGC (Society of Obstetricians and Gynaecologists of Canada)[22], SOMANZ (Society of Obstetric Medicine of Australia and New Zealand)[185], WHO (World Health Organization)[10].

Fluid management

Multiple guidelines recommend against plasma volume expansion (SOGC, NICE, SOMANZ). Fluid restriction in pre-eclampsia is recommended by two guidelines (SOGC, NICE), one of which recommends administration of no more than 80 mL/h of IV fluids (NICE).

Antihypertensive therapy

Seven guidelines discuss antihypertensive therapy (SOGC, WHO, NICE, ACOG, NVOG, SOMANZ, QLD).

For severe hypertension

There is uniform agreement in all seven guidelines that severe hypertension should be treated, although most guidelines do not rate the recommendation highly because of the lack of randomised controlled trials of antihypertensive versus placebo/no therapy (as discussed above under 'Antihypertensive therapy for severe hypertension'). Most guidelines recommend a blood pressure goal of <160/110 mmHg (SOGC, ACOG, QLD), but a goal of <150/80–100 mmHg is recommended in the UK (NICE), <160/100 mmHg in Australasia (SOMANZ), and ACOG makes a specific recommendation for women with chronic hypertension for whom blood pressure should be <160/105 mmHg. Recommended drugs of first choice are IV labetalol (SOGC, NICE, NVOG, SOMANZ), oral nifedipine (SOGC, NICE, NVOG, SOMANZ), and IV hydralazine (SOGC, NICE, SOMANZ); two CPGs leave the choice to the clinician (WHO, QLD). Two guidelines highlight that $MgSO_4$ should not be used as an antihypertensive (SOGC, SOMANZ).

For non-severe hypertension

Guidance for treatment of non-severe hypertension is reported by five guidelines and is highly variable, in part based on associated comorbidities and/or the type of hypertensive disease of pregnancy. All guidelines were published prior to release of the CHIPS Trial results (see 'Antihypertensive therapy for non-severe hypertension', above) which have clarified optimal management and will be incorporated into future updates. For women with end-organ dysfunction that can be exacerbated by elevated blood pressure, treatment to <140/90 mmHg is recommended (SOGC, NICE). For women without target-organ damage, treatment targets are: (1) for any hypertensive disorder of pregnancy, <150/80–100 mmHg (NICE), 130–159/80–105 mmHg (SOGC), 140–160/90–100 mmHg (SOMANZ), or <160/110 mmHg (NVOG); (2) for women with chronic hypertension, 120–159/80–104 mmHg (ACOG); and (3) for women with gestational hypertension or non-severe pre-eclampsia <160/110 mmHg (ACOG). Oral methyldopa (SOGC, NICE, ACOG, NVOG, SOMANZ), oral labetalol (SOGC, NICE, ACOG, NVOG, SOMANZ), and nifedipine (SOGC,

NICE, ACOG, NVOG, SOMANZ) are most commonly recommended.

ACE inhibitors and ARBs should not be used in pregnancy. For women with antihypertensive-treated chronic hypertension who are planning pregnancy, counselling should be undertaken (SOGC, NICE, NVOG, QLD). Alternatives to ACE inhibitors and ARBs should be discussed, and women should be instructed to stop ACE inhibitors and ARBs if inadvertently taken in early pregnancy (SOGC, NICE, ACOG, NVOG).

$MgSO_4$

There is general agreement that $MgSO_4$ is indicated for treatment of eclampsia (SOGC, WHO, NICE, ACOG, NVOG, QLD) and severe pre-eclampsia (SOGC, WHO, NICE, ACOG, NVOG), although ACOG recommends only intrapartum and postpartum treatment. There is less certainty about recommending $MgSO_4$ for non-severe pre-eclampsia (SOGC, ACOG, NVOG), although no guideline recommended *against* it. One guideline recommended that units define their own protocols for eclampsia prophylaxis (SOMANZ). $MgSO_4$ is otherwise indicated for fetal neuroprotection if women are delivering imminently at <34 weeks (SOGC, SOMANZ).

Therapies for HELLP

Corticosteroids are not recommended to improve clinical outcomes in HELLP syndrome (SOGC, WHO, NICE, ACOG, SOMANZ), but one guidelines suggests considering this therapy if an improvement in platelet count would be useful (ACOG).

One guideline discusses platelet thresholds for platelet transfusion (SOGC).

PRIORITIES FOR FUTURE RESEARCH

Significant progress has been and is being made to reduce the impact of pre-eclampsia in LMICs, but it remains a priority focus as we continue to struggle to achieve the 75% reduction in maternal mortality – the goal set in Millennium Development Goal 5 with a target date of 2015)[166].

Global priorities for hypertensive disorder of pregnancy management include: whether nifedipine is superior to parenteral agents for treatment of severe pregnancy hypertension; how to improve the cost-effectiveness of $MgSO_4$ for eclampsia prevention with regards to an abbreviated treatment course or reduced dose; and whether dexamethasone reduces severe maternal morbidity in HELLP syndrome without increasing maternal risk.

In general, hypertensive disorder of pregnancy management research has focused on institutional-level interventions. However, maternal lives lost from pre-eclampsia and eclampsia result from delays in triage, transport and treatment, such that if we limit ourselves to studying inpatient, facility-level interventions, many women will die or be irreversibly affected by pre-eclampsia complications prior to arriving at the inpatient facility. The future lies in getting diagnosis and care into the community, and improving transport to facility for definitive treatment.

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9

Timing and mode of delivery

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SYNOPSIS

The phrase 'planned childbirth on the best day in the best way' alludes to the fact that there is a myriad of considerations regarding timing (and mode of) childbirth in women with a hypertensive disorder of pregnancy, particularly pre-eclampsia[1]. Complicating this decision-making are inaccurate determination of gestational age, difficulty identifying those women who are at particular risk of an adverse outcome if pregnancy is prolonged, and the fact that 'severe' pre-eclampsia has been variably defined by international organisations and, yet, all list 'severe' pre-eclampsia as an indication for interventionist management, i.e. delivery.

Nevertheless, the past decade has seen publication of a significant body of work that informs our decisions about timing of delivery in women with a hypertensive disorder of pregnancy, particularly pre-eclampsia. Childbirth is recommended for women with pre-eclampsia or gestational hypertension at term for maternal benefit, although expectant care is recommended for women with any hypertensive disorder of pregnancy at late preterm gestational ages to reduce neonatal respiratory morbidity (associated with labour induction and Caesarean delivery). Small trials suggest that expectant care of women with pre-eclampsia from fetal viability to 33^{+6} weeks reduces neonatal morbidity, but the magnitude of maternal risk has not been fully quantified. To date, there are no trials to inform management of women with chronic hypertension.

Mode of delivery is usually determined by obstetric indications; however, if there is evidence of fetal compromise at a gestational age remote from term, women with a hypertensive disease of pregnancy may benefit from delivery by Caesarean. It is particularly important for women with a hypertensive disease of pregnancy to have the third stage of labour actively managed, particularly in the presence of thrombocytopaenia or coagulopathy. Ergometrine maleate should not be administered to women with any hypertensive disorder of pregnancy given its potential to precipitate severe hypertension.

TIMING OF DELIVERY

Optimising the timing of delivery involves striking a balance between the benefits and risks of pregnancy prolongation compared with those of induction or elective Caesarean delivery. Birth of the baby is always in the best interest of the woman. For her, pregnancy prolongation has no direct benefit, but for the baby, the benefits may be large at gestational ages remote from term. This can be a heart-wrenching decision for families and their care providers.

> "I remember asking one of the doctors to please be honest with me and to tell me how soon they thought I would deliver . . . would it be three weeks or three days? I will never forget that doctor as she pulled up a chair next to my bed and held my hand as I cried when she told me that I would probably only make it three days. I was 28 weeks along."
>
> Melissa M

Assessing gestational age

Accurate knowledge of gestational age is critical to decisions about timing of childbirth, diagnosis of intrauterine growth retardation (IUGR) and decisions about whether to administer antenatal corticosteroids for fetal lung maturity. This is of particular importance in low-resource settings where care for preterm infants may be limited to specialised health care facilities not easily accessible to all women.

The most accurate estimation of gestational age can be achieved by ultrasonographic examination in the first trimester. However, ultrasound is not always available in under-resourced settings and, when it is, many women do not present for their first antenatal care visit until the second trimester or later, when ultrasonographic examination is less accurate.

In the absence of an early ultrasonographic assessment of gestational age, it is advisable to use multiple methods. In addition to ultrasonographic assessment in the second trimester (or later), providers may estimate gestational age using last menstrual period (LMP) or clinical examination (abdominal palpation before 24 weeks' gestational age and symphysis–fundal height (SFH) after 24 weeks' gestational age). All of these are less accurate than first trimester ultrasonographic examination[2] (Table 9.1). For example, gestational age estimates were within 7 days when assessed by LMP (65%) or SFH (75%) in a prospective, population-based study in Pakistan[3]. Accuracy was improved by an algorithm that took LMP-based dating only when ultrasound-based values were not available[2]. Memory aids have been developed to assist women in remembering their LMP, such as those relating dates to festivals in Pakistan. In addition, job aids and algorithms have been developed to assist providers in accurately estimating gestational age.

INTERVENTIONIST VERSUS EXPECTANT CARE

When considering timing of delivery, the decision must be made between delivery (i.e., interventionist

Table 9.1 Comparison of methods to estimate gestational age

Method	*Accuracy*	*Limitations*
Ultrasonographic examination (US)	±5 days if first trimester ±7 days after first trimester	Controversial whether all women should undergo routine US screening in the first trimester May be less accurate if fetal malformation, severe IUGR, or maternal obesity If a single late examination is performed, it cannot reliably distinguish between a pregnancy that is misdated and younger than expected, and a pregnancy that is complicated by fetal growth restriction
Last menstrual period (LMP)	±14 days	May be inaccurate if the woman is not sure of the date of her LMP or does not have regular 28-day cycles There is lower accuracy in settings with low literacy Inaccurate assumption of the date of ovulation may be due to early pregnancy bleeding, implantation bleeding, non-ovulatory menstrual cycles, or use of hormonal contraceptives in the preceding 3 months
Symphysis–fundal height (SFH)	±3 weeks	Many factors interfere with accurate assessment, such as leiomyoma, obesity, other factors affecting uterine size or the ability to palpate the uterus (e.g., retroverted position), fetal anomalies affecting fetal size (e.g., hydrocephalus), IUGR, racial differences in SFH growth rates Inter- and intra-observer error Dating based on a single measurement is not recommended and might easily be inaccurate

IUGR, intrauterine fetal growth restriction

care) and pregnancy prolongation (i.e., expectant care).

- *Interventionist care* (also known as 'active management', 'aggressive management', or 'early delivery'): Childbirth by either induction of labour or Caesarean delivery after antenatal corticosteroids have been given to improve fetal lung maturation, which in practice, is after 24–48 hours.
- *Expectant care*: Administration of corticosteroids to improve fetal lung maturation, stabilisation of the woman's condition and then, if possible, delay of childbirth.

The goal of expectant management is to achieve fetal maturation *in utero*, thereby preventing or minimising complications associated with prematurity; there are no maternal benefits to expectant management. A decision to proceed with expectant management follows a period of maternal and fetal observation, assessment and maternal stabilisation. The latter may involve control of maternal blood pressure, magnesium sulphate for eclampsia prophylaxis (among women with pre-eclampsia), and corticosteroids to accelerate fetal pulmonary maturation if delivery is anticipated within the next 7 days and current gestational age is $\leq 34^{+6}$ weeks[4].

Expectant management with inpatient monitoring of maternal and fetal status may improve perinatal outcomes, but women should be chosen carefully and provided with counselling on the likelihood of perinatal survival and the risks of maternal complications. Ideally, candidates for expectant management are women who have been appropriately counselled, have made an informed choice for expectant management, have a viable fetus that is less than $37^{+0/7}$ weeks' gestational age, and have no contraindications (see below) to expectant management.

Although lists have been published of indications for delivery in pre-eclampsia, criteria will vary based on gestational age. These women have indictions for delivery that are consistent with expert opinion and study protocols[5,6]:

- Eclampsia or another serious maternal complications associated with pre-eclampsia[5]
- Severe end-organ complications
- Uncontrolled severe maternal hypertension
- Intrauterine fetal demise
- Fetal compromise that would be an indication for delivery in general obstetric practice (e.g., reversed end-diastolic flow in the umbilical artery)[7]
- Term gestational age.

There appears to be some agreement that risks of expectant management, regardless of gestational age, outweigh any potential benefits in the setting of severe pre-eclampsia, as defined in this book and by SOGC, the Canadian Society of Obstetrics and Gynaecology[8,9]. A pragmatic schema for consideration, and local modification, summarising the place, timing and mode of delivery is presented in Table 9.2[10].

Appropriate level of care

The place of care for women with a hypertensive disorder of pregnancy will depend on the woman's disorder and associated complications (if any), her gestational age, and the status of her fetus. Different levels of health care systems have different capacities to support the care of sick women and babies, based on levels of staffing, cadres of providers available, infrastructure and the availability of equipment, medications, or laboratory tests. Women with a hypertensive disorder of pregnancy, particularly non-severe pre-eclampsia, must be managed at a facility that can provide at least basic emergency obstetric and neonatal care (EmONC); women with severe pre-eclampsia, eclampsia, or severe hypertension, whether managed expectantly or with interventionist management, should be managed at facilities that can provide comprehensive EmONC; women with severe complications of a hypertensive disorder of pregnancy (e.g., oliguria that persists for 48 hours after delivery, coagulopathy, haemolysis, HELLP (haemolysis, elevated liver enzymes, low platelet) syndrome, persistent coma after convulsion) should be managed at a tertiary care facility. Recognised standards for basic and comprehensive EmONC have been published by the UNFPA[11].

Women with pre-eclampsia

Women with pre-eclampsia must be recognised as having the potential to develop life-threatening or life-altering complications. This has been emphasised by the Confidential Enquiries into Maternal Death (UK), which have consistently identified the failure to appreciate risk in

Table 9.2 Timing of delivery according to gestational age at presentation with pre-eclampsia (reproduced from Steegers EA *et al.*, *Lancet* 2010 Aug 21;376(9741): 631–44[10] with permission from Elsevier)

	Gestational age at diagnosis				
	20^{+0}– viability	*Viability – 29^{+6}*	*30^{+0}–33^{+6}*	*34^{+0}–36^{+6}*	*≥37^{+0}*
Perinatal prognosis	Survival: 18–50% Intact survival: 2–45%	Survival: 60–95% Intact survival: 15–90%	Survival: 98% Intact survival: 88–96%	Survival: >99% Intact survival: >96%	
Maternal risks (relative to normotensive pregnancy)	Significantly increased	Significantly increased	Significantly increased	Moderately increased	Minimally increased
In utero transfer to tertiary centre	NO as a routine, but centre should be competent with 2nd trimester termination and/or expectant management	YES if stable for transfer	Ideally, but perinatal outcomes unchanged if postpartum transfer	NO, but centre should be competent with expectant management	NO
Expectant management	NO as a routine, but at 22–23 weeks some may attempt to attain perinatal survival	YES rate of adverse maternal outcomes same with expedited delivery; significant perinatal gains		YES acute morbidity and school age issues are associated with late preterm birth	NO post-HYPITAT[38]
Betamethasone for fetal lungs	NO	YES	YES	YES if non-laboured Caesarean	NO
Assessment & surveillance	Minimum standard: on admission, day after admission, every Monday & Thursday until delivery, and on day of delivery; additional testing as indicated by changes in clinical state NOTE: this approach has been associated with >80% reduction in adverse maternal outcomes				
Maternal	Blood: CBC, INR, APTT, fibrinogen, creatinine, electrolytes, uric acid, AST, LDH, bilirubin, albumin, glucose (to R/O AFLP) Urine: dipstick, protein:creatinine ratio; pulse oximetry				
Fetal	Ultrasound: AFI, umbilical artery Doppler, ductus venosus Doppler; NST				
Deciding when to deliver	Women with 'severe pre-eclampsia, as defined in this textbook, should be delivered				Delivery, post-HYPITAT[38]
Route of delivery	Vaginal (misoprostol IOL)	Probable Cesarean, unless IUFD	Vaginal; fetal or uterine status may preclude vaginal delivery		

AFI, amniotic fluid index; AFLP, acute fatty liver of pregnancy; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CBC, complete blood count; INR, international normalised ratio; IOL, induction of labour; IUFD, intrauterine fetal death; LDH, lactate dehydrogenase; NST, non-stress test; PTB, preterm birth; R/O, role of

pre-eclampsia as responsible for potentially avoidable mortality or morbidity. As a result, subspecialty consultation has been advised[12] by telephone if necessary depending on the availability of obstetricians in the practice setting.

The optimal timing of birth for women with pre-eclampsia depends on evolving manifestations of pre-eclampsia in one/more organ systems for the woman and baby (Table 9.2). There is no tool available to guide the clinician in balancing the multitude of factors to consider, including the maternal and perinatal benefits and risks as perceived by the physician and the family, availability of personnel and conditions to monitor the woman and fetus, availability of specialist care for a preterm infant, and the preferences of the family. However, tools are available to identify women at increased risk of maternal complications.

Predicting adverse outcomes

Ideally, clinicians would identify women at particular risk of adverse maternal outcomes and undertake interventionist care. Models have not yet been developed and validated that will allow this to be done with a high degree of accuracy. This is discussed in detail in Chapter 3.

In brief, many individual factors (clinical, laboratory, or ultrasonographic) continue to be identified as related to latency (e.g., angiographic factor profile and shorter admission-delivery intervals[13]) or adverse clinical outcomes (e.g., higher uric acid and more adverse perinatal outcomes[14]). However, systematic study is unusual, particularly examinations of their added value over and above information from history and physical examination, with or without basic laboratory testing.

The Pre-eclampsia Integrated Estimate of RiSk (PIERS) score can identify women with pre-eclampsia who are at increased risk of adverse maternal outcomes in the subsequent 7 days, based on maternal history, symptoms, signs and laboratory parameters within the first 48 hours of hospital assessment with suspected pre-eclampsia. (Efforts to predict adverse outcomes farther into the future have not been successful[15].) The fullPIERS model was developed in well-resourced settings and the miniPIERS model in under-resourced settings, with areas under the receiver operating curves (AUC ROC) of 0.76 (95% CI 0.72–0.80) for fullPIERS[16], and 0.88 (95% CI 0.47–0.80) for miniPIERS[17]. (These models are discussed in detail in Chapter 3.)

If laboratory testing is available, then in addition to the clinical features of gestational age on admission and oxygen saturation, the following laboratory tests should be used as they were predictive of adverse maternal outcome in fullPIERS: platelet count, serum creatinine and alanine aminotransferase (https://piers.cfri.ca/PIERSCalculatorH.aspx)[16]. If laboratory testing is NOT available, then the focus should be on those clinical features that were independently predictive of adverse maternal outcome in the miniPIERS study: parity and gestational age on admission, headache/visual symptoms, chest pain/dyspnoea, systolic blood pressure and proteinuria (dipstick)[17]. An online calculator (cfri.ca/piers) is available for entry of continuous variables (such as gestational age) into the miniPIERS model to provide real-time personalised risks to all women whose caregivers have access to the internet.

Consideration of the severity of pre-eclampsia

The timing of birth literature on pre-eclampsia is heavily focused on the distinction between 'severe' and non-severe pre-eclampsia. Yet, there is little consistency between international guidelines in the definition of 'severe' pre-eclampsia[8,9,18–24].

Chapter 3 discusses the definition of 'severe' pre-eclampsia. In brief, when proteinuria is a mandatory criterion for pre-eclampsia in international guidelines[18–20], 'severe' pre-eclampsia is defined as the development of: (1) pre-eclampsia at <34 weeks[18], (2) one/more features of maternal end-organ dysfunction that is either not defined[18,19] or listed as 'symptoms'[20], (3) heavy proteinuria[18,20], or severe hypertension[18,20], or (4) one/more relevant fetal abnormalities[8,9,18]. When proteinuria is not a mandatory criterion for pre-eclampsia (which can be otherwise defined by hypertension and one/more pre-eclampsia-related maternal symptoms, signs, or abnormal laboratory tests or fetal monitoring abnormalities)[8,9,21–24], 'severe' pre-eclampsia is defined as the development of: (1) pre-eclampsia at <34 weeks[21], (2) proteinuria plus one/more feature(s) that alone would signify pre-eclampsia (cerebral/visual disturbances, pulmonary oedema, platelet count $<100 \times 10^9$/L, renal insufficiency, or elevated liver enzymes)[24], or

(3) one/more features of end-organ dysfunction described as: heavy proteinuria[21], one/more features of HELLP[22,23], new persistent and otherwise unexplained right upper quadrant/epigastric abdominal pain[24], severe hypertension[21,24], or those dysfunctions requiring delivery[8,9].

What further complicates timing of delivery related to the severity of pre-eclampsia is that there are women with non-severe pre-eclampsia who should be delivered (e.g., those at $\geq 37^{+0}$ weeks), and those with 'severe' pre-eclampsia (by all but Canadian guidelines[8,9]) who may reasonably undertake pregnancy prolongation (e.g., heavy proteinuria). This is why the Canadian guidelines have tried to single out as 'severe' pre-eclampsia, a group of women who are particularly 'severe' and require delivery by all guidelines. However, clinicians cannot be faulted for finding all of the 'severe' pre-eclampsia definitions difficult to follow.

What can be said is that the woman with pre-eclampsia who is at least 34 weeks' gestation and who is without symptoms, heavy proteinuria, laboratory evidence of end-organ complications, or fetal compromise has non-severe pre-eclampsia by all international guidelines. Also, the woman with pre-eclampsia with proteinuria and one or more end-organ manifestations of pre-eclampsia has 'severe' pre-eclampsia. The only exception is the Canadian guidelines that have tried to single out a particularly high risk group of women (within the women designated as 'severe' by other guidelines) who are inappropriate for ongoing pregnancy prolongation and should give birth.

Indications for delivery in pre-eclampsia vary with gestational age, and are discussed by gestational age below.

Gestational age $<24^{+0}$ weeks

Expectant management of pre-eclampsia at $<24^{+0}$ weeks (prior to fetal viability in well-resourced settings) is associated with high perinatal mortality (>80%) and maternal complication rates that have varied from 27 to 71% (including one maternal death; >40 studies, >4700 women)[6,25]. Given these risks, experts have recommended extensive counselling, which should include as an option termination of pregnancy regardless of the setting[6]. In under-resourced settings where there are limited neonatal services, this approach could be undertaken at gestational ages at which the fetus is 'non-viable' or unlikely to achieve viability within 1 or 2 weeks[18].

Gestational age 24^{+0}–33^{+6} weeks

Observational studies suggest that approximately 40% of women are eligible for expectant care following an initial period of observation and stabilisation (39 cohort studies, 4650 women)[5]. If women are eligible for expectant management of pre-eclampsia at 24^{+0}–33^{+6} weeks, such an approach may decrease neonatal morbidity, although the magnitude of maternal risk is unclear. Rates of serious maternal complications are very low (median <5%) in uncontrolled observational studies in well-resourced settings[5].

In the relevant Cochrane review (4 trials, 425 women[26]), interventionist care (i.e., antenatal corticosteroids if possible, followed by labour induction or emergency Caesarean delivery) compared with expectant care was associated with earlier birth by an average of 9.91 days (95% CI −16.37 to −3.45) and birth by Caesarean (4 trials, 425 women; RR 1.09, 95% CI 1.01–1.18), as well as more of the following adverse neonatal outcomes: neonatal intensive care admission (2 trials, 125 women; RR 1.35, 95% CI 1.16–1.58) and a longer stay there (2 trials, 125 women; mean difference of 11.14 days, 95% CI 1.57–20.72), respiratory distress syndrome (2 trials, 133 women; RR 2.30, 95% CI 1.39–3.81), ventilation (2 trials, 300 women; RR 1.50, 95% CI 1.11–2.02), neonatal intraventricular haemorrhage (1 trial, 262 women; RR 1.82, 95% CI 1.06–3.14), and necrotising enterocolitis (3 trials, 395 women; RR 2.10, 95% CI 0.93–4.79). The excess of morbidity associated with interventionist (vs. expectant) care occurred despite interventionist care being associated with fewer small for gestational age (SGA) babies (2 trials, 125 women; RR 0.30, 95% CI 0.14–0.65). There was no significant difference in adverse maternal outcomes between interventionist (vs. expectant) care, but the event rates were very low and the trials underpowered to find differences that would be clinically significant.

Subsequent to the most recent update of the Cochrane review discussed above, an additional randomised controlled trial (267 women) has been published that both failed to find neonatal benefit associated with expectant care and demonstrated increased maternal risk[27]. This trial was similar to

others in that women had to qualify for expectant care following a period of stabilisation, and interventionist care was associated with delivery an average of 8.1 days earlier (2.2 days in the prompt delivery group versus 10.3 days for the expectant management group). SGA babies were less common in the intervention (vs. expectant care) group (9.4% vs. 21.7%; RR 0.44, 95% CI 0.24–0.83), as in previous trials. However, interventionist (vs. expectant) care was not associated with more neonatal morbidity (56.4% vs. 55.6%; RR 1.01, 95% CI 0.81–1.26) or maternal morbidity (20.3% vs. 25.2%; RR 0.81, 95% CI 0.52–1.27). In fact, interventionist (vs. expectant) care was associated with fewer women with placental abruption (1.5% vs. 7.6%; RR 0.20, 95% CI 0.04–0.88). What makes the results of this trial different from others is not clear. The trial was carried out in South America in tertiary perinatal units, although others have been carried out in similar units in low- and middle-income countries[28]. However, following treatment of severe hypertension, only some units used oral antihypertensive therapy, something that may have been associated with the excess of placental abruption in expectant care and the failure to demonstrate less neonatal morbidity in babies born an average of 8.1 days later, compared with babies born in the interventionist care group.

In observational studies, expectant care of pre-eclampsia at 24^{+0}–33^{+6} weeks is associated with pregnancy prolongation of approximately 14 days. However, if pre-eclampsia is complicated by HELLP syndrome, only a median of 5 days are gained, and serious maternal morbidity is higher (median 15%). Therefore, brief expectant care would be appropriate if disseminated intravascular coagulation (DIC) is absent[29] and either regional anaesthesia or vaginal birth may be possible if there is temporary improvement of HELLP, something that is observed in more than 50% of women so managed[5].

Pending the results of a definitive randomised controlled trial powered to examine perinatal and maternal benefits and risks, timing of delivery in women with pre-eclampsia at 24^{+0}–33^{+6} weeks must be individualised. It would seem prudent to follow advice to clearly document a care plan that outlines the nature of fetal monitoring, indications for delivery, when corticosteroids should be given, and when discussions should take place with neonatology and obstetric anaesthesia staff[19].

Gestational age 34^{+0}–36^{+6} weeks

At these gestational ages, pregnancy prolongation is not expected to have substantial perinatal survival benefits. However, there may be advantages with regards to reduction in neonatal morbidity (particularly central nervous system[30]) and maternal morbidity. There are two published randomised controlled trials that inform timing of delivery at these late preterm gestational ages.

In HYPITAT II[31], 703 women with pre-eclampsia (60.2%, *de novo* or superimposed), gestational hypertension (25.9%), or pre-existing hypertension that was deteriorating (13.9%) were randomised to interventionist care (i.e., labour induction or Caesarean birth) or expectant care. Interventionist (vs. expectant) care was associated with possible maternal benefit, but definite perinatal risk. Women assigned to interventionist (vs. expectant) care experienced fewer adverse maternal outcomes (of thromboembolic disease, pulmonary oedema, eclampsia, HELLP syndrome, placental abruption, or maternal death, 1.1% vs. 3.1%; RR 0.36, 95% CI 0.12–1.11) without an increase in Caesarean delivery (30.4% vs. 32.5%; RR 0.94, 95% CI 0.75–1.16). However, interventionist (vs. expectant) care was associated with more admissions to neonatal intensive care (7.4% vs. 3.7%; RR 2.0, 95% CI 1.0–3.8) attributable to neonatal respiratory distress syndrome (5.7% versus 1.7%; RR 3.3, 95% CI 1.4–8.2). These findings did not differ by type of hypertensive disorder of pregnancy.

In a second, smaller randomised controlled trial of 169 women with mild pre-eclampsia without severe features, interventionist (vs. expectant) care was associated with fewer women who progressed to pre-eclampsia with severe features within 72 hours of randomisation (3.2% vs. 41.3%; RR 0.36, 95% CI 0.27–0.47), without an associated increase in Caesarean delivery (44.7% vs. 37.3%; RR not provided, $p = 0.35$) or neonatal intensive care unit admission (21.3% vs. 18.7%; RR not provided, $p = 0.89$)[32]. This trial was not of high quality, having been stopped early for unstated reasons.

In summary, it would appear that interventionist care may decrease the risk of adverse maternal outcome, however defined, among women who are stable and eligible for expectant care. However, the potential for interventionist (vs. expectant) care to increase neonatal respiratory morbidity justifies a

strategy of expectant care at these late preterm gestational ages.

Specific comment must be made about the impact of interventionist (vs. expectant) care on mode of delivery. Caesarean delivery rates have been about 70% in trials comparing one antihypertensive with another near or at term among women with pre-eclampsia who were not delivered immediately[33–37]. Although it has been long-believed that delaying childbirth may allow time for cervical ripening and successful vaginal birth (the preferred mode for all women if possible, including those with HELLP syndrome[29]), neither of the interventionist (vs. expectant) care trials mentioned above associated pregnant prolongation with lower rates of Caesarean delivery. Also, the large HYPITAT trial of women with pre-eclampsia at term (see below) failed to demonstrate this association[38].

Gestational age 37^{+0}–42^{+0} weeks

In the HYPITAT trial (756 women), interventionist (vs. expectant) care was associated with a decrease in progression of maternal disease (31.0% vs. 43.8%; RR 0.71, 95% CI 0.59–0.86); although primarily due to a decrease in severe hypertension (16.4% vs. 27.2%), a similar impact was seen on other serious maternal complications such as HELLP syndrome (1.1% vs. 2.9%)[38]. (Although women were recruited from 36^{+0} weeks, they consisted of only 9.9% of the trial population, so the results of the HYPITAT trial are not considered to be applicable to women at this gestational age.) Interventionist (vs. expectant) care was not associated with an increase in Caesarean birth (RR 0.75, 95% CI 0.55–1.04) or impact on long-term health-related quality of life[39]. Secondary analyses revealed that the benefits of labour induction (with regards to decreasing maternal complications) were even greater among women with an unfavourable cervix within the expectant care group and unrelated to those complications in the interventionist group[40].

Women with gestational hypertension (without pre-eclampsia)

Like those with pre-eclampsia, women with gestational hypertension at 37^{+0}–42^{+0} weeks probably benefit from labour induction by decreasing a composite measure of maternal morbidity[38]. Women with gestational hypertension comprised 65.6% of the relevant HYPITAT trial cohort, and the effect was similar in the gestational hypertension subgroup, although it did not reach statistical significance on its own (RR 0.81, 95% 0.63–1.03). The UK guidelines have interpreted these data as reflecting some uncertainty about whether labour induction is effective for women with gestational hypertension[19]. As discussed above, there was no increase in Caesarean births with labour induction (RR 0.75, 95% CI 0.55–1.04).

Using observational data from a multicentre American database of 3588 women with gestational hypertension at $\geq 36^{+0}$ weeks (1.6% of 228,668 deliveries), labour induction between 38^{+0} and 39^{+6} weeks appeared to offer the best balance between maternal and neonatal complications[41].

Women with pre-existing (chronic) hypertension

There are no randomised controlled trial data that inform timing of delivery in women with pre-existing hypertension.

Using observational data from an American population-based database of 179,669 women with otherwise uncomplicated pre-existing hypertension at 36^{+0}–41^{+6} weeks (half of all women with pre-existing hypertension who represented 1% of all deliveries), labour induction at 38^{+0}–39^{+6} weeks appeared to optimise the trade-off between the risk of adverse fetal (stillbirth) or maternal complications (superimposed pre-eclampsia and abruption) that increase in incidence with gestational age, and the adverse neonatal outcomes (neonatal mortality and morbidity) that decrease in incidence with gestational age[42].

Cost-effectiveness of interventionist management

We were unable to identify data on the cost-effectiveness of interventionist (vs. expectant) care for women with any of the hypertensive disorders of pregnancy before 34^{+0} weeks.

For women with pre-eclampsia or gestational hypertension near term (at 34^{+0}–36^{+6} weeks), we were unable to identify analyses from randomised controlled trials. The relevant analysis identified data from a retrospective controlled study of 4293 pregnant women of whom 1064 developed gestational hypertension or pre-eclampsia; although not recommended by randomised controlled trial

data[31], a policy of labour induction was cost-effective based on neonatal and maternal morbidity; labour induction cost CAD$299 more but was associated with better quality of life[19,43].

For women with pre-eclampsia or gestational hypertension (without pre-eclampsia) at term, labour induction was effective and cost-saving (by CAD$1065 overall) owing to less resource use antepartum[44].

MODE OF DELIVERY

While associated with greater than average rates of Caesarean delivery, the presence of a hypertensive disorder complicating a woman's pregnancy is not an automatic indication for Caesarean delivery. Randomised controlled trial data from India suggest that even women who have experienced antenatal eclampsia at or beyond 34^{+0} weeks of gestation can be considered for induction[45]. However, we do recognise that women with severe pre-eclampsia remote from term with clinical evidence indicative of fetal compromise (e.g., absent or reversed end-diastolic flow by umbilical artery Doppler) may best be delivered by Caesarean section. A randomised controlled trial conducted in India of 200 women with eclampsia identified an almost significant, but clinically important, improvement in adverse neonatal events with a policy of Caesarean delivery (9.90% vs. 19.19%; RR 0.52, 95% CI 0.25–1.05)[45].

Labour induction

Induction of labour in women with severe pre-eclampsia takes more time[46] and is less successful than in women with normotensive pregnancies[47]. However, an unfavourable cervix does not preclude successful induction[48], and neither IUGR nor oligohydramnios are contraindications to induction of labour[49]. Indeed, and against widely held opinion, the HYPITAT trial identified that women with gestational hypertension or mild pre-eclampsia at term who have an unfavourable cervix may benefit *more* from labour induction than other women[40].

For induction of labour, cervical ripening is recommended to increase the chance of successful vaginal delivery, recognising that this statement is supported by data derived from normotensive, rather than hypertensive pregnancies[50]. Cervical ripening could be by either mechanical (e.g., intracervical Foley balloon[51]) or prostaglandin-based (e.g., misoprostol, PGE_2); the use of vaginal PGE_2 is limited owing to both cost and cold chain requirements and may be less effective than oral misoprostol[52,53]. Adding vaginal oestradiol (50 μg) may improve the labour induction properties of vaginal misoprostol[54]. In women with asthma, mechanical approaches to labour induction may be safer and as effective, and do not appear to carry the excess maternal and perinatal morbidity previously associated with this method[55].

Fetal status

When considering the mode of delivery, both the gestational age and the fetal status should be considered. The rate of successful induction of labour with vaginal delivery is 47.5% at 28–32 weeks and 68.8% at 32–34 weeks of gestation. A success rate of 30% can be achieved even when birth weight is <1500 g[48,49]. Conversely, the success of induction at 24–28 weeks of gestation ranges from 6.7% to 10% suggesting that the potential maternal and fetal benefits to be derived by labour induction be carefully considered against the requirements for urgent or emergency delivery[56–58]. When there is increased resistance to diastolic flow in the umbilical artery, the vaginal delivery rate is significantly lower but still greater than 50%[59,60]. Most babies with absent or reversed end-diastolic flow by Doppler velocimetry of the umbilical artery, abnormal biophysical profile scores and abnormal sequential changes in Doppler studies of the fetal arterial and venous systems (e.g., appearance of ductal A waves) are delivered by Caesarean[61–64]. It should be remembered that the biophysical profile appears to be falsely reassuring when pregnancies are complicated by either pre-eclampsia[65] or IUGR[66,67].

In observational studies of women with severe pre-eclampsia, induction of labour (compared with Caesarean delivery) is associated with either similar or lower rates of adverse maternal and fetal outcomes[49,57,68,69]. For example, there was a 52% decrease in the odds for bronchopulmonary dysplasia and shorter duration of ventilator support in the infants born following labour induction compared with those delivered by elective Caesarean section. In addition, there are longer-term considerations relevant to Caesarean delivery, such as the risk of uterine rupture with subsequent pregnancies or morbidity associated with repeat Caesarean deliveries[70].

Potential for bleeding

Women with pre-eclampsia are at risk of thrombocytopaenia and coagulopathy (either antepartum or *de novo* postpartum), and all standard measures including the active management of the third stage of labour[71] should be taken to avoid postpartum haemorrhage. Oxytocin is the uterotonic drug of choice for such active management. Ergometrine (ergonovine maleate) is contraindicated in all forms of hypertensive disorder of pregnancy, particularly pre-eclampsia and gestational hypertension. If oxytocin is not available, safer alternative uterotonic drugs that have significantly fewer side-effects, especially acute elevations in blood pressure, are recommended[19,72–76].

Antenatal corticosteroids

Where delivery is believed to be in the best maternal and/or fetal interest, there are no clinical signs of maternal infection, and gestational age is between 24^{+0} and 34^{+6}, the clinician should offer a single course of antenatal corticosteroids (either IM dexamethasone or IM betamethasone – a total of 24 mg in two divided doses given 12 hours apart)[77]. The beneficial effects of antenatal corticosteroids can be observed within 4 hours of the first dose[77]. A single repeat course of corticosteroids can be considered if iatrogenic preterm birth at $\leq 34^{+6}$ weeks still seems likely within the next 7 days, and at least 7 days have transpired since the initial course of antenatal corticosteroids[78].

BEST PRACTICE POINTS

(Please see Appendix 9.1 for the evaluation of the strength of the recommendation and the quality of the evidence on which they are based.)

Management should be based on the understanding that giving birth is the only cure for pre-eclampsia, and women with gestational hypertension or pre-existing hypertension may develop pre-eclampsia antepartum or postpartum. Mode of delivery is usually driven by the usual obstetric indications, unless there is evidence of substantial fetal compromise or gestational age is <30 weeks. Recommendations for delivery or ongoing pregnancy are outlined in Table 9.2.

Place of delivery

1. All women with a hypertensive disorder of pregnancy of any type require delivery in a centre that can provide EmONC.
2. Women with a hypertensive disorder of pregnancy and serious maternal complications require delivery in a centre capable of providing CEmONC.

Timing of delivery

Women with pre-eclampsia

1. Consultation with an obstetrician is advised in women with pre-eclampsia. (If an obstetrician is not available in under-resourced settings, consultation with at least a physician is recommended.)
2. All women with severe pre-eclampsia or eclampsia should be delivered within 24 hours, regardless of gestational age.*
3. For women with non-severe pre-eclampsia at $<24^{+0}$ weeks' gestation, counselling should include information about delivery within days as an option.
4. For women with non-severe pre-eclampsia at 24^{+0}–33^{+6} weeks' gestation, expectant management should be considered, but only in centres capable of caring for very preterm infants.
5. For women with non-severe pre-eclampsia at 34^{+0}–36^{+6} weeks' gestation, expectant management is advised.
6. For women with pre-eclampsia at $\geq 37^{+0}$ weeks' gestation, delivery within 24 hours is recommended.
7. For women with non-severe pre-eclampsia complicated by HELLP syndrome at 24^{+0}–34^{+6} weeks' gestation, consider delaying delivery long enough to administer antenatal corticosteroids for acceleration of fetal pulmonary maturity as long as there is temporary improvement in maternal laboratory testing.

8. All women with HELLP syndrome at ≥35^{+0} weeks' gestation should be considered for delivery within 24 hours.

*"*Severe*"pre-eclampsia is defined according to Canadian criteria of potentially life-altering complications included within all other definitions of severe pre-eclampsia. There is consensus that these represent indications for delivery: (1) uncontrolled maternal hypertension; (2) maternal end-organ complications of the central nervous, cardiorespiratory, haematological, renal, or hepatic systems; or (3) stillbirth or substantial fetal compromise of abruption with maternal/fetal compromise or reversed ductus venosus A wave. Although these conditions are included in the WHO definition of severe pre-eclampsia, WHO also includes other criteria for severe pre-eclampsia that are not clear indications for delivery: heavy proteinuria, gestational age <34 weeks and evidence of any 'fetal morbidity'.

Women with gestational hypertension (without pre-eclampsia)

1. For women with gestational hypertension at <34^{+0} weeks, expectant management is advised.
2. For women with gestational hypertension at 34^{+0}–36^{+6} weeks', expectant management is advised.
3. For women with gestational hypertension at ≥37^{+0} weeks', childbirth within days should be discussed.

Women with pre-existing hypertension

1. For women with pre-existing hypertension at <34^{+0} weeks, expectant management is advised.
2. For women with pre-existing hypertension at 34^{+0}–36^{+6} weeks, expectant management is advised, even if women require treatment with antihypertensive therapy.
3. For women with uncomplicated pre-existing hypertension who are otherwise well at ≥37^{+0} weeks' gestation, childbirth should be considered at 38^{+0}–39^{+6} weeks' gestation.

Mode of delivery

1. For women with any hypertensive disorder of pregnancy, vaginal delivery should be considered unless a Caesarean delivery is required for the usual obstetric indications.
2. If vaginal delivery is planned and the cervix is unfavourable, then cervical ripening should be used to increase the chance of a successful vaginal delivery.
3. At a gestational age remote from term, women with a hypertensive disorder of pregnancy with evidence of fetal compromise may benefit from delivery by emergent Caesarean.
4. Antihypertensive treatment should be continued throughout labour and delivery to maintain systolic blood pressure at <160 mmHg and diastolic blood pressure at <110 mmHg.
5. The third stage of labour should be actively managed with oxytocin 5 units IV or 10 units IM, particularly in the presence of thrombocytopaenia or coagulopathy.
6. Ergometrine maleate should not be administered to women with any hypertensive disorder of pregnancy, particularly pre-eclampsia or gestational hypertension; alternative oxytocics should be considered.

PRIORITIES FOR UNDER-RESOURCED SETTINGS

A challenge with expectant management in low-resource settings is inadequate resources (human and material) to accurately assess gestational age or monitor the woman and fetus intensively. The minimum technology, staffing and infrastructure requirements by level of the health care system (beyond the need for EmONC) are yet to be determined. Also, although many technologies for assessing gestational age, maternal well-being and fetal well-being meet requirements for use in low-resource settings and many have been tested in those settings, there is no clear consensus on cost-effectiveness of their introduction into health systems and potential impact on maternal and perinatal mortality. Ministries of health must consider their budgetary constraints and multiple

priorities when making decisions about introducing new technologies that require capital investments, training interventions and maintenance costs. What is needed at this time is a guide that includes information on how they perform in relation to requirements for low-resource settings: portability, cost, ease of use, ability to record/print images, frequencies, power requirements, battery life, durability, frame rate, screen settings, user interface and ability to communicate with a variety of devices[79]. This will provide ministries of health with guidance for choosing and scaling up use of the technologies.

The authors have suggested priorities for different levels of the health care system in Table 9.3.

WHAT INTERNATIONAL GUIDELINES SAY (APPENDIX 9.2[80])

Abbreviations for Clinical Practice Guidelines: ACOG (American College of Obstetricians and Gynecologists)[24], NICE (National Institutes of Clinical Excellence)[19], NVOG (National Obstetrics and Gynaecology Society, Netherlands)[20], QLD (Queensland, Australia)[22,23], SOGC (Society of Obstetricians and Gynaecologists of Canada)[8,9], SOMANZ (Society of Obstetric Medicine of Australia and New Zealand)[81], WHO (World Health Organization)[18], ESC (European Society of Cardiology)[82], ASH (American Society of Hypertension)[83], AOM (Association of Onario Midwives)[21].

Timing of delivery

Seven international guidelines (NICE, NVOG, ESC, WHO, ACOG, SOGC, SOMANZ) make recommendations regarding timing of delivery.

Recommendations for delivery (and administration of antenatal corticosteroids, if appropriate) focus on women with pre-eclampsia (ACOG, NICE, NVOG, SOGC, WHO, SOMANZ). Uncontrolled severe hypertension is the most widely regarded maternal indication for delivery (and treatment) (NICE, WHO, ACOG, SOMANZ). Expectant care is considered appropriate depending on the type of hypertensive disorder and gestational age, assuming that women and fetuses can be appropriately managed and cared for when delivered.

Table 9.3 Priorities for timing and mode of delivery by level of health care system at which care is delivered

	Antepartum and postpartum	
	Initial priority	*Ultimate goal*
Community		
Primary health care centre (detect, stabilise and refer)	Assess gestational age accurately Use miniPIERS) model (±pulse oximetry to assess risk for individual women with HDPs[14]	mHealth-guided decision-making
Facility		
Secondary-level facility (detect, manage and refer if necessary)	Assess gestational age accurately Monitor maternal well-being with additional testing (blood, urine and pulse oximetry) to derive personalised risk through fullPIERS model (https://piers.cfri.ca/PIERSCalculatorH.aspx)[13]	mHealth-guided decision-making Monitor fetal well-being with NST and ultrasonographic assessment
Tertiary-level (referral) facility (detect and manage definitely)	Assess gestational age accurately Monitor maternal well-being with additional testing (blood, urine and pulse oximetry) to derive personalised risk through fullPIERS model (https://piers.cfri.ca/PIERSCalculatorH.aspx)[13] Monitor fetal well-being with NST and ultrasonographic assessment	mHealth-guided decision-making

NST, non-stress test

There is general consensus that women with pre-eclampsia should be delivered if pre-eclampsia is 'severe' or gestational age is either prior to fetal viability (WHO, ACOG, SOGC, SOMANZ 2014) or term (NICE, WHO, ACOG, SOGC, SOMANZ 2014). Definitions of severe pre-eclampsia vary, but none of the guidelines that have gestational age <34 weeks as a severity criterion indicate that women at <34 weeks with pre-eclampsia must be delivered (WHO, ASH 2008, AOM 2012). It should be noted that of 14 guidelines, only four indicate that 'heavy proteinuria' is a pre-eclampsia severity criterion; if applied strictly, it would mean that women with pre-eclampsia and heavy proteinuria should be delivered (WHO, ASH 2008, NVOG 2011, AOM 2012). There is consensus that women with pre-eclampsia should be considered for expectant management if they are at a gestational age associated with fetal viability and <34 weeks (WHO, NICE, ACOG, SOGC, SOMANZ 2014).

Women with gestational hypertension should be delivered at term (WHO, ACOG, SOGC), although this remains a controversial recommendation, with some guidelines recommending expectant care pending future studies (NICE, SOMANZ 2014).

There is no consistent guidance for women with chronic hypertension.

Mode of delivery

In terms of mode of delivery, the related issues have been addressed by five of the nine clinical practice guidelines (ACOG, AOM, QLD, NICE, SOGC). In pregnancies complicated by pregnancy hypertension, but without fetal compromise, the mode of delivery should be based on the clinical circumstances and usual obstetric indications (N = 4) (ACOG, QLD, NICE, SOGC). If a vaginal delivery is planned, and the cervix is unfavourable, then two guidelines recommend cervical ripening (QLD, SOGC). Active management of the third stage of labour with oxytocin is recommended (N = 2) (AOM, SOGC).

PRIORITIES FOR FUTURE RESEARCH

There is a need for better mechanisms for assessing gestational age in under-resourced settings where there is substantial reliance on inaccurate methods, such as LMP and SFH.

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10

Anaesthesia

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SYNPOSIS

This chapter is not designed to be an anaesthetic text but focuses on anaesthetic issues specifically related to parturients with hypertensive disorders of pregnancy. Early consultation and involvement of anaesthesia will result in the best possible outcome for women with a hypertensive disorder of pregnancy and their babies. Provision of effective analagesia for labour will not only decrease pain, but also attenuate its effects on blood pressure and cardiac output. In addition, epidural analgesia benefits the fetus by decreasing maternal respiratory alkalosis, compensatory metabolic acidosis, and release of catecholamines. An effective labour epidural can be used should a Caesarean delivery be required, avoiding the need for general anaesthesia. Both neuraxial (epidural, spinal, continuous spinal and combined spinal epidural) and general anaesthesia are appropriate for Caesarean delivery. The choice of technique will depend on the overall condition of the parturient, the urgency of the situation and whether there are contraindications to any particular technique. Challenges associated with anaesthesia include maintaining haemodynamic stability during laryngoscopy and intubation with general anaesthesia, or after sympathetic block secondary to neuraxial anaesthesia. Although neuraxial anaesthesia is preferred to general anaesthesia, owing to potential problems with the airway in the woman with pre-eclampsia, neuraxial anaesthesia may not be possible in the presence of a low platelet count or other coagulation abnormality. The interaction of non-depolarising muscle relaxants (as part of general anaesthesia) and magnesium sulphate will limit their use in the woman with pre-eclampsia. Adequate analgesia and ongoing monitoring are important components of overall postpartum management.

INTRODUCTION

A recurring lesson following investigation of maternal mortality secondary to complications of pre-eclampsia is the importance of teamwork and, in particular, the early involvement of anaesthesia. When possible, the anaesthetic team should be notified when a woman with pre-eclampsia is admitted to hospital. This notification allows for anaesthetic assessment, as well as clinical optimisation and care planning, all well in advance of anaesthetic intervention. Early anaesthetic consultation is associated with a reduction in both fetal and maternal morbidity[1].

Basic equipment and medications must be available in every labour and delivery area, and operating room in order to monitor maternal and fetal well-being, and resuscitate both should complications arise (Table 10.1). Essential

Table 10.1 Essential equipment for maternal resuscitation

Ventilation	Oxygen source Bag/mask Oral, nasopharyngeal airways
Intubation	Laryngoscope and different blades Different sizes of endotracheal tubes Gum elastic bougie McGill forceps Supraglottic airway device for rescue if failed intubation (e.g., laryngeal mask airway)
Intravenous access	Intravenous catheters (different gauges) Intravenous fluids (e.g., normal saline) Intravenous tubing
Emergency medications	Vasopressors (e.g., phenylephrine or ephedrine) Atropine Epinephrine $MgSO_4$ Cardiac medications such as amiodarone Nalaoxone (for neonatal and maternal resuscitation)
Other	Some means of providing left uterine displacement (e.g., wedge, blankets) Suction Defibrillator Equipment to perform perimortem Caesarean delivery

equipment includes oxygen, suction and a means of monitoring maternal blood pressure and heart rate. Ideally, one also would be able to monitor oxygen saturation and end-tidal carbon dioxide. Equipment for maternal resuscitation should always be immediately available (Table 10.1)[2]. A means of monitoring the fetus and equipment for newborn resuscitation also are required. While all of these resources are considered essential in well-resourced settings, they may not be available in less well-resourced areas. Some of the agents, techniques and equipment discussed in this chapter may not be available, but the basic principles of working as a team and using available resources to ensure the best possible outcome still apply.

The perspective taken in this chapter is that the anaesthetist should participate in a team-based multidisciplinary approach, that includes midwifery, obstetrics, nursing, neonatology and other medical specialties (e.g., haematology) or intensive care, as appropriate.

This chapter aims to highlight the potential issues faced by the anaesthetist when managing a patient with a hypertensive disorder of pregnancy, although the focus of this best anaesthetic practice is on pre-eclampsia. Throughout the chapter, analgesia refers to pain relief which may be provided through pharmacological means (e.g., opioids or gases, such as nitrous oxide) or through a central nerve (neuraxial) block (e.g., epidural) (Figure 10.1) whereby local anaesthetic is deposited close to the spinal cord and nerves to block the sensation of pain. Anaesthesia allows surgery to be performed and may be provided by a neuraxial block (e.g., epidural, spinal that can be continuous or 'single shot', or combined spinal epidural) which uses a stronger local anaesthetic than that used for analgesia. Neuraxial anaesthesia provides a denser sensory block in addition to muscle relaxation. Another way of providing anaesthesia is the use of a general anaesthetic that obtunds sensation to the whole body and the brain, resulting in unconsciousness, amnesia, analgesia, muscle relaxation and the inhibition of reflex activity. (For further information on overall anaesthetic concerns, the reader is referred to a basic text on anaesthesia, e.g., *Miller's Anaestheia*[3].)

INITIAL ASSESSMENT

The aim of the initial assessment is to plan in advance all aspects of both routine and emergency care, anticipate possible problems and the potential for anaesthetic intervention, and discuss any issues identified with the maternity care providers, the woman and her family. The risks and benefits associated with each anaesthetic technique can be explained, with the aim of expediting the process of informed consent should the need arise for an emergency procedure.

Anaesthetic planning should cover all aspects of prenatal maternal optimisation, including provision of analgesia for labour (as applicable), the appropriate choice of anaesthesia for assisted delivery or Caesarean delivery, and a plan for general postpartum care and pain management. Quotes from pre-eclampsia survivors illustrate just how much a multidisciplinary team is needed:

> "My blood pressure was 256/120 [mmHg] and doctors couldn't get it lowered. The doctors decided to put me into a medically induced coma to help stop the swelling of my brain and to try and lower my blood pressure. They

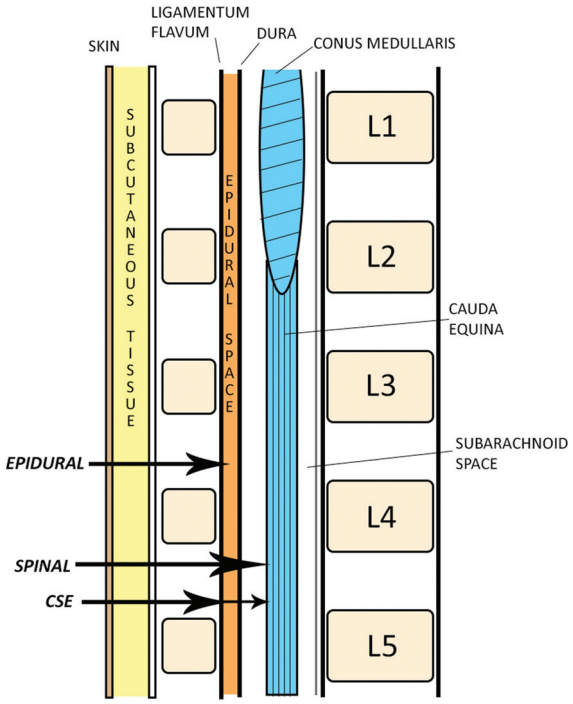

Figure 10.1 Schematic of spinal neuroanatomy, illustrating sites of needle insertion for neuraxial anaesthesia. (Image by DA de Silva © GLOWM)

> didn't successfully wake me until Friday morning when I was in labor and it was time to push. They had tried several times to wake me up but . . . I would thrash and struggle and try to pull the intubation tubes from my throat. The first thing I heard when I woke was that I was in the hospital and my baby had died. I was so sedated and drugged all I could say was, 'that's sad' . . . Looking back I realize I had no idea what was actually happening".
>
> Shelly S., HELLP syndrome survivor

A full anaesthetic history and physical examination should be completed, paying particular attention to the maternal airway in case emergency intubation is required, concurrent disease (which is common in this population, Table 10.2), drug history (including potential drug interactions) and end-organ involvement from pre-eclampsia (or another hypertensive disorder of pregnancy).

Women with a hypertensive disorder of pregnancy often have medical comorbidities for which they are receiving therapy, and women with pre-eclampsia have a multisystem disorder by definition (Table 10.3)[4,5]. Baseline haemoglobin, platelet count, tests of coagulation, renal function and liver enzymes should all be performed whether or not neuraxial analgesia/anaesthesia is considered. The initial results will guide the frequency of further investigations. Also, women with hypertensive disorders of pregnancy (including pre-eclampsia) are often treated with medications that may have implications for anaesthetic management, such as $MgSO_4$ for eclampsia prophylaxis or nifedipine for hypertension (Table 10.4)[6,7].

Table 10.2 Common comorbidities associated with the hypertensive disorders of pregnancy

Comorbidity	*Anaesthetic implications*
Diabetes mellitus	Regular blood glucose monitoring and BP <140/90 mmHg
Chronic hypertension	Consider the possibility of end-organ damage (e.g., renal disease, left ventricular hypertrophy, or coronary artery disease)
Renal disease	Consider the medication(s) given and their doses Avoid non-steroidal anti-inflammatory drugs Seek specialist advice as required (such as for dialysis)
Obesity	Difficulty with non-invasive monitoring (e.g., correct BP cuff size for accurate measurement, challenging venous access) May require invasive monitoring Increased failure/complications associated with neuraxial techniques Increased incidence of airway problems Need for thromboprophylaxis
Anti-phospholipid antibody syndrome	Patient likely to have been on prophylactic heparin therapy throughout pregnancy
Connective tissue disorders	Wide variety of effects that may require specialist advice

BP, blood pressure

ONGOING MONITORING

A basic standard of monitoring should be maintained throughout a woman's hospital stay. At minimum, blood pressure, heart rate, oxygen saturation and level of consciousness should be monitored

Table 10.3 Impact of the systemic effects of pre-eclampsia on anaesthesia

System Effect	*Anaesthetic implications*	*Planning considerations*
Vascular (BP)		
Hypertension	Potential for extreme hypertension during labour, in response to intubation, or during emergence from general anaesthesia	Regular BP monitoring, invasive monitoring may be required Maintain sBP <160 mmHg
Hypotension	Exaggerated hypotension secondary to neuraxial or general anaesthesia given high sympathetic tone Increased sensitivity to vasoactive drugs	Lateral uterine displacement to avoid aorto-caval compression Cautious boluses of ephedrine or phenylephrine to maintain sBP within 10% of patient's baseline
Generalised oedema	Anticipate that generalised oedema may make venous access challenging	May need central line
Airway		
Laryngeal oedema	Increased risk of difficult intubation or ventilation	Early and continuous assessment Anticipate possible need for intervention, and identify experienced assistance if possible Difficult airway equipment should be available Practice 'can't intubate, can't ventilate' drill[4]
Cardiac		
Pulmonary oedema	May require CPAP or invasive ventilatory support Potentially difficult ventilation	Careful input/output monitoring and fluid restriction
Cardiac failure with preserved ejection fraction[5]		Consider non-invasive cardiac monitoring or transthoracic echocardiography Early involvement of intensive care, if indicated
Renal		
Proteinuria	Pulmonary, cerebral, or generalised oedema, even in the absence of nephrotic-range proteinuria	Input/output monitoring
Oliguria		Fluid restriction (to a maximum of 80 mL/h in pre-eclampsia)
Acute kidney injury and electrolyte imbalance	Altered drug clearance Potential arrhythmias	Avoid NSAIDs and other nephrotoxic agents Electrolyte monitoring (including magnesium) and treatment of hyperkalaemia

Hepatic		
Epigastric or RUQ pain Elevated liver enzymes Sub-capsular haematoma or rupture	May have rapidly deteriorating function Mainly haematological implications (see below) May require surgical intervention	Early investigation of RUQ pain Frequent re-assessment of function Preparation for laparotomy if required
Haematology		
Haemolysis Thrombocytopaenia Coagulopathy	Increased risk of neuraxial haematoma with neuraxial techniques Risk of massive haemorrhage May require blood products	Regular platelet monitoring in respect to performing neuraxial anaesthesia Timely removal of epidural catheters, weighing the risk of removal with the risk of leaving the catheter *in situ* Avoid non-steroidal anti-inflammatories if there is thrombocytopaenia Monitor fibrinogen levels during haemorrhage Early advice from haematologists Preparation of blood products if required
Neurology		
Eclampsia or PRES Altered consciousness Stroke Subarachnoid haemorrhage	Emergency management of seizures An ongoing deficit and/or evolving clinical picture may affect informed consent or anaesthetic choice (e.g., if there is raised intracranial pressure)	Seizure prevention preferable (with $MgSO_4$) Avoidance or prompt treatment of severe hypertension Any persistent headache/neurological deficit warrants further investigation
Placenta		
Increased risk of abruption causing DIC	Major obstetric haemorrhage Immediate Caesarean delivery may be indicated	See Haematological system Inadequate time for neuraxial technique

BP, blood pressure; CPAP, continuous positive airway pressure; DIC, disseminated intravascular coagulation; sBP, systolic blood pressure; RUQ, right upper quadrant; PRES, posterior reversible encephalopathy syndrome; NSAIDs, non-steroidal anti-inflammatory drugs; $MgSO_4$, magnesium sulphate

Table 10.4 Pharmacological agents in pre-eclampsia and their impact on anaesthesia

Name of drug	*Effect*	*Anaesthetic considerations*
$MgSO_4$	Eclampsia prevention and treatment	Awareness of potential toxicity and reversal by calcium gluconate Increased risk of Caesarean delivery Prolonged effect of non-depolarising muscle relaxants No proven increase in the need for neonatal resuscitation[6]
Nifedipine	Effective, rapid hypertensive control Prolongation of pregnancy Calcium channel antagonist	Rebound tachycardia on induction of anaesthesia Caution when used with magnesium may have increased antihypertensive and negative inotropic effects
Labetalol	Well tolerated, good hypertensive control Specific alpha 1 and non-specific beta adrenoreceptor antagonist	Avoid in asthmatics Fatigue bronchospasm May cause neonatal hypotension and hypoglycaemia
Hydralazine	Increases intracellular cGMP causing decrease in intracellular calcium producing vasodilation	Tachycardia SLE-like syndrome Peripheral neuropathy with longer term use – assess prior to neuraxial block Delayed hypotension with fetal bradycardia
Alpha methyldopa	Central alpha-2 receptor blocker	May cause bradycardia and haemolytic anaemia
Aspirin	Reduced risk of pre-eclampsia	Low dose (<160 mg/d) should not preclude neuraxial technique in the absence of other clotting abnormalities[7]
Oxytocin	Augmentation of labour Reduced blood loss after delivery	May cause hypotension and should be given slowly and cautiously
Ergometrine	Increases uterine tone after delivery, reduces blood loss	Avoid – may cause severe hypertension
Misoprostol	Increases uterine tone and reduces blood loss after delivery	Hypertension but to a lesser degree than ergometrine
Carboprost	Increases uterine tone after delivery, reduces blood loss	Caution in asthmatics

cGMP, cyclic guanosine monophosphate; $MgSO_4$, magnesium sulphate; SLE, systemic lupus erythematosus

regularly. It is important to stress that postanaesthetic monitoring and documentation should be equivalent to postoperative monitoring seen in non-obstetric surgical patients[8].

Blood pressure monitoring should be frequent (and at times continuous) following neuraxial anaesthesia or general anaesthesia, regardless of the severity of hypertension pre-intervention. It may be appropriate to monitor it continuously using an intra-arterial line which is particularly useful when the woman has a very high systolic blood pressure, a very labile blood pressure, or when it cannot be accurately measured (such as in the obese woman for whom a large cuff is required but which fits poorly due to a short upper arm). An arterial line is also useful when frequent blood sampling is required.

Oliguria is a common finding in women with pre-eclampsia, given high sympathetic tone and intravascular volume depletion. There is currently no way of identifying women who will respond adversely to a fluid challenge with pulmonary oedema, so fluid restriction (i.e., administration of no more than 80 mL/h of intravenous fluid) is recommended in pre-eclampsia. (See Chapter 8 for a more detailed discussion of fluid management.)

Early warning systems – integrating routine observations

'Early warning systems' are red and yellow colour-coded observation charts onto which a patient's routine observations are plotted and

deviations from norms of vital signs, symptoms, or signs are flagged for review. These early warning systems have been used widely to trigger early review of 'at risk' medical and surgical patients and, in some circumstances, have been validated as a means of identifying patients who will require critical care[9].

There is growing enthusiasm for the use of early warning systems to monitor women in pregnancy and postpartum. Although evidence is lacking to fully support the implementation of early warning systems in maternity care, it seems logical that a standardised mechanism to enable early detection and appropriate reporting of the 'at risk' parturient is a prerequisite to reducing maternal morbidity and mortality[1]. Table 10.5 presents one published example of a Modified Early Obstetric Warning Systems (MEOWS), with one reading within the 'red zone' or two within the 'yellow zone' triggering urgent review by a consultant[10].

Central venous catheters

Central venous pressure (CVP) correlates poorly with left atrial pressures in severe pre-eclampsia, making absolute values of CVP measurements inaccurate[11]. However, central venous access may be required for the safe delivery of vasoactive drugs or if generalised oedema makes peripheral access impossible. Under those circumstances, the inserted central venous line may be used to measure *trends* in CVP as a guide to a woman's response to any fluid administered.

Although pulmonary artery catheters are the gold standard for measurement of left and right ventricular filling pressures, there is no evidence from randomised controlled trials to support their use in pre-eclampsia[12]. This is unlikely to change owing to the highly invasive nature of the intervention, the significant risk of complications, and the lack of physicians skilled in pulmonary arterial catheter insertion given their infrequent use.

Transthoracic echocardiography

Transthoracic echocardiography (TTE) provides a quick, non-invasive, accurate assessment of fluid status and contractility[5,13]. Right heart pre-load can be estimated from right and left ventricular end-diastolic volumes, and variations in inferior vena caval diameter with spontaneous respirations. As anaesthetists become more skilled in TTE use, there is potential to have additional information with which to care for women with hypertensive disorders of pregnancy.

Minimally invasive cardiac output monitoring devices

There is increasing availability of devices to estimate cardiac output at the bedside (e.g., PiCCO, LiDCO, FloTrac/Vigileo systems) and these are used widely in intensive care settings for non-pregnant patients. Although most techniques require that patients be undergoing positive pressure ventilation for accurate results, these devices may provide information about trends that can be used to guide fluid replacement when neuraxial anaesthesia is used. At present, unlike TTE[14], use of non-invasive cardiac output assessment has not been validated for use in maternity care.

Other

The addition of end tidal carbon dioxide monitoring is mandatory during general anaesthesia.

LABOUR ANALGESIA

Maternal pain has physiological effects that may be harmful to the mother and her fetus(es). Pain is associated with increased maternal cardiac output and blood pressure[15–17]. Maternal pain is also associated with the following effects that can harm the fetus: (1) respiratory alkalosis (that can shift the maternal haemoglobin-oxygen dissociation curve to the left and reduce oxygenation of umbilical venous blood, as well as cause vasoconstriction and restrict uterine artery blood flow); (2) compensatory metabolic acidosis (that is readily transferred to the fetus); and (3) release of catecholamines that are associated with uncoordinated uterine contractions[18].

Labour analgesia may benefit the hypertensive parturient by attenuating the pain-induced sympathetic response that may contribute to uncontrolled hypertension. In the past, lay individuals and some health care providers assumed that any form of medicinal pain relief was deleterious to the fetus. However, studies focusing on parameters of fetal well-being such as acid–base status, Apgar scores, fetal oxygen saturation and perinatal mortality have demonstrated that effective maternal pain relief (such as with epidural analgesia) is *beneficial* rather than harmful[18].

Table 10.5 Parameters to trigger a response in an early warning system. (Adapted from CEMACH recommended early warning system[10])

	Red trigger		*Yellow trigger*	
Observation	*Low*	*High*	*Low*	*High*
Systolic BP (mmHg)	<90	>160	90–100	150–160
Diastolic BP (mmHg)	—	>100	–	90–100
Heart rate (beats per minute)	<40	>120	40–50	100–120 or 40–50
Respiratory rate (breaths per min)	<10	>30	–	21–30
Oxygen saturation (%)	<95	Not applicable	–	Not applicable
Temperature (degrees C)	<35	>38	35–36	–
Pain score	Not applicable	–	Not applicable	2–3
Neurological response	Unresponsive, but responds to pain	Not applicable	Depressed responsiveness, but responds to voice	–
Lochia	Foul smelling	–	Not applicable	–
Proteinuria >2+	>2+	–	Not applicable	–
Amniotic fluid	Green	–	Not applicable	–
Looks unwell	Not applicable	–	Yes	–

BP, blood pressure

Labour analgesia can be provided pharmacologically through three different forms of administration: inhalation, parenteral (by intravenous (IV) or intramuscular (IM) injection), or neuraxial.

Inhalation analgesia

Inhalation analgesia is not used commonly with the exception of the 50:50 mix of nitrous oxide/oxygen (N_2O/O_2). The benefits of N_2O/O_2 include minimal placental transfer, minimal haemodynamic effects, and rapid onset and offset of analgesia. Disadvantages described include nausea and vomiting, and maternal sedation. A meta-analysis summarised the effectiveness of analgesia in 19 randomised controlled trials that compared N_2O/O_2 with other forms of analgesia – placebo, other gases and mixtures, or transcutaneous nerve stimulation (TENS)[19]; 17 of these studies were of poor quality and two of fair quality. In the N_2O/O_2 arms, maternal satisfaction with analgesia ranged from 30 to 80%. In a prospective cohort study of good quality, 54% of women who had had N_2O/O_2 were satisfied with their pain relief compared with 94% of women who received epidural analgesia[19].

Some hospitals have N_2O/O_2 'piped-in' to labour and delivery areas. Those that provide the 50:50 mixture in tanks should ensure that the tanks are stored and handled correctly to ensure that the correct mixture is delivered. When administering the N_2O/O_2 mixture, a demand valve system should be used to ensure that further gas will not be delivered if the woman becomes drowsy. Also, the room in which inhalational analgesia is used should be well ventilated and, ideally, there should be a system for scavenging waste gases. Simple scavenging systems can be made by connecting a corrugated tube that collects the exhaled gases to a vent or exhaust system.

Many centres no longer use N_2O/O_2 given these environmental concerns and the perceived lack of efficacy[20].

Parenteral analgesia

Parenteral analgesia is administered commonly in many centres where neuraxial analgesia is not readily available.

Historically, pethidine (meperidine) has been the opioid of choice for labour analgesia, but this practice has changed with the recognition that pethidine has both adverse fetal and neonatal side-effects, including depression of fetal muscular activity, reduction in fetal aortic blood flow, decreased short-term fetal heart rate variability, low Apgar scores, neonatal respiratory depression, reduced neonatal neurobehavioural scores, and weak suckling that could affect breastfeeding[18]. Of note, neonatal side-effects may occur up to 72 hours after birth owing to accumulation of pethidine's active metabolite, norpethidine.

The fact remains, however, that all opioids administered parenterally have undesirable maternal and neonatal side-effects. However, IM-administered opioid (pethidine, tramadol, or diamorphine) is not particularly effective compared with placebo[21], making IV opioid administration the route of choice.

When used during early labour, morphine and fentanyl have minimal neonatal effects. However, owing to their long half-lives, neither drug is recommended for routine use in advanced stages of labour or during delivery, as maternal sedation and neonatal respiratory depression may result[21].

Remifentanil is an ultra short-acting opioid that has been investigated for use in IV patient-controlled labour analgesia (PCA). In one meta-analysis of three studies (233 subjects), remifentanil (compared with pethidine) was more effective (as measured by a reduction of mean visual analogue scale scores for labour pain after 1 hour) and associated with higher patient satisfaction[22]. In another meta-analysis that reviewed 12 randomised controlled trials (2001–2011) comparing remifentanil with any other form of labour analgesia[23], 269 women received remifentanil, 209 pethidine, 10 nitrous oxide and 54 epidural analgesia. Remifentanil (compared with pethidine) provided superior analgesia, better patient satisfaction, and lower conversion rates to epidural analgesia[23]. However, compared with epidural analgesia, remifentanil was associated with poorer pain control as well as maternal respiratory depression (defined as a maternal oxygen saturation <95%); long-term adverse neonatal effects were not increased[23].

In summary, parenteral opioids should be used when neuraxial analgesia is contraindicated or unavailable. When parenteral opioids are used, careful attention must be paid to maternal respiration and oxygen saturation, and neonatal resuscitation may be required.

Neuraxial analgesia

Neuraxial analgesia provides the highest quality of pain relief and can be obtained through four different techniques: epidural, combined spinal-epidural, continuous spinal, or 'single-shot' spinal anaesthesia (Figure 10.1). Neuraxial analgesia/anaesthesia is contraindicated when: (1) the patient refuses to consent; (2) there is infection at the proposed site of insertion of the catheter or there is evidence of systemic infection; (3) there is haemodynamic compromise (severe hypotension); or (4) there is evidence of coagulopathy (see Table 10.6, discussed below)[24].

Neuraxial anaesthesia/analgesia may be contraindicated in women with pre-eclampsia owing to the presence of coagulopathy. There is debate about the lowest platelet count that is safe for neuraxial anaesthesia, even in normotensive patients[25]. Many anaesthetists will administer neuraxial anaesthesia when the platelet count is >75,000/mm^3 and relatively stable, and there is no clinical evidence of coagulopathy. Not only do platelets need to be sufficient for insertion of a neuraxial catheter, they need to be sufficient at the time of catheter removal. In all cases, the risk–benefit profile of removal versus leaving the epidural *in situ* needs to be addressed. In some cases of pre-eclampsia, the platelet count may take days to normalise; therefore, the risk of epidural infection or trauma from the catheter may outweigh the risk of neuraxial haematoma. Also, as a decreased platelet count may be an indication of disseminated intravascular coagulation (possibly secondary to placental abruption) or other co-existing conditions, one has to consider the relative merits of providing neuraxial anaesthesia with the potential risk of a neuraxial haematoma in each individual patient[26].

Epidural analgesia

Maternal pain can be treated effectively with epidural analgesia, without an associated increase in adverse fetal or neonatal effects among normotensive or hypertensive women[15,27]. In fact, when given to normotensive women, epidural analgesia (compared with either no labour analgesia or opioids, as discussed above) was associated with *better* fetal acid–base status and neonatal Apgar scores[18].

Table 10.6 Coagulation and neuraxial anaesthesia (reproduced from Magee *et al. J Obstet Gynaecol Can* 2014;36: 416–441, with permission)

Treatment with ASA or heparin	*Normal platelet count*	*Low platelet count & normal INR and aPTT*	*Abnormal INR or aPTT (regardless of platelet count)**
None *or* Low dose ASA	✓	✓ if platelets >75 × 10⁹/L Unclear if platelets 50–75 × 10⁹/L X if platelets <50 × 10⁹/L	
UFH			
≤10,000 IU/d (SC)	✓ 0–4 h after last dose	Unclear	X Contraindicated
>10,000 IU/d (SC)	✓ 4 h after last dose and aPTT normal	Unclear	
Therapeutic dose (IV)	✓ 4 h after last dose and aPTT normal	Unclear	
LMWH			
Prophylactic dose†	✓ 10–12 h after last dose	Unclear	
Therapeutic dose‡	✓ 24 h after last dose	Unclear	
Low dose ASA + prophylactic UFH or LMWH**	Unclear††	Unclear	

ASA, aspirin; aPTT, activated partial thromboplastin time; INR, international normalised ratio;LMWH, low molecular weight heparin; SC, subcutaneous; UFH, unfractionated heparin
These recommendations are based on the absence of a rapidly falling platelet count or KNOWN platelet dysfunction (e.g., von Willebrand's disease)
* Other than a lupus anticoagulant
† Prophylactic dosing is defined as ≤10,000 IU/d
‡ Therapeutic dosing (SC) is defined as >10,000 IU/d
** Prophylactic doses of unfractionated heparin are defined as ≤10,000 IU/d
†† Unless ASA is stopped 7 days or more before delivery

Among hypertensive pregnant women, epidural analgesia attenuates pain-induced elevations in blood pressure and cardiac output[16], as well as providing an option for neuraxial anaesthesia should urgent/emergent Caesarean delivery be necessary for maternal or fetal reasons. An extension of this effect is the potential for hypotension among women with pre-eclampsia who have systemic vasoconstriction and intravascular volume depletion. Although most studies have demonstrated no hypotension among women with pre-eclampsia compared with normotensive women[27–29], a recent retrospective controlled cohort study (200 women, 100 with severe pre-eclampsia) did demonstrate more frequent hypotension, late decelerations and vasopressor administration following epidural analgesia compared with normotensive controls[30]. Although this study did not use hypertensive controls provided with alternative analgesia, or ideally, randomise women, it highlights the theoretical risk of neuraxial-related hypotension among women with 'severe' pre-eclampsia.

It is of particular note that even among women with severe pre-eclampsia, epidural analgesia/anaesthesia does not increase the risk of Caesarean delivery[31].

Medications administered through the epidural catheter consist of a combination of a low-dose local anaesthetic (e.g., bupivacaine 0.08%) and an opioid (e.g., fentanyl 2 μg/mL) that provides effective labour analgesia with minimal haemodynamic effect.

Combined spinal-epidural analgesia

Combined spinal-epidural analgesia (CSE) combines the advantages of spinal analgesia (i.e., rapid onset of

pain relief and good analgesia from the insertion of medications into the subarachnoid space) with those of epidural analgesia so that one can provide ongoing continuous pain relief[32]. CSE analgesia is an acceptable technique for labour analgesia and anaesthesia, but there is some evidence that the use of intrathecal opioids may lead to transient fetal bradycardia (odds ratio 1.8, 95% confidence interval 1.0–3.1)[33,34]. This fetal bradycardia does not lead to the need for emergency Caesarean delivery (6.0% versus 7.8% for any non-intrathecal opioid technique)[34]. The proposed mechanism is that the rapid onset of analgesia causes a rapid decrease in beta-adrenergic agonists leading to a predominance of alpha activity. As a result, there is increased uterine contractility and reduced uteroplacental perfusion, with subsequent fetal bradycardia[34].

Continuous spinal analgesia

Continuous spinal analgesia (CSA) is more effective than epidural analgesia, as the medications for analgesia (opioid and local anaesthetic) are injected directly into the subarachnoid (intrathecal) space around the spinal cord and cauda equina. This technique is performed by inserting a needle directly into the subarachnoid space and then threading a catheter through that needle. Visual confirmation of cerebrospinal fluid in the hub of the needle identifies correct placement of the needle in the subarachnoid space (prior to insertion of the catheter), making it an easier technique to learn and perform in contrast to inserting a needle into the epidural space where loss of resistance is used to identify the space.

CSA is used in some patient populations as an initial labour analgesia technique (e.g., morbid obesity) as there is a defined end-point (i.e. cerebrospinal fluid) when the space is identified. One of the concerns in identifying the epidural space is that one might inadvertently puncture the dura, but obviously that is not a concern when one is deliberately puncturing it. Increasingly, CSA is used as a rescue technique after accidental dural puncture has occurred inadvertently during attempted epidural insertion; attempting again to identify the epidural space may result in multiple attempts and a second dural puncture.

CSA has the same side-effect profile as epidural analgesia, including risk of postdural puncture headache (see below). However, CSA is associated with a greater risk of neuraxial infection, as the catheter is in the subarachnoid space and cerebrospinal fluid is an excellent culture medium. Similar to the CSE technique, injection of intrathecal opioids may result in transient fetal bradycardia (see above). In addition, there is greater potential for drug error owing to the injection of medication, intended for the epidural space, through the spinal catheter (because the same type of catheter may be used by most anaesthetists for both techniques). As less medication is required in the subarachnoid space (1–2 mL) than in the epidural space (10–20 mL), inadvertent injection of medication intended for the epidural space into the subarachnoid space can result in a high anaesthetic block and cardiovascular and respiratory impairment. This mandates that an intrathecal catheter for CSA be well labelled and that information is communicated to all care givers that the catheter is intrathecal.

Although controversial, animal studies suggest that use of an indwelling spinal catheter may be associated with a lower incidence of postdural puncture headache. Although two recent meta-analyses did not find a lower incidence of postdural puncture headache in an intrathecal catheter group, compared with a group that had the epidural reinserted, nevertheless, fewer women in the intrathecal catheter group required an epidural blood patch[35,36].

'Single-shot' spinal analgesia

Low dose, single-shot spinal analgesia is easy to perform and provides rapid pain relief of a limited duration, depending on the medications used (i.e., 1–3 hours)[37,38]. This technique is used occasionally in women who are expected to deliver within an hour (because, for example, they are at full cervical dilatation).

Single-shot spinal analgesia is the neuraxial technique that uses the smallest needle (i.e., 24 gauge or smaller, compared with 16–18 gauge needles with other techniques). Some anaesthetists consider the single-shot spinal technique safer than the epidural technique, as the incidence of postdural puncture headache is lower and there is potentially less risk of trauma to neuraxial blood vessels[39,40]. However, the potential adverse effects are similar to combined spinal-epidural, and include maternal hypotension (that is dose-dependent) and fetal bradycardia[34].

CAESAREAN DELIVERY

Cesarean delivery is common, and particularly so among women with pre-eclampsia given uteroplacental dysfunction and the need to deliver some such women at early gestational ages.

Table 10.7 presents the principles of managing an anaesthetic in women with a hypertensive disorder of pregnancy. All neuraxial anaesthetic techniques are appropriate to consider, even in the woman with eclampsia. Among 66 conscious women who had suffered eclampsia but were stable, no major complications occurred in the 37 who underwent epidural anaesthesia and the 27 who underwent general anaesthesia, although the 1-minute Apgar score was higher in the epidural group (related to the temporary depressive effects of the medication used for general anaesthesia)[41]. This latter finding is not unexpected as babies born to healthy mothers having general anaesthesia have a lower 1-minute Apgar that recovers by 5 minutes. Factors that influence anaesthetic choice include the need for an emergent Caesarean delivery owing to maternal or fetal concerns, any contraindication to neuraxial anaesthesia, the presence of an existing epidural or spinal catheter in a labouring woman, and maternal choice.

General anaesthesia

The indications for general anaesthesia are similar to those in the general obstetric population. (For further details about mode of delivery, see Chapter 9.) These indications include insufficient time to induce neuraxial anaesthesia (generally owing to fetal concerns or maternal haemodynamic instability) or contraindication(s) to neuraxial anaesthesia, including coagulopathy (Table 10.6), systemic infection, cardiovascular instability, failure to obtain consent, and allergy to any of the anaesthetic agents.

The challenges associated with general anaesthesia are similar to those in normotensive women but the risks may be higher in women with pre-eclampsia. These challenges include the possibility of a difficult airway or failed intubation, the hypertensive response to endotracheal intubation, and haemodynamic instability. If a woman is comatose and has increased intracranial pressure, any further increase in blood pressure during intubation could cause irreversible brain damage. Similarly a drop in blood pressure secondary to sympathetic block with neuraxial anaesthesia, could compromise cerebral perfusion[42]. The risks associated with pulmonary aspiration secondary to gastric regurgitation have declined due to the almost universal administration of aspiration prophylaxis (with histamine$_2$ receptor antagonists and prokinetic agents) and 'nothing by mouth' policies once the possibility of Caesarean delivery is raised.

Difficult airway

Although obstetric anaesthetists are concerned about the risks of difficult or failed intubation in any parturient undergoing general anaesthesia, this is a particular concern in women with pre-eclampsia because they may have airway oedema[43,44]. Airway difficulties are responsible for a substantial part of the increased maternal morbidity and mortality associated with general anaesthesia in women with pre-eclampsia[45]. The Obstetric Anaesthetists' Association and the Difficult Airway Society of the UK have published guidelines for the management of difficult and failed intubation in obstetrics[46]. The algorithms and tables which summarize the management of this situation are available on the websites of the OAA[47] and the DAS[48].

Hypertensive response to intubation

In normotensive and hypertensive patients, tracheal intubation may trigger an increase in heart rate and blood pressure[49]. In women with a hypertensive disorder of pregnancy, this hypertensive response may precipitate severe hypertension and an adverse cerebrovascular event (e.g., stroke). As such, it is important to make every effort to attenuate this hypertensive response.

Various pharmacologic approaches to prevention of the hypertensive response to tracheal intubation have been studied in non-obstetric patients, with fewer studied in pregnancy. Randomised controlled trials have compared various agents (with or without control therapy) in patients with pre-eclampsia of various severity. These agents have included opioids (i.e., alfentanil, fentanyl, remifentanil), antihypertensive agents (i.e., nitroglycerin, labetalol, nifedipine), magnesium and lidocaine. The number of subjects in the individual studies were small and the patient populations were heterogeneous; although most women had received antihypertensive medications preoperatively, others had not and not all were

Table 10.7 Principles of anaesthetic management for Caesarean delivery in women with a hypertensive disorder of pregnancy

Stabilise the woman's BP prior to surgery, if possible. If the BP is severely elevated and uncontrolled, the risks of anaesthesia and surgery will have to be balanced against any potential benefits
Aim for haemodynamic stability perioperatively (avoid hypotension/hypertension)
For spinal anaesthesia, use the smallest available spinal needle, e.g., 24-gauge or smaller, preferably with a pencil point in order to decrease the risk of postdural puncture headache
Consider prophylactic phenylephrine infusion to prevent hypotension during neuraxial anaesthesia (possibly use lower dose than for normotensive parturients)
Avoid a hypertensive response to intubation during general anaesthesia by administering an opioid, remifentanil (0.0–1.0 μg/kg) or fentanyl (50–150 μg), with or without labetalol (20 mg followed by 10 mg increments until the dBP is decreased to <100 mmHg or mean arterial BP has decreased by 20% from baseline) prior to induction with an adequate dose of thiopental (5–7 mg/kg) or propofol (2–3 mg/kg). Esmolol (1.5 mg/kg) or nitroglycerin (2 μg/kg) combined with propofol (2 mg/kg) have been recommended[56]
Monitor: • Standard monitors: electrocardiogram, non-invasive BP, oxygen saturation with the addition of temperature and end tidal CO_2 for general anaesthesia • Consider intra-arterial BP monitoring if woman requires repeated blood sampling or there is difficulty controlling BP
Administer oxytocin as an infusion, rather than as a bolus

BP, blood pressure; dBP, diastolic blood pressure; MAP, mean arterial pressure

receiving magnesium. The agents and doses for induction of anaesthesia also varied.

These studies are presented in detail in Appendix 10.1[50–60]. The bottom-line is that the differences in the protocols of these studies make it difficult to draw firm conclusions as to the best method of attenuating the hypertensive response to intubation, in terms of the individual agent, combination of agents, and/or dose(s). Further study is needed of this important topic. In the meantime, a prudent approach would be to ensure that an optimum dose of an induction agent is used (e.g., thiopental 5–7 mg/kg or propofol 2–3 mg/kg) as well as an opioid. There is little to choose between the opioids, but the advantages of rapid onset and offset of remifentanil suggest it be used in a dose of 1 μg/kg, where it is available. Alfentanil (10 μg/kg) and fentanyl (50–100 μg) are alternatives to remifentanil. As most women with pre-eclampsia will be on magnesium, further magnesium should not be given. However, one could consider administering a loading dose of magnesium pre-induction in the circumstance where it has not been given. Sublingual nifedipine 10 mg or labetalol (20 mg loading dose followed by 10 mg increments) to control blood pressure preoperatively are other possible agents. Caution should be exercised, however, as many women with pre-eclampsia may already be on antihypertensive medication; additional antihypertensive medication may lead to hypotension.

Non-depolarising muscle relaxants

Non-depolarising muscle relaxants are used to produce muscle relaxation to facilitate surgery and mechanical ventilation. In women with pre-eclampsia, the combination of a standard dose of a non-depolarising muscle relaxant and $MgSO_4$ results in prolonged motor block[61], so many consider $MgSO_4$ to be a relative contraindication to the use of a non-depolarising muscle relaxant. If this combination of therapies cannot be avoided, the dose of the non-depolarising muscle relaxant must be titrated carefully according to monitoring by a peripheral nerve stimulator[62]. Calcium gluconate (or, alternatively, calcium chloride) is the antidote to magnesium and can be used if prolonged neuromuscular block occurs.

Haemodynamic management (i.e., hypotension and hypertension)

Maintenance of a stable blood pressure is key to the successful management of women with a hypertensive disorder of pregnancy. Ideally, the blood pressure will have been stabilised prior to the need for Caesarean delivery. Thereafter, assuming a baseline blood pressure that is <160/110 mmHg (i.e., not severely elevated), one should strive to avoid both falls and rises in blood pressure relative to that baseline.

Maternal blood pressure can be monitored during Caesarean delivery either non-invasively or invasively. If blood pressure monitoring is undertaken non-invasively, the cuff size has to be appropriate for the size of arm. (For more information, see Chapter 1.) Shivering, which often occurs in women having neuraxial anaesthesia (either epidural or spinal), may interfere with non-invasive blood pressure monitoring. Placing the cuff on the wrist (rather than on the upper arm) may decrease interference, although blood pressure measurements taken in this fashion would be used to evaluate trends in blood pressure as wrist measurement is known to overestimate blood pressure[63]. Invasive blood pressure monitoring achieved by insertion of an arterial line can provide continuous measurement when blood pressure proves difficult to stabilise, and provides the added benefit of allowing repetitive blood sampling.

Some authors suggest that it is more important to focus on cardiac output, rather than blood pressure, during neuraxial anaesthesia for Caesarean delivery in women with severe pre-eclampsia[64]. This can be done using minimally invasive cardiac output monitors[64,65] or transthoracic echocardiography[5], as discussed above. The authors who recommend the use of cardiac output suggest that it reflects uterine perfusion better than arterial blood pressure, but this is controversial[66].

For many years, anaesthetists routinely administered an intravenous bolus (1000–2000 mL) of crystalloid prior to neuraxial block for Caesarean deliveries to avoid hypotension. As most crystalloid intravenous fluid exits the vascular system within 20 minutes of administration, this therapy is ineffective[67,68]. Most authorities now recommend limiting the amount of intravenous fluid (unless there is ongoing bleeding) in healthy women, administering fluid as a co-load (i.e., administering intravenous fluid after rather than before induction of spinal anaesthesia)[69–71]. Hypotension is avoided and/or treated through the use of vasopressors (generally phenylephrine). (For further discussion on fluid management, see Chapter 8.)

Vasopressors

In normotensive women, phenylephrine has become the vasopressor of choice to prevent and/or treat hypotension, given its rapid onset and offset that allow for moment-to-moment control of blood pressure[66,72]. Ephedrine's popularity as a vasopressor in the setting of neuraxial anaesthesia declined following a study comparing prophylactic infusions of ephedrine and phenylephrine in elective Caesarean deliveries. This study found that umbilical arterial pH was significantly lower in the group receiving the ephedrine (vs. phenylephrine) infusion, even in the presence of good blood pressure control[66,72].

In women with pre-eclampsia, there are no studies comparing ephedrine with phenylephrine to prevent or treat hypotension. Although the majority of studies of neuraxial block for Caesarean delivery in women with pre-eclampsia used ephedrine as the vasopressor, the literature is not extensive (as summarised in Appendix 10.2). A prudent approach would be to start with a lower dose of medication (either ephedrine 3–5 mg bolus or phenylephrine 25–50 μg bolus) than one would for normotensive women and titrate the dose to the blood pressure[13].

Neuraxial anaesthesia

Neuraxial anaesthesia and hypotension

Henke *et al.* reviewed prospective studies that compared haemodynamic changes following spinal anaesthesia, or CSE anaesthesia, with epidural and/or general anaesthesia for Caesarean delivery in severe pre-eclampsia[68]. They reported on three trials that studied the haemodynamic changes after spinal anaesthesia for non-emergency Caesarean delivery, comparing women with severe pre-eclampsia (N = 115) with normotensive women (N = 121). In all three of these studies, the group with severe pre-eclampsia had a lower incidence of hypotension and required less ephedrine to treat hypotension than did the normotensive controls[68]. In two of these studies, many of the women with severe pre-eclampsia delivered at an earlier gestational age (lower fetal weight), raising the possibility that women with severe pre-eclampsia had less hypotension because their fetuses were smaller and caused less aortocaval compression[73,74]. Therefore, the third study compared normotensive women delivering at an earlier gestational age (fetal weight was similar); once again, the incidence of hypotension requiring treatment was lower in the pre-eclampsia group ($p < 0.03$).

In addition to the three studies identified by Henke *et al.*, a study by Tihtonen *et al.* used

non-invasive whole-body impedance cardiography to assess the impact of spinal anaesthesia for Caesarean delivery on maternal haemodynamics in women with pre-eclampsia (N = 10; 6 were severe) with comparative data from a historic cohort of normotensive (N = 10) women[75]. The incidence of hypotension differed between the groups (normal = 80% vs. pre-eclampsia = 30%). Women with pre-eclampsia had a low cardiac index and high systemic vascular resistance index preoperatively and, while cardiac index remained stable after induction of spinal anaesthesia, systemic vascular resistance index decreased. Following delivery, the mean cardiac index increased due to an increase in heart rate (with no associated increase in stroke index). The authors raised the possibility that women with pre-eclampsia were unable to increase stroke index and that this might increase the risk of pulmonary oedema[75]. One observational study looked at cardiac output using minimally invasive monitoring in 15 women with severe pre-eclampsia undergoing Caesarean delivery under spinal anaesthesia[65]; there was a modest afterload reduction with minimal cardiac output change following spinal anaesthesia in women with severe pre-eclampsia. This led them to conclude that spinal anaesthesia is associated with adequate haemodynamic stability[65].

Spinal anaesthesia versus epidural anaesthesia in women with pre-eclampsia

Two prospective studies compared epidural anaesthesia (N = 57) with spinal anaesthesia (N = 64) in women with severe pre-eclampsia[76,77]. The larger of these studies found a higher incidence of hypotension (systolic blood pressure <100 mmHg) in the spinal group compared with the epidural group (51% vs. 23%) but the duration of hypotension was short (median 1 min vs. 0 min). From induction of anaesthesia to delivery of the fetus, there was a significant difference in the lowest systolic blood pressure ($p < 0.001$), diastolic blood pressure ($p < 0.005$) and mean blood pressure ($p < 0.001$) between the epidural and spinal groups. The total dose of ephedrine to treat hypotension, although greater in the spinal group, was nevertheless small (12 mg – spinal; 6 mg – epidural)[76]. The smaller study (total of 21 subjects) found a similar incidence of hypotension and ephedrine dose between the two groups[77].

In addition to these prospective studies identified by Henke *et al.*, there have been two retrospective studies comparing spinal with epidural anaesthesia[78,79]. The study by Hood *et al.* looked at women with severe pre-eclampsia who received spinal anaesthesia (N = 103) or epidural anaesthesia (N = 35) for Caesarean delivery[78]. Similar to the prospective studies, the lowest mean blood pressure and ephedrine use were similar between the groups. In a similar retrospective study, the incidence of hypotension and ephedrine use were similar between spinal (N = 70) and epidural (N = 51) anaesthesia in women with pre-eclampsia[79]; the only difference in this study was that there were some women in each group who were classified as having mild-moderate pre-eclampsia (41 in the spinal group vs. 18 in the epidural group).

Only one prospective study compared CSE (N = 27) with epidural (N = 27) and general anaesthesia (N = 26)[80]. It is important to note that the dose of hyperbaric bupivacaine administered in the spinal component of the CSE in this study is similar to that used by many anaesthetists for single-shot spinal (11 mg). The authors do not report on whether the CSE group required epidural top-up doses but given the intrathecal dose, one could consider this group as receiving spinal anaesthesia. Blood pressure was lower at the time of skin incision ($p < 0.003$) and treatment with ephedrine boluses was higher in the CSE and epidural groups (compared to the general anaesthesia group) (0 mg general anaesthesia vs. 8 mg epidural vs. 6 mg CSE) ($p < 0.009$). As well, significantly more IV fluid was administered in the neuraxial groups (2387 ± 110 epidural, 2255 ± 102 mL spinal) compared to the general anaesthetic (1537 ± 101 mL) group ($p < 0.001$)[80].

Spinal anaesthesia (CSE) versus general anaesthesia in women with pre-eclampsia

In Henke *et al.*'s review[68] there was one study that compared general anaesthesia (N = 35) to spinal anaesthesia (N = 35) (other than for the Wallace study that used CSE, rather than single shot spinal)[81]. The primary outcome in this study was umbilical arterial base deficit; they considered a difference of >8 mEq/L to be clinically significant[81]. Of note, this study was done in women undergoing emergent Caesarean delivery for a non-reassuring fetal heart rate. Although there was a higher base

deficit (7.1 vs. 4.7 mEq/L, $p = 0.02$) and lower median umbilical artery pH (7.20 vs. 7.23, $p = 0.046$) in the spinal group compared to the general anaesthesia group, the authors felt that the clinical significance was uncertain, as there was no difference in requirement for neonatal resuscitation[81]. As with other studies, the dose of ephedrine used to treat hypotension was higher in the spinal group (14 vs. 8 mg, $p = 0.002$). The dose of ephedrine did not correlate with umbilical artery base deficit.

In conclusion, spinal anaesthesia is considered to be safe in women with severe pre-eclampsia, providing there are no contraindications to its use (such as coagulopathy). More research is needed in this area, particularly with respect to vasopressor use. Although phenylephrine is used by most anaesthetists for prophylaxis and treatment of hypotension in normotensive women receiving neuraxial anaesthesia, only one study used phenylephrine to treat hypotension[65]; the rest used ephedrine. Studies are required comparing phenylephrine with ephedrine in women with severe pre-eclampsia.

Spinal anaesthesia

Spinal (vs. epidural) anaesthesia provides more rapid onset, more profound block, and a lower incidence of patchy/failed anaesthesia[82]. Also, if a blood vessel is in advertently punctured during spinal anaesthesia, the hole is smaller than that from an epidural needle, potentially decreasing the risk of a neuraxial haematoma.

In the past, spinal anaesthesia was considered to be contraindicated in women with pre-eclampsia owing to the fear of precipitating potentially fatal hypotension. However, several randomised controlled trials of women with pre-eclampsia have shown that the incidence of hypotension following spinal anaesthesia is actually *lower* than among healthy women, and that hypotension is easier to treat[73,74,83].

Some anaesthetists now use continuous spinal anaesthesia for Caesarean delivery. With continuous spinal anaesthesia, the local anaesthetic can be titrated to achieve the desired level of anaesthesia. Although spinal microcatheters (27–32 gauge) have been used in the past for continuous spinal anaesthesia, many anaesthetists now use a macrocatheter (20–22 gauge epidural catheter) as it is easier to insert than the microcatheter. Not only will some anaesthetists insert a standard epidural catheter if an accidental dural puncture occurs during attempted epidural or CSE anaesthesia, but some will electively insert it in a patient when difficulty with insertion is anticipated, such as a morbidly obese parturient. Potentially, continuous spinal anaesthesia using a macrocatheter carries a greater risk of postdural puncture headache and neuraxial haematoma, than when single-shot spinal anaesthesia is done with a smaller needle, although this is controversial.

Epidural anaesthesia

Epidural anaesthesia is not used commonly for Caesarean delivery unless the woman already has an epidural catheter in place for labour analgesia. The larger epidural needle, the slower onset of anaesthesia, the higher incidence of shivering, and the higher incidence of patchy/failed anaesthesia are potential disadvantages of epidural anaesthesia. The major advantage of epidural anaesthesia, compared to single-shot spinal anaesthesia, is the slower onset of sympathetic block, making it easier to titrate vasopressors to avoid/treat hypotension.

Combined spinal–epidural analgesia

CSE combines the advantages and disadvantages of spinal and epidural anaesthesia. Some studies suggest that combined spinal-epidural is advantageous in women with pre-eclampsia as one can use a lower intrathecal dose to initiate anaesthesia and then use the epidural catheter to adjust the height of the block[84,85]. The effective dose of medication does not appear to be different in women with (as opposed to those without) pre-eclampsia[86].

Local anaesthetic infiltration

Rarely general anaesthesia and neuraxial anaesthesia may not be available for Caesarean delivery owing to a lack of anaesthetic services or contraindications to both techniques related to the parturient's underlying disease. Under these circumstances, the only option is for the obstetrician to infiltrate the layers of the wound with local anaesthetic[87,88]. This technique uses a dilute concentration of local anaesthetic (e.g., 0.5% lidocaine) combined with epinephrine (i.e., 1:200,000) to limit absorption

and decrease the risk of local anaesthetic toxicity. As there is less dense anaesthesia, the surgeon has to handle the tissues gently or the patient will complain of pain.

Other considerations

Ergometrine is contraindicated in women with pre-eclampsia.

Oxytocin is usually administered after delivery of the baby to prevent postpartum haemorrhage. However, oxytocin should be administered by infusion and carefully titrated to effect[13]. Oxytocin should not be administered by bolus injection; using continuous minimally invasive haemodynamic monitoring in 18 women with 'severe' pre-eclampsia, 5 IU of oxytocin by IV bolus was associated with an increase in heart rate, increase in systemic vascular resistance, and fall in blood pressure[89]. Five of the 18 women had a decrease in cardiac output as they could not increase their stroke volume.

POSTPARTUM ISSUES

It is essential that postpartum, anaesthesia assesses every woman who has received anaesthetic care for potential complications and pain control. In women whose labour and delivery was uncomplicated, little or no analgesia may be required, but those who have had a long, difficult labour or operative delivery may require a more complex plan.

Anaesthetic complications – early and delayed

Depending on the type of anaesthesia given, there is a range of complications that need to be addressed should they arise in the postoperative period.

Early

In the immediate postoperative period, respiratory depression, labile blood pressure, oxygen desaturation and cardiac changes can all occur. The woman should be closely monitored in a recovery unit by someone trained in recovery care until the patient is fully awake (i.e., able to appropriately answer questions and maintain her own airway) and stable from a cardiovascular perspective[8]. The type of monitoring should include, at minimum, measurement of blood pressure non-invasively, heart rate, oxygen saturation and level of consciousness. Also, as most women undergoing general anaesthesia will have received a neuromuscular blocking agent, it is important to monitor return of neuromuscular function. Several maternal deaths have occurred in the immediate postoperative period secondary to respiratory failure (sometime owing to inadequate reversal of neuromuscular blockade[90].

While postoperative nausea and vomiting may occur following neuraxial opioids, they are more likely to occur following general anaesthesia and postoperative orders should include provision for administration of anti-emetic medications.

The challenge of balancing the need to induce general anaesthesia rapidly for the sake of the fetus/newborn while anaesthetising the mother, may lead to maternal awareness (i.e., recall of events when the patient was thought to have been anaesthetised)[91]. Caesarean delivery is one of the most common surgical procedures that lead to awareness given the lower doses of anaesthetic agents used in an effort to minimise effects on the fetus(es)[92]. Specific questioning of the mother in the postoperative period should be undertaken following any obstetric general anaesthetic in order to detect awareness[93]. If awareness is detected, a full explanation should be provided and an appropriate referral should be made for psychological assistance as post-traumatic stress disorder may otherwise arise[94].

Also, if a complication(s) has(have) occurred during the provision of general anaesthesia (such as dental damage or difficult intubation), the woman should be informed about these. Consideration should be given to providing written information about the nature of the complication and how it was managed. Also, the woman should be instructed to give the letter to her anaesthetist prior to any future anaesthetic.

Delayed

Potentially delayed complications of regional anaesthesia vary in their severity and incidence (Table 10.8).

Dural puncture is one of the most common complications. A meta-analysis of obstetric studies in this area found the incidence of accidental dural puncture to be 1.5%, with 50% of these patients going on to develop a postdural puncture headache[95]. The incidence varies greatly from one centre to another, with the number of epidurals inversely related to the number of complications[96].

Table 10.8 Postoperative complications secondary to regional anaesthesia

Procedure	*Complication*	*Sign*
Epidural or spinal	Spinal haematoma	Back pain, neurological signs
	Epidural haematoma	Back pain, neurological signs
	Dural puncture	Severe postural fronto-occipital headache/neck ache, visual disturbances
	Direct nerve damage	History of pain on injection, neurological signs
	Epidural abscess	Back pain, neurological signs, fever
	Meningitis	Fever, headache
Local anaesthetic wound infiltration	Infection	Fever
	Displacement	Pain
	Local anaesthetic toxicity	Neurological and cardiac symptoms (end result cardiac arrest)

Serious complications are rare. For example, spinal haematoma occurs in about 1:168,000 epidurals[97], and even less frequently following spinal anaesthesia. Nerve damage can occur temporarily in about 1 in 3000 patients, and permanently (i.e., for more than 6 months) in about 1 in 15,000 patients[98]. Meningitis following neuraxial anaesthesia is also a very rare complication, ranging in reported incidence from 1:50,000[99] to fewer than 1:200,000[100].

Pain

Once the patient is stable and she has been transferred to the ward, the main challenge will be pain management, especially in the absence of any supplemental regional anaesthesia.

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. Table 10.9 outlines the physiological effects of pain which include, but are not limited to, an increase in blood pressure.

There is scant literature on postpartum analgesia in women with a hypertensive disorder of pregnancy, so the management approach is based on general principles of postpartum care. Ideally, the plan for pain control will include a means of preventing pain (prophylaxis) and a means of treating breakthrough pain. Regularly administered medication via a variety of routes (multimodal) provides a baseline level of analgesia and is generally ordered for 24–48 hours postpartum. Additional oral or IV analgesics are ordered for breakthrough pain. For women planning an elective Caesarean delivery, some form of preoperative patient education may be useful in managing patients' expectations and advising on coping strategies (e.g., finding alternative ways of performing tasks that may cause pain and limiting certain activities, such as lifting).

Table 10.9 The physiological effects of pain

System	*Effect*
Cardiovascular	Increased heart rate Increased blood pressure Increased peripheral vascular resistance Increased myocardial oxygen consumption → potential for myocardial ischaemia
Respiratory	Diaphragmatic splinting
Gastrointestinal	Delayed gastric emptying Decreased bowel motility
Psychological	Anxiety Sleeplessness Low morale Postpartum depression
Neurological	Chronic pain (in up to 10% of patients postCaesarean delivery

A commonly used approach to pharmacological management is the WHO analgesic ladder, beginning with: (1) non-opioid analgesic, then adding (2) opioid for mild to moderate pain, and then (3) spinal/epidural opioid or patient-controlled analgesia, with or without other techniques, as necessary (e.g., local wound infiltration with anaesthetic) (Figure 10.2)[101].

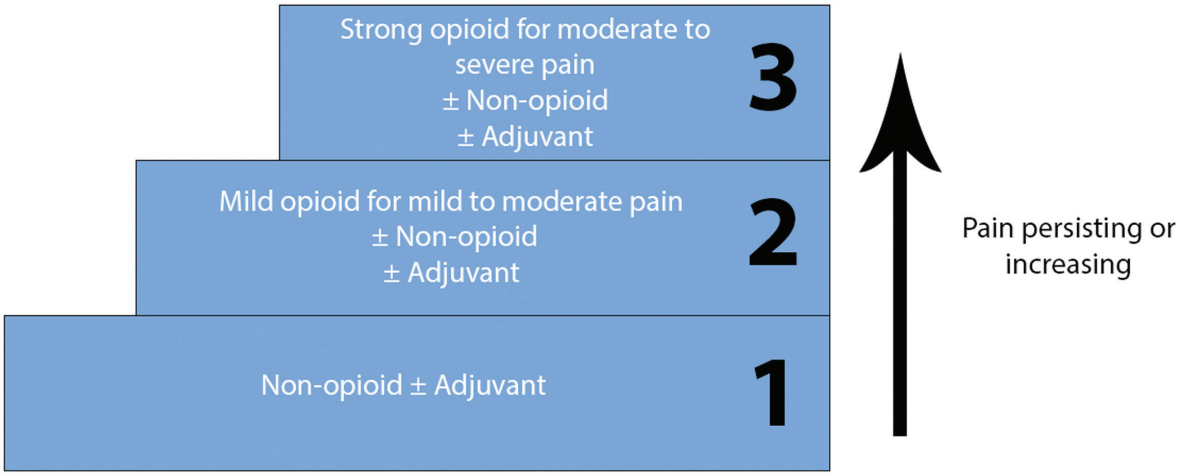

Figure 10.2 WHO analgesic ladder[101]. (Adapted for use with permission)

Oral/rectal analgesics

The non-opioid oral analgesics, paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) (Step 1, Figure 10.2) give a good base on which to build further medication needs. Both drugs are acceptable for use in breastfeeding mothers. Paracetamol (acetaminophen) is well-tolerated and demonstrates excellent synergy with many other analgesics. NSAIDs are very useful analgesics, but caution should be exercised in women with a hypertensive disorder of pregnancy. NSAIDs (e.g., ibuprofen, diclofenac, ketorolac) have antiplatelet effects (which may be an issue in the face of thrombocytopaenia); they may increase blood pressure[102], and they may reduce renal perfusion (and should therefore, not be used in the woman with renal dysfunction from pre-eclampsia).

Oral opioids (e.g., morphine, hydromorphone, oxycodone) are effective in managing moderate pain (Step 2, Figure 10.2). The American Academy of Pediatrics, the European Medicines Agency and the UK's Medicines and Healthcare Products Regulatory Agency all recommend against use of codeine during breastfeeding[103,104] as a maternal rapid acetylator phenotype may result in excessive levels of active metabolites in breast milk.

Non-opioids and opioids are usually administered orally, but an alternative route of administration is rectal. Of course, opioids can be administered by IV injection.

IV analgesics

When oral/rectal administration is not an option, pain is severe (e.g., postoperatively), or a rapid-onset of analgesia is required, IV analgesics may be used either alone or as a supplement to oral analgesics (Step 3, Figure 10.2). IV analgesics act more quickly because IV administration avoids 'first-pass' hepatic metabolism. IV analgesics are also often more potent than those administered via other routes.

The commonly used IV medications are morphine based. They are administered by the nurse or physician, or via a patient-controlled analgesia (PCA) pump. While IV opioids are an excellent option for urgent analgesia, their use should be limited as there is the potential for tolerance and addiction. In addition to IV opioids, some oral analgesics (e.g., paracetamol, ketorolac, NSAIDs) are available for intravenous use.

Some IV medications, that were not used previously for analgesia, such as ketamine and magnesium, are being investigated for their analgesic properties. When ketamine is used in low doses during general anaesthesia[105], it has a morphine-sparing effect that lasts longer (i.e., up to 24 hours) than one would anticipate based on the half-life of the drug. $MgSO_4$ also has some analgesic effect[106], an 'added bonus' in women who are administered it for eclampsia prophylaxis or treatment, or fetal neuroprotection; at present, $MgSO_4$ is not recommended for administration as an analgesic *per se*. (For more information, see Chapter 8.)

Neuraxial analgesia

A neuraxial catheter generally is removed postoperatively unless there are concerns about haemostasis or coagulation. Without a supplemental opioid, analgesia can be anticipated for 1–2 hours after spinal anaesthesia and 1–4 hours after epidural anaesthesia/analgesia, depending on the local anaesthetic used and the dose injected. When an opioid (e.g., morphine or diamorphine) is included in the spinal injectate or when an opioid is injected through the epidural catheter, effective postpartum analgesia may last up to 24 hours; the actual duration is dependent on the dose[107].

The commonly used opioids for this purpose are morphine, fentanyl and diamorphine, although some countries use pethidine (such as Australia). Other medications under investigation for neuraxial analgesia include $MgSO_4$ for its morphine-sparing action[108] and clonidine for prolonging spinal anaesthesia and improving early analgesia[109].

Another way of providing postoperative analgesia in a patient is to administer a continuous local anaesthetic ± opioid mixture through a pre-existing neuraxial catheter (epidural or spinal) by continuous infusion or patient-controlled epidural analgesia. While use of a neuraxial catheter is an effective way of providing postpartum analgesia, it is more complex. The catheter may limit patient mobility and the longer it is in place, the greater the risk of infection. This approach is generally avoided in obstetric cases unless extensive surgery has been required (e.g., laparotomy for complications) and postoperative pain control is a concern (e.g., in patients with contraindications to opioids and NSAIDs). Even in these rare cases, nurses caring for these patients postoperatively must be experienced in the management of neuraxial analgesia.

Other methods

Following general or neuraxial anaesthesia for Caesarean delivery, wound infiltration and abdominal nerve blocks reduce opioid consumption postpartum (20 trials, 1150 women)[110]. Bupivacaine-soaked sponges have been described to reduce postoperative opioid and diclofenac consumption[111].

Postoperative wound infusion is a technique whereby a catheter is inserted superficially into the abdominal wound and local anaesthetic is continuously infused. It is a technique with mixed reports of success[112–114]. A recent study suggests that subfascial placement is superior and that multiholed catheters provide better analgesic outcomes[115]. The catheter is generally placed intraoperatively just before closure of the fascia and should block superficial nerves around the wound. Inadvertent intravascular injection could result in cardiovascular and central nervous system collapse.

Transversus abdominis plane blocks often are used when neuraxial analgesia is unavailable (e.g., following general anaesthesia). They are often placed under ultrasound guidance into the transversus abdominal plane and are performed bilaterally. This is a single-shot technique and more nerves are blocked than during wound infusion. A correctly placed transversus abdominis plane block should block intercostal nerves (T7–T11), the subcostal nerves (T12) and the iliohypogastric and ilioinguinal nerves (L1). A meta-analysis by Mishriky *et al*. (9 trials, 554 patients) found that bilateral transversus abdominis plane blocks, in the absence of intrathecal morphine, are effective for post-Caesarean analgesia; however, when intrathecal (spinal) morphine has been used, there is no additional benefit of a transversus abdominis plane block. Intrathecal morphine alone provides better analgesia than transversus abdominis plane blocks alone, although this is at the expense of morphine-related side-effects[116]. A randomised controlled trial comparing transverse abdominal plane blocks with wound infiltration (both combined with paracetamol and NSAIDs) found no difference in cumulative morphine consumption following Caesarean delivery[117]. The authors recommended wound infiltration over transverse abdominal plane blocks owing to the resources and time required to do transverse abdominal plane blocks, but they acknowledged that further studies are required.

Intrathecal opioid followed by postoperative bilateral ilioinguinal nerve blocks is an approach associated with reduced morphine use postpartum[118], although there is no reduction in morphine-related side-effects[119].

BEST PRACTICE POINTS

(Please see Appendix 10.3 for the evaluation of the strength of the recommendation and the quality of the evidence on which they are based.)

1. The anaesthetist should be informed when a woman with pre-eclampsia is admitted to the delivery suite.
2. Women with pre-eclampsia should have a platelet count on admission to the delivery suite.
3. Planning for the care of women with pre-eclampsia should include members of the multi-disciplinary team.
4. The anaesthetist should assess the woman with pre-eclampsia from the standpoint of possible anaesthetic care and as her status may change, she should be reassessed.
5. Arterial line insertion may be used for continuous arterial blood pressure monitoring when blood pressure control is difficult or there is severe bleeding. An arterial line also is useful when repetitive blood sampling is required, e.g., in women with HELLP (haemolysis, elevated liver enzymes, low platelet) syndrome.
6. Central venous pressure monitoring is not routinely recommended and, if a central venous catheter is inserted, it should be used to monitor trends and not absolute values.
7. Pulmonary artery catheterisation is not recommended unless there is a specific associated indication and then only in an intensive care setting.
8. Early insertion of an epidural catheter (in the absence of contraindications) is recommended for control of labour pain.
9. In the absence of contraindications, all of the following are acceptable methods of anaesthesia for women undergoing Caesarean section: epidural, spinal, continuous spinal, combined spinal epidural and general anaesthesia.
10. A routine, fixed intravenous fluid bolus should not be administered prior to neuraxial anaesthesia.
11. Neuraxial analgesia and/or anaesthesia are appropriate in women with hypertensive disorders of pregnancy provided there are no associated coagulation concerns (Table 10.5) or specific contraindications as noted earlier in the text.

PRIORITIES FOR UNDER-RESOURCED SETTINGS

While all of the resources discussed in this chapter are considered to be essential for care of women with hypertensive disorders of pregnancy in well-resourced settings, these materials may not be available in less well-resourced areas. However, basic principles apply in all settings – working as a team to provide multidisciplinary care, and using available resources to ensure the best possible outcome for mother and baby(ies). Table 10.10 outlines suggested priorities according to the level of the health care service, with primary health centres designed to provide BEmONC and facilities designed to provide CEmONC.

A key feature of any priority-setting exercise is action and evaluation. As such, routine monitoring and evaluation of obstetric anaesthesia services must be undertaken to help improve the quality of maternity care[120]. A key component of future priorities is the proper training of non-physician anaesthesia providers, with emphasis on provision of resuscitation and regional anaesthesia techniques, since most of anaesthetics in sub-Saharan Africa are provided by this cadre of people[121]; also, these individuals can assist in providing adequate pain management for both Caesarean deliveries and vaginal deliveries, utilising simple and inexpensive methods such as single-shot spinals[122] (Figure 10.3). The availability of blood products is discussed in Chapter 8, but transfusion protocols for blood loss antenatally or postnatally should be in place in every unit[123,124].

WHAT INTERNATIONAL GUIDELINES SAY

In a review of international guidelines, only the Canadian guidelines[24,125] present a detailed list of recommendations for anaesthetic management. The latest update from the National Institute for

Table 10.10 Priorities for obstetric anaesthesia by level of health care system at which care is delivered

	Antepartum and postpartum	
	Initial priority	*Ultimate goal*
Community		
Primary health care centre for provision of BEmONC	Availability of essential equipment for monitoring, consisting of a means of measuring BP and heart rate Some means of providing left uterine displacement (e.g., wedge, blankets) Availability of essential equipment for maternal resuscitation, consisting of oxygen, suction, and intravenous access (see Table 10.1 for details) Provision of pain relief (inhalational or systemic opioids) for vaginal delivery	Ability of oxygen saturation monitoring
Facility		
Secondary-level (for provision of EmONC	Assess gestational age accurately Availability of essential equipment for monitoring, consisting of a means of measuring BP and heart rate Ability to monitor maternal well-being with laboratory testing* (blood and urine) Some means of providing left uterine displacement (e.g. wedge, blankets) Ability to monitor fetus with NST Availability of essential equipment for maternal resuscitation, consisting of oxygen, suction, equipment for intubation and ventilation, intravenous access, and emergency medications (see Table 10.1) Defibrillator Equipment to perform peri-mortem Caesarean delivery Provision of adequate pain relief for vaginal delivery and postCaesarean delivery (by inhalational of systemic means)	Ability to monitor oxygen saturation and end-tidal carbon dioxide Ability to monitor fetus with ultrasonographic assessment Provision of anaesthetic management (including neuraxial analgesia such as single-shot spinal) by non-physician provider Transfusion protocol
Tertiary-level (referral) for provision of EmONC	Assess gestational age accurately Availability of essential equipment for monitoring, consisting of a means of measuring BP and heart rate Ability to monitor maternal well-being with laboratory testing* (blood and urine) Some means of providing left uterine displacement (e.g., wedge, blankets) Monitor fetal well-being with NST and ultrasonographic assessment	Ability to monitor oxygen saturation and end-tidal carbon dioxide Provision of anaesthetic management (including neuraxial analgesia) by non-physician provider Transfusion protocol

continued

	Antepartum and postpartum	
	Initial priority	*Ultimate goal*
	Availability of essential equipment for maternal resuscitation, consisting of oxygen, suction, equipment for intubation and ventilation, intravenous access, and emergency medications (see Table 10.1)	
	Defibrillator	
	Equipment to perform peri-mortem Caesarean delivery	

BP, blood pressure; NST, non-stress test
* Complete blood count, coagulation, serum creatinine, and liver enzymes, at minimum

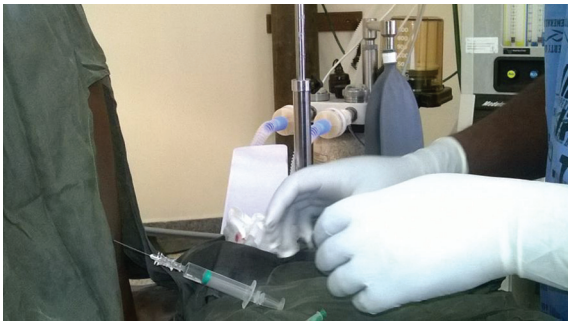

Figure 10.3 Performing single-shot spinal anaesthesia in Uganda

Health and Care Excellence (NICE) in the UK includes references to the use of remifentanil for labour analgesia and to ablate the hypertensive response to intubation[126]. The recommendations from this review of guidelines are presented in Appendix 10.4[127]. In addition, the Australasian guideline presents discussion of anaesthetic issues that are in agreement with the Canadian guideline, in terms of early involvement of the anaesthetist in the care of women with pre-eclampsia on delivery suite, no pre-loading with fluid prior to neuraxial anaesthesia, epidural analgesia as an adjunct to antihypertensive therapy, and low-dose aspirin as compatible with regional analgesia/anaesthesia; also the Australasian guidelines do a particularly good job of highlighting the potential airway problems associated with pre-eclampsia and the importance of attenuating the hypertensive response to endotracheal intubation[128].

PRIORITIES FOR FUTURE RESEARCH

Priorities for future research include:

- How can we improve maternal monitoring intrapartum, including maternal fluid status?
- Does haemodynamic monitoring during antihypertensive therapy improve maternal and perinatal outcomes?
- What is a safe platelet count for neuraxial block?
- What is the most appropriate vasopressor (and dose) for the prevention and treatment of hypotension following neuraxial block?
- What is the most appropriate strategy to manage postpartum pain?

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11

Treatment postpartum – immediate and long term

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SYNOPSIS

Hypertension may worsen transiently postpartum, especially between days 3 and 6 when blood pressure peaks. Hypertension and pre-eclampsia may even develop for the first time postpartum. Hypertension, proteinuria and the biochemical changes of pre-eclampsia begin to resolve by 6 weeks postpartum but may persist for longer, especially when those changes have been extreme. Care in the 6 weeks postpartum includes management of hypertension, ensuring resolution of biochemical changes, and screening for secondary causes of hypertension in women with resistant hypertension, impaired renal function, or abnormal urinalysis. Care providers should be aware of the mental health implications of the hypertensive disorders of pregnancy, such as anxiety, depression and post-traumatic stress disorder. The hypertensive disorders of pregnancy are also associated with a number of long-term complications and the postpartum period provides an ideal window of opportunity to address these risks, such as premature cardiovascular disease and chronic kidney disease. Women with a history of a hypertensive disorders of pregnancy should adopt a heart-healthy lifestyle and should be screened and treated for traditional cardiovascular risk factors according to locally accepted guidelines.

CARE IN THE FIRST 6 WEEKS AFTER BIRTH

Women and their maternity care providers may assume that, because delivery is the cure for pre-eclampsia, all aspects of the disease will improve postpartum. As such, it is important to manage expectations and prepare women for an alternative outcome.

Hypertension may antedate delivery in up to 50% of women with postpartum hypertension. Women with pre-existing hypertension who did not require antihypertensive medication antenatally may require such therapy after delivery[1]. Those at greatest risk of postpartum hypertension are those who delivered preterm and, for multiparous women, those with higher urate levels[2,3]. Postpartum deterioration of maternal end-organ function occurs in up to 25% of women with a hypertensive disorder of pregnancy; this deterioration usually occurs early in the puerperium, especially when women have had severe disease[4].

Hypertension that appears for the first time postpartum does so most commonly on days 3–6[5], when there is mobilisation of extracellular fluid and expansion of intravascular volume[2]. Postpartum hypertension may be isolated or associated with pre-eclampsia-related end-organ dysfunction. Two-thirds of women with postpartum pre-eclampsia have no antenatal hypertensive disorder of pregnancy and their postpartum

pre-eclampsia/eclampsia usually develops within days, but occasionally up to 3 weeks, after delivery[6].

Pre-eclampsia mimickers should be considered in women in whom pre-eclampsia worsens postpartum or in women who develop severe hypertension and HELLP (haemolysis, elevated liver enzymes, low platelet) syndrome in the postpartum period (see Chapter 3, for further details). The differential diagnosis includes disorders such as thrombotic thrombocytopaenic purpura/haemolytic uraemic syndrome (TTP/HUS), systemic lupus erythematosus and exacerbation of pre-existing renal disease. They are important to recognise because they require individualised therapeutic interventions. Key issues to consider are the urinary sediment (which must be collected by urinary catheter because of lochia), the time course of the abnormalities relative to delivery, and manifestations that may point to disease processes other than pre-eclampsia, such as a skin rash of lupus.

Management of hypertension

At minimum, blood pressure should be measured during the time of peak postpartum blood pressure elevation (for all postnatal women), on days 3–6 after delivery so that the rise in blood pressure, which may be to severe levels, does not go undetected[5,7]. All severe hypertension should be treated, be it antenatally or postpartum[8].

There are no reliable data to guide whether antenatal antihypertensive therapy should be continued postpartum. The potential advantages of continuing antihypertensives postpartum would be to decrease the risk of non-severe or severe hypertension postpartum. However, postnatal antihypertensive therapy has not been shown to decrease the development of postnatal severe hypertension, shorten hospital stay, or result in any other beneficial or adverse effects in very small published, randomised controlled trials (3 trials, 313 women)[9]. Based on data outside pregnancy, blood pressure should be treated to <140/90 mmHg but possibly to <130/80 mmHg in women with *pre-gestational* diabetes mellitus[10]. Generally, antihypertensives are needed longer in women with pre-eclampsia (approximately 2 weeks) versus gestational hypertension (about 1 week)[11].

There is no clear best choice of antihypertensive agent[9]. Any antihypertensive agent used should be based on a clinician's familiarity with the drug. Antihypertensives used most commonly in pregnancy, as well as captopril and enalapril are 'usually acceptable' for breastfeeding[12,13]. The available studies have been small and evaluated maternal serum/plasma drug and/or active metabolite concentrations, the same levels in breast milk, and infant serum/plasma/urine levels; few case reports or series have described any clinical adverse effects in infants. However, any breastfed baby who is potentially exposed to drugs through breast milk should be observed for any behavioural (e.g., excessive crying) and/or physiological (e.g., diarrhoea) concerns. Caution may be exercised in preterm and low birth weight infants owing to immature drug clearance and/or increased susceptibility to drug effects. There is particular concern about the angiotensin converting enzyme (ACE) inhibitors, at least initially until the premature baby is stabilised, but the concerns expressed by neonatologists are largely theoretical[14].

Analgesia

Control of postpartum pain is discussed in Chapter 10.

Thromboprophylaxis

Guidelines vary in their recommendations about risk factors, the number of risk factors that should prompt thromboprophylaxis, and the duration of that thromboprophylaxis. Risk factors agreed upon by most guidelines include pre-eclampsia, advanced maternal age, obesity, prolonged antenatal bed rest, postpartum haemorrhage and emergency Caesarean delivery[15–17]. Pre-eclampsia is associated with an increased risk of venous thromboembolism (VTE) (adjusted odds ratio 2.9–3.1)[17]. The risk is further increased in women with pre-eclampsia and fetal growth restriction (adjusted odds ratio 5.8)[17]. The duration of thromboprophylaxis from delivery may vary from treatment until full mobilisation, to 4–6 weeks postpartum.

CARE BEYOND THE FIRST 6 WEEKS AFTER BIRTH

Work-up to rule out underlying disease

After gestational hypertension

Gestational hypertension usually resolves by 6 weeks postpartum[18]. If it persists, particularly beyond 6 months postpartum, the woman has 'pre-existing' or 'chronic' hypertension, either

essential or secondary to another aetiology. Further investigation is warranted at that time.

Hypertension that is difficult to control (such as with three agents) in particular should prompt evaluation for a secondary cause of hypertension.

After pre-eclampsia

The hypertension of severe pre-eclampsia may take up to 3–6 months to resolve[18]. As following gestational hypertension, hypertension that persists beyond 6 months after delivery indicates chronic hypertension and warrants consideration of secondary causes.

Screening for underlying causes of pre-eclampsia may better inform management of the woman's health after the current pregnancy, between pregnancies, and/or in subsequent pregnancies. These efforts are best undertaken at 3–6 months postpartum when pregnancy-related physiology can be relied upon to have resolved.

Screening for pre-existing hypertension and underlying renal disease should be undertaken if pre-eclampsia was: (1) of onset before 34 weeks or 'severe', or (2) was followed at 3–6 months postpartum by ongoing proteinuria, estimated glomerular filtration rate (eGFR) <60 mL/min, or abnormal urinary sediment. While it is essential to ensure resolution of target organ damage (e.g., proteinuria), routine measurement of microalbuminuria after pre-eclampsia resolution is not recommended without a specific renal indication. Appropriate specialist referral (e.g., internal medicine or nephrology) should be considered for women in whom blood pressure is difficult to control or a secondary cause (including renal disease) is suspected.

Special mention of thrombophilia screening is warranted. Thrombophilia confers, at most, a weakly increased risk of pre-eclampsia (and other placentally mediated pregnancy complications). Routine thrombophilia screening following pre-eclampsia is not recommended[20] because of this weak association and, also, because treatment with thromboprophylaxis has not been demonstrated to improve outcomes[21]; an individual patient data meta-analysis is being performed to examine whether there is a high-risk subgroup of women who may benefit from thromboprophylaxis and therefore, could be screened for thrombophilia[22]. Until such time, the one subgroup of women who may benefit from antiphospholipid antibody screening is pre-eclampsia with delivery at <34 weeks, as these women would meet criteria for the antiphospholipid antibody syndrome (APAS) and the diagnosis would influence future management outside pregnancy (e.g., choice of contraception) at minimum[23].

Future pregnancy planning

The recurrence risk of a hypertensive disorder of pregnancy depends in part on the disorder and its characteristics in the previous pregnancy and characteristics of the woman, particularly obesity. Recurrence is discussed in detail in Chapter 5. In brief, gestational hypertension is followed by a hypertensive disorder of pregnancy risk of about 25% in the subsequent pregnancy, and almost all is gestational hypertension (21%) rather than pre-eclampsia (4%). In contrast, pre-eclampsia is followed by a higher hypertensive disorder of pregnancy risk of 40%, with just over half as pre-eclampsia (22%) and the rest as gestational hypertension (15%); recurrence rates are higher (exceeding 50% in some reports) when pre-eclampsia was 'severe' or associated with HELLP syndrome specifically.

Implications for long-term paediatric health

The short-term implications for the fetus and newborn are discussed in Chapter 3. Discussed here is the fact that the hypertensive disorders of pregnancy may have long-term implications for the child beyond the complications of preterm delivery and/or fetal growth restriction. Although any potential impact on neurodevelopment is of keen interest to practitioners, there are other chronic diseases associated with the hypertensive disorders of pregnancy and/or preterm delivery of which the clinician should be aware.

Neurodevelopment

Pre-eclampsia superimposed on pre-existing hypertension (versus pre-existing hypertension alone) has no adverse effect on (or slightly better) intellectual development[24]. There is no literature available on the independent impact of antihypertensive therapy.

Gestational hypertension and pre-eclampsia may predict generally modest long-term effects on child development. Children of women with pre-eclampsia had better outcomes (i.e., *reduced*

internalising morbidity such as anxiety) at ages 5 and 8 years, but children of women with gestational hypertension were more likely to have poorer behaviour from 8 years onwards, with the largest difference seen at 14 years; no information was provided on the potential impact of antihypertensive therapy[25]. Both types of hypertensive disorders of pregnancy were associated with a small reduction in verbal ability of uncertain clinical significance[26]. The neurodevelopmental effects of pre-eclampsia persisted even when matched or adjusted for gestational age and growth restriction[27]. Although placental abruption is an additional risk factor for adverse neurodevelopmental outcomes, it has not been studied in conjunction with pre-eclampsia[28].

It should be noted that not all studies provide a consistent picture of the association between the hypertensive disorders of pregnancy and paediatric cognitive function. The mixed pattern of results likely arises from methodological differences, particularly varying study populations and study designs[27]. The lack of much information on antihypertensive therapy is a major drawback to this literature. There are a handful of small randomised controlled trials that have examined paediatric neurodevelopment. Babies of antihypertensive (mainly methyldopa)-treated mothers (versus normotensive controls) more often had delayed fine-motor function at 6 months of age, while those of placebo-treated hypertensive mothers more frequently had 'questionable' neurological assessment and delayed gross-motor function at 12 months[29]. In other small randomised controlled trials, antihypertensive therapy was not associated with negative effects on child development when assessed at 1 year, 18 months, or 7.5 years (methyldopa, 242 children)[30], 18 months (atenolol, 190 children)[31], or 7.5 years (nifedipine, 110 children)[32]. In contrast, in an observational controlled study, methyldopa (25 exposed children) (but not labetalol, 32 exposed children) was associated with lower intelligence quotient (IQ) scores, but in multivariable regression, IQ was associated with maternal IQ and duration of antihypertensive treatment[33].

Other long-term outcomes

Higher blood pressure A systematic review and meta-analysis found that children exposed to pre-eclampsia had higher systolic and diastolic blood pressure values during childhood and young adulthood when compared with controls[34,35]. The degree of elevated blood pressure is related to preterm birth and higher body mass index (BMI) of the children[34,35]. The blood pressure effects were present at age 21 years[36].

Stroke In the Helsinki birth cohort (6410 pregnancies), pre-eclampsia was associated with an increased risk of stroke in the adult offspring[37].

Pregnancy complications of their own In a population-based cohort study (24,119 women), hypertensive disorders of pregnancy and gestational diabetes mellitus (GDM) were increased in women who were themselves born preterm, especially before 32 weeks[38]. Although this was a study of preterm birth in general, the hypertensive disorders of pregnancy were found to be an important cause of iatrogenic preterm birth.

Implications for long-term maternal health

Pregnancy is considered a biological 'stress test' that can predict a woman's health in later life[39]. The hypertensive disorders of pregnancy, particularly pre-eclampsia, are associated with a number of future health risks. Identifying women at risk by virtue of the physiologic stress test of a pregnancy complicated by pre-eclampsia is a unique opportunity to address and prevent chronic illnesses.

Cardiovascular risk factors and disease

The American Heart Association has recognised pre-eclampsia and gestational hypertension as 'major' cardiovascular risk factors for women[40–42]. Pre-eclampsia has a pathophysiology remarkably similar to cardiovascular disease, in terms of metabolic abnormalities (such as hyperlipidaemia and insulin resistance), a heightened inflammatory response, a hypercoagulable state and endothelial dysfunction[43].

It is likely that some women are predisposed to pre-eclampsia because of an adverse pre-pregnancy cardiovascular risk profile, which lowers the threshold for a hypertensive response to placentally derived products[44]. The alternative hypothesis is that pre-eclampsia itself damages a woman's endothelium and produces permanent metabolic sequelae, leading to increased long-term cardiovascular risk[39,43].

A large prospective study examined the cardiovascular risk profiles of women who developed a hypertensive disorder of pregnancy and found that women with gestational hypertension and pre-eclampsia, compared with women who had a normotensive pregnancy, had higher BMI, lower levels of high density lipoprotein (HDL), and higher levels of triglycerides, low density lipoprotein (LDL) and total cholesterol[45].

A small case–control study conducted at 1 year postpartum showed asymptomatic left ventricular moderate–severe dysfunction/hypertrophy was significantly higher in women who had suffered from preterm pre-eclampsia (56%) compared with term pre-eclampsia (14%) or matched controls (8%; $p<0.001$)[46]. This suggests that pre-eclampsia is associated with persistent postpartum cardiovascular impairment.

Three large systematic reviews have consistently demonstrated that women with a history of pre-eclampsia have a higher risk of cardiovascular and cerebrovascular disease[47–49] (Table 11.1). The 2007 systematic review by Bellamy *et al.* included 25 studies, and approximately 3 million women of whom 25,000 had pre-eclampsia[47]. McDonald *et al.* in their 2008 review included 15 studies and a total of 118,990 women with a history of pre-eclampsia/eclampsia and 2,259,576 women with unaffected pregnancies[49]. A recent review by Brown *et al.* in 2013 included 50 papers but did not state the number of women included[48]. While there are methodological differences, the results have been generally similar amongst the reviews.

KEY POINT

Pre-eclampsia is associated with a number of long-term health complications including hypertension, heart disease, stroke, renal disease and diabetes

Hypertension

Bellamy *et al.* found that pre-eclampsia was associated with development of hypertension later in life, after a mean follow-up of 14 years with a relative risk of 3.7 (95% CI 2.70–5.05)[47]. For women with gestational hypertension, the risk of developing subsequent hypertension was similar to women with a risk of hypertension (RR 3.39, 95% CI 0.82–13.92) at a mean of 11 years postpartum[47]. Brown *et al.* had similar results with a relative risk of 3.13 (95% CI 2.51–3.89) for women with a history of pre-eclampsia/eclampsia[48].

Ischaemic heart disease

In the systematic review of Bellamy *et al.*, the relative risk of fatal or non-fatal ischaemic heart disease in women with pre-eclampsia was over twice that of women without pre-eclampsia (RR 2.16, 95% CI 1.86–5.20)[47]. The risk of ischaemic heart disease also occurred earlier at a mean of 11.7 years after the index pregnancy. In McDonald *et al.*'s review, women with a history of pre-eclampsia/eclampsia had an increased risk of subsequent cardiac disease, in both case–control studies (odds ratio 2.47, 95% CI 1.22–5.01) and cohort studies (RR 2.33, 95% CI 1.95–2.78)[49]. Brown *et al.* found that women who experienced pre-eclampsia were at more than two fold increased odds of cardiovascular disease (OR 2.28, 95% CI 1.87–2.77) with similar results between the cohort and control studies[48].

Bellamy *et al.* found that women with severe pre-eclampsia had a greater risk of developing later ischaemic heart disease (RR 2.86, 95% CI

Table 11.1 Risk of cardiovascular disease after pre-eclampsia (95% CI presented in parentheses)

	Bellamy[47] (2007)	*McDonald[49] (2008)*	*Brown[48] (2013)*
Hypertension	Pre-eclampsia: RR 3.7 (2.70–5.05) Gestational hypertension: RR 3.39 (0.82–13.92)	Not analysed	RR 3.13 (2.51–3.89)
Ischaemic heart disease	RR 2.16 (1.86–5.20)	OR 2.47 (1.22–5.01)* RR 2.33 (1.95–2.78)†	OR 2.28 (1.87–2.77)
Stroke	RR 1.81 (1.45–2.27)	OR 2.6 (1.5–4.3)* RR 2.03 (1.54–2.67)†	OR 1.77 (1.43–2.21)

* Case–control studies; †cohort studies

1.65–2.24) compared to women who had mild pre-elampsia (RR 1.92, 95% CI 1.65–2.24) particularly if pre-eclampsia occurred before 37 weeks (RR 7.71, 95% CI 4.40–13.52)[47]. This 'dose response' effect was not, however, demonstrated in the review by Brown. The review by Brown compared outcomes for pre-eclampsia both with and without preterm birth using three studies whilst the data from Bellamy came from only one study[48].

The risk of cardiovascular disease may be further increased in the presence of poor fetal outcomes. In a population-based retrospective cohort study of women with maternal placental syndrome (defined as pre-eclampsia, gestational hypertension, placental abruption, and/or placental infarction), the risk of premature cardiovascular disease was higher in the presence of poor fetal growth (adjusted hazard ratio (aHR) 3.1, 95% CI 2.2–4.5) or intrauterine fetal death (aHR 4.4, 95% CI 2.4–7.9)[50]. A Canadian population-based retrospective cohort study of 1985 women found that in middle-aged women (mean age 45 years) who underwent coronary revascularisation, prior maternal placental syndrome (such as pre-eclampsia) doubled the risk of death (aHR 1.61, 95% CI 1.00–2.58)[51].

Stroke

Bellamy's review found that the overall risk of fatal and non-fatal cerebrovascular disease (stroke or non-fatal stroke) after pre-eclampsia was 1.81 (95% CI 1.45–2.27) compared with women who had not developed pre-eclampsia. Subgroup analysis showed that the risk of fatal stroke (RR 2.98, 95% CI 1.11–7.96) was greater than that of non-fatal stroke (RR 1.76, 95% CI 1.40–2.2) after pre-eclampsia[47]. A diagnosis of pre-eclampsia before 37 weeks was associated with a further elevation in risk (RR 5.08, 95% CI 2.09–12.35) compared with pre-eclampsia after 37 weeks (RR 0.98, 95% CI 0.50–1.92). McDonald included only one eligible case–control study which reported an increased risk of 2.6 (95% CI 1.5–4.3) consistent with the pooled estimate in the six cohort studies (RR 2.03, 95% CI 1.54–2.67)[49].

Renal disease

Pre-eclampsia has been associated with an increased risk of end-stage kidney disease in large observational studies.

A large retrospective cohort study from Norway (20,918 women with pre-eclampsia) found that pre-eclampsia in the first pregnancy was associated with a relative risk of end-stage kidney disease of 4.7 (95% CI 3.6–6.1). This risk increased further to 6.7 (95% CI 4.3–10.6) among women who also had pre-eclampsia only in their second pregnancy, and increased again if women had pre-eclampsia in both their first and second pregnancies or in three pregnancies (RR 15.5, 95% CI 7.8–30.8)[52].

In a population-based study from Taiwan (8653 women with gestational hypertension, 17,998 women with pre-eclampsia), having had either gestational hypertension or pre-eclampsia was associated with a greater risk of chronic kidney disease (aHR 9.4, 95% CI 7.1–12.4) and end-stage renal disease (aHR 12.4, 95% CI 8.5–18.0), even after controlling for several factors including coronary artery disease, congestive heart failure, hyperlipidaemia and abruption[53]. The greatest risk of end-stage renal disease was associated with having had pre-eclampsia or eclampsia (aHR 14.0, 95% CI 9.4–20.7) compared with gestational hypertension (aHR 9.0, 95% CI 5.2–15.7)[53].

Other chronic diseases

Diabetes In a population-based study (50,598 women with a hypertensive disorder of pregnancy), women with a prior hypertensive disorder of pregnancy had a two-fold increased risk of developing diabetes when followed up to 16.5 years after pregnancy, even in the absence of a prior history of gestational diabetes[54]. A history of a hypertensive disorder of pregnancy and gestational diabetes together increased the risk associated with GDM alone[54].

Elevated thyroid stimulating hormone (TSH) In a nested case–control study of women with pre-eclampsia from two large cohort studies (Calcium for Pre-eclampsia Prevention trial[55] and the Nord-Trondelag Health Study[56]), women with prior pre-eclampsia had higher thyroid stimulating hormone (TSH) levels compared with controls who had no history of a hypertensive disorder of pregnancy[57]. Of note, women with prior pre-eclampsia were less likely to have thyroid peroxidase antibodies, suggesting that their hypothyroidism was occurring in the absence of an autoimmune process. The association between

pre-eclampsia and elevated TSH was especially strong (adjusted OR 5.8, 95% CI 1.3–25.5) if pre-eclampsia had occurred in both the first and the second pregnancies[57].

Central nervous system white-matter lesions Several studies have shown that women whose pregnancies were complicated by pre-eclampsia or eclampsia are more likely than controls to have white matter lesions; although these may reflect a predisposition to vascular disease, the significance of these lesions is currently unknown[58,59].

Mental health Pre-eclampsia can be very stressful for women and their partners[60], especially relative to expectations of a routine, normal pregnancy and no prior significant illness[60]. Women may have to deal with postpartum recovery from hypertension, end-organ complications, and frequently, Caesarean delivery. In addition, women may have to deal with perinatal loss or illness, such as care in the neonatal intensive care unit (NICU).

A systematic review showed that while the evidence is not entirely consistent, in general, there is an association with prior pre-eclampsia or HELLP syndrome and more anxiety, depression and post-traumatic stress disorder (6 studies, 5636 women)[61]. Women who experienced severe maternal morbidity were shown to be at particular risk of post-traumatic stress disorder (1824 women)[62]. Women with severe pre-eclampisa who must deal with a perinatal death or NICU admission are at particular risk of poor health-related (especially mental health-related) quality of life[63]. These effects of pre-eclampsia on mental health may persist beyond the short term; women with preterm birth owing to severe, early-onset pre-eclampsia (compared with women with preterm birth for other reasons) more often experienced post-traumatic stress symptoms an average of 7 years postpartum[64].

Postpartum care of women with pre-eclampsia should include evaluation and referral for postpartum psychological care. It is important for women to receive relevant information about not only their medical condition, but their psychological condition as well. It is also necessary to examine coping strategies after pre-eclampsia and offer adequate supportive interventions when they are needed[60].

Investigations and interventions to improve long-term health

Pregnancy and the immediate postpartum period may be one of the few times in a woman's life when she accesses the health care system regularly. Therefore, the postpartum period provides a unique window of opportunity for early identification and reduction of primary cardiovascular risk.

Education/awareness

Among women A small study using focus groups found that women with prior pre-eclampsia were unaware of the link between pre-eclampsia and future cardiovascular disease, but were eager to learn about the link and motivated to achieve a healthy lifestyle[65]. Another study found that women generally had a low level of cardiovascular risk factor knowledge[66].

Although some guidelines, such as those from NICE (UK), recommend that future cardiovascular risk should be communicated to the woman before discharge from maternal services, some argue that it may be too early for most women[67,68]. Women may be recovering from serious morbidity whilst balancing the demands of the neonate; this may limit the efficacy of the communication. Women's reactions to learning about the link between pre-eclampsia and future cardiovascular disease included both positive feelings (i.e., motivation, empowerment) and negative ones (i.e., being scared, angry, guilty, or isolated)[65]. Therefore, it is important that women are followed on an ongoing basis and receive information about cardiovascular health over time.

Recently, an educational intervention to promote cardiovascular knowledge and awareness was tested amongst women with a history of pre-eclampsia. The intervention, delivered by telephone given that postpartum women have many demands on their time, had several components: diet, exercise, medication compliance, screening for risk factors and symptoms of myocardial infarction. It was found to be a practical and effective method of contacting postpartum women following pre-eclampsia and increasing perception of cardiovascular risk[66].

Among health care providers There is also a lack of awareness amongst health care providers and gaps in identification and routine follow-up.

Though the American Heart Association recommends that health professionals disclose the future risk of cardiovascular disease to women with a history of pre-eclampsia, a study revealed that only a third of health professionals provide that counselling[69]. A review of the existing literature on engaging obstetricians and gynaecologists in cardiovascular risk reduction found that while they agreed that their role extended beyond reproductive care, there was variation in practice and they were unlikely to manage hypertension or elevated cholesterol. Obstetricians and gynaecologists identified knowledge and skill deficits, concerns about liability, and barriers to prevention presented by their practice structure. Some providers also emphasised difficulties completing referrals to primary care providers[70]. A Canadian survey of maternity care providers found that only 54% of participants were familiar with the long-term cardiovascular risks of pre-eclampsia[71]. A small retrospective review from The Netherlands examined cardiovascular risk factor management and found that only 50% of women with pre-eclampsia had their blood pressure measured by 3 months postpartum. Blood glucose and lipids were infrequently checked even though some of the women had cardiovascular risk factors prior to the index pregnancy[72]. Appendix 11.1 contains training materials for health care providers including multiple choice questions and a case study. Knowledge translation tools for health care providers are included in Appendix 11.2.

Cardiovascular risk factor screening

At present, there are no guidelines advising when to screen women with a prior hypertensive disorder of pregnancy or pre-eclampsia for cardiovascular risk factors. (Cardiovascular risk factor screening in women with pre-existing or chronic hypertension has been published by all national societies.) The very earliest would be at 3–6 months postpartum when the metabolic changes of pregnancy (such as dyslipidaemia) have resolved.

Traditional cardiovascular markers appear to be more abnormal in women who have suffered from pre-eclampsia, as early as 1 year postpartum[73]. A small study from the Maternal Health Clinic, a postpartum cardiovascular risk reduction clinic in Kingston, Canada, sought to determine whether women with a history of pre-eclampsia (N = 99) compared with those without pre-eclampsia (N = 118) had 10-year, 30-year and lifetime cardiovascular risk estimates that were high enough at 1 year postpartum to identify them as warranting further counselling and follow-up regarding lifestyle modification and/or pharmacotherapy[74]. Using traditional cardiovascular risk markers (i.e., sex, age, smoking, serum total cholesterol, serum LDL cholesterol, serum HDL cholesterol, fasting plasma glucose, systolic blood pressure, diastolic blood pressure and antihypertensive use), the study found that women who had suffered from pre-eclampsia (versus those who had not) more often had elevated 10-year cardiovascular risk (i.e., 18.2% vs. 1.7%, respectively; OR 13.1, 95% CI 3.4–85.5), 30-year cardiovascular risk (i.e., 31.3% vs. 5.1%, respectively, OR 8.4, 95% CI 3.5–23.2), and lifetime cardiovascular risk (i.e., 41.4% vs. 17.8%, respectively; OR 3.3, 95% CI 1.8–6.1)[74]. A follow-up study showed that the Maternal Health Clinic could identify a population of postpartum patients with increased 10- and 30-year cardiovascular risk[75].

KEY POINT

Following pre-eclampsia, it would seem prudent to screen women for traditional cardiovascular risk markers according to national guidelines which should also dictate intervention for abnormal results

It remains unclear whether traditional risk factors, such as those used in the Maternal Health Clinic, are sufficient for cardiovascular risk screening. First, global risk assessment tools like the Framingham Risk Score may not accurately estimate cardiovascular risk in young women, especially in the short term; a study of 2333 women using the Framingham Offspring cohort showed that the 10-year model estimates negligible risks for young women, whereas the 30-year model suggests a risk that is 10 times higher[76]. Second, cardiovascular risk factors used in prediction models like the Framingham or Reynolds Risk Score may not fully explain the risk of cardiovascular disease after pre-eclampsia; in a literature based study that included 16 studies, a major part of the observed OR of cardiovascular disease after pre-eclampsia remained after adjustment for these traditional cardiovascular risk factors[77].

In summary, it remains unclear both *when* cardiovascular risk screening should take place

following pre-eclampsia, and at *what threshold* treatment should begin. There are public health implications and costs to consider. Although it may be appropriate to intervene at earlier stages in this population, we should await supportive research findings. In the meantime, it would seem prudent to screen women who have had pre-eclampsia for traditional cardiovascular risk markers according to national guidelines which should also dictate intervention for abnormal results.

A simple approach that has been proposed in this population of women is the identification of any of the components of metabolic syndrome as the syndrome does not predict clinical outcomes better than its individual components[78]. These components include:

- Blood pressure
- Weight and height are measured to calculate the BMI
- Lipid panel
- Glucose intolerance screening.

All women with gestational diabetes should undergo postpartum glucose tolerance testing. In addition, some recommend that postpartum testing for glucose intolerance should be ordered for all women with one of the other components of metabolic syndrome, such as obesity[78]. Abnormalities in any of the above components should be treated as per current national guidelines or prompt referral to an internal medicine specialist.

Lifestyle change

What is appropriate and evidence-based for all is adoption of a heart-healthy diet and lifestyle to decrease cardiovascular risk (Table 11.2)[40]. Of course, neither is an easy intervention and there are barriers to change that are specific to postpartum women.

Women may be motivated by the knowledge that weight *gain* between pregnancies predicts pre-eclampsia and other pregnancy complications (e.g., gestational diabetes and Caesarean delivery)[80,81], and weight *loss* between pregnancies may improve future pregnancy outcome in addition to long-term cardiovascular risk. However, there are many competing demands on a new mother's time.

Major perceived barriers to lifestyle change identified in a qualitative (American) study of 20 postpartum women were lack of time, cost of healthy foods and family responsibilities[65]. Another (Dutch) study of 36 women identified additional barriers of poor postpartum physical and psychological recovery, and lack of postpartum medical and psychological support from health care providers[82]. Perceived facilitators have included knowledge of the link between pre-eclampsia and cardiovascular disease, a desire to stay healthy, and creating a healthy home for their children[65]. This link to child health may be a key motivator of change.

Currently, postpartum lifestyle interventions tailored specifically for women following a hypertensive disorder of pregnancy are lacking, although those demonstrated to be effective outside

Table 11.2 Dietary and lifestyle modifications recommended for all women[40] (with permission from Society of Obstetricians and Gynaecologists of Canada)

Intervention	*Details*
Heart-healthy diet	Maintain a healthy balanced diet (high in fruits, vegetables, low-fat dairy products, reduced in saturated fat and cholesterol) in addition to dietary and soluble fibre, whole grains and protein from plant sources[79]
Regular physical activity	Undertake 150 minutes/week of moderate to vigorous-intensity aerobic physical activity (such as walking, jogging, cycling or swimming)
Alcohol consumption	Reduce alcohol consumption to <2 drinks/day and <9/week
Weight reduction	Attain and maintain ideal body weight (i.e., BMI 18.5–24.9 kg/m^2)
Reduce waist circumference	Attain and maintain a waist circumference of <88 cm
Salt intake	Reduce intake to <1500 mg/d
Smoking cessation	Quit smoking in addition to ensuring a smoke-free environment

BMI, body mass index

pregnancy have been tested in unselected postpartum populations[83]. Among postpartum women in general (21 studies, 6288 women), most weight loss interventions (6 of 8) were effective, as were most smoking cessation interventions (4 of 5). Also effective were individualised tailoring of counselling, group counselling sessions, and use of diaries or other correspondence material. Of note, the Maternal Health Clinic (Kingston, ON) has designed 'The Postpartum Mother's Health Record', a card that allows women to set goals and track weight loss[84]. The timing of data collection coincides with the infant's scheduled visits and immunisations, linking maternal and child health going forward – a practical and potentially more feasible approach for the new mother. Appendix 11.2 highlights knowledge translation tools for women including mobile apps, programmes and research studies.

Focus groups with women with prior pre-eclampsia indicated potential interest in a web-based programme focused on lifestyle strategies to decrease cardiovascular risk[65]. This approach was tested in a small feasibility study (20 women) of a web-based, tailored health education intervention related to diet and exercise, in conjunction with counselling by a psychologist (Dutch ProActive study, Postpartum Rotterdam Appraisal of Cardiovascular Health and Tailored Intervention)[85]. The intervention was initiated at 6 months postpartum and continued for 3 months. In all 60% of women participated and anthropometric measurements at 13 months postpartum improved significantly, although metabolic parameters did not[85].

Bariatric surgery for women with morbid obesity

Women who are morbidly obese and have failed lifestyle interventions to achieve weight loss are candidates for bariatric surgery without considering potential effects on future pregnancy, which are mixed. There are no randomised controlled trials for women planning pregnancy, but in a retrospective cohort study of insurance claims data (585 women)[86] and two controlled registry studies (identifying 1085 women with prior bariatric surgery)[87,88], women who had undergone bariatric surgery (vs. those who had not) experienced lower rates of all hypertensive disorders of pregnancy (including pre-eclampsia)[86], gestational diabetes and large-for-gestational infants[87], as well as fewer emergency Caesarean deliveries[88] following adjustment for confounders. However, these benefits have not been consistently demonstrated, with one registry study demonstrating *higher* rates of hypertension and gestational diabetes following bariatric surgery[88]. In addition, potential benefits appear to come at the price of more gastrointestinal problems[88,89], lower birth weight[88], more small-for-gestational age (SGA) infants[87], earlier delivery[87] and, possibly, higher perinatal mortality[87,88] and admission to NICU[88]. Therefore, at present, there are insufficient data to support recommendations to undergo bariatric surgery to favourably affect future pregnancy outcomes.

BEST PRACTICE POINTS

(Please see Appendix 11.3 for the evaluation of the strength of the recommendations and the quality of the evidence on which they are based.)

Care in the 6 weeks after birth

1. Blood pressure should be measured during the time of peak postpartum blood pressure, at days 3–6 after delivery.
2. Women with postpartum hypertension should be evaluated for pre-eclampsia (either arising *de novo* or worsening from the antenatal period).
3. Antihypertensive therapy may be continued postpartum, particularly in women with antenatal pre-eclampsia and those who delivered preterm.
4. Severe postpartum hypertension must be treated with antihypertensive therapy, to keep systolic blood pressure <160 mmHg and diastolic blood pressure <110 mmHg.
5. Antihypertensive therapy may be used to treat non-severe postpartum hypertension, to keep blood pressure at <140/90 mmHg for all but women with pre-gestational diabetes mellitus among whom the target should be <130/80 mmHg.

6. Antihypertensive agents acceptable for use in breastfeeding include nifedipine XL, labetalol, methyldopa, captopril and enalapril.
7. There should be confirmation that end-organ dysfunction of pre-eclampsia has resolved.
8. Non-steroidal anti-inflammatory druds (NSAIDs) should not be given postpartum if hypertension is difficult to control, there is evidence of kidney injury (oliguria and/or an elevated creatinine) (≥90 μmol/L) or platelets are $<50 \times 10^9$/L.
9. Postpartum thromboprophylaxis should be considered in women with pre-eclampsia who have other risk factors for thromboembolism.

Care beyond the first 6 weeks after birth

1. Women with a history of severe pre-eclampsia (particularly those who presented or delivered at <34 weeks) should be screened for pre-existing hypertension and underlying renal disease.
2. Referral for internal medicine or nephrology consultation should be considered for women with postpartum hypertension that is difficult to control, or women who had pre-eclampsia and have at 3–6 months postpartum ongoing proteinuria, decreased eGFR (<60 mL/min), or another indication of renal disease (such as abnormal urinary sediment).
3. Women who are overweight should be encouraged to attain a healthy body mass index to decrease risk in future and for long-term health.
4. Women with pre-existing hypertension or persistent postpartum hypertension should undergo the following investigations (if not done previously): urinalysis; serum sodium, potassium and creatinine; fasting glucose; fasting lipid profile; and standard 12-lead electrocardiography.
5. Women who are normotensive but who have had a hypertensive disorder of pregnancy, may benefit from assessment of traditional cardiovascular risk markers.
6. All women who have had a hypertensive disorder of pregnancy should pursue a healthy diet and lifestyle.

PRIORITIES FOR UNDER-RESOURCED SETTINGS

The priorities for postpartum care of women with hypertensive disorders of pregnancy in under-resourced settings are outlined in Table 11.3. A sample policy brief that focuses on postnatal care is contained in Appendix 11.4.

In LMICs, routine postnatal care has the potential to improve both maternal and neonatal outcomes. In LMICs, almost 40% of women experience complications after delivery and an estimated 15% develop potentially life-threatening problems[90]. More than half of maternal deaths occur postpartum and the vast majority (i.e., 80%) of those occur in the first week postpartum[91]. Such visits are most likely to detect early complications that may be addressed by referral for specialist care.

Also, postnatal care has the potential to identify neonatal sepsis and asphyxia/hypothermia, the leading causes of neonatal death in LMICs. Finally, postnatal care helps to promote healthy maternal behaviours, such as exclusive breastfeeding and proper care of babies with low birth weight.

> "By the 6th week the child is due for pentavalent. That is . . . the diphtheria, tetanus and all . . . at that 6 week [mark]. That is the time (when) the lady is also due for the 6 week postnatal review. But many a time the postnatal review is not done . . . because of lack of manpower at the PHC. You have a lot of children and . . . so sometimes to attend to mother, and educate and counsel takes time."
>
> Stakeholder, Local Government in Ogun, Nigeria

Postnatal care is reported at much lower rates than for other maternal and infant health services[92]. In a review of Demographic and Health Survey (DHS) data from 1990 to 2009 in 38 countries in four regions (i.e., sub-Saharan Africa; North Africa/West Asia/Europe; South/Southeast Asia; and Latin America and the Caribbean), approximately half of the countries with data (i.e., 8 of 18) provided at least one demonstrated postnatal visit to more than half (64–92%) of postpartum women within 41 days after giving birth[93]. Even within those countries, postnatal visits varied from 64% to

Table 11.3 Priorities for postpartum care in under-resourced settings

	Initial priority	*Ultimate goal*
Community		
Primary health care centre (detect, stabilise and refer)	A health care visit within 24 hours after the birth	A health care visit within 24 hours after the birth and then again at least three more times – on day 3, in the second week, and again at 6 weeks
	BP measurement shortly after birth and at 6 hours	BP measurement shortly after birth and at 6 hours
	Counselling about the signs and symptoms of pre-eclampsia at each postpartum visit	Counselling about the signs and symptoms of pre-eclampsia at each postpartum visit
Facility		
Secondary-level facility (detect, manage and refer if necessary) Tertiary-level (referral) facility (detect and manage definitively)	Delivery in facility of all women with a HDP	Delivery in facility of all women with a HDP
	Management of women with HDPs, including postpartum pre-eclampsia (see Table 4.4, Chapter 4)	Management of women with HDPs, including postpartum pre-eclampsia (see Table 4.4, Chapter 4)
		Counselling about BP monitoring as well as heart-healthy diet and lifestyle following a HDP

BP, blood pressure; HDP, hypertensive disorder of pregnancy

92% of relevant women. Although there was a strong relationship between receiving postnatal care and both more antenatal visits and having skilled birth attendance, the major determinant of postnatal care was delivery in facility. (A recent systematic review found that inequities in the use of postnatal services is also based on socioeconomic status, education, ethnicity and geographical location[94].) Following delivery in facility, at least two-thirds of women reported postnatal care in all countries except Uganda and Zimbabwe where less than half of the women reported postnatal checkups. Women who delivered in a health facility (compared with those who did not) were more likely to report postnatal visits, to have the first visit within 2 days after birth, and to receive postnatal care from a doctor, nurse, or midwife. Among women who did not deliver at a health facility, postnatal care was reported for less than 50% with the exception of a few countries in South/Southeast Asia (i.e., Cambodia and the Philippines), sub-Saharan Africa (i.e., Ghana and Madagascar), and Latin America and the Caribbean (i.e., Bolivia, the Domincan Republic and Peru).

In recognition of the postnatal period as ". . . a critical phase in the lives of mothers and newborn babies", the 2013 WHO guidelines on postnatal care[95] recommend the following:

- A health care visit within 24 hours after the birth and then again at least three more times – on day 3, in the second week, and again at 6 weeks;
- Blood pressure measurement shortly after birth and at 6 hours, although there is no guidance around blood pressure measurement during the rest of the postpartum period;
- Counselling about the signs and symptoms of pre-eclampsia at each postpartum visit.

It is important to recognise that in a LMIC, postpartum care may be provided in the community rather than in facility, and by varying cadres of health care workers. For example, lay health workers may undertake promotion of postpartum care, while nurses and midwives may initiate treatment of pre-eclampsia[96]. All of these workers need to be trained accordingly.

Global initiatives that address the link between a woman's reproductive health and long-term health are lacking. To prevent non-communicable diseases in the offspring, the International Federation of Gynaecology and Obstetrics (FIGO) recently announced that it is partnering with other agencies and organisations that focus on enforcing interventions, such as good nutrition and minimisation of harmful environmental exposures during pregnancy[97]. While this initiative

acknowledges the role of non-communicable diseases within the reproductive, maternal, neonatal and child health continuum, it does not address the long-term chronic illnesses that may develop as a result of a complicated pregnancy.

WHAT INTERNATIONAL GUIDELINES SAY (APPENDIX 11.5)

Abbreviations for Clinical Practice Guidelines: ACOG (American College of Obstetricians and Gynecologists)[99], AOM (Association of Ontario Midwives), NICE (National Institutes of Clinical Excellence)[67], NVOG (National Obstetrics and Gynaecology Society, Netherlands)[100], QLD (Queensland, Australia)[101,102], SOGC (Society of Obstetricians and Gynaecologists of Canada)[103,104], SOMANZ (Society of Obstetric Medicine of Australia and New Zealand)[105,106], WHO (World Health Organization)[107].

Most international guidelines highlighted that pre-eclampsia may develop *de novo* or worsen in the postpartum period (AOM, ACOG, NICE, SOGC, QLD).

The majority of guidelines stated that blood pressure may increase postpartum and recommended continuing antihypertensive therapy that women had been taking antepartum (NICE, ACOG, SOGC). Importantly, no guideline recommended that antenatal antihypertensive therapy be stopped. Although the treatment of severe hypertension followed similar recommendations to those antenatally, treatment targets for non-severe hypertension were generally lower and varied amongst guidelines (NICE, SOGC, ACOG); most commonly, clinicians are recommended to aim for a blood pressure <150/100 mmHg for women with gestational hypertension or pre-eclampsia (NICE, ACOG).

Most of the guidelines specifically mentioned the association between the hypertensive disorders of pregnancy (particularly pre-eclampsia) and future cardiovascular health, and suggested lifestyle counselling as the logical response (AOM, ACOG, NICE, SOGC, QLD, SOMANZ).

SUMMARY

Care in the immediate postpartum period should focus on the management of hypertension using treatment options that are acceptable during breastfeeding. Consideration should be given to postpartum thromboprophylaxis in women with a hypertensive disorder of pregnancy if other risk factors are present. NSAIDs should be avoided if hypertension is difficult to control or there is either a coagulopathy or renal dysfunction. All women with pre-eclampsia should be followed closely after delivery to ensure resolution of end-organ damage. Women should be screened for underlying disease that may have predisposed to pre-eclampsia and pre-eclampsia mimickers should also be ruled out. Finally, the postpartum period offers a unique window of opportunity to address short- and long-term risks of hypertensive disorders of pregnancy. Women should be counselled about the ideal inter-pregnancy interval as well as risks in future pregnancies. Women should be evaluated for risk factors for premature cardiovascular disease as well as other complications such as chronic kidney disease. Currently, the focus should be on the adoption of a heart-healthy lifestyle and screening for traditional cardiovascular risk factors.

PRIORITIES FOR FUTURE RESEARCH

Given the global rise in non-communicable diseases and the risk stratification that pregnancy appears to provide, there is an urgent need to identify how a woman's pregnancy history can be added to currently available cardiovascular disease risk scoring systems to identify and manage women at increased risk for cardiovascular disease.

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Appendices

The reference numbers cited in the appendices refer to the references given at the end of the relevant chapter in the main section of the textbook

Appendix 1.1

Training module for automated blood pressure measurement by community health care workers – adapted from materials from the CLIP Trial for use with the Microlife 3AS1-2 with guidance from the Piers On the Move (POM) app

The CRADLE BP device (Microlife 3AS1-2) is a hand-held, upper-arm, semi-automated blood pressure device that has been successfully validated for use in a non-pregnant population[108] and for use in pregnancy (including pre-eclampsia)[109]. It is being used for BP measurement in the community setting in the CLIP Trial.

Instructions for use of the Microlife 3AS1-2 by community health care workers are as follows:

1. Have the woman rest for at least 5 minutes. She should be seated, without talking or reading.
2. Position the woman properly. She should be seated with her back against a chair. Both feet should be on the floor.
3. Place the cuff on her arm. Either arm may be used. Ensure that there is no tight clothing around her upper arm. The cuff should be placed so that the bottom is 1–2 cm above the elbow. The arm should then rest on a table or the arm rest of the chair if the arm rest is high enough. The woman must remain still, with no movement and no talking.
4. Take the blood pressure. Turn on machine and inflate the cuff by hand, the cuff will then deflate automatically. Keep the device as still as possible during cuff deflation or alternatively, let it rest on the table during deflation. If the cuff has not been inflated to the correct pressure, the device will indicate this with a 'beeping' sound; if this occurs, inflate the cuff to 30 mmHg higher than the previous inflation pressure that caused the beeping and then try letting the cuff deflate again.
5. Record the first blood pressure measurement.
6. Wait 1 minute during which time the woman should remain still, without moving, talking, or reading.

7. Repeat the blood pressure measurement (i.e., step #4). All women will receive two blood pressure measurements, and an average of the two measurements should be used to indicate the blood pressure for that visit (i.e., the two measurements are added and divided by two).
8. If the second measurement differs significantly (>10 mmHg) from the first, a third measurement is required. In this case the second and third measurements will be averaged to determine the blood pressure.
9. If at any time an 'error' message is received, repeat the measurement.

Appendix 1.2

GRADE evaluation of best practice points regarding hypertension

Recommendation	*Quality of evidence**	*Strength of recommendation†*
Diagnosis of hypertension		
1. The diagnosis of hypertension should be confirmed by health facility BP measurements.	Low	Strong
2. Hypertension in pregnancy should be defined as a sBP ≥140 mmHg and/or dBP ≥90 mmHg, based on the average of at least two measurements, taken at least 15 minutes apart, using the same arm.	Low	Weak (sBP) Strong (dBP)
3. For the purposes of defining superimposed pre-eclampsia in women with pre-existing hypertension, resistant hypertension should be defined as the need for three antihypertensive medications for BP control at ≥20 weeks' gestation.	Low	Weak
4. A 'transient' hypertensive effect should be defined as a sBP ≥140 mmHg or a dBP ≥90 mmHg which is not confirmed on the same visit after the woman rests, or on subsequent visits.	Very low	Weak
5. A 'white coat' hypertensive effect refers to BP that is elevated in a health facility (i.e., sBP ≥140 mmHg or dBP ≥90 mmHg) but by ABPM or HBPM, sBP is <135 mmHg and dBP is <85 mmHg.	Very low	Strong
6. 'Masked' hypertension refers to BP that is normal in the health facility (i.e., sBP <140 mmHg and dBP <90 mmHg) but elevated by ABPM or HBPM (i.e., sBP of ≥135 mmHg or dBP ≥85 mmHg).	Very low	Weak
7. Severe hypertension should be defined as a sBP of ≥160 mmHg or a dBP of ≥110 mmHg based on the average of *at least* two measurements, taken at least 15 minutes apart, using the same arm.	Low	Strong
BP measurement		
1. BP should be measured using standardised technique, particularly with the woman seated and her arm at the level of the heart.	Low	Strong
2. An appropriately sized cuff (i.e., length of 1.5 times the circumference of the arm) should be used.	Low	Strong
3. Korotkoff phase V (marked as disappearance of Korotkoff sounds) should be used to designate dBP.	Moderate	Strong
4. If BP is consistently higher in one arm, the arm with the higher values should be used for all BP measurements.	Very low	Weak
5. BP can be measured using a mercury sphygmomanometer, calibrated aneroid device, or an automated BP device that has been validated for use in pre-eclampsia.	Low	Strong
6. Automated BP machines that have not been validated for use in pre-eclampsia may under- or over-estimate BP, so those readings should be compared with those using mercury sphygmomanometry or a calibrated aneroid device.	Low	Strong

continued

Appendix 1.2 *continued*

Recommendation	*Quality of evidence**	*Strength of recommendation†*
7. In a health facility setting, when BP elevation is non-severe and pre-eclampsia is not suspected, ABPM or HBPM is useful to confirm persistently elevated BP.	Very low	Weak
8. When HBPM is used, maternity care providers should ensure that women have adequate training in measuring their BP and interpreting the readings taken.	Very low	Strong
9. The accuracy of all BP measurement devices used in health facilities should be checked regularly (e.g. annually) against a calibrated device.	Very low	Strong
10. The accuracy of all automated devices used for HBPM should be checked regularly against a calibrated device (e.g., at multiple ANC for an individual woman).	Very low	Strong

* The judgements about the quality of evidence is based on the confidence that available evidence reflects the true effect of the intervention or service. Evidence is considered to be of *high quality* when the true effect is thought to lie close to that of the estimate of the effect (e.g., if there is a wide range of studies included in the analyses with no major limitations, there is little variation between studies, and the summary estimate has a narrow confidence interval). Evidence is considered to be of *moderate quality* when the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different (e.g., if there are only a few studies and some have limitations but not major flaws, there is some variation between studies, or the confidence interval of the summary estimate is wide). Evidence is considered to be of *low quality* when the true effect may be substantially different from the estimate of the effect (e.g., the studies have major flaws, there is important variation between studies, or the confidence interval of the summary estimate is very wide)

† A *strong recommendation* should be interpreted as meaning that most people in this situation would want the recommended course of action and only a small number would not. Clinicians should regard the recommendation as applying to most individuals. Policy-makers can adopt the recommendation as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. A *weak recommendation* should be interpreted as meaning that the majority of people in this situation would want the recommended course of action, but many would not; patients' values and preferences should be considered in reaching a decision. Decision aids may support people in reaching these decisions. Policy-making will require substantial debate and involvement of various stakeholders. An appropriately documented decision making process could be used as a quality indicator

Appendix 1.3

Sample policy brief for blood pressure measurement

ELEVATED BLOOD PRESSURE IS AN ESSENTIAL DIAGNOSTIC CRITERIA FOR THE HYPERTENSIVE DISORDERS OF PREGNANCY

Approximately 99% of all global maternal deaths occur in resource-constrained regions. Between one-third and one-half of those deaths result from the hypertensive disorders of pregnancy which cannot be diagnosed if blood pressure is not measured.

WE ARE FALLING SHORT OF OUR BLOOD PRESSURE MEASUREMENT TARGETS

Routine blood pressure measurement is part of prescribed antenatal and postnatal care in all countries for the purpose of detecting the hypertensive disorders of pregnancy and preventing complications for mothers and babies. WHO recommends blood pressure measurement at each antenatal visit, shortly after birth, and again within 6 hours after birth. Furthermore, hypertension may worsen transiently postpartum, especially between days 3 and 6 when blood pressure peaks. Monitoring of blood pressure should continue in the 6 weeks postpartum to prevent long-term complications.

Although blood pressure measurement is one of the more commonly received components of antenatal care in LMICs, many women still do not have their blood pressure measured and rates are as low as 40%.

WHICH BLOOD PRESSURE MEASUREMENT DEVICE SHOULD BE USED?

There are three types of blood pressure measurement devices available: mercury sphygmomanometers, aneroid (dial) devices and automated devices. Availability and accuracy in pregnancy are the key concepts that need to be considered when choosing a device.

Mercury manometers and aneroid (dial) devices require a trained health care provider to use a stethoscope. For health and safety reasons, mercury devices are largely unavailable outside of biomedical departments that check the accuracy of institutional blood pressure measurement devices. Those devices are usually aneroid. These need to be checked ('calibrated') at least once every 2 years, something that is often not done.

Automated blood pressure measurement devices can be used without stethoscopes by all health care workers, or in the home by the woman herself. While training/instruction in their use is necessary, they do not demand the skill required to use a stethoscope, therefore enabling task-sharing across health worker cadres. They maintain their accuracy over time and many are inexpensive. A critically important point is that devices used must be accurate for use in pregnancy; most devices have been neither tested nor found to be accurate. Furthermore, devices must be validated for use specifically in pre-eclampsia, the most dangerous of the hypertensive disorders of pregnancy; many of the devices used in pregnancy that have been tested have not been found to be accurate for this purpose. Microlife and OMRON have marketed devices suitable for use in pre-eclampsia. The Microlife 3AS1-2 is a low-cost device suitable for use in pre-eclampsia as well as in under-resourced settings.

ACTIONS

Ensure provision of accurate blood pressure devices at the primary and all health care levels.

Integrate blood pressure measurement into routine antenatal and postnatal care, especially at the primary health centre level.

Task shift to enable midwives, nurses and lower-level workers to correctly measure and

interpret blood pressure, and subsequently refer women to the appropriate level of care.

Update national protocols and clinical guidelines to facilitate education and training about blood pressure measurement by health care workers, including all of those in the community.

Integrate blood pressure measurement into quality assurance checklists and initiatives.

Appendix 1.4

Recommendations for blood pressure measurement and diagnosis from international clinical guidelines*

	SOMANZ 2014	*PRECOG II (DAU) 2009*	*PRECOG 2005*
Measurement of BP			
Position	BP should be measured with the woman seated comfortably with her legs resting on a flat surface		
Cuff size	An appropriately sized cuff (i.e., use large cuff with inflatable bladder covering 80% of arm circumference when upper arm circumference is greater than 33 cm) should be used	Measure BP with equipment that is accurate in individual hypertensive pregnant women Use appropriate *cuff size*–thigh cuffs (18×36 cm) for women with an arm circumference of 41 cm or more. Follow PRECOG recommendation 6 for reducing errors in BP measurement	
Korotkoff phase for BP	Disappearance of Korotkoff (K) phase V should be used to designate diastolic BP First sound heard of K phase I defines the systolic BP		
Which arm to use	Measurements should be undertaken in both arms at the initial visit to exclude vascular abnormalities		
Type of device	Mercury sphygomomanometers remain the gold standard. Other devices that may be used are automated BP recorder and aneroid devices		
Choice of automated BP device	Automated BP recorders and aneroid devices are prone to errors and each unit should maintain a mercury sphygmomanometer for validation of those devices		

NICE 2010	*NVOG 2011*	*WHO 2011*	*ACOG 2013*	*SOGC 2014*
				BP should be measured with the woman in the sitting position with the arm at the level of the heart
				An appropriately sized cuff (i.e., length of 1.5 times the circumference of the arm) should be used Weak
				Korotkoff phase V should be used to designate diastolic BP Weak
				If BP is consistently higher in one arm, the arm with the higher values should be used for all BP measurements
				BP can be measured using a mercury sphygmomanometer, calibrated aneroid device, or an automated BP device that has been validated for use in PE
				Automated BP machines that have not been validated for use in PE may under- or over-estimate BP in those women and comparison of readings using mercury sphygmomanometry or a calibrated aneroid device is recommended

continued

Appendix 1.4 *continued*

	SOMANZ 2014	*PRECOG II (DAU) 2009*	*PRECOG 2005*
Measurement of BP			
Home and ambulatory BP monitoring	24-h ambulatory BP monitoring or repeated home BP monitoring can be used to diagnose white coat hypertension in early pregnancy		
Precautions to take when choosing HBPM			
Maintenance of hospital BP measurement devices	All devices should be calibrated on a regular basis (ideally monthly)		
Maintenance of home BP measurement devices			
Diagnosis of hypertension			
Location/type for measurements			
Defining hypertension	Defined as sBP ≥140 mmHg and/or dBP ≥90 mmHg confirmed by repeated readings over several hours		dBP ≥90 mmHg
Defining resistant hypertension			

NICE 2010	*NVOG 2011*	*WHO 2011*	*ACOG 2013*	*SOGC 2014*
			For women with GH we suggest BP be monitored at least once weekly with proteinuria assessment in the office and with an additional weekly *measurement of BP at home* or in the office. For pregnant women with chronic hypertension and poorly controlled BP we suggest the use of HBPM For women with suspected white coat hypertension, we suggest the use of ABPM to confirm the diagnosis before the initiation of antihypertensive therapy	In the office setting, when BP elevation is non-severe and PE is not suspected, ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) are useful to confirm persistently elevated BP
				When HBPM is used, maternity care providers should ensure that patients have adequate training in measuring their BP and interpreting the readings taken
				The accuracy of all BP measurement devices used in hospitals or offices should be checked regularly against a calibrated device
				The accuracy of all automated devices used for HBPM should be checked regularly against a calibrated device
				The diagnosis of hypertension should be based on office or in-hospital BP measurements
			sBP ≥140 mmHg and/or a dBP ≥90 mmHg Two occasions at least 4 h apart	Hypertension in pregnancy should be defined as an office (or hospital) sBP ≥140 mmHg and/or dBP ≥ 90 mmHg, based on the average of at least two measurements, taken at least 15 minutes apart, using the same arm
				For the purposes of defining superimposed PE in women with pre-existing hypertension, resistant hypertension should be defined as the need for three antihypertensive medications for BP control at ≥20 weeks' gestation

continued

Appendix 1.4 *continued*

	SOMANZ 2014	*PRECOG II (DAU) 2009*	*PRECOG 2005*
Diagnosis of hypertension			
Defining transient hypertension	Defined as women referred for assessment of new onset hypertension with normal BP and investigations *Repeat assessment should be arranged within 3–7 days* *Synonymous for labile hypertension*		
Defining white coat hypertension	Defined as hypertension in a clinical setting with normal BP away from this setting assessed by 24-h ABPM		
Defining masked hypertension			
Defining severe hypertension	Defined as a sBP ≥170 mmHg or a dBP of ≥110 mmHg		

PE, pre-eclampsia
* SOMANZ 2014 is included in the chapter text, but not in this table adapted from Gillon 2014[118]
† Techniques for measurement of BP in pregnancy are described in 'Antenatal care' (NICE clinical guidance 62)
ACOG 2013: American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013 Nov; 122(5):1122–1131
NICE 2010: National Collaborating Centre for Women's and Children's Health (UK). CG107: Hypertension in pregnancy: The management of hypertensive disorders during pregnancy. NICE: Guidance 2010 Aug
NVOG 2011: Nederlandse Vereniging voor Obstetrie en Gynaecologie. Hypertensieve aandoeningen in de zwangerschap. 2011

NICE 2010	*NVOG 2011*	*WHO 2011*	*ACOG 2013*	*SOGC 2014*
				A 'transient' hypertensive effect should be defined as office sBP ≥140 mmHg or a dBP ≥90 mmHg which is not confirmed after rest, on repeat measurement on the same or on subsequent visits
				A 'white coat' hypertensive effect refers to BP that is elevated in the office (i.e., sBP ≥140 mmHg or dBP ≥90 mmHg) but ABPM or HBPM sBP is <135 mmHg and dBP is <85 mmHg
				A 'masked' hypertensive effect refers to BP that is normal in the office (i.e., sBP <140 mmHg and dBP <90 mmHg) but elevated by ABPM or HBPM (i.e., sBP of ≥135 mmHg or dBP ≥85 mmHg)
			sBP ≥160 mmHg and/or a dBP ≥110 mmHg Diagnosis can be confirmed within a shorter interval (even minutes) to facilitate timely antihypertensive therapy	Severe hypertension should be defined, in any setting, as a sBP of ≥160 mmHg or a dBP of ≥110 mmHg based on the average of *at least* two measurements, taken at least 15 minutes apart, using the same arm

PRECOG: Milne F, Redman C, Walker J, Baker P, Bradley J, Cooper C, et al. The pre-eclampsia community guideline (PRECOG): how to screen for and detect onset of pre-eclampsia in the community. BMJ 2005 Mar 12;330(7491):576–80
PRECOG II: Milne F, Redman C, Walker J, Baker P, Black R, Blincowe J et al. Assessing the onset of pre-eclampsia in the hospital day unit: summary of the pre-eclampsia guideline (PRECOG II). BMJ 2009; 339:b3129
SOGC 2014: Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. Pregnancy Hypertens 2014;4(2):105–145
SOMANZ 2014: Lowe SA, Bowyer L, Lust K, McMahon LP, Morton MR, North RA, et al. The SOMANZ guideline for the management of hypertensive disorders of pregnancy. Sydney: SOMANZ; 2014
WHO 2011: World Health Organization. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. 2011

Appendix 2.1

Proteinuria – policy brief

PROTEINURIA – Policy brief

Urinary dipsticks should be made consistently available wherever antenatal and postnatal care is provided.

WHY SCREEN FOR PROTEINURIA IN PREGNANCY?

The presence of proteinuria identifies women who are at increased risk of adverse outcomes for themselves and their babies.

Although a level of proteinuria above which risk is substantially increased has not been determined, in resource-constrained settings where maternal symptoms and signs alone are used to guide treatment, dipstick proteinuria of 4+ is associated with an increased risk of stillbirth.

Above: A diagram showing the procedure of proteinuria measurement.

HOW TO SCREEN FOR PROTEINURIA AND BY WHOM?

Use of urinary dipsticks for proteinuria screening is easy and inexpensive. Testing can be performed following minimal training and is a method well-suited to task-shifting.

Dipsticks should be used for screening in preference to other methods until such time that another method proves to be superior.

ACTIONS

- Screening for proteinuria should be integrated into existing antenatal and postnatal programmes.
- Urinary dipsticks should be made consistently available wherever antenatal and postnatal care is provided. This will require strengthening of the supply chain and procurement services at national and sub-national levels.
- National and international guidelines should include guidance around proteinuria measurement.
    - At minimum, proteinuria should be performed at first of the four WHO recommended antenatal visits AND whenever hypertension is detected.
    - Proteinuria testing should be performed at the six-week postpartum visit in women who developed proteinuria in pregnancy.

At minimum, proteinuria testing should be performed at the first of the four WHO-mandated antenatal visits, when hypertension is detected, and at the 6-week postpartum visit in women who developed proteinuria in pregnancy.

Appendix 2.2

Methods of proteinuria assessment

	Advantages	*Disadvantages*	*Comments**
Random urine samples	*Easy to perform*	*Excretion may vary over a 24-hour period*	
Dipstick testing			
For protein	Widely used in pregnancy	Poor sensitivity and specificity for quantification of proteinuria Results vary according to urine concentration	Results vary according to test strips and analyser used; testing using automated analyser may decrease reading bias
For albumin	More specific for glomerular proteinuria	Results vary according to urine concentration	No studies for diagnosis of significant proteinuria
For PrCr	Urinary creatinine 'correction' for concentration	No information in pregnancy	No studies for diagnosis of significant proteinuria
For ACR	More specific for glomerular proteinuria	Less information and validation for use in pregnancy compared with urinary dipstick	Available on strips for visual read, point of care or on laboratory automated analyser More costly than urinary dipstick for protein
*Spot testing**			
Urinary PrCr	Widely studied	Less reliable at high range proteinuria	Current cut-off is 30 mg/mmol to detect 0.3 g/d of proteinuria but optimal threshold may be slightly higher and published cut-offs range from 17 to 71 mg/mmol
Urinary ACR	More specific for glomerular proteinuria	Less information and validation for use in pregnancy compared with PrCr	Ideal cut-off to identify 0.3 g/d of proteinuria unclear, possibly within the range of 2–8 mg/mmol.
Other methods			
Heat coagulation test	Low cost	Requires test tubes, burner, and test reference card	This is an alternative to urinary dipstick testing when test strips are not available and pre-eclampsia (or renal disease) is suspected
Sulfosalicylic acid test	Low cost	False positive in alkaline or dilute urine	Same as for heat coagulation test

continued

Appendix 2.2 *continued*

	Advantages	*Disadvantages*	*Comments**
*Timed urine collections**	*Reflect total 24 h excretion in complete collection*	*Inconvenient* *Inaccurate when incomplete*	*Urinary creatinine excretion is helpful to estimate under or over-collection*
24 hour			
For proteinuria	Traditional gold standard for quantification of proteinuria		
For albuminuria		Less studied in pregnancy compared with total proteinuria	
2–12 hour			
For proteinuria or albuminuria		Less studied and used in clinical practice	

ACR, albumin : creatinine ratio; PrCr, protein : creatinine ratio
* The values of proteinuria and albuminuria vary according to local laboratory methods; urinary creatinine reporting is now standardized in many laboratories

Appendix 2.3

GRADE evaluation of best practice points regarding proteinuria

	*Quality of evidence**	*Strength of recommendation†*
1. All pregnant women should be assessed for proteinuria, at minimum, at their first antenatal visit.	Low	Weak
2. Urinary dipstick testing (or SSA or heat coagulation testing if dipsticks are not available) may be used for screening for proteinuria when the suspicion of pre-eclampsia is low.	Low	Weak
3. Significant proteinuria should be strongly suspected when urinary dipstick proteinuria is ≥2+.	Moderate	Strong
4. Definitive testing for proteinuria (by urinary protein : creatinine ratio or 24-hour urine collection) is encouraged when there is a suspicion of pre-eclampsia.	Moderate	Strong
5. Significant proteinuria is ≥0.3 g/d in a complete 24-hour urine collection or ≥30 mg/mmol (≥0.3 mg/mg) urinary creatinine in a random urine sample.	Moderate	Strong
6. There is insufficient information to make a recommendation about the accuracy of the urinary albumin:creatinine ratio, although values <2 mg/mmol (<18 mg/g) are normal and all values ≥8 mg/mmol (≥71 mg/g) are elevated..	Low	Strong
7. In well-resourced settings with sophisticated fetal monitoring, proteinuria testing does not need to be repeated once the significant proteinuria of pre-eclampsia has been confirmed.	Moderate	Strong
8. In under-resourced settings, proteinuria testing should be repeated to detect 4+ dipstick proteinuria that is associated with an increased risk of stillbirth.	Low	Weak

GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; SSA, sulfosalicylic acid

* The judgements about the quality of evidence is based on the confidence that available evidence reflects the true effect of the intervention or service. Evidence is considered to be of high quality when the true effect is thought to lie close to that of the estimate of the effect (e.g., if there is a wide range of studies included in the analyses with no major limitations, there is little variation between studies, and the summary estimate has a narrow confidence interval). Evidence is considered to be of moderate quality when the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different (e.g., if there are only a few studies and some have limitations but not major flaws, there is some variation between studies, or the confidence interval of the summary estimate is wide). Evidence is considered to be of low quality when the true effect may be substantially different from the estimate of the effect (e.g., the studies have major flaws, there is important variation between studies, or the confidence interval of the summary estimate is very wide)

† A strong recommendation should be interpreted as meaning that most people in this situation would want the recommended course of action and only a small number would not. Clinicians should regard the recommendation as applying to most individuals. Policy-makers can adopt the recommendation as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. A weak recommendation should be interpreted as meaning that most people in this situation would want the recommended course of action, but many would not; patients' values and preferences should be considered in reaching a decision. Decision aids may support people in reaching these decisions. Policy-making will require substantial debate and involvement of various stakeholders. An appropriately documented decision making process could be used as a quality indicator

Appendix 2.4

Recommendations for proteinuria diagnosis in international pregnancy hypertension guidelines*

See next page – this appendix requires a double-page layout

	PRECOG II (DAU) 2009	*PRECOG 2005*	*AOM 2012*
General considerations			Urinary protein should also be reassessed by dipstick at the time of the second BP measurement
Screening means/ method	Estimate proteinuria by dipsticks and follow PRECOG recommendation 7 to improve reliability; 6 Accuracy is not increased by retesting a new sample. Use the higher of the dipstick results from the community and the day assessment unit		
Definition of significant proteinuria	Exclude significant proteinuria by calculating the urinary protein to creatinine ratio from a random sample or confirm and quantify by 24 hour urine collection. Use a threshold ratio of 30 to exclude significant proteinuria	≥1+ (300 mg/L) on dipstick testing, a protein : creatinine ratio of ≥30 mg/mmol on a random sample, or a urine protein excretion of ≥300 mg/24 h	For urine dipstick values equivalent to ≥0.3 g/L (≥+1 on urine dipstick) in addition to other signs or symptoms of pre-eclampsia, further investigation and/or a prompt medical consult should be arranged
Reading urinary dipstick tests			

BP, blood pressure; PE, pre-eclampsia; PET, pre-eclamptic toxaemia
* SOMANZ 2014 is included in the chapter text, but not in this table adapted from Gillon 2014[63]
ACOG 2013: American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013 Nov; 122(5):1122–1131
AOM 2012: Salehi P, Association of Ontario Midwives HDP CPG, Working Group. Hypertensive disorders of pregnancy (Clinical Practice Guideline 15). 2012; Available: http://www aom on ca/Health_Care_Professionals/Clinical_Practice_ Guidelines/
NICE 2010: National Collaborating Centre for Women's and Children's Health (UK). CG107: Hypertension in pregnancy: The management of hypertensive disorders during pregnancy. NICE: Guidance 2010 Aug
NVOG 2011: Nederlandse Vereniging voor Obstetrie en Gynaecologie. Hypertensieve aandoeningen in de zwangerschap. 2011

NICE 2010	*QLD 2013*	*NVOG 2011*	*WHO 2011*	*ACOG 2013*	*SOGC 2014*
					All pregnant women should be assessed for proteinuria ideally at each routine antenatal visit
Use an automated reagent-strip reading device or a spot urinary protein : creatinine ratio for estimating proteinuria in a secondary care setting					Urinary dipstick testing (by visual or automated testing) may be used for screening for proteinuria when the suspicion of PE is low
Diagnose significant proteinuria if the urinary protein : creatinine ratio is >30 mg/mmol or a validated 24-hour urine collection shows >300 mg protein Where 24-hour urine collection is used to quantify proteinuria, there should be a recognized method of evaluating completeness of the sample	–	Definition of PET lists ≥0.3 g/d	Definition of PET lists ≥0.3 g/d	–	Significant proteinuria should be defined as ≥0.3 g/d in a complete 24-hour urine collection or ≥30 mg/mmol urinary creatinine in a spot (random) urine sample
If an automated reagent-strip reading device is used to detect proteinuria and a result of ≥1+ is obtained, use a spot urinary protein : creatinine ratio or 24-hour urine collection to quantify proteinuria	Proteinuria should be strongly suspected when urinary dipstick proteinuria is ≥"2+"				Significant proteinuria should be suspected when urinary dipstick proteinuria is ≥1+

QLD 2013: Queensland Maternity and Neonatal Clinical, Guidelines Program. Hypertensive disorders of pregnancy. 2013;MN10.13-V4-R15
PRECOG: Milne F, Redman C, Walker J, Baker P, Bradley J, Cooper C, et al. The pre-eclampsia community guideline (PRECOG): how to screen for and detect onset of pre-eclampsia in the community. BMJ 2005 Mar 12;330(7491):576–80
PRECOG II: Milne F, Redman C, Walker J, Baker P, Black R, Blincowe J et al. Assessing the onset of pre-eclampsia in the hospital day unit: summary of the pre-eclampsia guideline (PRECOG II). BMJ 2009; 339:b3129
SOGC 2014: Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. Pregnancy Hypertens 2014;4(2):105–145
WHO 2011: World Health Organization. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. 2011

Appendix 3.1

GRADE evaluation of best practice points regarding classification of hypertensive disorders of pregnancy

	*Quality of evidence**	*Strength of recommendation†*
1. HDPs should be classified as pre-existing hypertension or gestational hypertension with or without pre-eclampsia, or 'other' hypertension on the basis of different diagnostic and therapeutic considerations.	Low	Strong
2. The presence or absence of pre-eclampsia must be ascertained, given its clear association with more adverse maternal and perinatal outcomes.	Low	Strong
3. In women with pre-existing hypertension, pre-eclampsia should be defined as resistant hypertension, new *or* worsening proteinuria, one or more adverse conditions, or one or more severe complications.	Low	Strong
4. In women with gestational hypertension, pre-eclampsia should be defined as new-onset proteinuria, one or more adverse conditions, or one or more severe complications.	Low	Strong
5. The assessment of maternal angiogenic factor balance appears to inform the diagnosis of pre-eclampsia, and other placental complications of pregnancy, where uncertainty exists, especially when 'superimposed pre-eclampsia' is suspected.	Moderate	Strong
6. Severe pre-eclampsia should be defined as pre-eclampsia complicated by one or more severe complications.	Low	Strong
7. For women with pre-existing hypertension, serum creatinine, fasting blood glucose, serum potassium, and urinalysis should be performed in early pregnancy if not previously documented.	Low	Weak
8. Among women with pre-existing hypertension or those with a strong clinical risk marker for pre-eclampsia, additional baseline laboratory testing may be based on other considerations deemed important by health care providers.	Very low	Weak
9. Women with suspected pre-eclampsia should undergo the maternal laboratory and a schedule of pertinent fetal testing described in Table 3.3.	Moderate	Strong
10. Doppler velocimetry-based assessment of the fetal circulation may be useful to support a placental origin for hypertension, proteinuria, and/or adverse conditions (including IUGR), and for timing of delivery.	Moderate except for timing of delivery which is high	Weak except for timing of delivery which is strong
11. The BPP is not recommended as part of a schedule of fetal testing in women with a HDP.	Moderate	Weak
12. If initial testing is reassuring, maternal and fetal testing should be repeated if there is ongoing concern about pre-eclampsia (e.g., change in maternal and/or fetal condition).	Low	Weak

continued

Appendix 3.1 *continued*

	*Quality of evidence**	*Strength of recommendation†*
13. In resource-constrained settings, the miniPIERS model can provide personalised risk estimation for women with any HDP. In many of these women, the ultimate diagnosis cannot be confirmed until at least three months after delivery.	High	Strong
14. Health care providers should be alert to symptoms of post-traumatic stress following a HDP; and refer women for appropriate evaluation and treatment.	Low	Weak
15. Health care providers should inform their patients, antepartum and postpartum, about pre-eclampsia, its signs and symptoms, and the importance of timely reporting of symptoms to health care providers.	Very low	Weak
16. Information should be re-emphasised at subsequent visits.	Very low	Weak

GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; HDP, hypertensive disorder of pregnancy; BPP, biophysical profile

* The judgements about the quality of evidence is based on the confidence that available evidence reflects the true effect of the intervention or service. Evidence is considered to be of high quality when the true effect is thought to lie close to that of the estimate of the effect (e.g., if there is a wide range of studies included in the analyses with no major limitations, there is little variation between studies, and the summary estimate has a narrow confidence interval). Evidence is considered to be of *moderate quality* when the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different (e.g., if there are only a few studies and some have limitations but not major flaws, there is some variation between studies, or the confidence interval of the summary estimate is wide). Evidence is considered to be of low quality when the true effect may be substantially different from the estimate of the effect (e.g., the studies have major flaws, there is important variation between studies, or the confidence interval of the summary estimate is very wide).

† A *strong recommendation* should be interpreted as meaning that most people in this situation would want the recommended course of action and only a small number would not. Clinicians should regard the recommendation as applying to most individuals. Policy-makers can adopt the recommendation as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. A weak recommendation should be interpreted as meaning that most people in this situation would want the recommended course of action, but many would not; patients' values and preferences should be considered in reaching a decision. Decision aids may support people in reaching these decisions. Policy-making will require substantial debate and involvement of various stakeholders. An appropriately documented decision making process could be used as a quality indicator.

Appendix 3.2

Classification of the hypertensive disorders of pregnancy according to international clinical practice guidelines*

See next page – this appendix requires a double-page layout

	PRECOG 2005	*PRECOG II 2009*	*QLD 2013*	*NICE 2010*	*WHO 2011*
Pre-existing (chronic) hypertension					
Definition	dBP ≥90 mmHg before pregnancy or at booking before 20 weeks	dBP ≥90 mmHg before pregnancy or at booking before 20 weeks	(specify essential without known cause) BP >140/90 mmHg before pregnancy or 20 weeks or if woman taking antihypertensive(s) when she conceives	"Hypertension" at booking or before 20 weeks or if woman taking antihypertensives when referred to maternity services.	
With comorbid conditions			"Secondary" causes are listed		
Superimposed PET	New features of ET (includes women with pre-existing proteinuria)	New features of PET	New systemic features of PET after 20 weeks		
Includes women with pre-existing proteinuria	√				
Superimposed PET without severe features					
Superimposed PET with severe features					
Resistant hypertension					

NVOG 2011	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
BP ≥140/90 mmHg before pregnancy or 20 weeks	Hypertension before pregnancy or 20 weeks	Hypertension (≥140/90) before pregnancy or 20 weeks	Hypertension (≥140/90) before pregnancy or 20 weeks
	Comorbid conditions are listed and some include some secondary causes (e.g., CKD)		Comorbid conditions are listed and some include some secondary causes (e.g., CKD)
Symptoms of PET after 20 weeks	One/more at ≥20 weeks: resistant hypertension or new or worsening proteinuria or one or more other adverse conditions	"More likely" when: New proteinuria after 20 weeks Sudden, substantial, and sustained increase in proteinuria AND (1) sudden increase in BP or need to increase antihypertensive dose; sudden signs and symptoms of PET, such as (2) abnormal liver enzymes; (3) platelet count <100,000 cells/mm^3; (4) PET symptoms such as right upper quadrant pain and severe headaches; (5) pulmonary congestion or edema; (6) renal insufficiency (creatinine level doubling or rising to ≥1.1 mg/dL (97.2 μM) in women without other renal disease	One/more at ≥20 weeks: Resistant hypertension, *or* New or worsening proteinuria, *or* One/more adverse condition(s), *or* One/more severe complication(s)
	√	√	√
		Without organ system dysfunction #2–6 above (i.e., only hypertension and proteinuria)	
		With one/more organ dysfunctions (#2–6 above)	
			Need for three antihypertensives for BP control at ≥20 weeks

continued

Appendix 3.2 *continued*

	PRECOG 2005	*PRECOG II 2009*	*QLD 2013*	*NICE 2010*	*WHO 2011*
Gestational or 'new' hypertension					
Definition	New hypertension at ≥20 weeks	New hypertension at ≥20 weeks	New hypertension at >20 weeks, without features of PET, with normal BP by 12 weeks postpartum	New hypertension at >20 weeks without proteinuria	
With comorbid conditions					
With evidence of pre-eclampsia					
Pre-eclampsia					
Definition	Gestational hypertension and quantified proteinuria that resolves after delivery	Gestational hypertension and proteinuria that resolves after delivery	Gestational hypertension (confirmed twice) and proteinuria or one/more of: renal involvement (creat ≥90 μmol/L or oliguria), haematological involvement (thrombocytopaenia, haemolysis, DIC), liver involvement (raised transaminases, severe epigastric or RUQ pain), neurological involvement (severe headache, persistent visual disturbances of photopsia, scotomata, or cortical blindness, retinal vasospasm, hyperreflexia with sustained clonus, convulsions (eclampsia), stroke, pulmonary oedema, IUGR, placental abruption	Gestational hypertension and proteinuria	Gestational hypertension and proteinuria (>0.3 g/24 h)

NVOG 2011	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
New sBP ≥140 mmHg and/or dBP ≥90 mmHg (KV) at >20 weeks, measured twice, with normal BP at 12 weeks postpartum	New hypertension at ≥20 weeks	New hypertension at >20 weeks without proteinuria, with normal BP "postpartum"	New hypertension at ≥20 weeks
	Co-morbid conditions are listed and some include some secondary causes (e.g., CKD)		Co-morbid conditions are listed and some include some secondary causes (e.g., CKD)
	New proteinuria *or* one or more of the other adverse conditions (see Table 3.3)		New proteinuria or one/more of: adverse condition(s)[¥] *or* severe complication(s)[¥]
Gestational hypertension and proteinuria (>0.3 g/24 h) Also defines mild pre-eclampsia	Hypertension and proteinuria or one/more of signs and symptoms associated with end-organ dysfunction	Gestational hypertension and new proteinuria or one/more of: thrombocytopenia (<100,000 platelets/mL), impaired liver function (elevated blood levels of live transaminases to 2× normal), new development of renal insufficiency (creat >1.1 mg/dL or a doubling of serum creat in the absence of other renal disease), pulmonary edema, or cerebral or visual disturbances	Gestational hypertension and new proteinuria or one/more of: adverse condition(s)[¥] *or* *severe* complication(s)[¥]

continued

Appendix 3.2 *continued*

	PRECOG 2005	*PRECOG II 2009*	*QLD 2013*	*NICE 2010*	*WHO 2011*
Pre-eclampsia					
Eclampsia			With PET, one/more seizures	With PET, a convulsive condition	With PET, generalized seizures not attributable to other causes
Severe pre-eclampsia			One/more of: platelet count $<100{,}00 \times 10^9$/L, elevated transaminases, microangiopathic haemolytic anaemia with fragments/schistocytes on blood film (essentially HELLP syndrome)	Severe hypertension and/or symptoms, and/or biochemical and/or haematological impairment	One/more of: severe hypertension, heavy proteinuria, and substantial maternal organ dysfunction Onset at <32–34 weeks and fetal morbidity are used in some parts of the world
HELLP syndrome			HELLP spelled out Highlighted as variant of severe pre-eclampsia	HELLP spelled out	
Other 'hypertensive effects'					
Transient hypertensive effect					
White-coat effect			BP that is elevated in a clinical setting but normal in a non-clinical setting by (24 h) ABPM or HBPM using an appropriately validated device		
Masked hypertensive effect					
Hypertension (sBP and/or dBP)	dBP ≥90 mmHg	dBP ≥90 mmHg	sBP ≥140 mmHg and/or dBP ≥90 mmHg	dBP ≥90 mmHg (on two occasions, >4 hours apart) or dBP >110 mmHg (measured once)	-

NVOG 2011	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
	With PET, new onset of convulsions	With PET, new onset grand mal seizures	
Severe hypertension or PET symptoms (headache, epigastric pain, nausea, malaise), or proteinuria >5 g/24 h	PET with onset at <34 weeks, with heavy proteinuria (>0.3–0.5 g/24 h) or with one/more adverse conditions	(p32) ** ". . . consideration of pre-eclampsia as mild should be avoided."	PET with one/more severe complications‡
		HELLP spelled out Highlighted as a pre-eclamptic subtype	
			Elevated BP may be due to environmental stimuli or the, pain of labour, for example
			BP that is elevated in a clinical setting but normal in a non-clinical setting (<135/85 mmHg) by ABPM or HBPM
			BP that is normal in the clinical setting but elevated in a non-clinical setting (≥135/85 mmHg) by ABPM or HBPM
sBP ≥140 mmHg and/or dBP ≥90 mmHg	dBP ≥90 mmHg	sBP ≥140 mmHg or dBP ≥90 mmHg	sBP ≥140 mmHg and/or dBP ≥90 mmHg (based on average ≥2 measurements, taken ≥15 min apart, using the same arm)

continued

Appendix 3.2 *continued*

	PRECOG 2005	*PRECOG II 2009*	*QLD 2013*	*NICE 2010*	*WHO 2011*
Other 'hypertensive effects'					
Mild				sBP 140–149 mmHg dBP 90–99 mmHg	
Moderate				sBP 150–159 mmHg dBP 100–109 mmHg	
Severe			≥160/ and/or 110 mmHg	≥160/110 mmHg	
Late postpartum hypertension					
Definition					

ABPM, ambulatory blood pressure monitoring); ACOG, American College of Obstetricians and Gynecologists; AOM, Association of Ontario Midwives; BP, blood pressure; CKD, chronic kidney disease; Creat, creatinine; dBP, diastolic blood pressure; DIC, disseminated intravascular coagulation; HBPM, home blood pressure monitoring; HELLP syndrome, Haemolysis, Elevated Liver enzymes and Low Platelet count syndrome; NICE, National Institute for Health and Clinical Excellence; NVOG, Nederlandse Vereniging voor Obstetrie en Gynaecologie; PET, pre-eclampsia; PRECOG, pre-eclampsia community guideline; QLD, Queensland Maternity and Neonatal Clinical Guidelines Program; RUQ, right upper quadrant; sBP, systolic blood pressure; SOGC, Society of Obstetricians and Gynaecologists of Canada; WHO, World Health Organisation

* SOMANZ 2014 is included in the chapter text, but not in this table adapted from Gillon 2014[58]

ACOG 2013: American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013 Nov; 122(5):1122–1131

AOM 2012: Salehi P, Association of Ontario Midwives HDP CPG, Working Group. Hypertensive disorders of pregnancy (Clinical Practice Guideline 15). 2012; Available: http://www aom on ca/Health_Care_Professionals/Clinical_Practice_Guidelines/

NVOG 2011	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
		sBP 140–159 mmHg or dBP 90–109 mmHg	
sBP 140–159 mmHg or dBP 90–109 mmHg			
≥160/or 110 mmHg	≥160/or 110 mmHg	≥160/or 110 mmHg (as greater than mild)	≥160/or 110 mmHg (based on average ≥2 measurements, taken ≥15 min apart, using the same arm)
		Hypertension (usually mild) that develops 2 weeks to-6 mos postpartum, usually normalizing by the end of the first year	

NICE 2010: National Collaborating Centre for Women's and Children's Health (UK). CG107: Hypertension in pregnancy: The management of hypertensive disorders during pregnancy. NICE: Guidance 2010 Aug
NVOG 2011: Nederlandse Vereniging voor Obstetrie en Gynaecologie. Hypertensieve aandoeningen in de zwangerschap. 2011
QLD 2013: Queensland Maternity and Neonatal Clinical, Guidelines Program. Hypertensive disorders of pregnancy. 2013;MN10.13-V4-R15
PRECOG: Milne F, Redman C, Walker J, Baker P, Bradley J, Cooper C, et al. The pre-eclampsia community guideline (PRECOG): how to screen for and detect onset of pre-eclampsia in the community. BMJ 2005 Mar 12;330(7491):576–80
PRECOG II: Milne F, Redman C, Walker J, Baker P, Black R, Blincowe J et al. Assessing the onset of pre-eclampsia in the hospital day unit: summary of the pre-eclampsia guideline (PRECOG II). BMJ 2009; 339:b3129
SOGC 2014: Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. Pregnancy Hypertens 2014;4(2):105–145
WHO 2011: World Health Organization. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. 2011

Appendix 3.3

Definitions of pre-eclampsia and severe pre-eclampsia

	Define pre-eclampsia in association with hypertension								
	PRECOG 2005	*PRECOG II 2009*	*QLD 2013*	*NICE 2010*	*WHO 2011*	*NVOG 2011*	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
Proteinuria	✓	✓	✓	✓	✓	✓	✓	✓	✓
Heavy proteinuria									
Proteinuria is not mandatory – one/more other manifestations sufficient			✓				✓	✓	✓
Gestational age at onset <34 weeks									
Maternal symptoms									
Headache/visual symptoms			✓				✓	✓	✓
Chest pain/dyspnoea							✓		✓
Nausea/vomiting							✓		✓
Right upper quadrant/ epigastric pain			✓				✓		✓
Maternal signs									
Cardiac/cardiovascular									
Severe hypertension							✓		✓
Uncontrolled severe hypertension									

Define SEVERE pre-eclampsia									
PRECOG 2005	*PRECOG II 2009*	*QLD 2013*	*NICE 2010*	*WHO 2011*	*NVOG 2011*	*AOM 2012*	*ACOG 2013*	*SOGC 2014*	*Notes*
									1. Not mandatory. In absence of proteinuria, one or more of ✓
				✓	✓	✓			
				✓		✓			1. <32–34 weeks 2. Mentioned in text as risk factor for poor outcome
			✓		✓	✓	✓		1. Cerebral or visual disturbances 2. Cerebral or visual disturbances (with proteinuria)
			✓			✓			
			✓		✓	✓			
			✓		✓	✓	✓		1. Severe, persistent, unresponsive to medication, not otherwise explained (with proteinuria)
			✓	✓	✓	✓	✓		
			(✓)	(✓)				✓	

continued

Appendix 3.3 *continued*

	Define pre-eclampsia in association with hypertension								
	PRECOG 2005	*PRECOG II 2009*	*QLD 2013*	*NICE 2010*	*WHO 2011*	*NVOG 2011*	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
Maternal signs									
Positive inotropic support									
Myocardial ischaemia/ infarction									
Neurologic									
Eclampsia			✓				✓		
PRES									
Cortical blindness or retinal detachment			✓						
Glasgow coma scale <13									
Stroke, TIA or RIND			✓						
Hyperreflexia (with clonus)			✓						
Pulmonary									
Oxygen saturation <97%									✓
Oxygen saturation <90%									
Pulmonary oedema			✓				✓	✓	
Need for ≥50% oxygen for >1 h									
Intubation (other than for Caesarean delivery),									
Renal									
Oliguria			✓						

Define SEVERE pre-eclampsia									
PRECOG 2005	*PRECOG II 2009*	*QLD 2013*	*NICE 2010*	*WHO 2011*	*NVOG 2011*	*AOM 2012*	*ACOG 2013*	*SOGC 2014*	*Notes*
				(✓)				✓	
				(✓)				✓	
				(✓)		✓		✓	
				(✓)				✓	
				(✓)		✓		✓	
				(✓)				✓	
				(✓)				✓	
				(✓)				✓	
				(✓)		✓	✓	✓	1. With proteinuria
				(✓)				✓	
				(✓)				✓	

continued

Appendix 3.3 *continued*

	Define pre-eclampsia in association with hypertension								
	PRECOG 2005	*PRECOG II 2009*	*QLD 2013*	*NICE 2010*	*WHO 2011*	*NVOG 2011*	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
Abnormal maternal laboratory tests									
Haematology/coagulation									
Elevated WBC count									✓
Platelet count decreased but ≥50 × 10^9/L									✓
Platelet count decreased but <50 × 10^9/L			✓				✓	✓	
Elevated INR or aPTT			✓ 1						✓
Renal									
Elevated serum uric acid									✓
Elevated serum creatinine			✓				✓		✓
Acute kidney injury (creatinine >150 μM with no prior renal disease)								✓	
New indication for dialysis									
Hepatic									
Elevated serum AST, ALT, LDH or bilirubin			✓				✓	✓	✓
Hepatic dysfunction (INR >2 in absence of DIC or warfarin)									
Low plasma albumin							✓		✓
Hepatic haematoma or rupture									

Define SEVERE pre-eclampsia									
PRECOG 2005	*PRECOG II 2009*	*QLD 2013*	*NICE 2010*	*WHO 2011*	*NVOG 2011*	*AOM 2012*	*ACOG 2013*	*SOGC 2014*	*Notes*
		✓							1. "Microangiopathic haemolytic anaemia"
		✓	(✓)	(✓)		✓	✓	✓	1. Thrombocytopaenia 2. <100,000/mL 3. <100,000/mL with proteinuria
									1. Haemolysis and DIC
						✓			
			(✓)	(✓)			✓	✓	1. Progressive renal insufficiency (serum creatinine >1.1 mg/dL or a doubling of serum creatinine concentration in absence of other renal disease) 2. With proteinuria
			(✓)	(✓)				✓	
		✓				✓	✓		1. Twice normal 2. With proteinuria
			(✓)	(✓)				✓	
						✓			
			(✓)	(✓)				✓	

continued

Appendix 3.3 *continued*

	Define pre-eclampsia in association with hypertension								
	PRECOG 2005	*PRECOG II 2009*	*QLD 2013*	*NICE 2010*	*WHO 2011*	*NVOG 2011*	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
Fetoplacental manifestations									
Non-reassuring FHR									✓
IUGR			✓				✓		✓
Oligohydramnios							✓		✓
Absent/reversed end-diastolic flow by Doppler velocimetry							✓		✓
Abruption *without* evidence of maternal or fetal compromise			(✓)				(✓)		✓
Abruption with evidence of maternal or fetal compromise			(✓)				(✓)		
Reverse ductus venosus A wave									
Stillbirth							✓		
Interventions									
Transfusion of any blood product									

ACOG, American College of Obstetricians and Gynecologists; AOM, Association of Ontario Midwives; aPTT, activated partial thromboplastic time; ASH, American Society of Hypertension; AST, aspartate aminotransferase; ALT, alanine aminotransferase; FHR, fetal heart rate; INR, international normalised ratio; IUGR, intrauterine fetal growth restriction; LDH, lactate dehydrogenase; NICE, National Institute for Health and Clinical Excellence; NVOG, Nederlandse Vereniging voor Obstetrie en Gynaecologie; PRECOG, pre-eclampsia community guideline; PRES, posterior reversible encephalopathy syndrome; QLD, Queensland Maternity and Neonatal Clinical Guidelines Program; RIND, reversible ischaemic neurological deficit; SOGC, Society of Obstetricians and Gynaecologists of Canada; TIA, transient ischaemic attack; WBC, white blood cell count; WHO, World Health Organization

* A checkmark indicates that the diagnostic criterion was listed by the guideline. A checkmark in brackets indicates that although not listed specifically, the criterion could reasonably be interpreted as being part of the definition in the relevant guideline

† The NICE 2010 guidelines include "symptoms, and/or biochemical and/or haematological impairment" as part of the definition of severe pre-eclampsia. It is assumed that those complications indicated by ( ) would meet this definition

** The WHO 2011 guidelines include "substantial maternal end-organ dysfunction" as part of the definition of severe pre-eclampsia. It is assumed that those complications indicated by ( ) would meet this definition. "Fetal morbidity" also required interpretation

*** Pre-eclampsia with severe feature

Define SEVERE pre-eclampsia									
PRECOG 2005	*PRECOG II 2009*	*QLD 2013*	*NICE 2010*	*WHO 2011*	*NVOG 2011*	*AOM 2012*	*ACOG 2013*	*SOGC 2014*	*Notes*
				✓					
				✓		✓			1. Not included (as IUGR with PET managed the same way as IUGR w/o PET)
				✓		✓			
				✓		✓			
						(✓)			
				(✓)		(✓)		✓	
				✓				✓	
				✓		✓		✓	
								✓	

ACOG 2013: American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013 Nov; 122(5):1122–1131

AOM 2012: Salehi P, Association of Ontario Midwives HDP CPG, Working Group. Hypertensive disorders of pregnancy (Clinical Practice Guideline 15). 2012; Available: http://www aom on ca/Health_Care_Professionals/Clinical_Practice_Guidelines/

NICE 2010: National Collaborating Centre for Women's and Children's Health (UK). CG107: Hypertension in pregnancy: The management of hypertensive disorders during pregnancy. NICE: Guidance 2010 Aug

NVOG 2011: Nederlandse Vereniging voor Obstetrie en Gynaecologie. Hypertensieve aandoeningen in de zwangerschap. 2011

QLD 2013: Queensland Maternity and Neonatal Clinical, Guidelines Program. Hypertensive disorders of pregnancy. 2013;MN10.13-V4-R15

PRECOG: Milne F, Redman C, Walker J, Baker P, Bradley J, Cooper C, et al. The pre-eclampsia community guideline (PRECOG): how to screen for and detect onset of pre-eclampsia in the community. BMJ 2005 Mar 12;330(7491):576–80

PRECOG II: Milne F, Redman C, Walker J, Baker P, Black R, Blincowe J et al. Assessing the onset of pre-eclampsia in the hospital day unit: summary of the pre-eclampsia guideline (PRECOG II). BMJ 2009; 339:b3129

SOGC 2014: Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. Pregnancy Hypertens 2014;4(2):105–145

WHO 2011: World Health Organization. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. 2011

Appendix 4.1

Literature searches

PREGNANCY-INDUCED HYPERTENSION SEARCHES: COMPLICATIONS, EPIDEMIOLOGY

Removed duplicates, non-Eng, non-Fre, animal research using EndNote searches and de-duping function.

COMPLICATIONS

Database(s): **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)** 1946 to Present Search Strategy:

#	*Searches*	*Results*
1	complications.fs. or exp Infant, Newborn, Diseases/et, cn or exp Pregnancy Outcome/ or (sequel* or later life or late life).mp. or Pregnancy Complications/et, cn or exp Abortion, Spontaneous/et, cn or exp Chorea Gravidarum/et or exp Diabetes, Gestational/et or exp Fetal Death/et or exp Fetal Diseases/et, cn or exp Maternal Death/et or exp Morning Sickness/et or exp Nuchal Cord/et or exp Obstetric Labor Complications/et or exp Oligohydramnios/et or exp Pelvic Floor Disorders/et or exp Pemphigoid Gestationis/et, cn or exp Perinatal Death/et or exp Phenylketonuria, Maternal/et or exp Placenta Diseases/et, cn or exp Polyhydramnios/et, cn or exp Pregnancy Complications, Cardiovascular/et or exp Pregnancy Complications, Hematologic/et, cn or exp Pregnancy Complications, Infectious/et or exp Pregnancy Complications, Neoplastic/et, cn or exp Pregnancy in Diabetics/et or exp Pregnancy, Ectopic/et or exp Pregnancy, Prolonged/et or exp Prenatal Injuries/et or exp Puerperal Disorders/et, cn	1759552
2	exp Hypertension, Pregnancy-Induced/ or ((exp Pregnancy/ or exp Pregnancy Complications/) and exp Hypertension/)	34751
3	1 and 2	10375
4	limit 3 to yr="2011 -Current"	1499
5	limit 4 to (humans and (english or french))	1358
6	(complicat* and (((pregnan* or gestation* or obstetric*) and hypertens*) or (pre-eclamp* or preeclamp* or toxemia* or toxaem* or gestosis or pre eclamp* or eclamp* or EPH Complex))).ti,ab.	9813
7	limit 6 to yr="2013 -Current"	1505
8	5 or 7 EXPORTED THESE	2668

Database(s): **EBM Reviews – Cochrane Central Register of Controlled Trials** March 2015, **EBM Reviews – Database of Abstracts of Reviews of Effects** 1st Quarter 2015 Search Strategy:

#	*Searches*	*Results*
1	(complicat* and (((pregnan* or gestation* or obstetric*) and hypertens*) or (pre-eclamp* or preeclamp* or toxemia* or toxaem* or gestosis or pre eclamp* or eclamp* or EPH Complex))).mp.	735
2	limit 1 to yr="2011 -Current" [Limit not valid in DARE; records were retained] EXPORTED THESE	221

EPIDEMIOLOGY

Database(s): **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)** 1946 to Present Search Strategy:

#	*Searches*	*Results*
1	exp Hypertension, Pregnancy-Induced/ or ((exp Pregnancy/ or exp Pregnancy Complications/) and exp Hypertension/)	34751
2	(epidemiology or ethnology).fs.	1328387
3	exp Epidemiology/	22151
4	exp incidence/ or exp prevalence/	368169
5	(incidence or prevalen* or epidemiol*).ti,ab.	1178435
6	2 or 3 or 4 or 5	2053499
7	1 and 6	6092
8	limit 7 to (yr="2010 -Current" and (english or french))	1736
9	(((pregnan* or gestation* or obstetric*) and hypertens*) or (pre-eclamp* or preeclamp* or toxemia* or toxaem* or gestosis or pre eclamp* or eclamp* or EPH Complex)).ti,ab.	41767
10	(incidence or prevalen* or epidemiol*).ti,ab.	1178435
11	9 and 10	5706
12	limit 11 to yr="2013 -Current"	945
13	8 or 12 EXPORTED THESE	2383

Database(s): **EBM Reviews – Cochrane Central Register of Controlled Trials** March 2015, **EBM Reviews – Database of Abstracts of Reviews of Effects** 1st Quarter 2015 Search Strategy:

#	*Searches*	*Results*
1	(((pregnan* or gestation* or obstetric*) and hypertens*) or (pre-eclamp* or preeclamp* or toxemia* or toxaem* or gestosis or pre eclamp* or eclamp* or EPH Complex)).mp.	2235
2	(incidence or prevalen* or epidemiol*).mp.	76380
3	1 and 2	447
4	limit 3 to yr="2010 -Current" [Limit not valid in DARE; records were retained] EXPORTED THESE	208

Appendix 5.1

Studies of predictive tests for pre-eclampsia

See next page – this appendix requires a double-page layout

Risk factor¥ or predictor	*First author (year)*	*Study design*	*Type of HDP*	*No. of women (rate %)*	*RR or OR**	*AUC ROC*	*Sensitivity (%)*	*Specificity (%)*	*LR+*	*LR–*
Predictors										
Clinical examination										
BP	Cnossen† (2008)[96]	Systematic review and meta-analysis	Any PET	60,599 (5.51%)		0.76	35	90	3.5	0.72
UAD	Cnossen† (2008)[96]	Systematic review and bivariable meta-analysis	Any PET	79,547 (3.14 %)		–	90	70	3.0	0.14
	Papageorghiou† (2002)[108]	Review	Any PET	18,683 (2.5%)			24–89	86–96	5.90	0.55
	Afrakhteh† (2014)[162]	Prospective	PET, stillbirth, placental abruption and preterm labour	205 (17.5%)			57.5	98.2	31.9	0.43
	Napolitano† (2012)[112]	Retrospective observational	Any PET Early-onset pre-eclampsia Preterm PET	3549 (3.6%) (0.6%) (1.2%)		0.682 0.851 0.786	–	–	–	–
Laboratory markers										
Podocyturia	Jim† (2014)[104]	Prospective	Any PET	91 (15.4%)			36	96	9	0.67
	Craici† (2013)[105]	Prospective	Any PET Any HDP (PET and GH)	267 (5.6%) (11.2%)		 1 0	 100 54	 100 100	 ∞ ∞	 0 0.46
	Kelder† (2012)[103]	Case–control	Any PET	69 (50.7%)		0.82	68.6	88.2	5.81	0.36
IPG/creatinine ratio	Dawonauth† (2014)[107]	Prospective longitudinal	Any PET	416 (8.2%)		0.862	84.2	83.6	5.13	0.19
Calcium/creatinine ratio	Vahdat† (2012)[106]	Prospective cohort	Any PET	150 (9.3%)		–	77	78	3.5	0.29

Hs-CRP	Kashanian† (2013)[121]	Prospective cohort	Any PET	394 (10.7%)		0.855	78.1	72.1	2.80	0.30
Fibronectin	Leeflang (2007)[122]	Systematic review	Any PET	573 (19.0%)		–	50–100	43–88	1.24–11.5	0–0.74
Platelets	Yang† (2011)[169]	Case–control	Any HDP (PET and GH)	1288 (35.8%)		0.662	47.12	81.67	2.57	0.65
Angiogenic factors										
PlGF sFLT1 sENG	Kleinrouweler (2012)[165]	Systematic review and meta-analysis	Any PET	29 to 3098 –		–	32 26 18	95 95 95	6.4 5.2 3.6	0.72 0.78 0.86
PlGF	Ghosh† (2013)[128]	Prospective cohort	EO-PET (1st vs 2nd trimester)	1244 (1.5%)	18.83* 2.76*	0.98 0.97	84 58	78 66	3.82 1.71	0.21 0.67
	Ghosh† (2013)[129]	Prospective cohort	EO-PET in Obese/overweight	1678 (1.7%)	7.64*	0.98	79	68	2.46	0.31
	Chappell (2013)[125]	Prospective	PET delivered within 14 days	625 (55%)		0.87	96	55	2.13	0.07
	Ghosh† (2013)[123]	Prospective cohort	EO-PET EO-IUGR	722 (1.5%)	8.35* 10.73*	0.982 0.982	82 84	65 67	2.36 2.54	0.28 0.24
Sflt/PlGF	Hanita (2014)[132]	Prospective	Any PET	84 (14.3%)		0.873	92	68	2.89	0.12
	Engels (2013)[130]	Prospective	PET/HELLP	338 (64%)		0.964	70.3	95.1	14.3	0.31
	Teixeira† (2013)[131]	Prospective longitudinal	Any PET	71 (16.9%)		0.95	–	–	–	–
	Delic† (2014)[163]	Prospective	Any PET	69 (49.2%)		0.895	–	–	–	–
	Villa (2013)[134]	Nested case–control	EO-PET	106 (5.7%)		1	100	99.8	500	0
	Forest† (2014)[133]	Nested case–control	EO-PET	7929 (0.2%)		0.977	88.9	90	8.89	0.12
PlGF/sFlt-1	McElrath† (2012)[124]	Prospective longitudinal	Any PET	2243 (6.2%)		0.74	61	75.1	2.45	0.52

continued

Risk factor¥ or predictor	*First author (year)*	*Study design*	*Type of HDP*	*No. of women (rate %)*	*RR or OR**	*AUC ROC*	*Sensitivity (%)*	*Specificity (%)*	*LR+*	*LR–*
Predictors										
Multivariables										
BP and UAD	Kleinrouweler (2013)[111]	Individual patient data meta-analysis	Any PET	6708 (4.5%)		0.85				
MC, PP-13, β-hCG	Schneuer† (2012)[142]	In-house study and systematic review	Any PET EO-PET	2678 (2.7%) (0.2%)		0.72 0.82	24 45	95 95	4.8 9	0.8 0.58
MC, UAD, Biomarkers	Kuc (2011)[143]	Systematic review	Any PET	138,571 (2.6%)		–	43–100	90	–	–
MC, UAD and PAPP-A	Goetzinger† (2014)[148]	Prospective cohort	Any PET	1200 (8.5%)		0.76	36.7	93.2	5.4	0.68
MC and UAD	Lai† (2013)[110]	Prospective screening	Intermediate PET LO-PET	4,294 (0.9%) (3.4%)		0.838 0.792	70.3 54.6	90 90	7.03 5.46	0.33 0.51
MC and BP	Gallo† (2014)[98]	Prospective	Any PET EO-PET Preterm PET	17,383 (3.1%) (0.4%) (0.8%)		0.893 0.88 0.813	52.5 84.3 65.7	90 90 90	5.25 8.43 8.13	0.12 0.17 0.21
MC, BP and UAD	Caradeux† (2013)[99]	Prospective cohort	EO-PET	627 (1.5%)		0.895	62.5	95.5	13.9	0.39
MC, PlGF, BP and UAD	Myers† (2013)[149]	Prospective cohort	Preterm PET	3529 (1.3%)	0.65*	0.81	45	95	9	0.58
MC, PIGF and free β-hCG	Di Lorenzo† (2012)[144]	Prospective cohort	EO-PET	2118 (0.57%)		0.893	75	90	7.5	0.28
MC, BP PAPPA, ADAM12 and PlGF	Myatt† (2012)[137]	Observational study	Any PET	2218 (7.9%)		0.73	46.1	80	2.31	0.67
MC, hCG-h , PAPP-A and BP	Keikkala† (2013)[145]	Nested case–control	EO-PET	707 (4.1%)		0.863	69	90	6.9	0.34

MC, UAD, PlGF, sFlt-1 and lipid-related markers	Diguisto† (2013)[153]	Prospective observational study	Any PET	235 (23.8%)		0.795	39.6	90	3.96	0.67
MC, PlGF, and UAD	Rizos† (2013)[150]	Case–control	Any PET	116 (10.3%)		–	46	99	19	0.56
PAPP-A and sFlt-1/PlGF	Park† (2014)[90]	Prospective cohort	LO-t PET	262 (3%)		0.969	87.5	95	17.5	0.13
PWV and sFlt-1	Katsipi† (2014)[151]	Prospective	Any PET EO-PET	118 (17.8%) (9.3%)		0.965 0.963	90 92	90 90	9 9.2	0.11 0.09
IPG/creatinine	Dawonauth† (2014)[107]	Prospective longitudinal	Any PET	416 (8.2%)		0.862	84.2	83.6	5.13	0.19
MC, BP, PAPPA, ADAM12 and PlGF	Kuc† (2013)[97]	Nested case–control	EO-PET LO-PET EO-PET + SGA LO-PET+SGA	667 (10.2%) (14.8%) (1.9%) (7.3%)		0.88 0.88 0.95 0.95	72 49 92 57	90 90 90 90	7.2 4.9 9.2 5.7	0.31 0.57 0.09 0.48
MC, BP and taurine	Kuc† (2014)[143]	Case–control	EO-PET	167 (10.2%)		0.93	55	90	5.5	0.5
BP and sENG	Abdelaziz† (2012)[162]	Nested case–control	Any HDP EO-PET LO-PET	1898 (4.69%) (0.84%) (3.16%)		0.83 0.86 0.83	71.8 83.8 80.3	90 90 90	7.18 8.38 8.03	0.31 0.18 0.22
HRG and UAD	Bolin† (2012)[109]	Case–control	Preterm PET	175 (15.4%)		0.85	91	62	2.39	0.15
PlGF, PP13, PAPP A and IL-1β	Siljee† (2013)[168]	Retrospective case–control	EO-PET	70 (50%)		0.830	55.9	90	5.59	0.49
Uric acid and BP	Martell-Claros (2013)[167]	Prospective cohort	GH	283 (6.0%)	4.02* 3.6*	0.75	50	84.2	3.16	0.59

† Studies including proteinuria for the definition of pre-eclampsia; ¥Risk factors, *Odd ratios
PET, pre-eclampsia; GH, gestational hypertension; EO, early onset; LO, late onset; UAD, uterine artery Doppler; BP, blood pressure; SGA, small for gestational age; MC, maternal characteristics

Appendix 5.2

Predictors of pre-eclampsia

Demographics and family history	*Past medical or obstetric history*	*Current pregnancy*	
Independent predictors			
Maternal			
		Clinical examination	
		First trimester	*Second or third trimester*
		• MAP	• MAP
			• Uterine artery Doppler
		Laboratory markers	
		First trimester	*Second or third trimester*
		• Fibronectin	• sFlt-1:PlGF
		• hs-CRP	• Podocyturia
		• Platelets	• PlGF
		• PlGF	• Calcium:creatinine ratio
		• sFLT-1	• Fibronectin
		• sENG	
Multivariable predictors			
Maternal			
Maternal age	Previous pre-eclampsia	Multiple pregnancy	Excessive weight gain in pregnancy
Afro-Caribbean or South Asian race	Pre-existing medical condition(s)	Overweight/obesity (BMI)	
Family history of pre-eclampsia (mother)	Pre-existing hypertension	First ongoing pregnancy	
Education level	Pre-existing diabetes mellitus		
	Preterm labour/delivery		
	Non-smoking		
		Clinical examination	
		First trimester	*Second or third trimester*
		• MAP	• MAP
		• sBP	• Uterine artery Doppler
		• dBP	
		• Uterine artery Doppler	

continued

Appendix 5.2 *continued*

Demographics and family history	*Past medical or obstetric history*	*Current pregnancy*	
Multivariable predictors			
		Laboratory markers	
		First trimester	*Second or third trimester*
		• PIGF	• PIGF
		• Uric acid	• sFlt-1
		• PP-13	• PAPP-A
		• sENG	• HRG
		• β-hCG	• PWV
		• PAPP-A	• Leptin,
		• ADAM12	• Triglycerides
		• Taurine	
		• IL-1β	

Appendix 5.3

Performance of predictors (summary of evidence by trimester)

See next page – this appendix requires a double-page layout

Appendix 5.3

Predictor	*First author (year)*	*Study design*	*Type of HDP*	*No. of women (rate %)*	*AUC ROC*	*Sensitivity (%)*	*Specificity (%)*	*LR+*	*LR–*
First trimester predictors									
Individual predictors									
Clinical examination									
BP (MAP)	Cnossen† (2008)[96]	Systematic review and meta-analysis	Any PET	60,599 (5.51 %)	0.79	–	–	–	–
Laboratory markers									
hs-CRP	Kashanian† (2013)[121]	Prospective cohort	Any PET	394 (10.7%)	0.855	78.1	72.1	2.80	0.30
Fibronectin	Leeflang (2007)[122]	Systematic review	Any PET	573 (19.0%)	–	50–100	63–88	1.47–4.0	0–0.74
Platelets	Yang† (2011)[169]	Case–control	Any HDP (PET and GH)	1288 (35.8%)	0.662	47.12	81.67	2.57	0.65
Angiogenic factors									
PlGF sFLT-1 sENG	Kleinrouweler (2012)[165]	Systematic review and meta-analysis	Any PET	29 to 3098 –	–	32 26 18	95 95 95	6.4 5.2 3.6	0.72 0.78 0.86
PlGF	Ghosh† (2013)[128]	Prospective cohort	EO-PET	1244 (1.5%)	0.972	58	66	1.71	0.64
Multivariables									
MC, PP-13, β-hCG	Schneuer† (2012)[142]	In-house study and systematic review	Any PET EO-PET	2678 (2.7%) (0.2%)	0.72 0.82	24 45	95 95	4.8 9	0.8 0.58
MC, UAD, Biomarkers	Kuc (2011)[166]	Systematic review	Any PET	138,571 (2.6%)	–	43–100	90	–	–
MC, UAD and PAPP-A	Goetzinger† (2014)[148]	Prospective cohort	Any PET	1200 (8.5%)	0.76	36.7	93.2	5.4	0.68
MC, BP and UAD	Caradeux† (2013)[99]	Prospective cohort	EO-PET	627 (1.5%)	0.895	62.5	95.5	13.9	0.39
MC, PIGF and free b-hCG	Di Lorenzo† (2012)[144]	Prospective cohort	EO-PET	2118 (0.57%)	0.893	75	90	7.5	0.28
MC, BP PAPPA, ADAM12 and PlGF	Myatt† (2012)[137]	Observational study	Any PET	2218 (7.9%)	0.73	46.1	80	2.31	0.67

MC, hCG-h, PAPP-A and BP	Keikkala† (2013)[145]	Nested case–control	EO-PET	707 (4.1%)	0.863	69	90	6.9	0.34
MC, PlGF, and UAD	Rizos† (2013)[150]	Case–control	Any PET	116 (10.3%)	–	46	99	19	0.56
MC, BP, PAPP-A, ADAM12 and PlGF	Kuc† (2013)[97]	Nested case–control	EO-PET LO-PET EO-PET + SGA LO-PET + SGA	667 (10.2%) (14.8%) (1.9%) (7.3%)	0.88 0.88 0.95 0.95	72 49 92 57	90 90 90 90	7.2 4.9 9.2 5.7	0.31 0.57 0.09 0.48
MC, BP and taurine	Kuc† 2014[143]	Case–control	EO-PET	167 (10.2%)	0.93	55	90	5.5	0.5
BP and sENG	Abdelaziz† (2012)[164]	Nested case–control	Any HDP EO-PET LO-PET	1898 (4.69%) (0.84%) (3.16%)	0.83 0.86 0.83	71.8 83.8 80.3	90 90 90	7.18 8.38 8.03	0.31 0.18 0.22
PlGF, PP13, PAPP A and IL-1β	Siljee† (2013)[168]	Retrospective case–control	EO-PET	70 (50%)	0.830	55.9	90	5.59	0.49
Uric acid and BP	Martell-Claros (2013)[167]	Prospective cohort	GH	283 (6.0%)	0.75	50	84.2	3.16	0.59
Second and third trimester predictors (summary of the evidence)									
Individual predictors									
Clinical examination									
BP (MAP)	Cnossen† (2008)[96]	Systematic review and meta-analysis	Any PET	60,599 (5.51 %)	0.76	35	90	3.5	0.72
UAD	Cnossen† (2008)[96]	Systematic review and bivariable meta-analysis	Any PET	79,547 (3.14 %)	–	90	70	3.0	0.14
	Papageorghiou† (2002)[108]	Review	Any PET	18683 (2.5%)		24–89	86–96	5.90	0.55
	Afrakhteh† (2014)[162]	Prospective	PET, stillbirth, placental abruption and preterm labor	205 (17.5%)		57.5	98.2	31.9	0.43
	Napolitano† (2012)[112]	Retrospective observational	Any PET Early-onset pre-eclampsia Preterm PET	3549 (3.6%) (0.6%) (1.2%)	0.682 0.851 0.786	–	–	–	–

continued

Appendix 5.3 *continued*

Predictor	*First author (year)*	*Study design*	*Type of HDP*	*No. of women (rate %)*	*AUC ROC*	*Sensitivity (%)*	*Specificity (%)*	*LR+*	*LR–*
Second and third trimester predictors (summary of the evidence)									
Individual predictors									
Laboratory markers									
Podocyturia	Jim† (2014)[104]	Prospective	Any PET	91 (15.4%)		36	96	9	0.67
	Craici† (2013)[105]	Prospective	Any PET Any HDP (PET and GH)	267 (5.6%) (11.2%)	1 0	100 54	100 100	∞ ∞	0 0.46
	Kelder† (2012)[103]	Case–control	Any PET	69 (50.7%)	0.82	68.6	88.2	5.81	0.36
Calcium: creatinine ratio	Vahdat† (2012)[106]	Prospective cohort	Any PET	150 (9.3%)	–	77	78	3.5	0.29
Fibronectin	Leeflang (2007)[122]	Systematic review	Any PET	573 (19.0%)	–	50–85	43–96	1.24–11.5	0.20–0.69
Angiogenic factors									
PlGF	Ghosh† (2013)[128]	Prospective cohort	EO-PET	1244 (1.5%)	0.98	84	78	3.82	0.21
	Ghosh† (2013)[129]	Prospective cohort	EO-PET in obese/ overweight	1678 (1.7%)	0.98	79	68	2.46	0.31
	Chappell (2013)[125]	Prospective	PET delivered within 14 days	625 (55%)	0.87	96	55	2.13	0.07
	Ghosh† (2013)[123]	Prospective cohort	EO-PET	722 (1.5%)	0.982	82	65	2.36	0.28
sFlt-1:PlGF	Hanita (2014)[130]	Prospective	Any PET	84 (14.3%)	0.873	92	68	2.89	0.12
	Engels (2013)[130]	Prospective	PET/HELLP	338 (64%)	0.964	70.3	95.1	14.3	0.31
	Teixeira† (2013)[131]	Prospective longitudinal	Any PET	71 (16.9%)	0.95	–	–	–	–
	Delic† (2014)[163]	Prospective	Any PET	69 (49.2%)	0.895	–	–	–	–
	Villa (2013)[134]	Nested case–control	EO-PET	106 (5.7%)	1	100	99.8	500	0
	Forest† (2014)[133]	Nested case–control	EO-PET	7929 (0.2%)	0.977	88.9	90	8.89	0.12
PlGF/sFlt-1	McElrath† (2012)[124]	Prospective longitudinal	Any PET	2243 (6.2%)	0.74	61	75.1	2.45	0.52

Multivariables									
BP and UAD	Kleinrouweler (2013)[111]	Individual patient data meta-analysis	Any PET	6708 (4.5%)	0.85				
MC, PlGF, BP and UAD	Myers† (2013)[149]	Prospective cohort	Preterm PET	3529 (1.3%)	0.81	45	95	9	0.58
MC, UAD, PlGF, sFlt-1 and lipid-related markers	Diguisto† (2013)[153]	Prospective observational study	Any PET	235 (23.8%)	0.795	39.6	90	3.96	0.67
PAPP-A and sFlt-1/PlGF	Park† (2014)[90]	Prospective cohort	LO-PET	262 (3%)	0.969	87.5	95	17.5	0.13
PWV and sFlt-1	Katsipi† (2014)[151]	Prospective	Any PET EO-PET	118 (17.8%) (9.3%)	0.965 0.963	90 92	90 90	9 9.2	0.11 0.09
HRG and UAD	Bolin† (2012)[109]	Case–control	Preterm PET	175 (15.4%)	0.85	91	62	2.39	0.15
Not specified (any) trimester predictors (summary of the evidence)									
IPG/creatinine ratio (2 weeks prior to diagnosis)	Dawonauth† (2014)[107]	Prospective longitudinal	Any PET	416 (8.2%)	0.862	84.2	83.6	5.13	0.19
PlGF sFlt-1 sENG (Combination of trimesters)	Kleinrouweler (2012)[165]	Systematic review and meta-analysis	Any PET	29 to 3098 –	–	32 26 18	95 95 95	6.4 5.2 3.6	0.72 0.78 0.86
PlGF (confirmed PET and delivered within 14 days)	Chappell (2013)[125]	Prospective	PET	625 (55%)	0.87	96	55	2.13	0.07
MC and BP (Combination of 1st and 2nd trimester)	Gallo† (2014)[98]	Prospective	Any PET EO-PET Preterm PET	17,383 (3.1%) (0.4%) (0.8%)	0.893 0.88 0.813	52.5 84.3 65.7	90 90 90	5.25 8.43 8.13	0.12 0.17 0.21
MC, PlGF, and UAD (Combination of trimesters)	Rizos† (2013)[150]	Case–control	Any PET	116 (10.3%)	–	46	99	19	0.56

† Studies including proteinuria for the definition of pre-eclampsia

PET, pre-eclampsia; GH, gestational hypertension; EO, early onset; LO, late onset; UAD, uterine artery Doppler; BP, blood pressure; SGA, small for gestational age; MC, maternal characteristics

Appendix 5.4

Recommendations for prediction of pre-eclampsia from international clinical guidelines

	PRECOG 2005	*NICE 2010*
Prediction		
Risk assessment		

Prediction

Clinical risk markers for pre-eclampsia	History of previous PET Multiple pregnancy Antiphospholipid antibodies Significant proteinuria at booking or pre-existing renal disease Pre-existing diabetes mellitus Pre-existing hypertension First pregnancy ≥10 years since last baby Age ≥40 years BMI ≥35 Family history of preeclampsia (mother/sister) Booking diastolic BP ≥80 mmHg	"High" risk markers: HDP in prior pregnancy Autoimmune disease (e.g., SLE) Antiphospholipid syndrome Renal disease Pre-existing diabetes mellitus Pre-existing hypertension "Moderate" risk factors: Multiple pregnancy First pregnancy Age ≥40 years >10 years since 1st baby BMI ≥35 kg/m^2 at first visit Family history of PET ≥10 year since last baby

ACOG, American Congress of Obstetricians and Gynecologists; AOM, Association of Ontario Midwives; BMI, body mass index; DM, diabetes mellitus; GP, general practitioner; GPP, good practice point; NICE, National Institute for Health and Clinical Excellence; PET, pre-eclampsia; PRECOG, pre-eclampsia community guideline; WHO, World Health Organization; SOGC, Society of Obstetricians and Gynaecologists of Canada

ACOG 2013: American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013 Nov; 122(5):1122–1131

AOM 2012: Salehi P, Association of Ontario Midwives HDP CPG, Working Group. Hypertensive disorders of pregnancy (Clinical Practice Guideline 15). 2012; Available: http://www aom on ca/Health_Care_Professionals/Clinical_Practice_Guidelines/

WHO 2011	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
	Screening for PET should be assessed by known clinical risk factors assessment in early pregnancy, and decide whether or not to undertake preventive measures (IIIB) (IIIA/B)	Screening for PET except the use of medical history is not recommended (Moderate, Strong)	Screening for PET risk should be offered by clinical risk assessment in early pregnancy (II-2C/Low, Strong) Screening using biomarkers or Doppler ultrasound velocimetry of uteroplacental circulation, is not recommended (II-2C/Very low,Weak)
Obesity, chronic hypertension, DM, nulliparity, adolescent pregnancy, conditions leading to hyperplacentation and large placentas (e.g., twin pregnancy)	Presence of antiphospholipid antibodies, previous PET, pre-existing DM, multiple pregnancy, nulliparity, family history of PET, raised pre-pregnancy BMI, maternal age ≥40 years	First degree relative with history of PET, PET in previous PET, multiple gestation, maternal age ≥40 years, DM, obesity, pre-existing hypertension	History of previous pre-eclampsia Multiple pregnancy Antiphospholipid antibody syndrome Significant proteinuria at booking or pre-existing renal disease Pre-existing diabetes mellitus Pre-existing hypertension (II-2 B/Very low, Strong)

NICE 2010: National Collaborating Centre for Women's and Children's Health (UK). CG107: Hypertension in pregnancy: The management of hypertensive disorders during pregnancy. NICE: Guidance 2010 Aug
PRECOG: Milne F, Redman C, Walker J, Baker P, Bradley J, Cooper C, et al. The pre-eclampsia community guideline (PRECOG): how to screen for and detect onset of pre-eclampsia in the community. BMJ 2005 Mar 12;330(7491):576–80
SOGC 2014: Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. Pregnancy Hypertens 2014;4(2):105–145
WHO 2011: World Health Organization. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. 2011

Appendix 5.5

GRADE evaluation of best practice points

	*Quality of evidence**	*Strength of recommendation*†
1. Women should be screened for clinical risk markers of pre-eclampsia from early pregnancy.	Low	Strong
2. Consultation with an obstetrician or an obstetric internist/physician should be offered to women with a history of previous pre-eclampsia or another clinical marker of increased risk, particularly multiple pregnancy, antiphospholipid antibody syndrome, significant proteinuria at booking, or a pre-existing condition of hypertension, diabetes mellitus, or renal disease.	Very Low	Strong
3. Screening for non-clinical risk markers cannot be recommended routinely at present for women at low or increased risk of pre-eclampsia until such screening has been shown to improve pregnancy outcome.	Very Low	Weak

* The judgments about the quality of evidence is based on the confidence that available evidence reflects the true effect of the intervention or service. Evidence is considered to be of *high quality* when the true effect is thought to lie close to that of the estimate of the effect (e.g., if there is a wide range of studies included in the analyses with no major limitations, there is little variation between studies, and the summary estimate has a narrow confidence interval). Evidence is considered to be of *moderate quality* when the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different (e.g., if there are only a few studies and some have limitations but not major flaws, there is some variation between studies, or the confidence interval of the summary estimate is wide). Evidence is considered to be of *low quality* when the true effect may be substantially different from the estimate of the effect (e.g., the studies have major flaws, there is important variation between studies, or the confidence interval of the summary estimate is very wide)

† A *strong recommendation* should be interpreted as meaning that most people in this situation would want the recommended course of action and only a small number would not. Clinicians should regard the recommendation as applying to most individuals. Policy-makers can adopt the recommendation as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. A *weak recommendation* should be interpreted as meaning that most people in this situation would want the recommended course of action, but many would not; patients' values and preferences should be considered in reaching a decision. Decision aids may support people in reaching these decisions. Policy-making will require substantial debate and involvement of various stakeholders. An appropriately documented decision making process could be used as a quality indicator

Appendix 6.1

Randomised trials and systematic reviews of trials of interventions in pregnancy to prevent pre-eclampsia in women at low (to moderate) risk (unless indicated by an '*' when all women were presented together)

See next page – this appendix requires a double-page layout

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)				
		Maternal outcomes		
Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Aspirin				
Duley 2007[6] (systematic review of 59 trials, 37,500 women with only moderate-risk women included here when possible; see Appendix 6.2 for data on high-risk women)	25 trials (N = 28,469)	". . . *wide variation in study quality. The poorer quality studies were mostly the small early trials, with the more recent large studies tending to be of higher quality.*"	Low-dose aspirin or dipyridamole (N = 14,326)	Placebo or no anti-platelet agent (N = 14,143)
Henderson 2014[81] (systematic review of 23 trials, 22,988 women with both low and high-risk women included here; see Appendix 6.2 for data on high-risk women)	23 trials (N = 22,988) 8 trials (average-risk women) (N not specified)	(Of 23 trials) "*18 described adequate randomisation, with 2 trials not clearly reporting appropriate allocation concealment*" OAB: "*all RCTs reported valid outcome measures*" LFU <20%: 14/23 trials	Aspirin (50–150 mg/d) (N = not specified)	Placebo or no treatment (N = not specified)
Calcium				
Hofmeyr 2014[7] (systematic review of 24 trials, 17,954 women with only low-risk women included here when possible; see Appendix 6.2 for data on high-risk women. Data on women at unclear risk not presented)	HIGH-DOSE 8 trials (N = 15,143)	Alloc con low risk: 11/19 trials. OAB low risk: 12/19 trials IOD low risk: 10/19 trials	HIGH-DOSE (≥1 g/d) (N = 7821)	Placebo or no calcium (N = 8935)
	LOW DOSE 10 trials (N = 2234 with low and high risk women combined)		LOW DOSE (<1 g/d) (N = 1178)	

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)			
Maternal outcomes		*Neonatal outcomes*	
PET	*Other*	*SGA infants*	*Other*
RR 0.86 [0.79–0.95] NNT 119 [73,333] (25 trials, N = 28,469) Eclampsia RR 0.94 [0.59–1.48]* (9 trials, N = 22,584)	GH RR 1.00 [0.92–1.08] (22 trials, N = 19,863) Abruption RR 1.17 [0.93–1.48] (12 trials, N = 2 2,272) Maternal death RR 2.57 [0.39–17.06]* (3 trials, N = 12,709) CS RR 1.02 [0.98–1.06]* (24 trials, N = 31,834) IOL RR 1.03 [0.98–1.08]* (5 trials, N = 19,295) Hospital admission during pregnancy RR 1.03 [0.97–1.10]* (3 trials, N = 12,964)	RR 0.91 [0.83–0.99] (23 trials, N = 19,399)	Perinatal death RR 0.92 [0.80–1.07] NNT 243 [131–1666] (23 trials, N = 28655) PTB <37 weeks RR 0.93 [0.88–0.99] (19 trials, N = 27,899)
	Abruption RR 1.17 [0.93–1.48]* (8 trials, N = 22,988)		Perinatal death RR 0.92 [0.76–1.11]* (14 trials, N = 22,848)
HIGH-DOSE RR 0.59 [0.41–0.83] (8 trials, N = 15,143)	HIGH-DOSE Hypertension (+/–PET) RR 0.71 [0.57–0.89] (8 trials, N = 15,143) Death or serious morbidity RR 0.80 [0.65–0.97] (4 trials, N = 9732) HELLP RR 2.67 [1.05–6.82] (2 trials, N = 12,901)	HIGH-DOSE RR 1.05 [0.86–1.29]* (4 trials, N = 13,615)	
LOW DOSE Calcium alone RR 0.36 [0.23–0.57]* (4 trials, N = 980) Calcium ± supplements RR 0.38 [0.28–0.52] (9 trials, N = 2234)	LOW DOSE Calcium with or without co-supplements Hypertension (±PET) RR 0.53 [0.38–0.74]* (5 trials, N = 665)	LOW DOSE Calcium alone Not estimable Calcium plus supplements RR 0.81 [0.54–1.21]* (4 trials, N = 854)	

continued

Appendix 6.1 *continued*

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)				
		Maternal outcomes		
Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Calcium				
Imdad 2012[10] (systematic review)	15 trials (N = 16,754)	"*The studies included in this review were in general of good methodological quality… allocation concealment [was] adequate in most of the studies*."	500 mg–2 g/d starting at <32 weeks (N = 8,367)	Placebo or no calcium (N = 8387)
Villar 2006[9] (single trial)	N = 8325	Alloc con: yes. OAB: yes LFU <20%: yes	Calcium (1.5 g/d) (N = 4157)	Placebo (N = 4168)
Dietary changes				
Duley 2005[13] (systematic review)	2 trials (N = 603)	Alloc con low risk: 1/2 trials. OAB: NR. IOD low risk: 2/2 trials.	Advice to reduce dietary salt intake to 20 or 50 mmol/d (N = 294)	Advice to continue normal diet (N = 309)

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)			
Maternal outcomes		*Neonatal outcomes*	
PET	*Other*	*SGA infants*	*Other*
Any PET RR 0.48, [0.34–0.67] (15 trials, N = 16,490) Severe PET RR 0.75, [0.57–0.98] (5 trials, N = 13,724)	Mortality/severe morbidity RR 0.80 [0.65–0.97] (2 trials, N = 9732) ("*No increased risk of kidney stones*")	RR 1.01 [0.84–1.21] (7 trials, N = 14,438] LBW RR 0.85 [0.72–1.01] (6 trials, N = 14,479) BWt (g) Mean difference 85.75 [37.91–133.58] (13 trials, N = 8574)	PTB <37 weeks RR 0.76 [0.60–0.96] (10 trials, N = 15,275) Perinatal mortality RR 0.90 [0.74–1.09] (11 trials, N = 15,665]
PET/eclampsia RR 0.91 [0.69–1.19] Severe PET/eclampsia RR 0.73 [0.49–1.07] Early onset PET or eclampsia RR 0.77 [0.54–1.11] Eclampsia RR 0.68 [0.48–0.97]	Abruption RR 0.77 [0.43–1.39] GH RR 0.96 [0.86–1.06] Severe GH RR 0.71 [0.61–0.82] Gestational proteinuria RR 1.04 [0.93–1.17] Severe PET complications^ RR 0.76 [0.66–0.89] Any ICU/SCBU admission RR 0.85 [0.75–0.95] ICU admission ≥2 d RR 0.84 [0.57–1.21] Maternal death RR 0.17 [0.03–0.76] Severe maternal M&M index+ RR 0.80 [0.70–0.91]		PTB <37 weeks RR 0.91 [0.79-1.05] PTB <32 weeks RR 0.82 [0.71–0.93] Stillbirth RR 0.93 [0.74–1.17] NND RR 0.70 [0.56–0.88]
RR 1.11 [0.46–2.66] (2 trials, N = 603)	GH RR 0.98 [0.49–1.94] (2 trials, N = 242) Visit to day care unit RR 1.05 [0.48–2.32] (1 trial, N = 361) Antenatal hospital admission RR 0.82 [0.56–1.22] (1 trial, N = 361) Abruption RR 0.19 [0.01–3.98] (1 trial, N = 361) CS RR 0.75 [0.44–1.27] (1 trial, N = 361)	RR 1.5 [0.73–3.07] (1 trial, N = 242)	Perinatal death RR 1.92 [0.18–21.03] (2 trials, N = 409) PTB RR 1.08 [0.46–2.56] (1 trial, N = 242) 5 min Apgar <7 RR 1.37 [0.53–3.53] (1 trial, N = 361) NICU admission RR 0.98 [0.69–1.40] (1 trial, N = 361)

continued

Appendix 6.1 *continued*

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)				
Maternal outcomes				
Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Dietary changes				
Ota 2015[15] (systematic review)	17 trials (N = 9030)	Alloc con low risk: 6/17 trials. OAB low risk: 3/17 trials. IOD low risk 11/17 trials.	Nutritional education to increase energy and protein intake or actual energy and protein supplementation	No education, no supplement or placebo
			NUTRITIONAL EDUCATION (5 trials, N = 553)	No nutritional education (5 trials, N = 544)
			BALANCED ENERGY AND PROTEIN (12 trials, N = 2856)	No intervention (12 trials, N = 2684)
			HIGH-PROTEIN (1 trial, N = 259)	Low or no protein supplement (1 trial, N = 270)

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)			
Maternal outcomes		*Neonatal outcomes*	
PET	*Other*	*SGA infants*	*Other*
–	Protein intake (g/d) Mean difference 6.99 [3.02–10.97] (e trials, N = 632] Energy intake (kcal/d) Mean difference 105.61 [–18.94–230.15]	RR 0.97 [0.45–2.11] (1 trial, N = 404) LBW RR 0.04 [0.01–0.14] (1 trial, N = 300) BWt (g) Undernourished Mean difference +489.76 [427.93–551.59] (2 trials, N = 320) BWt (g) Adequately nourished Mean difference +15.0 [–76.30–+106.30] (1 trial, N = 406	PTB RR 0.46 [0.21–0.98] (2 trials, N = 449) Stillbirth RR 0.37 [0.07–1.90] (1 trial, N = 431) Neonatal death RR 1.28 [0.35–4.72] (1 trial, N = 448)
RR 1.48 [0.82–2.66] (2 trials, N = 263)	Weekly gestational weight gain Mean difference 18.63 [–1.81–39.07] (9 trials, N = 2391)	RR 0.79 [0.69–0.90] (7 trials, N = 4408) BWt (g) Mean difference +40.96 [4.66–77.26] (11 trials, N = 5385)	PTB RR 0.96 [0.80–1.16] (5 trials, N = 3384) Stillbirth RR 0.60 [0.39–0.94] (5 trials, N = 3408) NND RR 0.68 [0.43–1.07] (5 trials, N = 3381) Bayley Mental Score at 1 year Mean difference of –0.74 [–1.95–0.47] (1 trial, N = 411)
–	Weekly gestational weight gain (g/week) Mean difference 4.5 [–33.55–42.55] (1 trial, N = 486)	RR 1.58 [1.03–2.41] (1 trial, N = 505) BWt (g) Mean difference –73.0 [–171.26–+25.26] (1 trial, N = 504) Weight at 1 year (g) Mean difference 61.0 [–184.60–+306.60] (1 trial, N = 409)	PTB RR 1.14 [0.83–1.56] (1 trial, N = 505) Stillbirth RR 0.81 [0.31–2.15] (1 trial, N = 529) NND RR 2.78 [0.75–10.36] (1 trial, N = 529)

continued

Appendix 6.1 *continued*

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)				
Maternal outcomes				
Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Dietary changes				
			ISOCALORIC PROTEIN	Protein replaced by an equal quantity of non-protein energy (2 trials, N = 93)
Allen 2014[12] (systematic review of 18 trials, 8712 women with low and high-risk women presented together here; 7 of the trials were with women with no risk factors for preeclampsia; see Appendix 6.2 for data on high-risk women. Data for women at unclear risk not presented)	18 trials (N = 8712)	Alloc con: low risk 9/18 trials OAB: low risk 7/18 trials IOD low risk: 17/18 trials	Dietary change alone or with other change	Placebo or no dietary change
			DIET (6 trials, N = 1334)	Control (6 trials, N = 1361)
			MIXED (Diet, physical activity & lifestyle) (6 trials, N = 733)	Control (not specified) (6 trials, N = 705)
			ESSENTIAL ACIDS (6 trials, N = 2275)	Control (not specified) (6 trials, N = 2304)
Micronutrients other than calcium				
Kubik 2004[23] (single trial)	N = 138	"*double blinded trial*"	Vitamin and mineral supplement containing 15 mg zinc, 2 mg copper, and 20 μg selenium	Placebo

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)			
Maternal outcomes		*Neonatal outcomes*	
PET	*Other*	*SGA infants*	*Other*
–	Weekly gestational weight gain (g/week) Mean difference 110.45 [–82.77–303.76] (2 trials, N = 184)	BWt (g) Mean difference 108.25 [–220.89–437.40] (2 trials, N = 184)	
ANY DIETARY CHANGE RR 0.81 [0.69–0.94] (18 trials, N = 8712) (I^2 = 0%)			
RR 0.67 [0.53–0.85] (6 trials, N = 2695)	–	–	–
RR 0.93 [0.66–1.32 (6 trials, N = 1438)	–	–	–
RR 0.92 [0.71–1.18] (6 trials, N = 4579)	–	–	–
"*6.25% vs. 7.7%*"	SVD ("*natural deliveries*") "*75.0% vs. 53.8%*"		

continued

Appendix 6.1 *continued*

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)				
Maternal outcomes				
Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Micronutrients other than calcium				
Makrides 2014[40] (systematic review of 10 trials, 9090 low and high risk women for whom outcomes were not reported by risk)	(Low and high risk women reported together) 10 trials (N = 9090)	Alloc con low risk: 2/10 trials. OAB low risk: 7/10 trials. IOD low risk: 3/10 trials.	Oral Mg (N = 4516) "*compositions of the Mg supplements, gestational ages at commencement, and doses administered varied*"	Placebo (8 trials, 3241) or no therapy (2 trials, N = 939) (Total N = 4180)

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)			
Maternal outcomes		*Neonatal outcomes*	
PET	*Other*	*SGA infants*	*Other*
RR 0.87 [0.58–1.32] (3 trials, N = 1042)* Eclampsia RR 0.14 [0.01–2.70] (1 trial, N = 100)	Hospitalisation during pregnancy RR 0.65 [0.48–0.86]* (3 trials, N = 1158) Abruption RR 0.96 [0.48–1.94] (1 trial, N = 4082) Pregnancy-induced HTN RR 0.39 [0.11–1.41] (3 trials, N = 4284)	RR 0.76 [0.54–1.07]* (3 trials, N = 1291 infants)	Stillbirth RR 0.73 [0.43–1.25]* (4 trials, N = 5526] Perinatal mortality RR 1.10 [0.72–1.67]* (5 trials, N = 5903 infants NND before hospital discharge RR 2.21 [1.02–4.75]‡* (4 trials, N = 5373 infants) Miscarriage <20 weeks RR 0.85 [0.49–1.49]* (6 trials, N = 3704] (6 trials, N = 3704) Gestational age at birth (weeks) Mean difference 0.06 [–0.07–0.20]* (5 trials, N = 5564] PTB <37 weeks RR 0.89 [0.69–1.14]* (7 trials, N = 5981] LBW <2500 g RR 0.95 [0.83–1.09]* (5 trials, N = 5577) NICU admission RR 0.74 [0.50–1.11]* (3 trials, N = 1435) Apgar <5 at 5 min RR 0.83 [0.41–1.67]* (1 trial, N = 377) Apgar <7 at 5 min RR 0.34 [0.15–0.80]* (4 trials, 1083 infants) Meconium-stained liquor RR 0.79 [0.63–0.99]* (1 trial, 4082 infants) Late FH decelerations RR 0.68 [0.53–0.88]* (1 trial, 4082 infants) Mild HIE RR 0.38 [0.15–0.98]* (3 trials, 4082 infants) Breech presentation RR 1.25 [0.81–1.92]* (1 trial, N = 4082)

continued

Appendix 6.1 *continued*

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)				
Maternal outcomes				
Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Micronutrients other than calcium				
Bullarbo 2013[42] (single trial)	N = 59	"*double-blind randomisa-tion*"	Magnesium (300 mg/d from 25 weeks) (N = 29)	Placebo (N = 30)
Mori 2012[43] (systematic review)	20 trials "*over 15,000 women and their babies*"	Alloc con low risk: 10/20 trials. OAB low risk: 13/20 trials. IOD low risk: 5/20 trials.	ZINC (5–90 mg/d) starting before conception to 26 weeks (N not specified)	Placebo or no zinc (N not specified)
Parrish 2013[44] (single trial of 684 low and high-risk women with data on low-risk women reported here; see Appendix 6.2 for data on high risk women)	N = 113	Alloc con: yes OAB: yes Loss to follow up <20%: No (f/u was available for N = 267 low and high risk combined)	Fruit and vegetable juice powder concentrate (N = 56)	Placebo (N = 57)

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)			
Maternal outcomes		*Neonatal outcomes*	
PET	*Other*	*SGA infants*	*Other*
Average dBP at 37 weeks significantly lower (mmHg) (72/1.4 mean/SEM vs 77/1.2, $p = 0.03$)	Fewer women developed an increase in dBP ≥15 mmHg ($p = 0.01$)		
PET or GH RR 0.83 [0.64–1.08] (7 trials, N = 2975)	APH 2nd trimester RR 1.59 [0.57–4.45] (1 trial, N = 1206) APH 3rd trimester RR 0.96 [0.39–2.33] (1 trial, N = 1206) PROM RR 0.93 [0.78–1.11] (2 trials, N = 1691) Post-term birth RR 1.09 [0.74–1.60] (3 trials, N = 1554) IOL RR 0.27 [0.10–0.73] (1 trial, N = 52) CS RR 0.95 [0.58–1.53] (6 trials, N = 2164) Instrumental vaginal birth RR 1.12 [0.79–1.59] (1 trial, N = 1206) PPH RR 1.13 [0.78–2.26] (3 trials, N = 718)	RR 1.02 [0.94–1.11] (8 trials, N = 4252 babies)	PTB RR 0.86 [0.76–0.97] (16 trials, N = 7637) BWt Mean difference −9.48 [−4.28–15.33] (16 trials, N = 5780) LBW RR 0.93 [0.78–1.12] (14 trials, N = 5643) Meconium in liquor RR 1.16 [0.86–1.56] (2 trials, N = 1385) FHR (beats/min) Mean difference −1.20 [−3.31–0.91] (1 trial, N = 176)
RR 1.22 [0.40–3.77] Mild PET RR 1.02 [0.31–3.32]	GH RR 1.02 [0.21–4.83]	RR 2.04 [0.39–10.7] RR 1.40 [0.45–4.26]	Live birth RR 1.02 [0.96–1.08] RDS RR 1.53 [0.27–8.79] NICU admission RR 1.03 [0.27–3.96] NND RR 0.20 [0.01–4.09]* NICU admission RR 0.57 [0.25–1.30]* IVH gr 3 or 4 RR 0.99 [0.06–15.7]*

continued

Appendix 6.1 *continued*

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)				
Maternal outcomes				
Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Prostaglandin precursors				
Makrides 2006[45] (systematic review of 2783 low- and high-risk women with data on low-risk women reported here; see Appendix 6.2 for data on high risk women)	4 trials (N = 2056)	Alloc con low risk: 3/6 trials OAB: NR IOD "*Most trials reported outcome for at least 83% of all women recruited*"	Marine oil (N = 1024)	Placebo or no marine oil (N = 1032)
Zhou 2012[46] (single trial)	N = 2399	Alloc con: yes OAB: NR Loss to f/u <20%: NR	Fish oil (800 mg DHA/d in second half of pregnancy) (N = 1197)	Placebo (N = 1202)

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)			
Maternal outcomes		*Neonatal outcomes*	
PET	*Other*	*SGA infants*	*Other*
RR 1.01 [0.52–1.98] (3 trials, N = 1130)	GH RR 1.09 [0.90–1.33] (5 trials, N = 1831)	RR 1.12 [0.93–1.35] (1 trial, N = 1111)	PTB <37 weeks RR 0.95 [0.80–1.13] (3 trials, N = 1393) Length of gestation (days) Mean difference 2.23 [0.67–3.80] (3 trials, N = 1393) Prolonged gestation (>42 weeks) RR 1.19 [0.73–1.93] (1 trial, N = 533) BWt (g) Mean difference 55.79 [4.83—106.74] (3 trials, N = 1946) LBW <2500 g RR 0.99 [0.87–1.13] (2 trials, N = 1413) Stillbirth ≥24 weeks) RR 1.00 [0.06–15.96] (1 trial, N = 533) NND RR 2.01 [0.18–22.01] (1 trial, N = 579)
PET aRR 1.03 (0.72–1.48] (N = 2399) Clinical PET aRR 0.87 [0.60–1.25]	GH aRR 0.93 [0.71–1.21] GDM aRR 1.04 [0.75–1.44] Clinical GDM aRR 0.97 [0.74–1.27]	For weight aRR 0.90 [0.66–1.22] For length aRR 0.93 [0.75–1.16] (N = 2399) For head circum aRR 0.96 [0.78–1.19] (N = 2399)	LBW aRR 0.65 [0.44–0.96] Macrosomia aRR 1.27 [1.05–1.55]

continued

Appendix 6.1 *continued*

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)				
Maternal outcomes				
Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Smoking cessation				
Chamberlain 2013[54] (systematic review)	86 trials (N = >29,000 women)	Alloc con low risk: 10/86 trials. OAB: "*not calculable due to insufficient numbers of studies with low risk of bias*" IOD low risk: 22/86 trials.	Smoking cessation interventions (N = 4298)	Routine care (N = 4264)
Coleman 2012[55] (single trial)	N = 1050	Alloc con: yes OAB: yes Loss to f/u <20%: yes (18.5%)	Nicotine patches (15 mg every 16 h for 8 weeks) (N = 521)	Placebo (N = 529)

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)			
Maternal outcomes		*Neonatal outcomes*	
PET	*Other*	*SGA infants*	*Other*
		LBW <2500 g RR 0.87 [0.70–1.08] (6 trials, N = 3836) Very LBW RR 1.27 [0.60–2.71] (2 trials, N = 1666) Mean BWt Mean difference 36.72 [0.70–72.74] (9 trials, N = 4846)	PTB <37 weeks RR 0.82 [0.70v0.96] (14 trials, N = 7852) Stillbirths RR 1.08 [0.51–2.30] (4 trials, N = 2212] NND RR 2.06 [0.61–6.92] (3 trials, N = 2095) NICU admission RR 0.82 [0.52–1.29] (2 trials, N = 1140)
PET or eclampsia 3 (0.6%) vs. 5 (0.9%), p = NR	BP >140/90 mmHg on at least 2 occasions 24 (4.6%) vs. 25 (4.7%), p = NR Caesarean OR 1.45 [1.05–2.01] (N = 1024)	LBW OR 1.38 [0.90–2.09] BWt, unadjusted (kg) –0.02 [–0.10–0.05]	Miscarriage OR 1.52 [0.25–9.13] Stillbirth OR 2.59 [0.50–13.4] (N = 1041) PTB OR 0.90 [0.58–1.41] (N = 1024) NICU admission OR 0.95 [0.58–1.57] (N = –1024) 5 min Apgar <7 OR 0.91 [0.45–1.80] (N = 1024) Cord blood arterial pH <7 OR 0.57 [0.17–1.97] (N = 1024) IVH OR 0.67 [0.11–4.05] (N = 1024) Neonatal convulsions OR 1.02 [0.29–3.54] (N = 1024) NEC OR 0.50 [0.12–2.03] (N = 1024)

continued

Appendix 6.1 *continued*

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)				
Maternal outcomes				
Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Thiazide diuretics				
Churchill 2007[56] (systematic review of 5 trials, N = 1836 low and high-risk women of which low and high-risk women are reported together here; see Appendix 6.2 for data on high-risk women)	5 trials (N = 1836)	"*The quality of all five studies was unclear*" Alloc con: unclear OAB: 4/5 trials LFU <20%: 5/5 trials	Thiazide diuretic (N = 1016)	Placebo or no thiazide (N = 820)
Vitamins C & E				
Rumbold 2008[57] (systematic review of 10 trials, N = 6533 low/ moderate- and high-risk women, of which the low/ moderate-risk women are presented here when possible; see Appendix 6.2 for data on the high-risk women)	5 trials (N = 3307)	Alloc con low risk: 3/5 trials. OAB low-risk: 5/5 trials (explicitly stated in 4). OAB low risk: 3/5 trials.	One/more antioxidants (N = 1858 as calculated from tables)	Placebo or no antioxidant (N = 1449)

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)			
Maternal outcomes		*Neonatal outcomes*	
PET	*Other*	*SGA infants*	*Other*
RR 0.68 [0.45–1.03]* (4 trials, N = 1391) Severe PET RR 1.56 [0.26–9.17]* (2 trials, N = 1297)	HTN (new or worsening) RR 0.85 [0.68–1.08]* (2 trials, N = 1475) Nausea and vomiting RR 5.81 [1.04–32.46]* (2 trials, N = 1217) CS RR 1.0 [0.26–3.81]* (1 trial, N = 20)	None in the 1 trial that reported this outcome	Perinatal death RR 0.72 [0.40–1.27]* (5 trials, N = 1836) Stillbirth RR 0.60 [0.27–1.34]* (5 trials, N = 1836) NND RR 0.88 [0.40–1.97]* (4 trials, N = 1816) PTB RR 0.67 [0.32–1.41]* (2 trials, N = 465) BWt Mean difference 139.0 [–484.40–762.40]* (1 trial, N = 20) Gestation at birth Mean difference 0.70 [–0.71–2.11]* (1 trial, N = 20) Postmaturity >42 weeks RR 7.0 [0.41–120.16]* (1 trial, N = 20) 5 min Apgar <7 RR 3.0 [0.14–65.90]* (1 trial, N = 20)
RR 0.85 [0.48–1.51] (4 trials, N = 2441)	Antihypertensive therapy RR 1.77 [1.22–2.57]* (2 trials, N = 4272) Require antenatal hospital admission for HTN RR 1.54 [1.00–2.39]* (1 trial, N = 1877)	RR 0.71 [0.42–1.19]* (2 trials, N = 2104)	PTB RR 1.17 [0.92–1.48]* (2 trials, N = 2067) Any baby death RR 0.90 [0.53–1.51]* (2 trials, N = 2077)

continued

Appendix 6.1 *continued*

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)				
Maternal outcomes				
Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Vitamins C & E				
Mahdy 2013[60] (single trial)	N = 299	Alloc con: yes. OAB: NR. LFU <20%: yes (6.3%).	Tocotrienol-rich fraction (TRF) of palm oil (100 mg/d) from early 2nd trimester until delivery (N = 151)	Placebo (N = 148)
Kiondo 2014[61] (single trial)	N = 932	Alloc con: yes OAB: yes LFU <20%: yes (10.6%)	Vitamin C 1000 mg/d from 12–22 weeks until delivery (N = 466)	Placebo (N = 466)
NO donors				
Schleussner 2014[141] (single trial of 111 low and high-risk women with data on low-risk women reported here; see Appendix 6.2 for data on high risk women)	N = 74	Allocation method not clear	Nitric oxide donor pentaerithrityl-tetranitrate (PTN) tablet twice daily (N = 33)	Placebo (N = 41)

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)			
Maternal outcomes		*Neonatal outcomes*	
PET	*Other*	*SGA infants*	*Other*
RR 0.20 [0.02–1.66]	PET or GH RR 0.36 [0.12–1.09]		
Any PET RR 0.77 [0.37–1.56] Severe PET RR 1.25 [0.34–4.65]	GH RR 0.67 [0.43–1.03] APH RR 0.78 [0.29–2.1] PROM RR 0.79 [0.41–1.54] Abruption RR 0.5 [0.04–5.53] Vaginal delivery RR 1.0 [0.82–1.22]	LBW RR 1.07 [0.72–1.59]	BWt <2500 g RR 1.07 [0.72–1.59] Apgar <7 RR 1.17 [0.76–1.81] Admission to SCU RR 1.53 [0.95–2.43] Stillbirth RR 1.01 [0.54–1.87] Early NND RR 0.71 [0.27–1.83] Abortion RR 1.01 [0.40–2.51] PTB RR 0.92 [0.63–1.34] Stillbirth RR 1.01 [0.54–1.87]
PET/HELLP 6(21.2%) vs. 8 (19.5%) PET <32 weeks 3 (50%) vs. 5(62.5%)	Abruption 0 vs. 4(9.8%) CS 14 (41.2%) vs. 21 (53.8%)		IUGR or perinatal death 9 (27.3%) vs. 17 (41.5%) PTD <37 weeks 10 (30.3%) vs. 12 (29.3%) PTD <32 weeks 1 (3%) vs. 8 (19.5%) 1 min Apgar score 7.7 (+/–1.9) vs. 7.4 (+/–2.2) 5 min Apgar score 8.5 (+/–1.4) vs. 8.7 (+/–1.1) UA pH 7.3 (+/–0.1) vs. 7.3 (+/–0.1) BWt (g) 2734 (+/–889) vs. 2460 (+/–01004) Ventilation (NICU) 9 (30) vs. 7 (20.0)

continued

Appendix 6.1 *continued*

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)				
		Maternal outcomes		
Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Lifestyle changes				
Meher 2006[73] (systematic review)	2 trials (N = 106)	Alloc con low risk: "inadequately reported". OAB: "not possible" LFU <20%: "completeness of follow-up was not reported in either trial"	4–6 h rest/d (N = 16)	Normal activity (N = 16)
			4–6 h rest/d + Nutrient supplementation (N = 37)	Normal activity + placebo (N = 37)
Kramer 2006[26] (systematic review)	14 trials (N = 1014)	Alloc con: "in most of the trials, the method of treatment allocation was either by alternation or was not described". OAB: not specified LFU<20%: not specified	Increase in exercise in sedentary women (N = 280)	Maintain activity level (N = 276)
			Reduction in exercise in physically fit women (N = 28)	Maintain activity level (N = 33)
			Increase then reduction in exercise in physically fit women (N = 25)	Maintain activity level (N = 24)

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)			
Maternal outcomes		*Neonatal outcomes*	
PET	*Other*	*SGA infants*	*Other*
RR 0.05 [0.00–0.83] (1 trial, N = 32)	GH RR 0.25 [0.03–2.00] (1 trial, N = 32)		
RR 0.13 [0.03–0.51] (1 trial, N = 74)	GH RR 0.15 [0.04–0.63] (1 trial, N = 74) CS RR 0.82 [0.48–1.41] (1 trial, N = 74)		
RR 1.17 [0.44–3.08] (2 trials, N = 82)	CS RR 0.96 [0.60–1.53] (3 trials, N = 386] Total gestational weight gain (kg) Mean difference 0.79 [–0.73–2.31] (4 trials, N = 122) Change in maternal fat mass (kg) Mean difference –1.51 [–3.06–0.04] (1 trial, N = 41) Change in maternal lean mass (kg) Mean difference 1.59 [0.38–2.80] (1 trial, N = 41)	BWt (g) Mean difference 49.49 [–27.74–126.73] (6 trials, N = 556)	PTB RR 1.82 [0.35–9.57] (3 trials, N = 111) 1 min Apgar Mean difference 1.0 [–1.37–3.37] (1 trial, N = 20) 5 min Apgar Mean difference 0.15 [–0.10–0.39] (4 trials, N = 462)
			PTB RR 1.18 [0.08–17.99] (1 trial, N = 61) BWt (g) Mean difference –135.0 [–368.66, 98.66] (1 trial, N = 61)
			Gestational weight gain (kg) Mean difference 0.90 [–1.59–3.39] (1 trial, N = 49) Bwt (g) Mean difference 460.0 [251.63–668.37] (1 trial, N = 49)

continued

Appendix 6.1 *continued*

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)				
Maternal outcomes				
Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Lifestyle changes				
			Reduction, then increase in exercise in physically fit women (N = 26)	Maintain activity level (N = 24)
			Increase in exercise in overweight women (N = 37)	Maintain activity level (N = 35)
Periodontal therapy				
Niederman 2010[143]	N = 1082	Alloc con: yes OAB: yes LFU <20%: yes	Periodontal treatment in midpregnancy (N = 542)	Periodontal treatment after pregnancy (N = 540)

Alloc con, allocation concealment; APH, antepartum haemorrhage; aRR, adjusted relative risk; BWt, birth weight; CI, confidence interval; circum, circumference; CS, Caesarean section; ctx, contraction; dBP, diastolic blood pressure; DHA, docosahexanenoic acid; FHR, fetal heart rate; FM, fetal movement; GDM, gestational diabetes mellitus; GH, gestational hypertension; HELLP, haemolysis, elevated liver enzymes, low platelets; HIE, hypoxic ischaemic encephalopathy; IOD, incomplete outcome data; IOL, induction of labour; LBW, low birth weight; LFU, loss to follow up; IUGR, intrauterine growth restriction; IVH, intraventricular haemorrhage; LBW, low birth weight; Mg, magnesium; NEC, necrotising enterocolitis; NICU, neonatal intensive care unit; NND, neonatal death; NNT, number needed to treat; NR, not reported; OAB, outcome assessment blinding; OR, odds ratio; PET, pre-eclampsia; PPH, postpartum haemorrhage; PROM, premature rupture of membranes; PTB, preterm birth; RDS, respiratory distress syndrome; RR, relative risk; SEM, standard error of mean; SGA, small-for-gestational age; SVP, spontaneous vaginal delivery

Outcomes (summary statistic [95% CI]) (N trials, N women for systematic reviews)			
Maternal outcomes		*Neonatal outcomes*	
PET	*Other*	*SGA infants*	*Other*
			Gestational weight gain (kg) Mean difference −2.60 [−4.96-9-0.24)] (1 trial, N = 50) BWt (g) Mean difference −100.0 [−308.39–108.39] (1 trial, N = 50)
			PTB RR 1.89 [0.18–19.95] (1 trial, N = 72) BWt (g) Mean difference −5.0 [−241.27–231.27]
OR 0.82 [0.44–1.56]		BWt 3450 vs. 3410 g ($p = 0.12$)	PTB OR 1.05 [0.7–1.58]

† "Sensitivity analysis after excluding women with GDM showed that the reduction in pre-eclampsia did not persist by combining all interventions (RR 0.91 [0.75–1.11]) or in diet only group (RR 0.86 [0.45–1.64])." "2 studies on women with GDM had . . . insulin. We cannot rule out the possibility that insulin use could have been an important contributor to the beneficial effect observed"

‡ These results should be interpreted with caution as a large number of severe congenital anomalies and deaths of two sets of twins (with birth weights <750 g) in the supplemented group likely accounted for the increased risk of death observed. When deaths due to severe congenital abnormalities were excluded from the meta-analysis, no increased risk of NND was seen.

^ Severe PET complications: 1+ of the following outcomes: severe pre-eclampsia or early onset pre-eclampsia (32 weeks gestation), eclampsia, HELLP syndrome, placental abruption, severe gestational HTN (≥160 mmHg and/or ≥110 mmHg systolic and diastolic pressures, respectively)

Appendix 6.2

Randomised trials and systematic reviews of trials of interventions to prevent pre-eclampsia in women at increased risk (unless indicated by an '*' when all women were presented together)

Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Antihypertensive drugs				
Abalos 2014[78] (systematic review)	49 trials (N = 4723)	Alloc con low risk: 17/49 trials. OAB low risk: 10/49 trials. IOD low risk: 45/49 trials.	ANY HYPERTENSIVE DRUG (N = 1476)	NO DRUG OR PLACEBO (N = 1375)
			ANY ANTIHYPERTENSIVE DRUG (N = 689)	METHYLDOPA (N = 650)
			ANY ANTIHYPERTENSIVE DRUG (N = 74)	CALCIUM CHANNEL BLOCKER (N = 62)

PET	*Other*	*SGA infants*	*Other*
Proteinuria/PET RR 0.93 [0.80–1.08] (23 trials, N = 2851) Severe PET RR 0.54 [0.24–1.23] (3 trials, N = 416) Eclampsia RR 0.34 [0.01–8.15] (5 trials, N = 578)	Maternal death RR 1.08 [0.24–4.83] (5 trials, N = 525) Severe HTN RR 0.49 [0.40–0.60] (20 trials, N = 2558) HELLP RR 2.02 [0.38–10.78] (1 trial, N = 197)	RR 0.97 [0.80–1.17] (20 trials, N = 2586)	RR 0.71 [0.49–1.02] (27 trials, N = 3230)
Proteinuria/PET RR 0.73 [0.54–0.99] (11 trials, N = 997)	Severe HTN RR 0.54 [0.30–0.95] (11 trials, N = 638) Antenatal hospital admission RR 0.77 [0.58–1.03] (2 trials, N = 275) CS RR 0.93 [0.78–1.12] (10 trials, N = 878) Abruption RR 2.02 [0.19–21.90] (1 trial, N = 173)	RR 0.80 [0.53–1.21] (7 trials, N = 597)	Perinatal death RR 0.73 [0.42–1.27] (19 trials, N = 1339) PTB< 37 weeks RR 0.76 [0.55–1.05] (9 trials, N = 623) Admission to SCBU RR 0.92 [0.67–1.26] (4 trials, N = 478)
Proteinuria/PET RR 2.15 [0.73–6.38] (2 trials, N = 128)	Severe HTN RR 2.09 [0.96–4.57] (2 trials, N = 136) HELLP RR 1.5 [0.26–8.60] (1 trial, N = 100) CS RR 1.57 [0.91–2.71] (1 trial, N = 100)	RR 1.0 [0.10–9.96] (1 trial, N = 36)	Total fetal or NND RR 1.0 [0.06–15.55] (2 trials, N = 136) PTB <37 weeks RR 0.63 [0.20–1.91] (1 trial, N = 36) Admission to SCBU RR 1.47 [0.44–4.89] (1 trial, N = 99)

continued

Appendix 6.2 *continued*

Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Antihypertensive drugs				
Magee 2007[79] (single trial)	N = 132		Less tight BP control (N = 66)	Tight BP control (N = 65)
Aspirin				
Duley 2007[6] (systematic review of 59 trials, 37,500 women with only high-risk women included here; see Appendix 6.1 for data on moderate-risk women)	18 trials (N = 4121)	". . . *wide variation in study quality. The poorer quality studies were mostly the small early trials, with the more recent large studies tending to be of higher quality*."	Low-dose aspirin or dipyridamole (N = 14,326)	Placebo or no anti-platelet agent (N = 14,143)
Bujold 2010[86] (systematic review and meta-analysis)	27 trials (N = 11,348)	Alloc con: 12/12 trials. OAB: 4/12 trials. LFU <20%: 12/12 trials.	Low-dose (50–150 mg/d) aspirin started ≤16 weeks or earlier (N = 389)	Placebo or no treatment (N = 375)
		Alloc con: 22/22 trials. OAB: double blinding 16/22 trials LFU <20%: 22/22 trials	Low-dose aspirin (50–150 mg/d) started ≥16 weeks (N = 5691)	Placebo or no treatment (N = 5657)
Groeneveld 2013[84] (meta-analysis)	4 trials (N = 268)	Alloc con: 4/4 trials. OAB: 4/4 trials. LFU <20%: ? (No information provided)	Aspirin 100 mg/d in IVF patients (N = 131) Singletons (N = 96) Twins (N = 24)	Placebo (N = 137) Singletons (N = 91) Twins (N = 41)

PET	*Other*	*SGA infants*	*Other*
16 (24.2) vs. 20 (30.8)	Serious maternal complications 3 (4.6%) vs. 2 (3.1%) CS 35 (53.0%) vs. 37 (56.9%) Antenatal corticosteroids for fetal lung maturation 16 (24.2%) vs. 15 (23.1%) $MgSO_4$ for PET 10 (15.2%) vs. 12 (18.5%)		GA at delivery 36.9 ± 3.0 vs. 36.3 ± 3.3 BWt (g) 2675 ± 858 vs. 2501 ± 855 5 min Apgar <7 0 (0.0) vs. 2 (3.1) 5 min serious perinatal complications 9 (13.6%) vs. 14 (21.5%) NICU stay 15 (22.7%) vs. 22 (34.4%)
RR 0.75 [0.66–0.85] (18 trials, N = 4121)	GH RR 0.54 [0.41–0.70] (12 trials, N = 838) Abruption RR 0.75 [0.42–1.34] (4 trials, N = 2710)	RR 0.89 [0.74–1.08] (13 trials, N = 4239)	Fetal and neonatal death RR 0.69 [0.53–0.90] (17 trials, N = 4443) PTB <37 weeks RR 0.89 [0.81–0.97] (10 trials, N = 3252)
RR 0.47 [0.34–0.65] (9 trials, N = 765) Severe PET RR 0.09 [0.02–0.37] (3 trials, N = 278)	GH RR 0.62 [0.45–0.84] (3 trials, N = 278) Abruption RR 0.62 [0.08–5.03] (4 trials, N = 360)	IUGR (any definition) 16 weeks or less: RR 0.44 (0.30–0.65) (9 trials, N = 853) >16 weeks: RR 0.98 (0.87–1.10) (15 trials, N = 7027)	PTB RR 0.22 [0.10–0.49] (4 trials, N = 387)
RR 0.81 [0.63–1.03) (18 trials, N = 10,584) Severe PET RR 0.26 [0.05–1.26] (2 trials, N = 669)	GH RR 0.63 [0.47–0.85) (14 trials, N = 4303) Abruption RR 1.56 [0.96–2.55] (6 trials, N = 3583)	IUGR RR 0.98 [0.87–1.10] (15 trials, N = 7027)	PTB RR 0.90 [0.83–0.97] (16 trials, N = 10,398)
	"Hypertensive pregnancy complications" Singletons: OR 0.62 [0.22–1.7] Twins: OR 1.2 [0.35–4.4]		PTB Singletons: OR 0.52 [0.16–1.7] (N = 180) Twins: OR 1.6 [0.51–5.0)

continued

Appendix 6.2 *continued*

Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Aspirin				
Villa 2013[85] (single trial + meta-analysis)	Single trial (N = 152) Meta-analysis 2 trials: Vainio 2002, Ebrashy 2005 (N = 346)	Alloc con: yes OAB: "double-blinded" LFU <20%: no (20.4%)	Aspirin (100 mg/d) (N = 61)	Placebo (N = 60)
Roberge *et al* 2012[88] (systematic review and meta-analysis)	4 trials (N = 392)	"*Studies with high risk of bias were considered for exclusion*"	Aspirin (50–150 mg/d) (≤16 weeks) (N = 201)	Placebo or no treatment (N = 191)
Henderson 2014[81] (systematic review of 23 trials, 22,988 women with only high-risk women included here; see Appendix 6.1 for data on moderate-risk women	15 trials (N = 12,656)	(Reported only for all 23 trials of low and high risk women together – See 'Henderson 2014', Appendix 6.1)	Aspirin (50–150 mg/d) (N = 6123)	Placebo or no treatment (N = 6522)
Cantu 2015[92] (secondary analysis of single trial)	Stratification by initiation (< or >16 weeks) N = 2539 Stratification by BMI N = 2479	Alloc con: not specified. OAB: no. LFU <20%: yes.	Aspirin (60 mg/d) <16 weeks (N = 225) Aspirin (60 mg/d) >16 weeks (N = 1029) BMI <30 (N = 756) BMI ≥30 (N = 487)	Initiation Placebo <16 weeks (N = 236) Placebo >16 weeks (N = 1013) BMI <30 (N = 756) BMI ≥30 (N = 480)
Bergeron 2016[82] (systematic review of 6 trials, 898 women with multiple gestations)	6 trials (N = 898)	Alloc con low risk: 5/6 trials. OAB low risk: 5/6 trials. IOD low risk: 4/6 trials	Aspirin (61–100 mg/d)	Placebo

PET	*Other*	*SGA infants*	*Other*
SINGLE TRIAL RR 0.70 [0.30–1.7] Severe PET RR 0.4 [0.1–1.2] Early onset PET RR 0.2 [0.03–2.1] META-ANALYSIS 2 trials (N = 346) RR 0.6 [0.37–0.83] Severe PET RR 0.3 [0.11–0.69) Preterm PET RR 0.2 [0.02–1.26] Term PET RR 1.0 [0.25–4.26]	GH RR 1.6 [0.6–4.2]	RR 0.3 [0.1–1.6]	
Severe PET RR 0.22 [0.08–0.57] Mild PET RR 0.81 [0.33–1.96]			
RR 0.76 [0.62–0.95] (13 trials, N = 12,184)	Abruption RR 1.12 [0.86–1.46] (3 trials, N = 12,366)	IUGR RR 0.80 [0.65–0.99] (13 trials, N = 12,504)	Perinatal death RR 0.81 [0.65–1.01] (10 trials, N = 12,240) PTB RR 0.86 [0.76–0.98] (10 trials, N = 11,779)
LDA <16 weeks RR 0.93 [0.67–1.31] LDA >16 weeks RR 0.90 [0.75–1.08] BMI <30 RR 0.91 [0.7–1.13] BMI ≥30 RR 0.89 [0.7–1.13]			
RR 0.67 [0.48–0.94] (5 trials, N = 898) Mild PET RR 0.44 [0.24–0.82] (# trials not specified, N = 724) Severe PET RR 1.02 [0.61–1.72] (# trials not specified, N = 724)		RR 1.09 [0.80–1.47] (4 trials, N = 1573 neonates)	PTB <37 weeks RR 1.11 [0.83–1.49] (# trials not specified, N = 1554 neonates)

continued

Appendix 6.2 *continued*

Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Calcium				
Hofmeyr 2014[7] (systematic review of 24 trials, 17,954 women with only high-risk women included here when possible; see Appendix 6.1 for data on low-risk women. Data on women at unclear risk not presented.)	5 trials (N = 587)	Alloc con low risk: 4/5 trials. OAB low risk: 4/5 trials. IOD low risk: 3/5 trials	Calcium (≥1 g/d) (N = 281)	Placebo or no calcium (N = 306)
Calcium + Aspirin				
Asemi 2012[101] (single trial)	N = 42	Alloc con: yes. OAB: no. LFU <20%: yes	Calcium carbonate (500 mg/d) + aspirin (80 mg/d) for 9 weeks (N = 20)	Placebo (N = 22)
Souza 2014[102] (single trial)	N = 49	Alloc con: yes. OAB: yes LFU <20%: yes	Calcium (2 g/d) + aspirin (100 mg/d) (N = 23)	Placebo (N = 26)
Dietary Changes				
Allen 2014[12] (systematic review of 18 trials, 8712 women with low and high-risk women presented together here; see Appendix 6.1 for data on low-risk women. Data for women at unclear risk not presented.)	18 trials (N = 8712)	Alloc con: low risk 9/18 trials OAB: low risk 7/18 trials IOD low risk: 17/18 trials	Dietary change alone or with other change (N = 4342)	Placebo or no dietary change (N = 4370)
			DIET (6 trials, N = 1334)	Control (not specified) (6 trials, N = 1361)
			MIXED (Diet, physical activity & lifestyle) (6 trials, N = 733)	Control (not specified) (6 trials, N = 705)

PET	*Other*	*SGA infants*	*Other*
RR 0.22 [0.12–0.42] (5 trials, N = 587)	Hypertension (±PET) RR 0.47 [0.22–0.97] (4 trials, N = 327)		PTB RR 0.45 [0.24–0.83] (4 trials, N = 568) Admission to NICU RR 0.29 [0.03–2.48] (1 trial, N = 63) Stillbirth or death before hospital discharge RR 0.39 [0.02–9.20] (3 trials, N = 512)
	Serum hs-CRP 102.87 ± 1828.52 vs. 3227.75 ± 4760.70 ($p = 0.001$) Plasma TAC 68.96 ± 236.39 vs. 74.46 ± 199.07 ($p = 0.04$) GSH 304.33 ± 709.32 vs. –39.33 ± 174/33 ($p = 0.03$)		
Superimposed PET 42.2 vs. 73.1% ($p = 0.112$)		IUGR 25.0% vs. 2.8% ($p = 0.07$) BWt (g) 2563 ± 0 1033 vs. 2604 ± 811 ($p = 0.88$)	PTB 33.3% in both treatment and placebo groups LBW (<2500 g) 11 (42.3%) vs. 7 (30.4%) ($p = 0.40$) Very LBW (<1500 g) 5 (19.2%) vs. 3 (13.0%) ($p = 0.71$)
ANY DIETARY CHANGE RR 0.81 [0.69–0.94]† (18 trials, N = 8712) ($I^2 = 0\%$)			
RR 0.67 [0.53–0.85]* (6 trials, N = 2695)			
RR 0.93 [0.66–1.32]* (6 trials, N = 1438)			

continued

Appendix 6.2 *continued*

Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Dietary Changes				
			ESSENTIAL FATTY ACIDS (6 trials, N = 2275)	Control (not specified) (6 trials, N = 2304)
Ziaei 2001[103] (single trial)	N = 100	Alloc con: not specified. OAB: no. LFU <20%: not specified	Allicin (100 mcg/d) in 3rd trimester (N = 50)	Placebo (N = 50)
Teran 2009[104] (single trial)	N = 235	Alloc con: yes. OAB: yes. LFU <20%: yes	CoQ10 (200 mg/d) (20 weeks GA to delivery (N = 118)	Placebo (N = 117)
Heparin				
Rodger 2014[111] (single trial)	N = 292	Alloc con: yes. LFU <20%: yes	Antepartum dalteparin N = 146	No antepartum dalteparin N = 143
			On-treatment analysis (N = 143)	On-treatment analysis (N = 141)

PET	*Other*	*SGA infants*	*Other*
RR 0.92 [0.71–1.18]* (6 trials, N = 6579)			
7 (14%) vs. 9 (18%) ($p = 0.799$)	–9 (18%) vs. 18 (36%) (***p*** = 0.043)		
RR 0.56 [0.33–0.96]	–		
8 (5.5%) vs. 5 (3.5%) difference –0.7 [–3.1–1.6] Severe or early onset PET 7 (4.8%) vs. 4 (2.8%) difference 2.0 (–2.8–6.8)	Symptomatic major VTE 1 (0.7%) vs. 2 (1.4%) difference –0.7 (–3.1–1.6) Abruption 4 (2.7%) vs. 3 (2.1%) difference 0.6 (–2.9–4.2)	SGA <10% 9 (6.2%) vs. 12(8.4%) difference –2.2 (–8.2–3.8) SGA <5% 2 (1.4%) vs. 3 (2.1%)	Pregnancy loss (any) 12 (8.2%) vs. 10 (7.0%) difference 1.2 (–4.9–7.3) Early pregnancy loss (≥3 at <10 weeks) 4 (2.7%) vs. 5 (3.5%) difference 0.8 (–4.8–3.2) Late pregnancy loss (≥2 at >10 weeks or ≥1 at >16 weeks) 6 (4.1%) vs. 2 (1.4%) difference 2.7(–1.0–6.5) PTB <37 weeks (23 (15.8%) vs. 17 (11.9%) difference 3.9 (–4.1–11.8) BWt of live births (g) 3186.2 vs. 3241.4 difference –55.2 [–238.6–128.1]
	Major bleeding 3 (2.1%) vs. 2 (1.4%) difference 0.7(–2.4–3.7) Minor bleeding (non-major) 28 (19.6% vs. 13 (9.2%) difference 10.4 (2.3–18.4) BMD 6 weeks postpartum 2.16 (0.35) vs. 2.23 (0.42) difference –0.07(–0.19–0.04)		

continued

Appendix 6.2 *continued*

Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Heparin				
Rodger 2014[110] (systematic review)	6 trials (N = 848)	Alloc con low risk: 5/6 trials. AB low risk: 3/6 trials. IOD low risk: 5/6 trials	Prophylactic LMWH (N = 425)	No LMWH (N = 423)
Lifestyle				
Meher 2006[126] (systematic review)	2 trials (N = 45)	Alloc con low risk: 2/2 trials. OAB: 1/2 trials. IOD low risk:2/2 trials	Moderate intensity aerobic exercise program (N = 23)	Normal physical activity (N = 22)
Yeo 2008[128] (single trial)	N = 79 (only have access to abstract)		Walking (N = 41)	Stretching (N = 38)
Periodontal therapy				
Kunnen 2010[142] (systematic review of 12 observational studies and 3 RCTs, of which results for 3 RCTs are reported here)	N = 3650	Alloc con: methods not reported. OAB: methods not reported. LFU <20% not reported	Periodontal treatment in midpregnancy (N = 1827)	Periodontal treatment after delivery (N = 1823)

PET	*Other*	*SGA infants*	*Other*
RR 0.46 [0.28–0.75] (N = 739) Severe or early PET RR 0.16 [0.07–0.36] (N = 665)	Abruption RR 0.42 [0.13–1.4] (N = 756)	SGA <10th centile RR 0.42 [0.29–0.59] (N = 713) SGA <5th centile RR 0.52 [0.28–0.94] (N = 604)	Pregnancy loss <20 weeks RR 0.89 [0.50–1.6] (N = 591) Pregnancy loss >20 weeks RR 0.41 [0.17–1.02] (N = 611) NND RR 0.31 [0.07–1.3] (N = 623) PTB <37 weeks RR 0.77 [0.62–0.96] (N = 556) PTB <34 weeks RR 0.45 [0.30–0.69] (N = 678)
RR 0.31 [0.01–7.09] (2 trials, N = 45)	GH RR 1.00 [0.07–13.37] (1 trial, N = 16) CS RR 0.93 [0.22–3.88] (1 trial, N = 29)	RR 3.00 [0.14–64.26] (1 trial, N = 16)	PTB RR 1.00 [0.07–13.37] (1 trial, N = 45)
14.6% [5.6–29.2] vs. 2.6% [0.07–13.8]			
RR 1.0 [0.78–1.28] (3 trials, N = 3650)			

continued

Appendix 6.2 *continued*

Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Micronutrients other than calcium				
Kubik 2004[23] (single trial)	N = 138	"*double blinded trial*"	Vitamin and mineral supplement containing 15 mg zinc, 2 mg copper, and 20 μg selenium	Placebo
Makrides 2014[40] (systematic review of 10 trials, 9090 low and high risk women for whom outcomes were not reported by risk)	(Low and high risk women reported together) 10 trials (N = 9090)	Alloc con adequate: 2/10 trials. OAB adequate: 7/10 trials. IOD: low risk of attribution bias 3/10 trials	ORAL Mg (N = 4516) "*compositions of the Mg supplements, gestational ages at commencement, and doses administered varied*"	Placebo (8 trials, 3241) or no therapy (2 trials, 939 women) (Total N = 4180)
Bullarbo 2013[42] (single trial)	N = 59	"*double-blind randomisation*"	Mg (300 mg/d from 25 weeks) (N = 29)	Placebo (N = 30)
Mori 2012[43] (systematic review)	20 trials "*over 15,000 women and their babies*"	Alloc con adequate: 10/20 trials. OAB adequate: 13/20 trials. LFU "*ranged from 1% to 40%. Attrition bias was judged to be at high risk in only 3 trials*	ZINC (5–90 mg/d) starting before conception to 26 weeks (N not specified)	Placebo or no zinc (N not specified)
Parrish 2013[44] (single trial of 684 low and high-risk women with data on high-risk women reported here; see Appendix 6.1 for data on moderate risk women)	N = 154	Alloc con: yes OAB: yes LFU <20%: No (f/u was available for N = 267 low and high risk combined)	Fruit and vegetable juice powder concentrate (N = 76)	Placebo (N = 78)

PET	*Other*	*SGA infants*	*Other*
"*6.25% vs. 7.7%*"	SVD ("*natural deliveries*") "*75.0% vs. 53.8%*"		
RR 0.87 [0.58–1.32]* (3 trials, N = 1042)	Hospitalisation during pregnancy RR 0.65 [0.48–0.86]* (3 trials, N = 1158)	RR 0.76 [0.54–1.07]* (3 trials, N = 1291 infants)	Perinatal mortality RR 1.10 [0.72–1.67]* (5 trials, N = 5903 infants NND before hospital discharge RR 2.21 [1.02–4.75]‡* (4 trials, N = 5373 infants) Apgar <7 at 5 min RR 0.34 [0.15–0.80]* (4 trials, 1083 infants) Meconium-stained liquor RR 0.79 [0.63–0.99]* (1 trial, 4082 infants) Late FH decelerations RR 0.68 [0.53–0.88]* (1 trial, 4082 infants) Mild HIE RR 0.38 [0.15–0.98]* (3 trials, 4082 infants)
Average dBP at 37 weeks significantly lower (mmHg) (72/1.4 mean/SEM vs. 77/1.4, $p = 0.03$)	Fewer women developed an increase in dBP ≥15 mmHg ($p = 0.01$)		
PET or GH RR 0.83 [0.64–1.08] (7 trials, N = 2975)	IOL RR 0.27 [0.10–0.73] (1 trial, N = 52)	RR 1.02 [0.94–1.11] (8 trials, N = 4252 babies)	PTB RR 0.86 [0.76–0.97] (16 trials, N = 7637)
PET RR 0.91 [0.49–1.68] Mild PET RR 1.03 [0.07–16.1] Severe PET RR 1.37 [0.32–5.91] Superimposed PET RR 0.71 [0.32–1.56] (N = 154)	GH RR 1.37 [0.32–5.91]	RR 0.77 [0.17–3.32]	Live birth RR 104 [0.95–1.14] NND RR 0.21 [0.01–4.31] RDS RR 0.34 [0.12–1.01] NICU admission RR 0.34 [0.12–1.01]

continued

Appendix 6.2 *continued*

Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Prostaglandin precursors				
Makrides 2006[45] (systematic review of 2783 low and high risk women with high risk women reported here. See Appendix 6.1 for data on low risk women)	3 trials (N = 1725)	Alloc con low risk: 3/6 trials OAB: NR LFU <20%: "*Most trials reported outcome for at least 83% of all women recruited*"	Marine oil (N = 858)	Placebo or no marine oil (N = 877)
Zhou 2012[46] (single trial)	N = 2399	Alloc con: yes OAB: NR LFU <20%: NR	Fish oil (800 mg DHA/d in second half of pregnancy) (N = 1197)	Placebo (N = 1202)
Smoking cessation				
Chamberlain 2013[54] (systematic review)	86 trials (N = >29,000 women)	Alloc con: low risk of bias 10/86 trials OAB: "*not calculable due to insufficient numbers of studies with low risk of bias*" Incomplete outcome data attrition bias: low risk 22/86 trials	Smoking cessation interventions (N = 4298)	Routine care (N = 4264)
Coleman 2012[55] (single trial)	N = 1050	Alloc con: yes OAB: yes LFU <20%: yes (18.5%)	Nicotine patches (15 mg every 16 h for 8 weeks) (N = 521)	Placebo (N = 529)

PET	*Other*	*SGA infants*	*Other*
RR 0.80 [0.50–1.29] (2 trials, N = 553)		RR 1.17 [0.81–1.69] (1 trial, N = 263)	PTB <37 weeks RR 0.82 [0.60–1.12] (3 trials, N = 523) BWt 47 g [1–93 g] (3 trials, N = 2440) LBW RR 1.03 [0.80–1.33] 3 trials, N = 789) Stillbirth (≥24 weeks) RR 0.68 [0.11–4.08] (2 trials, N = 295) NND RR 1.01 [0.32–3.24] (3 trials, N = 1724)
PET aRR 1.03 (0.72–1.48] (N = 2399)	GH aRR 0.93 [0.71–1.21]	For wt aRR 0.90 [0.66–1.22] For length aRR 0.93 [0.75–1.16] (N = 2399) For head circum aRR 0.96 [0.78–1.19] (N = 2399)	
		LBW <2500 g RR 0.82 [0.71–0.94] (14 trials, N = 8562)	PTB <37 weeks RR 0.82 [0.70–0.96] (14 trials, N = 7852)
PET or eclampsia 3 (0.6%) vs. 5 (0.9%), *p* = NR	BP >140/90 mmHg on at least 2 occasions 24 (4.6%) vs. 25 (4.7%), *p* = NR CS OR 1.45 [1.05–2.01]	LBW OR 1.38 [0.90–2.09]	PTB OR 0.90 [0.58–1.41]

continued

Appendix 6.2 *continued*

Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Thiazide diuretics				
Churchill 2007[56] (systematic review of 5 trials, N = 1836 low and high-risk women of which low and high-risk women are reported here; see Appendix 6.1 for data on low-risk women)	5 trials (N = 1836)	"*The quality of all five studies was unclear*" Alloc con: unclear OAB: 4/5 trials LFU <20%: 5/5 trials	Thiazide diuretic (N = 1016)	Placebo or no thiazide (N = 820)
Vitamins C & E				
Rumbold 2008[57] (systematic review of 10 trials, 6533 low/ moderate-and high-risk women, of which the high-risk women are presented here when possible; see Appendix 6.1 for data on the low/ moderate-risk	5 trials (N = 3226)	Alloc con low risk: 2/5 trials (3/5 trials "unclear, as no information was provided about the methods of randomsation and alloc con") OAB low risk: 4/5 trials ("degree of blinding, if any, was unclear for 1 trial") LFU <20%: 3/5 trials. (2/5 did not mention any losses to follow-up)	One/more antioxidants (N = 1858 as calculated from tables)	Placebo or no antioxidant (N = 1449)

PET	*Other*	*SGA infants*	*Other*
RR 0.68 [0.45–1.03]* (4 trials, N = 1391) Severe PET RR 1.56 [0.26–9.17] (2 trials, N = 1297)	HTN (new or worsening) RR 0.85 [0.68–1.08]* (2 trials, N = 1475) Nausea and vomiting RR 5.81 [1.04–32.46]* (2 trials, N = 1217) CS RR 1.0 [0.26–3.81]* (1 trial, N = 20)	None in the 1 trial that reported this outcome	Perinatal death RR 0.72 [0.40–1.27]* (5 trials, N = 1836) Stillbirth RR 0.60 [0.27–1.34]* (5 trials, N = 1836) NND RR 0.88 [0.40–1.97]* (4 trials, N = 1816) PTB RR 0.67 [0.32–1.41]* (2 trials, N = 465) BWt Mean difference 139.0 [–484.40–762.40]* (1 trial, N = 20) Gestation at birth Mean difference 0.70 [–0.71–2.11]* (1 trial, N = 20) Postmaturity >42 weeks RR 7.0 [0.41–120.16]* (1 trial, N = 20) 5 min Apgar <7 RR 3.0 [0.14–65.90]* (1 trial, N = 20)
RR 0.56 [0.29–1.11] (5 trials, N = 3005) Severe PET RR 1.25 [0.89–1.76] (2 trials, N = 2495)	Antihypertensive therapy RR 1.77 [1.22–2.57]* (2 trials, N = 4272) Require antenatal hospital admission for HTN RR 1.54 [1.00–2.39]* (1 trial, 1877 women)	RR 0.92 [0.63–1.34] (3 trials, N = 3167)	PTB RR 1.09 [0.97–1.22] (3 trials, N = 3131) Any baby death RR 1.27 [0.85–1.90] (2 trials, N = 3067)

continued

Appendix 6.2 *continued*

Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Vitamins C & E				
Villar 2009[137] (single trial)	N = 1365	Alloc con: method yes. OAB: not specified. LFU <20%: yes	Vitamin C (1000 mg/d) and Vitamin E (400 IU/d) (N = 687)	Placebo (N = 678)

PET	*Other*	*SGA infants*	*Other*
RR 1.0 [0.9–1.3] (N = 1355) Severe PET RR 0.8 [0.4–1.3] (N = 1355)	Eclampsia RR 1.5 [0.2–8.9) (N = 1355) HELLP RR 1.2 [0.5–3.1] (N = 1355) Abruption RR0.7 [0.2–1.8] (N = 1355) GH RR 1.2 [0.9–1.7] (N = 1355) Severe GH RR 0.9 [0.5–1.8] (N = 1355) Maternal ICU admission RR 0.2 [0.02–1.7] (N = 1355)		PTB <37 weeks RR 0.9 [0.7–1.0] (N = 1343) Delivery for PET <37 weeks RR 0.9 [0.6–1.2] (N = 1343) PTB <34 weeks RR 0.8 [0.6–1.0] (N = 1343) Delivery for PET <34 weeks RR 0.9 [0.6–1.5] (N = 1343) LBW <2500 g RR 0.9 [0.8–1.0] (N = 1515) LBW <1500 g RR 0.8 [0.6–1.1] (N = 1515) Any admission to NICU RR 0.8 [0.6–1.1] (N = 1515) >7 days in NICU (RR 0.9 [0.5–1.4] (N = 1515) Perinatal death RR 0.8 [0.6–1.2] (N = 1515) Any congenital malformation RR 1.6 [0.8–3.3] (N = 1515)

continued

Appendix 6.2 *continued*

Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
Vitamins C & E				
Spinnato 2007[138] (single trial)	N = 739	Alloc con: yes. OAB: not specified. LFU <20%: yes	Vitamin C (1000 mg/d) + Vitamin E (400 IU/d) (N = 371)	Placebo (N = 368)
L-arginine				
Dorniak-Wall 2014[117] (systematic review of 7 trials)	N = 884	Alloc con low risk: 3/7 trials. OAB low risk: 7/7. IOD low risk: 4/7 trials.	L-arginine (N = 228)	Placebo (N = 222)
Zhu 2013[114] (meta-analysis of 5 trials)	N = 277	Alloc con: not clear. OAB: 4/5 trials. LFU: "*2 of the 5 studies reported the details of withdrawals, whereas other 3 studies did not address this issue*"	L-arginine (N = 140)	Placebo (N = 137)

PET	*Other*	*SGA infants*	*Other*
aRR 0.78 [0.61–1.25]			Fetal and NND aRR 1.00 [0.53–1.87] PTD <37 weeks aRR 1.15 [0.89–1.50] PTD <34 weeks aRR 1.10 [0.65–1.84] LBW <2500 g aRR 0.98 [0.71-–1.36] Very LBW <1500 g aRR 1.08 [0.58–2.00] Apgar <4 at 1 min aRR 0.72 [0.37–1.39] Apgar <7 at 5 min aRR 0.72 [0.29–1.77] Baby died before discharge, or received NICU care aRR 0.93 [0.61–1.43] RDS aRR 1.11 [0.72–1.71] Ventilator support aRR 1.29 (0.60–2.74] Seizures aRR 2.08 [0.10–134.08)
PET or eclampsia OR 0.34 [0.21–0.55] (1 trial, N = 450)			PTB OR 0.48 [0.28–0.81] (1 trial, N = 450)
	Change in dBP Mean difference fixed −3.07 [−5.17–(−0.98)] (5 trials, 177)		GA at delivery Mean difference fixed 1.23 [0.46–1.99] (5 trials, N = 289)

continued

Appendix 6.2 *continued*

Author (study design)	*N trials (N women)*	*Quality of trials*	*Intervention (N women)*	*Controls (N women)*
NO donors				
Schleussner 2014[141] (single trial of 111 low and high-risk women with high-risk women reported here; see Appendix 6.1 for data on low-risk women)	N = 36	Allocation method not clear	Nitric oxide donor pentaerithrityl-tetranitrate (PTN) tablet twice daily (N = 20)	Placebo (N = 16)

Alloc con, allocation concealment; APH, antepartum haemorrhage; aRR, adjusted relative risk; BMI, body mass index; BWt, birth weight; CI, confidence interval; circum, circumference; CS, Caesarean section; ctx, contraction; dBP, diastolic blood pressure; DHA, docosahexanenoic acid; FH, fetal heart; FHR, fetal heart rate; FM, fetal movement; GA, gestational age; GH, gestational hypertension; GSH, total glutathione; HELLP, haemolysis, elevated liver enzymes, low platelets; HIE, hypoxic ischaemic encephalopathy; hs-CRP, high-sensitivity C-reactive protein; HTN, hypertension; IOD, incomplete outcome data; IOL, induction of labour; LBW; low birth weight; IUGR, intrauterine growth restriction; IVH, intraventricular haemorrhage; LBW, low birth weight; LFU, loss to follow-up; M&M, morbidity and mortality; Mg, magnesium; $MgSO_4$, magnesium sulphate; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; NND, neonatal death; NNT, number needed to treat; NR, not reported; OAB, outcome assessment blinding; OR, odds ratio; PET, pre-eclampsia; PPH, postpartum haemorrhage; PROM, premature rupture of membranes; PTB, preterm birth; RDS, respiratory distress syndrome; RR, relative risk; SCBU, special care baby unit; SEM, standard error of mean; SGA, small-for-gestational-age infants; SVP, spontaneous vaginal delivery; TAC, total antioxidant capacity; UA, umbilical artery; VTE, venous thromboembolism); WMD, weighted mean difference

PET	*Other*	*SGA infants*	*Other*
PET/HELLP 6 (30%) vs. 6 (37.5%) PET <32 weeks 5 (62.5%) vs. 1 (16.7%)	0 vs. 1 (6.2%) CS 12 (63.2%) vs. 7 (38.9%)		IUGR or perinatal death 7 (35%) vs. 11 (68.8%) PTD <37 weeks 4 (20%) vs. 7 (43.85) PTD <32 weeks 2 (10%) vs. 4 (25%)

‡ These results should be interpreted with caution as a large number of severe congenital anomalies and deaths of two sets of twins (with birth weights <750 g) in the supplemented group likely accounted for the increased risk of death observed. When deaths due to severe congenital abnormalities were excluded from the meta-analysis, no increased risk of NND was seen

Appendix 6.3

GRADE evaluation of best practice points for preventing pre-eclampsia

Recommendation
Prevention of pre-eclampsia in women at low risk
1. Calcium supplementation (of at least 1 g/d, orally) is recommended for women with low dietary intake of calcium (<600 mg/d, corresponding to less than two dairy servings per day
2. The following are recommended for other established beneficial effects in pregnancy: abstention from alcohol for prevention of fetal alcohol effects, exercise for maintenance of fitness, periconceptional use of a folate-containing multivitamin for prevention of neural tube defects, and smoking cessation for prevention of low birth weight and preterm birth
3. The following may be useful: periconceptional and ongoing use of a folate-containing multivitamin or exercise
4. The following are not recommended for pre-eclampsia prevention, but may be useful for prevention of other pregnancy complications: prostaglandin precursors or supplementation with magnesium or zinc
5. The following are not recommended: dietary salt restriction during pregnancy, calorie restriction during pregnancy for overweight women, low-dose aspirin, vitamins C and E, or thiazide diuretics
6. There is insufficient evidence to make a recommendation about the following: a heart-healthy diet, workload or stress reduction, supplementation with iron with/without folate, vitamin D, pyridoxine, or food rich in flavanoids.
Prevention of pre-eclampsia in women at increased risk
1. The following are recommended for prevention of pre-eclampsia: low-dose aspirin and calcium supplementation (of at least 1 g/d) for women with low calcium intake
2. Low-dose aspirin (75–100 mg/d) should be administered at bedtime (I-B) and initiated after diagnosis of pregnancy but before 16 weeks' gestation (I-B) and may be continued until delivery (I-C)
3. Prophylactic doses of LMWH may be considered in women with previous placental complications (including pre-eclampsia) to prevent the recurrence of 'severe' or early-onset pre-eclampsia, preterm delivery, and/or SGA infants (I-B)

*Quality of the evidence**	*Strength of the recommendation†*
High	Strong
Low (alcohol), moderate (exercise for fitness), moderate (folate-containing vitamin), high (smoking cessation)	Strong (for all)
Low (folate-containing vitamin), Very low (exercise)	Weak (for both)
Low (prostaglandin precursors), low (magnesium), low (zinc)	Weak (for all)
Moderate (salt restriction), moderate (calorie restriction in obesity), moderate (low-dose aspirin), high (vitamins C & E), moderate (thiazides)	Strong (for all but aspirin) Weak (for aspirin)
Very low (heart healthy diet), very low (workload/stress reduction), low (iron supplementation), very low (pyridoxine), low (vitamin D), very low (food rich in flavonoids)	Weak (for all)
High (low-dose aspirin), high (calcium)	Strong (for both)
Moderate (for aspirin at bedtime), high (aspirin initiated after diagnosis of pregnancy but before 16 weeks' gestation), moderate (aspirin continued until delivery)	Weak (for aspirin initiated after diagnosis of pregnancy but before 16 weeks' gestation and for aspirin continued until delivery) Strong (for aspirin at bedtime)
High	Weak

continued

Appendix 6.3 *continued*

Recommendation
Prevention of pre-eclampsia in women at increased risk
4. The following may be useful: L-arginine (I-B), metformin in PCOS and/or overweight women (1-C), increased rest at home in the third trimester (I-C), and reduction of workload or stress (III-C)
5. The following may be useful for prevention of other pregnancy complications: prostaglandin precursors (I-B), magnesium supplementation (I-C), and heparin thromboprophylaxis (I-B)
6. The following are recommended for other established beneficial effects in pregnancy (as discussed for women at low risk of pre-eclampsia): abstention from alcohol (II-2E) , periconceptional use of a folate-containing multivitamin (I-A), and smoking cessation (I-E)
7. The following are **not** recommended: calorie restriction in overweight women during pregnancy (I-D), weight maintenance in obese women during pregnancy (III-D), antihypertensive therapy specifically to prevent pre-eclampsia (I-D), vitamins C and E (I-E)
8. There is insufficient evidence to make a recommendation about the usefulness of the following: the heart-healthy diet (III-L), exercise (I-L), selenium (I-L), garlic (I-L); zinc, pyridoxine, iron (with or without folate), or multivitamins with/ without micronutrients all (III-L)

* The judgements about the quality of evidence is based on the confidence that available evidence reflects the true effect of the intervention or service. Evidence is considered to be of *high quality* when the true effect is thought to lie close to that of the estimate of the effect (e.g., if there is a wide range of studies included in the analyses with no major limitations, there is little variation between studies, and the summary estimate has a narrow confidence interval). Evidence is considered to be of *moderate quality* when the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different (e.g., if there are only a few studies and some have limitations but not major flaws, there is some variation between studies, or the confidence interval of the summary estimate is wide). Evidence is considered to be of *low quality* when the true effect may be substantially different from the estimate of the effect (e.g., the studies have major flaws, there is important variation between studies, or the confidence interval of the summary estimate is very wide)

*Quality of the evidence**	*Strength of the recommendation*†
High (L-arginine), high (metformin), high (rest), low (workload or stress reduction)	Weak (for all)
Moderate (prostaglandin), moderate (magnesium), moderate (heparin)	Weak (for all)
Moderate (alcohol), moderate (folate), high (smoking)	Strong (for all)
Moderate (calorie restriction), moderate (weight maintenance), high (antihypertensive therapy), moderate (vitamins C and E)	Weak (for calorie restriction and weight maintenance) Strong (for antihypertensive therapy and vitamins C and E)
Low (heart healthy diet), moderate (exercise), moderate (selenium), moderate (garlic), low (zinc, pyridoxine, iron, multivitamins)	Weak (for all)

† A *strong recommendation* should be interpreted as meaning that most people in this situation would want the recommended course of action and only a small number would not. Clinicians should regard the recommendation as applying to most individuals. Policy-makers can adopt the recommendation as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. A *weak recommendation* should be interpreted as meaning that most people in this situation would want the recommended course of action, but many would not; patients' values and preferences should be considered in reaching a decision. Decision aids may support people in reaching these decisions. Policy-making will require substantial debate and involvement of various stakeholders. An appropriately documented decision making process could be used as a quality indicator

Appendix 7.1

GRADE evaluation of best practice points for diet, lifestyle and place of care

	*Quality of evidence**	*Strength of recommendation†*
1. There is insufficient evidence to make a recommendation about the usefulness of the following: ongoing salt restriction among women with pre-existing hypertension, new severe dietary salt restriction for women with any HDP, and a heart-healthy diet or calorie restriction for obese women specifically.	Very low	Weak
2. There is insufficient evidence to make a recommendation about the usefulness of: exercise, workload reduction, or stress reduction.	Very low	Weak
3. For women with gestational hypertension (without pre-eclampsia), some bed rest in hospital (compared with unrestricted activity at home) may be useful to decrease severe hypertension and preterm birth.	Low	Weak
4. For women with pre-eclampsia who are hospitalised, strict bed rest is not recommended.	Moderate	Weak
5. For all other women with HDP, the evidence is insufficient to make a recommendation about the usefulness of some bed rest, which may nevertheless, be advised based on practical considerations.	Very low	Weak
6. Inpatient care should be provided for women with severe hypertension or severe pre-eclampsia, however defined.	Low	Strong
7. A component of care through hospital day units or home care can be considered for women with non-severe pre-eclampsia or non-severe (pre-existing or gestational) hypertension.	Moderate (day units) Low (home care)	Strong
8. Transport from community to facility must be considered a responsibility of women, their communities, and their care providers.	Moderate	Strong

* The judgments about the quality of evidence is based on the confidence that available evidence reflects the true effect of the intervention or service. Evidence is considered to be of high quality when the true effect is thought to lie close to that of the estimate of the effect (e.g., if there is a wide range of studies included in the analyses with no major limitations, there is little variation between studies, and the summary estimate has a narrow confidence interval). Evidence is considered to be of moderate quality when the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different (e.g., if there are only a few studies and some have limitations but not major flaws, there is some variation between studies, or the confidence interval of the summary estimate is wide). Evidence is considered to be of low quality when the true effect may be substantially different from the estimate of the effect (e.g., the studies have major flaws, there is important variation between studies, or the confidence interval of the summary estimate is very wide)

† A *strong recommendation* should be interpreted as meaning that most people in this situation would want the recommended course of action and only a small number would not. Clinicians should regard the recommendation as applying to most individuals. Policy-makers can adopt the recommendation as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. A *weak recommendation* should be interpreted as meaning that most people in this situation would want the recommended course of action, but many would not; patients' values and preferences should be considered in reaching a decision. Decision aids may support people in reaching these decisions. Policy-making will require substantial debate and involvement of various stakeholders. An appropriately documented decision making process could be used as a quality indicator

Appendix 7.2

Diet, lifestyle and place of care recommendations from international guidelines*

	PRECOG II 2009	*QLD 2013*	*NICE 2010*	*WHO 2011*
Dietary & lifestyle change				
General comments				
Dietary changes			For women with chronic hypertension, ongoing salt restriction recommended	
Exercise				
Workload reduction				
Stress reduction				
Bed rest			For women with GH, (any) NOT recommended	For women with any HDP, (strict) NOT recommended (Low, Weak)
Place of care				
Transfer of care from midwifery				
Assessment in 2° care setting by health care provider trained in HDP			Women with GH	
Hospital day unit or antepartum home care				
Admit to hospital	Women with any HDP and BP ≥170/110 mmHg PET & protein-ur3a of ≥2+, or protein : creatinine ratio of ≥30	Women with any HDP and severe hypertension or severe PET	Women with GH	
Refer to critical care setting			Women with any HDP and severe hypertension or severe PET with specific end-organ dysfunction	

NVOG 2011	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
For women with chronic hypertension, ongoing salt restriction recommended		For women with chronic hypertension, extreme salt restriction NOT recommended For women with chronic hypertension, weight loss NOT recommended)	For women with chronic hypertension, insufficient evidence to recommend ongoing salt restriction or extreme (new) salt restriction For women with chronic hypertension and obesity, insufficient evidence to recommend calorie restriction or heart healthy diet
		For women with chronic hypertension and BP that is controlled, ongoing exercise recommended	For women with any HDP, insufficient evidence to recommend
			For women with any HDP, insufficient evidence to recommend
			Stress reduction for any HDP – insufficient evidence to recommend
		For women with GH or PET without severe features, (strict) NOT recommended (Low, Qualified)	For women with GH, (In hospital vs. unrestricted activity at home) may be useful For women with PET, (in hospital) NOT recommended For women with chronic hypertension or any HDP out of hospital, Insufficient evidence to recommend
	Women with PET		
			Consider for women with non-severe pre-existing hypertension, GH, or PET
			Women with any HDP and severe hypertension or "severe" PET

continued

Appendix 7.2 *continued*

BP, blood pressure; GH, gestational hypertension; HDP, hypertensive disorder of pregnancy; PET, pre-eclampsia
* SOMANZ 2014 is included in the chapter text, but not in this table adapted from Gillon 2014[41]
ACOG 2013: American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013 Nov; 122(5):1122–1131
AOM 2012: Salehi P, Association of Ontario Midwives HDP CPG, Working Group. Hypertensive disorders of pregnancy (Clinical Practice Guideline 15). 2012; Available: http://www aom on ca/Health_Care_Professionals/Clinical_Practice_Guidelines/
NICE 2010: National Collaborating Centre for Women's and Children's Health (UK). CG107: Hypertension in pregnancy: The management of hypertensive disorders during pregnancy. NICE: Guidance 2010 Aug
NVOG 2011: Nederlandse Vereniging voor Obstetrie en Gynaecologie. Hypertensieve aandoeningen in de zwangerschap. 2011
QLD 2013: Queensland Maternity and Neonatal Clinical, Guidelines Program. Hypertensive disorders of pregnancy. 2013;MN10.13-V4-R15
PRECOG II: Milne F, Redman C, Walker J, Baker P, Black R, Blincowe J et al. Assessing the onset of pre-eclampsia in the hospital day unit: summary of the pre-eclampsia guideline (PRECOG II). BMJ 2009; 339:b3129
SOGC 2014: Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. Pregnancy Hypertens 2014;4(2):105–145
WHO 2011: World Health Organization. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. 2011

Appendix 8.1

Treatment wall charts

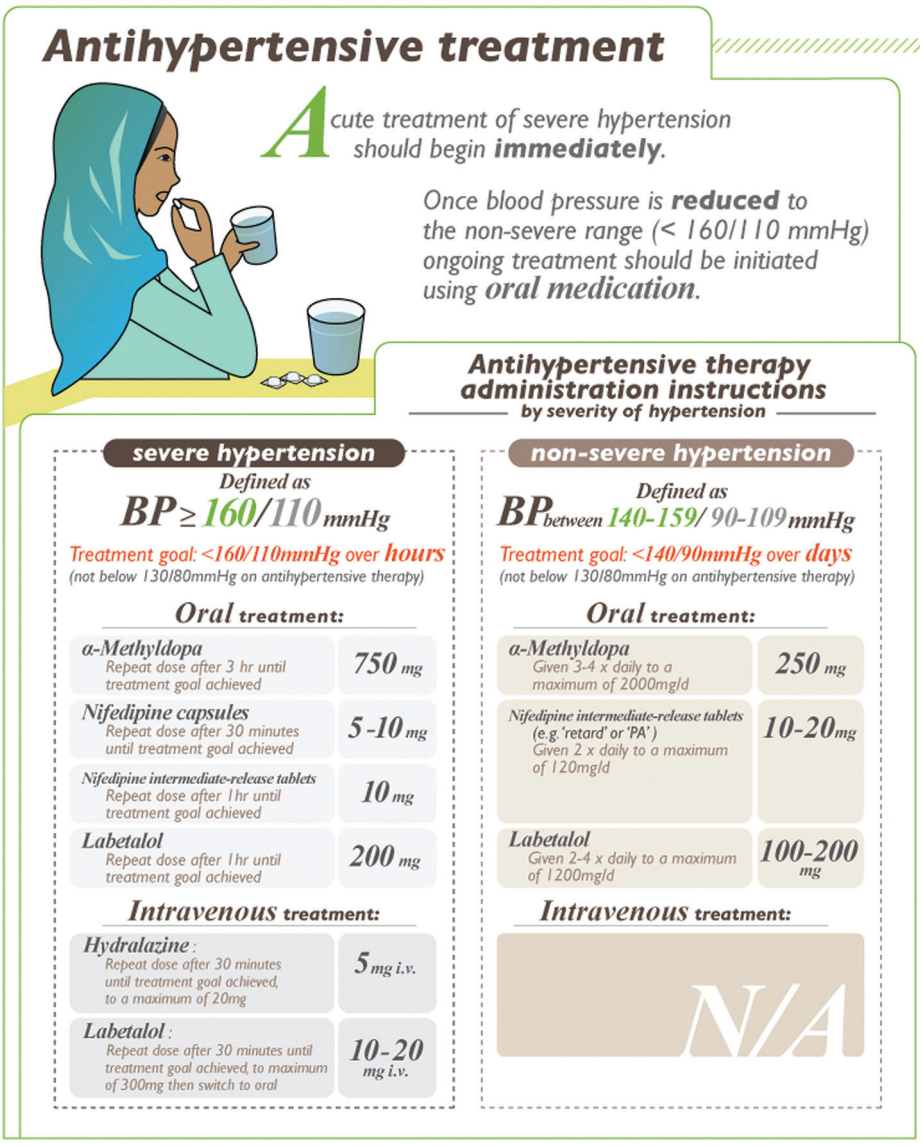


Figure S8.1 Wall chart for treatment of hypertension

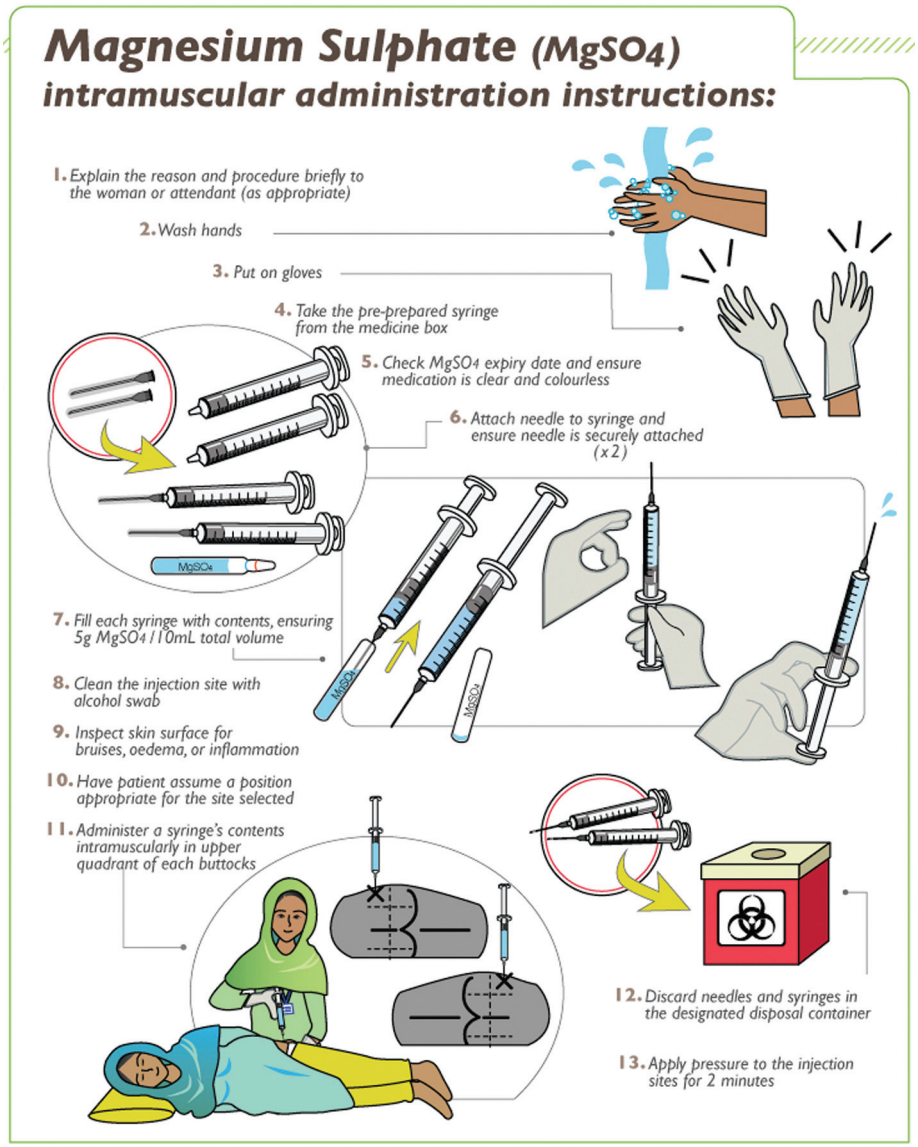


Figure S8.2 Wall chart for intramuscular administration of magnesium sulphate ($MgSO_4$)

Appendix 8.2

Essential Steps in Managing Obstetric Emergencies (ESMOE) – Emergency Obstetric Simulation Training (EOST)

The three drills listed here for eclampsia/pre-eclampsia are part of a more comprehensive set of drills designed for training in South Africa for a variety of obstetric emergencies, both maternal and neonatal. The instructions listed for these drills were adapted, with permission, from the ESMOE-EOST training manual.

Emergency drills (also known as 'fire drills') provide a simulated experience for participants to practice problem-solving and decision-making skills in the management of an obstetric or newborn emergency, with emphasis on thinking quickly, reacting (intervening) rapidly, and working as a team. Also, they provide opportunities to both revise essential skills and develop confidence in dealing with emergencies that do not occur frequently. Enquiries into poor outcomes from obstetric emergencies revealed the following common errors:

- Confusion in roles and responsibilities
- Failure to prioritise
- Failure to perform clinical tasks in a structured coordinated manner
- Poor communication
- Lack of organisational support?

Emergency drills should be carried out in the most realistic setting possible, such as the labour and delivery area of a hospital, clinic or maternity centre, where equipment and supplies are available for emergency interventions.

Drills should occur every 3 or 6 months. Try to avoid postponing a drill. The same drills should be repeated regularly to help health care workers to 'keep on their toes'. Ask yourself the following questions when you prepare your schedule:

- How will I/we ensure that all the emergency drills take place on time?
- How will I/we ensure that all staff are covered for each topic?
  - Day staff?
  - Night staff?
- Which skills do I/we not feel confident enough about?
- What will I/we do to improve my/our skills before doing the relevant emergency drill with the rest of the staff?
- How am I/are we going to improve the skills of staff members not feeling comfortable with certain skills after an emergency drill has been conducted?

The drills provided here cover eclampsia and pre-eclampsia.

- Scenario 1 (Eclampsia), version 1.2
- Scenario 2 (Pre-eclampsia), version 1.2
- Scenario 3 (Pre-eclampsia)

Start with Scenario 1 and proceed in order. Complete one scenario sheet for EVERY emergency drill. Please ensure that you complete the back page of the sheet where all participants should sign the attendance register.

Start a file for each scenario. Each time you have completed a drill, add that scenario sheet on top of the others in that file. Complete the summary sheets that should be kept in the front of this file.

Prepare for the drill by:

- Familiarising yourself with the requirements in terms of skills to demonstrate and materials to prepare for each scenario.
- Read the scenarios carefully before conducting the emergency drills. You must be comfortable and familiar with the different scenarios.
- Prepare all materials, medications, equipment, and manikins. Each scenario sheet has a list of materials needed for that drill on the first page.

Conducting an emergency drill: You or someone else should act as the "director" or "conductor" who facilitates the drill (10–15 min). The different roles for participants are illustrated on the diagram found on the first page of each scenario sheet.

Before beginning the drill, instruct the participants on which role they will play: (1) Team leader, (2) Helper 1, (3) Helper 2, or (4) Helper 3. The discoverer can become the team leader or a helper.

- One participant plays the role of patient.
- Invasive procedures are practised on the manikin/model that serves as the patient's "body".
- Procedures such as starting an IV and giving oxygen should be role played, using the appropriate equipment.
- A second participant plays the role of the "discoverer", while other participants are called on to assist the provider. It is important that during different drills, participants change their roles.
- The idea is to create a simulation that is as near as possible to a real emergency. Do not prompt participants as they participate in the drill and do not interrupt the drill with any discussion. However, throughout, participants should demonstrate what they would do and explain what they are doing and why they are doing it.

The facilitator/director/conductor uses the scenario sheet to orchestrate the drill. For information on how to do this and how to score the drill, see the instructions below under the heading "How to use the scenario sheets".

After the drill has been completed, give feedback (5–10 minutes) about how the team carried out the emergency drill (clinical skills and skills in conducting the drill). Facilitate an interactive discussion with participants who "acted" in the drill by asking them to:

- Comment on their performance, starting with strengths and then working towards areas that need improvement. Include aspects relating to clinical skills and to teamwork. Ask questions and encourage participants to ask questions. Review roles of providers who assist with the emergency, discuss what order there was, how the order could be improved and get participants to understand how to work as a team.
- Then, calculate the score for the drill (see scenario sheet) and review strengths and areas needing improvement based on the scenario sheet (where the column is blank).

Demonstrate each clinical skill with which problems were identified (clinical and teamwork) (5–10 minutes). Give participants a chance to return and demonstrate the skill(s) (10–30 minutes). Identify participants who need additional time to practise specific skills and arrange time after the session to work with each one.

Repeat the same drill (10 minutes) to give participants a chance to put together all of the skills in a repeat simulation. If you still identify serious problems with the drill (especially teamwork), repeat it for a third time.

Participants are evaluated by their ability to respond to an emergency as a team. Ideally this score will be 80% or higher. If one member of the team does well, the whole team will do well. If one member of the team is not performing to standard, the entire team will not pass. Participants must understand that they have a responsibility to themselves, team members, and women and newborns.

How to use the scenario sheet

- At the top of each scenario sheet, complete the line that indicates the topic of the scenario. (The number of the Module relates only to the ESMOE-EOST programme and can be ignored if not part of that programme in South Africa.)
- Complete the page of the sheet which is your summary record of what has happened in the drill, with space provided for: the before- and after-scores; observations and remarks on follow-up needed (e.g. for improvement of skills); and an attendance list to be signed by each participant.
- The scenarios are presented in a table with four columns:
  1. Information provided and questions asked
     - The scenario starts with *information about the patient's condition* written in italics across the first two columns. Give the information in the first block in italics to the participant who will act as "discoverer" (in front of the other participants) and ask him/her to repeat the information before starting with the drill. Provide the rest of the information in the blocks in italics as the drill progresses.
     - Each block with information in italics is followed by a question in bold that you should ask the participants. There are also discussion questions to use during feedback on the initial drill to push participants to problem-solve and give you an opportunity

to provide additional information about the condition and/or care provision.

2. Key reactions/responses expected from participants
   - Key reactions/responses expected from participants are provided in the second column of each scenario. The participant should demonstrate and explain what he/she is doing and also talk to the patient/family member of the patient.
   - Participants are expected to think quickly and react (intervene) rapidly when you provide information and ask questions.
3. Before (B)
   - Complete this during the initial drill.
   - Put a "Y" or "√" beside each step or task that the team performed correctly. If the team did NOT perform the step/task or did not perform it correctly, leave that space blank.
   - After the drill is complete, add up the number of "Y"s or "√"s and calculate the score for the drill.
4. After (A)
   - Complete this during the repeat drill.
   - Put a "Y" or "√" beside each step or task that the team performed correctly. If the team did NOT perform the step/task or did not perform it correctly, leave that space blank.
   - After the drill is complete, add up the number of "Y"s or "√"s and calculate the score for the drill.

Table S8.1 contains a fictitious example of a template for scoring a drill. Overall, the evaluation

Table S8.1 Example of how to score a drill

	BEFORE	AFTER
CLINICAL SCORE: Assessment, diagnosis, monitoring and emergency management	*43*	*43*
CLINICAL SCORE: Total number of boxes ticked above	23	32
EXECUTION OF DRILL SCORE:		
A. Activation/Communication skills		
1. Appropriate equipment brought (emergency trolley)	√	√
2. Discoverer exchanges information with team leader and helpers using SBAR approach		√
3. Team leader assigns essential roles to helpers (care for the woman, calling a doctor, etc.)	√	√
4. Team leader addresses team members by name		√
5. All observations are communicated clearly and loudly	√	√
6. Communication done correctly: instruction → repeat instruction → inform team when instruction is completed		√
7. The delegated helper informs the patient and family of what is happening and what will be done for the woman		
B. Response/Team work		
8. Team responds appropriately to team leaders' instructions	√	√
9. Team members cooperate with each other		√
10. The team determines the disposition of the patient (transfer, plan for further management)	√	√
C. Sign out/Documentation		
11. Person allocated to do documentation	√	√
12. Care (actions) completely documented (timing of intervention and administration of drugs)		√
D. Sequence of activities		
13. Activities performed in the correct order of priority		√
EXECUTION OF DRILL SCORE (A-D above)	*13*	*13*
EXECUTION OF DRILL SCORE (A-D above): Number of boxes ticked	6	12
TOTAL SCORE (CLINICAL SCORE + EXECUTION OF DRILL SCORE)	29	44
Out of a possible score of	*56*	*56*

of the response to an emergency is graded according to the sum of two sub-scores: a 'clinical score' and 'execution of drill score' (made up of scores for A. Activation/communication skills, B. Response/ team work, C. Sign-out/documentation, and D. Sequence of activities). To calculate the score, add the two subs-cores together to get the total score. You can get the percentage by dividing the score received by the possible score and then multiplying by 100. In the example in Table S8.1, the "before" drill was scored as follows: total score: $23 + 6 = 29$ (for clinical + execution) out of a possible total of $43 + 13 = 56$ points, giving a percentage score of $(29/56) \times 100 = 52\%$. The "after" drill was scored as $32 + 13 = 45$ points out of a possible 56 points, giving a percentage score of $(45/56) \times 100 = 80\%$, a passing score.

Date: …… Name of health facility: ……

Name(s) of evaluator(s): Signature(s):

…… ……

…… ……

SCORE:

BEFORE	AFTER

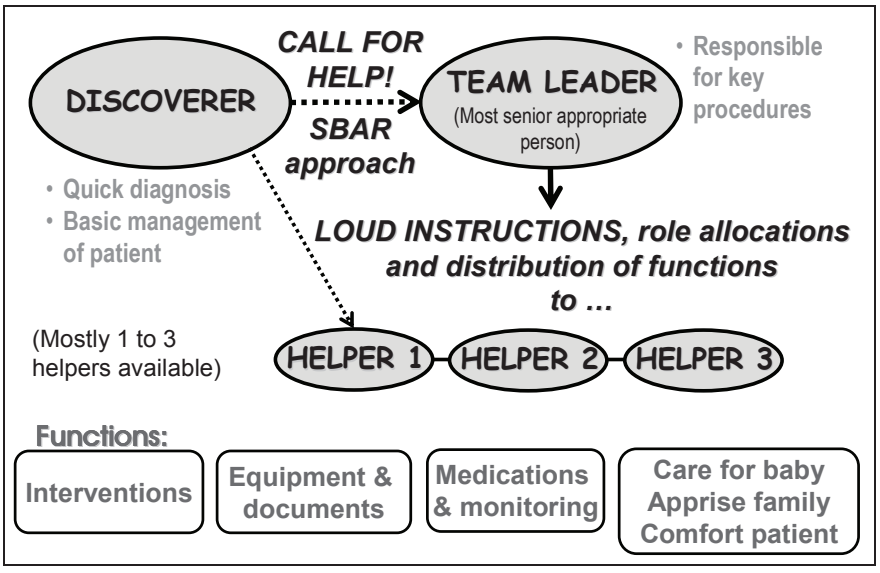
NOTES AND FOLLOW-UP

ATTENDANCE

	Name	Rank	Ward	Signature
1.				
2.				
3.				
4.				
5.				
6.				
7.				
8.				

PRE-ECLAMPSIA AND ECLAMPSIA
Scenario 1 (Eclampsia)

MATERIALS TO BE READY AND AVAILABLE BEFORE STARTING THE SESSION:	
General • Ask one of the participants to be the patient. Brief the "patient" on the scenario. • Blank clinical notes sheet • Clock **Drugs and supplies** • Syringes and needles • IV giving sets and IV pole • Test tubes for taking blood samples • Ringer's Lactate **Learning materials** • Flip charts Module 4	**Equipment** • Sphygmomanometer • Stethoscope • Pulse oximeter if available • A supplemental oxygen source. o If cylinders are used, check that they have adequate oxygen o Flow meter and air oxygen blender o Tubing • Ambu bag and mask • Oxygen mask Oxygen tubing • Oropharyngeal airway • Yankauer sucker • Pinardfetal stethoscope • Patellar hammer



For all of the steps, please demonstrate what you would do.
Explain what you are doing as you do it and why you are doing it.

ESMOE-EOST Module 4: Pre-eclampsia and eclampsia: Scenario 1 Version 1.2

B = Before / A = After		B	A
Information provided and questions asked	**Key reactions/responses expected from participants**		
Ms X is 16 years old and is 37 weeks pregnant. This is her first pregnancy. She has presented to the labour unit with contractions and says that she has had a bad headache all day. She also says that she cannot see properly. While she is getting up from the examination table, she falls back onto the pillow and begins to have a convulsion.			
1. What will you do?	Call for HELP! Mobilise all available personnel!!		
	Checks airway to ensure that it is open, and turns Ms X onto her left side		
	Secure circulation, airway, and breathing (CAB), if needed		
	Protect her from injuries (fall) but do not attempt to restrain her		
	While caring for the woman, find out the history of the woman's present and past illnesses from her relatives. Ask if she has epilepsy, history of previous convulsions, other signs and symptoms (fever, vaginal bleeding, severe headache/blurred vision, epigastric pain, severe abdominal pain)		
Ms X has stopped fitting.			
2. What will you do now?	Ensure the woman's airway is open: aspirate the mouth and throat as necessary. Observe colour for cyanosis and need for oxygen (if available, place a pulse oximeter).		
	Keep the woman on her side or place a wedge under the woman's right side so she tilts toward her left side to reduce the risk of aspiration of secretions, vomit and blood.		
	Check lungs for aspiration: Lungs should always be auscultated after the convulsion has ended.		
	Give oxygen at 4-6L per minute by mask or nasal cannulae, if available.		
	Put in a large bore IV (16 gauge or largest available) cannulae or needle with Ringer's Lactate		
	Obtain blood for the laboratory before infusing IV fluids (haematocrit, clotting profile, creatinine, AST, liver function tests) [Do bedside Hb]		
	Prepare and give magnesium sulfate IV 4g (20% solution) made up to 200mls (normal saline for injection) over 20 mins followed by 100 ml RL		
	Follow promptly with 10 g of 50% magnesium sulfate solution, 5 g in each buttock deep IM injection with 1 mL of 2% lignocaine in the same syringe		
	Infuse IV fluids (Ringer's Lactate) at 125 ml/hour when patient is ready for transfer to prevent accidental fluid overload en route to next level of care.		
	Catheterise the bladder and monitor fluid intake and output, test urine for proteinuria		
	Listen for fetal heart		
	At the same time, tells Ms X (and family members) what is going to be done, listens to her and responds attentively to her questions and concerns		
	Plan for transfer to a level 2 or 3 hospital if in a PHC, CHC, or Level 1 Hospital.		
Discussion Question 1			
Ms X's airway is clear, pulse is 110 bpm, BP 170/90 mmHg, AVPU = V, colour is pink. Breathing is shallow, lung sounds are clear, RR 28 breaths / minute. Urine protein is 3+, Hb is 9 g/dL, glucose if 4.5mmol/l.			
3. What will you do now?	This BP is dangerously high and needs management. Depends on drugs available in the clinic and presence of contraindications in the woman: • Labetalol, as stat IV doses 20 mg stat (increasing by 40, 80, 80 80mg every 20 minutes to achieve hypertension control or to a maximum of 300 mg in 24 hours. • An alternative if Labetalol is not available: give nifedipine 10 mg orally swallowed (not chewed, sublingual or buccal) stat; repeat @15 min x 3 or until BP less than 160/110		
	Conduct a **targeted history and physical examination.** Perform a secondary survey (Big 5, Forgotten 4, Core 1)		
	Plan to monitor lung sounds, BP, respirations, reflexes, oxygenation, colour, level of consciousness, maternal pulse, urine output, and fetal heart rate, temperature, liver tenderness, and labour signs		
Discussion Question 2			
It is now 1 hour since Ms X received MgSO4 following her convulsion. Her airway is clear, pulse is 110 bpm, BP 150/90 mmHg, AVPU = V, colour is pink. Breathing is shallow, you note creps in the lung bases, RR 32 breaths / minute. Urine output was 40 mL over the past hour. Reflexes are hyper-reactive. Her cervix is closed and she has no uterine contractions. (You are in an institution with safe C/S facilities).			
4. What will you do now?	Diagnose pulmonary oedema; give furosemide 40 mg IV once, reduce fluids but keep line open. (She is already on oxygen).		
	Plan for delivery. (Either induction or C/S depending on blood results and fetal condition)		
	Monitor level of consciousness. reflexes, BP, maternal pulse, lung sounds, respiratory rate, oxygenation, (Saturation if possible) liver tenderness (and AST), urine output (and urea and creatinine), Haemoglobin and platelets, temperature, and fetal heart rate and labour signs		
CLINICAL SCORE = TOTAL NUMBER OF TICKS ABOVE			

ESMOE-EOST Module 4: Pre-eclampsia and eclampsia: Scenario 1 Version 1.2

	B = Before / A = After	B	A
Information provided and questions asked	**Key reactions/responses expected from participants**		
DISCUSSION QUESTIONS			
1. What would you do if there was no magnesium sulfate?	*If cannot give magnesium because it is unavailable drug of choice is lorazepam (Ativan) 1-2mg IV (max= 4mg/24 hours) or clonezepam (Rivotril) 1mg IV repeated in 30 minutes if required (beware respiratory depression) If not available prescribe valium 10mg IV slowly and further 10mg IV slowly if convulsions recur.*		
2. What other diagnoses must you rule out?	*Epilepsy, meningitis, encephalitis, tetanus, severe/complicated malaria.*		

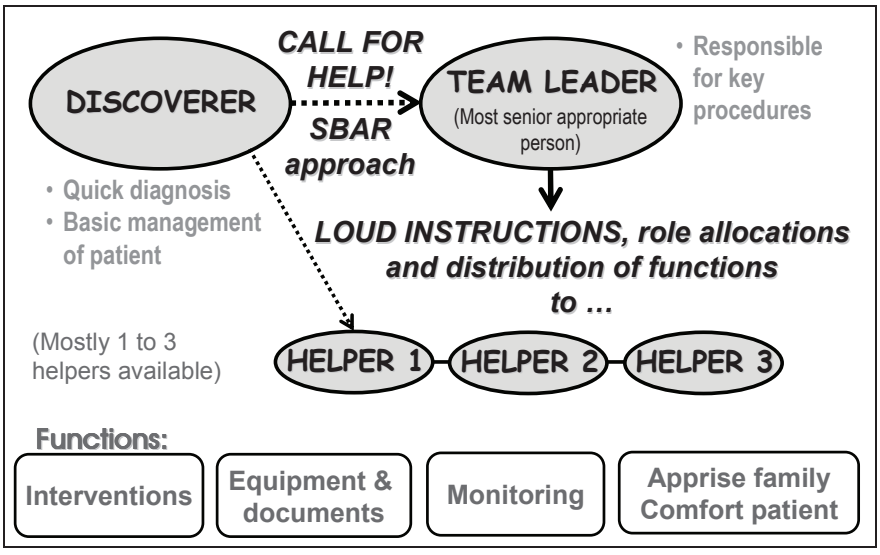
	BEFORE	AFTER
CLINICAL SCORE: Assessment, diagnosis, monitoring and emergency management	***24***	***24***
CLINICAL SCORE: Total number of boxes ticked above		
EXECUTION OF DRILL SCORE:		
A. Activation/Communication skills		
1. Appropriate equipment brought (eclampsia box; emergency trolley)		
2. Discoverer exchanges information with team leader and helpers using SBAR approach		
3. Team leader assigns essential roles to helpers (care for the woman, calling a doctor, etc.)		
4. Team leader addresses team members by name		
5. All observations are communicated clearly and loudly		
6. Communication done correctly: instruction → repeat instruction → inform team when instruction is completed		
7. The delegated helper informs the patient and family of what is happening and what will be done for the woman		
B. Response/Team work		
8. Team responds appropriately to team leaders' instructions		
9. Team members cooperate with each other		
10. The team determines the disposition of the patient (transfer, plan for further management)		
C. Sign out/Documentation		
11. Person allocated to do documentation		
12. Care (actions) completely documented (timing of intervention and administration of drugs)		
D. Sequence of activities		
13. Activities performed in the correct order of priority		
EXECUTION OF DRILL SCORE (A-D above)	***13***	***13***
EXECUTION OF DRILL SCORE (A-D above): Number of boxes ticked		
TOTAL SCORE (CLINICAL SCORE + EXECUTION OF DRILL SCORE)		
Out of a possible score of	***37***	***37***

DISCUSSION POINTS

1. Remember to replace drugs etc (on emergency trolley)
2. Equipment to be cleaned and sterilised appropriately
3. During drill there are no arguments or in-between discussions of opinions on how something should be done. Only the necessary actions are performed as swiftly and efficiently as possible
4. The environment should be quiet. Only instructions and feedback allowed
5. Observations are given clearly and loudly
6. Importance of the correct sequence of events
7. Documentation

PRE-ECLAMPSIA AND ECLAMPSIA
Scenario 2 (Pre-eclampsia)

MATERIALS TO BE READY AND AVAILABLE BEFORE STARTING THE SESSION:	
General • Request colleague to be the patient **Drugs and supplies** • Syringes and needles • IV giving sets and IV pole • Test tubes for taking blood samples • Ringer's Lactate • Magnesium sulphate **Learning materials** • Flip charts Module 4	**Equipment** • Sphygmomanometer • Stethoscope • Pulse oximeter if available • A supplemental oxygen source. o If cylinders are used, check that they have adequate oxygen o Flow meter and air oxygen blender o Tubing • Oxygen mask • Pinard fetal stethoscope • Patellar hammer



For all of the steps, please demonstrate what you would do.
Explain what you are doing as you do it and why you are doing it.

ESMOE-EOST Module 4: Pre-eclampsia and eclampsia: Scenario 2 Version 1.2

B = Before / A = After		B	A
Information provided and questions asked	**Key reactions/responses expected from participants**		
Mrs P is aged 19, P2, who is 36/40 pregnant has presented to the antenatal clinic. She complains of headache, blurred vision and had some epigastric pain this morning.			
1. What will you do?	Call for HELP! Mobilise all available personnel!!		
	Place the patient on the examination table with left lateral tilt		
	Perform a rapid evaluation of the general condition of the woman, including circulation (pulse, BP), airway, breathing, oxygenation, level of consciousness (AVPU), skin colour, presence of anxiety and/or confusion, blood loss, and skin temperature		
	Check patellar reflexes		
	Simultaneously ask about the history of Ms P's present illness		
The nurse reports that her BP is 148/96 mmHg, pulse is 100 bpm, respirations 20 breaths per minute, temperature is 37.2 ℃, and 2+ proteinuria is present. On examination, you find her to have hyper-reflexia, clonus and to be jittery. AVPU = A. The FHR is 120/min and regular.			
Discussion Question 1			
3. What will you do now?	Give oxygen at 4-6L per minute by mask or nasal cannulae, if available		
	Put in a large bore IV (16 gauge or largest available) cannulae or needle		
	Prepare and give magnesium sulfate IV 4g (20% solution) made up to 200mls (normal saline for injection) over 20 mins followed by 100 ml RL		
	Follow promptly with 10 g of 50% magnesium sulfate solution, 5 g in each buttock deep IM injection with 1 mL of 2% lignocaine in the same syringe		
	Infuse IV fluids (normal saline or Ringer's Lactate) at 80 ml/hour when patient is ready for transfer to prevent accidental fluid overload en route to next level of care		
	Listen to the fetal heart		
	Catheterise the bladder and monitor fluid intake and output		
	At the same time, tells Ms P (and family members) what is going to be done, listens to her and responds attentively to her questions and concerns		
	Check the BP every 15 minutes until ambulance arrives. Give nifedipine if BP systolic >160mmHg or diastolic >110mmHg		
	Plan for transfer to a level 2 or 3 hospital if in a PHC, CHC, or Level 1 Hospital and complete SBAR form		
Discussion Question 2			
3. What will happen once Ms P arrives as the referral hospital?	Conduct a **targeted history and physical examination.** Perform a secondary survey (Big 5, Forgotten 4, Core 1)		
	Obtain blood for laboratory investigations: haematocrit, clotting profile, creatinine, AST, liver function tests		
After 15 minutes at the referral hospital, Ms P is resting quietly. She still has a headache and hyper-reflexia.			
4. How will you plan to monitor her condition?	Check respirations, reflexes, oxygenation, colour, level of consciousness, maternal pulse,urine output, and fetal heart rate (FHR) at least hourly, or more frequently as needed		
	Check BP every 15 minutes for the first hour, and decide if antihypertensive medications are needed		
	Check temperature every four hours (hyperpyrexia may occur)		
	Check for liver tenderness		
	Check for signs of labour		
Discussion Question 3			
Her pulse is now 98 bpm, BP 156/110 mm Hg, respiration rate 20 breaths/minute, and urine output was 40 mL since catheterization at the clinic. She still has hyper-reflexia. You detect that the fetal heart rate is 120 bpm, slowing to 100 bpm after a contraction.			
5. What will you do now?	This BP is dangerously high and needs management. Depends on drugs available in the clinic and presence of contraindications in the woman: • Give nifedipine 10 mg orally swallowed (not chewed, sublingual or buccal) stat; repeat @15 min x 3 or until BP less than 160/110 • [An alternative is labetalol, as an IV infusion at 20 mg/hour (200 mg in 200 mL of normal saline, run at 20 mL/hour), increasing by 20 mg/hour every 20 minutes to achieve hypertension control or to a maximum of 300 mg in 24 hours].		
	Continue monitoring the woman and fetus.		
	Plan to keep the BP between dBP 90 and 100 mmHg		
Discussion Question 4			
6. What is your further plan of action?	Ms P needs delivery .The main concern now is fetal heart abnormality		
	Ms P should be prepared to go to the operating room for cesarean section. Only once stable, position Ms P on her side		
	Tells Ms P (and family members) what is happening, listens to her concerns and provides reassurance		
Discussion Question 5			

ESMOE-EOST Module 4: Pre-eclampsia and eclampsia: Scenario 2 Version 1.2

B = Before / A = After		B	A
Information provided and questions asked	**Key reactions/responses expected from participants**		
	CLINICAL SCORE = TOTAL NUMBER OF TICKS ABOVE		
DISCUSSION QUESTIONS			
1. What is Ms P's problem?	*Ms P's symptoms and signs are consistent with severe pre-eclampsia*		
2. What is your main concern at the moment?	*The main concern at the moment is to prevent Ms P from convulsing*		
3. What are signs of magnesium toxicity that you should check for before giving an additional dose?	• *Respiratory rate falls below 16 per minute.* • *Patellar reflexes are absent.* • *Urinary output falls below 30 mL per hour over preceding 4 hours.*		
4. What counselling will you give the woman and her family?	*Explain the severity of the illness, the necessity for organ system evaluation and then delivery. Reassure at this pregnancy duration there should not be any problems with the baby*		
5. What is the appropriate time for delivery?	*Mother must be fully resuscitated before a caesarean section is performed for fetal distress*		

	BEFORE	AFTER
CLINICAL SCORE: Assessment, diagnosis, monitoring and emergency management	***28***	***28***
CLINICAL SCORE: Total number of boxes ticked above		
EXECUTION OF DRILL SCORE:		
A. Activation/Communication skills		
1. Appropriate equipment brought (emergency trolley)		
2. Discoverer exchanges information with team leader and helpers using SBAR approach		
3. Team leader assigns essential roles to helpers (care for the woman, calling a doctor, etc.)		
4. Team leader addresses team members by name		
5. All observations are communicated clearly and loudly		
6. Communication done correctly: instruction → repeat instruction → inform team when instruction is completed		
7. The delegated helper informs the patient and family of what is happening and what will be done for the woman		
B. Response/Team work		
8. Team responds appropriately to team leaders' instructions		
9. Team members cooperate with each other		
10. The team determines the disposition of the patient (transfer, plan for further management)		
C. Sign out/Documentation		
11. Person allocated to do documentation		
12. Care (actions) completely documented (timing of intervention and administration of drugs)		
D. Sequence of activities		
13. Activities performed in the correct order of priority		
EXECUTION OF DRILL SCORE (A-D above)	***13***	***13***
EXECUTION OF DRILL SCORE (A-D above): Number of boxes ticked		
TOTAL SCORE (CLINICAL SCORE + EXECUTION OF DRILL SCORE)		
Out of a possible score of	***40***	***40***

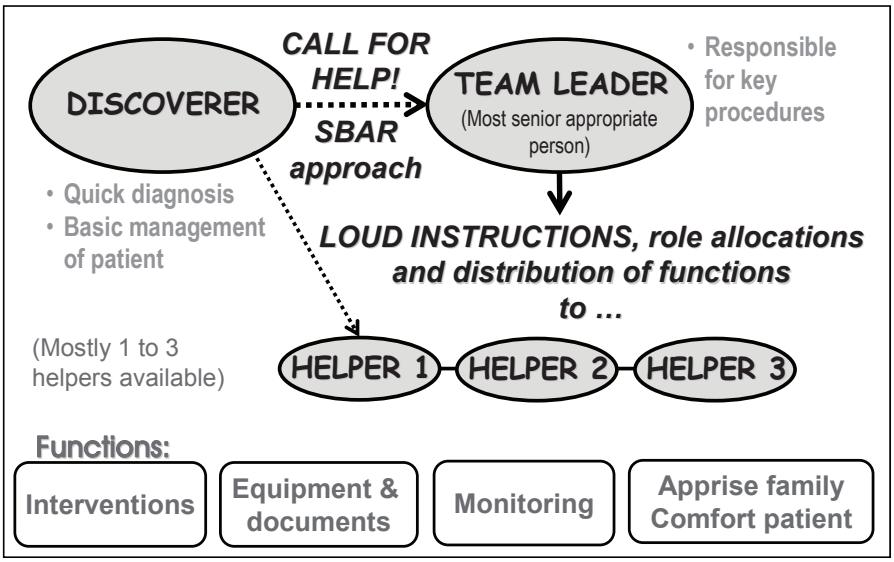
DISCUSSION POINTS

1. Remember to replace drugs etc (on emergency trolley)
2. Equipment to be cleaned and sterilised appropriately
3. During drill there are no arguments or in-between discussions of opinions on how something should be done. Only the necessary actions are performed as swiftly and efficiently as possible
4. The environment should be quiet. Only instructions and feedback allowed
5. Observations are given clearly and loudly
6. Importance of the correct sequence of events
7. Documentation

ESMOE-EOST: Preeclampsia. Module , Scenario 3

PRE-ECLAMPSIA
Scenario 3

MATERIALS TO BE READY AND AVAILABLE BEFORE STARTING THE SESSION:	
General • "Actor" • Blank clinical notes sheet • Clock **Drugs and supplies** • Syringes and needles • IV giving sets and IV pole • Test tubes for taking blood samples • Ringer's Lactate **Learning materials** • Flip charts Module	**Equipment** • Sphygmomanometer • Stethoscope • Pulse oximeter if available • A supplemental oxygen source. o If cylinders are used, check that they have adequate oxygen o Flow meter and air oxygen blender o Tubing • Ambu bag and mask • Oxygen mask • Oxygen tubing • Oropharyngeal airway • Yankauer sucker • Model of larynx • Defibrillator if available



For all of the steps, please demonstrate what you would do.
Explain what you are doing as you do it and why you are doing it. As you perform each step the facilitator will give you the results of your actions

ESMOE-EOST: Preeclampsia. Module , Scenario 3

	B = Before / A = After	B	A
Information provided and questions asked	**Key reactions/responses expected from participants**		
Mrs C a 25 year old Gravida 1, para 0, presents at casualty complaining she is feeling nauseaous. She is 31 weeks pregnant by early ultrasound done by her family physician. ***What will you do?***			
1. Shake and Shout	Responds appropriately to your greeting		
2. Call a CAB	*Assess circulation; pulse 120 beats per minute, blood pressure 205/118mmHg*		
	Assess Airway: Clear		
	Assess Breathing: Respiratory rate 24		
	Call for Help		
	Lie on bed in left lateral position		
The doctor/ senior sister and two other nurses arrive **(What must be done now?)**			
	Insert a IV line and obtain blood for Hb, platelets, AST, U&E		
	Run IV line of ringers lactate at 100ml/minute		
	Put 4g MgSO4 into 200ml normal saline and run in as a side drip over 20 minutes		
	Put up oxygen mask		
	Insert catheter		
	Repeat observations		
More information **(What must be done now?)**			
3. Big 5, Forgotten 4, Core 1 (Secondary survey)	*Further History: Ask about symptoms, etc.: No headache, blurred vision or epigastric pain*		
	CNS: Very brisk reflexes		
	CVS: Pulse 110 after, BP 170/115 mmHg after 10 minutes; heart sounds normal; repeat BP every 5 minutes		
	Resp: RR 20 breaths per minute; saturation 98% on oxygen mask; lung bases clear		
	Liver and GIT; Not tender, no jaundice		
	Renal: Catheter drains 20 mls concentrated urine, 3+ proteinuria		
	Heamatological: Not pale, no signs ecchymosis		
	Endocrine: Breast, thyroid normal; Glucose 5.1mmol/l		
	Musculo-skeletal: No DVTs		
	Immune: HIV neg, Temp. 36.4^{0}C		
	Core 1:, SF measurement 23 cm, Uterus not tender but irritable, Cephalic presentation, oligohydramnios, FH beat present,		
	Core 2: No vaginal bleeding (vaginal examination not done)		
4. Diagnosis	*Severe Pre-eclampsia at 31 weeks gestation*		
5. Further management	*Repeat observations At 20 minutes BP175/115mmhg, pulse 110, RR 18 breaths/min.*		
	Give labetalolol if available, or nifedipine		
	Give corticosteroids		
	Run fluids in at 100ml/hour		
Blood results: Hb 14g%, Platelets 120, AST 40, Urea 4.2, Creatinine 110, Sonar examination: 930gm, AEDF, AFI 3 **(What must be done now? Discussion)**			
	CLINICAL SCORE = TOTAL NUMBER OF TICKS ABOVE		
CLINICAL SCORE: Assessment, diagnosis, monitoring and emergency management		***23***	***23***

DISCUSSION QUESTIONS	
1. Should the baby be monitored	*Discuss management at every level of care; if cannot refer what actions should be taken.*
2. What is the place of expectant management	*Only in tertiary units*

ESMOE-EOST: Preeclampsia. Module , Scenario 3

EXECUTION OF DRILL SCORE:	Before (B)	After (A)
A. Activation/Communication skills		
1. Appropriate equipment brought (emergency trolley)		
2. Discoverer exchanges information with team leader and helpers using SBAR approach		
3. Team leader assigns essential roles to helpers (care for the woman, calling a doctor, etc.)		
4. Team leader addresses team members by name		
5. All observations are communicated clearly and loudly		
6. Communication done correctly: instruction → repeat instruction → inform team when instruction is completed		
7. The delegated helper informs the patient and family of what is happening and what will be done for the woman		
B. Response/Team work		
8. Team responds appropriately to team leaders' instructions		
9. Team members cooperate with each other		
10. The team determines the disposition of the patient (transfer, plan for further management)		
C. Sign out/Documentation		
11. Person allocated to do documentation		
12. Care (actions) completely documented (timing of intervention and administration of drugs)		
D. Sequence of activities		
13. Activities performed in the correct order of priority		
EXECUTION OF DRILL SCORE (A-D above)	***13***	***13***
EXECUTION OF DRILL SCORE (A-D above): Number of boxes ticked		
TOTAL SCORE (CLINICAL SCORE + EXECUTION OF DRILL SCORE)		
Out of a possible score of	***36***	***36***

DISCUSSION POINTS

1. Remember to replace drugs etc (on emergency trolley)
2. Equipment to be cleaned and sterilised appropriately
3. During drill there are no arguments or in-between discussions of opinions on how something should be done. Only the necessary actions are performed as swiftly and efficiently as possible
4. The environment should be quiet. Only instructions and feedback allowed
5. Observations are given clearly and loudly
6. Importance of the correct sequence of events
7. Documentation

Appendix 8.3

GRADE evaluation of best practice points regarding fluids, drugs and transfusion

	*Quality of evidence**	*Strength of recommendation†*
Fluid therapy		
1. Plasma volume expansion is not recommended for women with pre-eclampsia.	Moderate	Strong
2. IV fluid intake should be minimized to 80 mL/h in women with pre-eclampsia to avoid pulmonary oedema.	Low	Strong
3. Fluid should not be routinely administered to treat oliguria (<15 mL/h for 6 consecutive hours) for the sole purpose of increasing urine output.	Very low	Weak
4. For treatment of persistent oliguria, neither dopamine nor furosemide is recommended.	Moderate	Strong
Antihypertensive therapy for severe hypertension		
1. BP should be lowered to <160 mmHg systolic and <110 mmHg diastolic.	Low	Strong
2. Initial antihypertensive therapy in the hospital setting should be with nifedipine short-acting (capsules), parenteral hydralazine, or parenteral labetalol	High	Strong
3. Alternative antihypertensive medications include oral methyldopa, oral labetalol, oral clonidine, oral captopril (only postpartum), or a nitroglycerin infusion	Moderate (labetalol, nitroglycerin) Low (clonidine, captopril postpartum) Very low (methyldopa)	Weak
4. Refractory hypertension may be treated with sodium nitroprusside	Low	Weak
5. Nifedipine and $MgSO_4$ can be used contemporaneously	Moderate	Weak
6. $MgSO_4$ is not recommended solely as an antihypertensive agent.	High	Strong
7. Continuous FHR monitoring is advised until BP is stable.	Very low	Weak
Antihypertensive therapy for non-severe hypertension		
1. Antihypertensive drug therapy should aim for a dBP of 85 mmHg.	High	Strong
2. The choice of antihypertensive agent for initial treatment should be based on characteristics of the patient, contraindications to a particular drug, and physician and patient preference.	Very low	Weak
3. Initial therapy in pregnancy can be with one of a variety of antihypertensive agents methyldopa, labetalol, other beta-blockers (acebutolol, metoprolol, pindolol, and propranolol and calcium channel blockers (nifedipine).	High (methyldopa, labetalol, nifedipine), moderate (other beta-blockers)	Strong

continued

Appendix 8.3 *continued*

	*Quality of evidence**	*Strength of recommendation†*
Antihypertensive therapy for non-severe hypertension		
4. ACE inhibitors and ARBs should not be used during pregnancy.	Moderate	Strong
5. Atenolol and prazosin are not recommended prior to delivery.	Low	Weak
6. Captopril, enalapril, or quinapril may be used postpartum, even during breastfeeding.	Low	Weak
7. There is no compelling evidence that antihypertensive treatment of hypertension (with labetalol, nifedipine, and probably methyldopa) is associated with adverse effects on child development.	Low	Weak
8. Gestational hypertension and pre-eclampsia may each be associated with an increase in adverse paediatric neurodevelopmental effects, such as inattention and externalising behaviours.	Very low	Weak
$MgSO_4$		
1. $MgSO_4$ is recommended for first-line treatment of eclampsia.	High	Strong
2. $MgSO_4$ is recommended for eclampsia prevention in women with severe pre-eclampsia.	High	Strong
3. $MgSO_4$ may be considered for eclampsia prevention in women with non-severe pre-eclampsia based on cost considerations.	Moderate (based on effectiveness; cost from only one trial)	Strong
4. $MgSO_4$ should be used in standard dosing, usually 4 g IV loading dose followed by 1 g/h	Moderate	Strong
5. Routine monitoring of serum Mg levels is not recommended.	Low	Strong
6. Phenytoin and benzodiazepines should not be used for eclampsia prophylaxis or treatment, unless there is a contraindication to $MgSO_4$ or it is ineffective.	High (phenytoin) Moderate (diazepam)	Strong
7. In women with pre-existing or gestational hypertension, $MgSO_4$ should be considered for fetal neuroprotection in the setting of imminent preterm birth within the next 24 hours at $\leq 33^{+6}$ weeks.	Moderate (extrapolating from preterm labour)	Strong
Therapies for HELLP syndrome		
1. Every obstetrical centre should be aware of the local delay between ordering and receiving platelets units	Very low	Strong
2. For a platelet count $<20 \times 10^9$/L, platelet transfusion is recommended, regardless of mode of delivery.	Low	Strong
3. For a platelet count $20–49 \times 10^9$/L platelet transfusion is recommended prior to Caesarean delivery.	Low	Strong
4. For a platelet count $20–49 \times 10^9$/L, platelet transfusion should be considered prior to vaginal delivery if there is excessive active bleeding, known platelet dysfunction, a rapidly falling platelet count, or coagulopathy.	Low	Weak

continued

Appendix 8.3 *continued*

	*Quality of evidence**	*Strength of recommendation†*
Therapies for HELLP syndrome		
5. For a platelet count of $\geq 50 \times 10^9$/L, platelet transfusion should be considered prior to either Caesarean or vaginal delivery if there is excessive active bleeding, known platelet dysfunction, a rapidly falling platelet count, or coagulopathy.	Low	Weak
6. We do not recommend corticosteroids for treatment of HELLP until they have been proven to decrease maternal morbidity	Moderate/Low (RCTs did not show change in hard outcomes but underpowered)	Weak
7. We recommend against plasma exchange or plasmapheresis for HELLP, particularly within the first 4 days postpartum.	Low	Strong
Other therapies for treatment of pre-eclampsia (from 2008 document)		
1. Women with pre-eclampsia before 34 weeks' gestation should receive antenatal corticosteroids for acceleration of fetal pulmonary maturity.	High	Strong
2. Thromboprophylaxis may be considered antenatally among women with pre-eclampsia who have two or more additional thromboembolic risk markers, postnatally among women with pre-eclampsia who have at least one additional thromboembolic risk marker, or postnatally among women any HDP who were on antenatal bed rest for at least 7 days	Low	Weak

FHR, fetal heart rate; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; HELLP, Haemolysis, Elevated Liver enzyme, Low Platelet syndrome; $MgSO_4$, magnesium sulphate

* The judgements about the quality of evidence is based on the confidence that available evidence reflects the true effect of the intervention or service. Evidence is considered to be of high quality when the true effect is thought to lie close to that of the estimate of the effect (e.g., if there is a wide range of studies included in the analyses with no major limitations, there is little variation between studies, and the summary estimate has a narrow confidence interval). Evidence is considered to be of moderate quality when the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different (e.g., if there are only a few studies and some have limitations but not major flaws, there is some variation between studies, or the confidence interval of the summary estimate is wide). Evidence is considered to be of low quality when the true effect may be substantially different from the estimate of the effect (e.g., the studies have major flaws, there is important variation between studies, or the confidence interval of the summary estimate is very wide).

† A strong recommendation should be interpreted as meaning that most people in this situation would want the recommended course of action and only a small number would not. Clinicians should regard the recommendation as applying to most individuals. Policy-makers can adopt the recommendation as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. A weak recommendation should be interpreted as meaning that most people in this situation would want the recommended course of action, but many would not; patients' values and preferences should be considered in reaching a decision. Decision aids may support people in reaching these decisions. Policy-making will require substantial debate and involvement of various stakeholders. An appropriately documented decision making process could be used as a quality indicator.

Appendix 8.4

Sample policy briefs

ANTIHYPERTENSIVE THERAPY– Policy brief

"… the report of the 'Confidential Enquiries into Maternal Deaths in the UK' that covered the hypertensive disorders of pregnancy (2005-8) identified the **failure to treat** the **severe** (particularly systolic) **hypertension** of pre-eclampsia as the **single most serious failing** in the clinical care of these women who died."

WHY IS ANTIHYPERTENSIVE THERAPY IMPORTANT?

Women with severe hypertension, defined as BP of ≥ 160 mmHg systolic or ≥ 110 mmHg diastolic in pregnancy (or postpartum), should be treated with antihypertensive therapy. The World Health Organization (WHO) 'Prevention and Treatment of Pre-eclampsia and Eclampsia' recommendations strongly recommend use of antihypertensive therapy for treatment of severe hypertension during pregnancy, because treatment of severe hypertension in pregnancy or postpartum decreases maternal risk, particular that of stroke. This has been demonstrated in the 'Confidential Enquiries into Maternal Deaths in the UK (2009-12) and through a similar process in South Africa.

Antihypertensive therapy for **non-severe** pregnancy hypertension decreases the risk of severe hypertension and the associated risks.

WHICH ANTIHYPERTENSIVE SHOULD BE USED?

The choice of antihypertensive agent for initial treatment should be based on characteristics of the patient, contraindications to a particular drug, and physician and patient preference.

Severe hypertension

The antihypertensive agents used most commonly are oral nifedipine (capsules or tablets) or intravenous labetalol or hydralazine. Hydralazine is on the WHO Model List of Essential Medicines (2015) for treatment of severe hypertension, although nifedipine capsules (10mg) are listed as a tocolytic. Both of these medications are on the essential medicines lists of most LMICs.

Oral agents (such as methyldopa or labetalol) are far better-suited to management of severe hypertension than are parenteral agents, especially in resource-limited settings, as they do not require an investment in either physical resources (i.e. intravenous tubing, syringes and needles) or human resources (as administration of parenteral agents is by nurses or often, doctors). Also, oral antihypertensive agents do not mandate the same level of monitoring given a lower risk of dropping the blood pressure quickly and causing fetal compromise.

Non-severe hypertension

Oral methyldopa and oral labetalol are used most frequently for treatment of non-severe hypertension, but there are a wide variety of agents that can be used. Only methyldopa is on the WHO Model List of Essential Medicines (2015) for non-severe pregnancy hypertension.

Above: An instructional chart for Mozambique health workers showing the administration of methyldopa to a woman who has non-severe hypertension in pregnancy

ACTIONS

- **Create regulatory efficiency by** updating the National Essential Medicines List to include antihypertensive agents for treatment of severe and non-severe hypertension.
- **Identify and promote opportunities** where maternal health commodities can be integrated into the broader Health Management Information System.
- **Task-shift** to enable midwives, nurses, and lower-level providers to prescribe and safely administer the appropriate antihypertensive agent.
- **Strengthen the treatment at the community level** where few centers initiate treatment for pre-eclampsia and eclampsia. Taken in the context of the 'three delays' model of maternal mortality, this represents a lost opportunity for improving maternal outcome.
- **Update national protocols and clinical guidelines** to facilitate education, training and proper use of antihypertensive therapy among health care workers, particularly those in the community Materials should include a standardised toolkit that includes treatment guidance such as a visual record of monitoring and treatment, as well as other drugs needed for women with severe pre-eclampsia/eclampsia.

MAGNESIUM SULFATE ($MgSO_4$) – Policy brief

WHY USE MAGNESIUM SULFATE?

Magnesium sulfate ($MgSO_4$) has been on the World Health Organization(WHO) Model List of Essential Medicines since 1996. $MgSO_4$ is recommended by the WHO as the most effective, safe, and low-cost treatment for eclampsia prevention and treatment.

"…(F)ewer than half of centres initiated treatment for pre-eclampsia (40.0%) or eclampsia (28.0%) prior to transfer to facility (rural Nigeria). Taken in the context of the 'three delays' model of maternal mortality (delays in triage, **treatment,** transport), this represents a **lost opportunity** for improving maternal outcome"

- **First-line treatment of eclampsia**
  $MgSO_4$ more than halves the risk of recurrent eclampsia compared with other agents. Also, $MgSO_4$ is associated with a lower risk of both maternal death (compared with either diazepam or a lytic cocktail) and maternal pneumonia and respiratory support (compared with either phenytoin or a lytic cocktail). Although the WHO Model List of Essential Medicines (2015) also lists benzodiazepines as anticonvulsants, they are not recommended for eclampsia treatment.
- **First-line therapy for eclampsia prevention in severe pre-eclampsia**
  Compared with placebo or no treatment, $MgSO_4$ more than halves the risk of eclampsia among women with pre-eclampsia. $MgSO_4$ may be considered for eclampsia prevention in women with non-severe pre-eclampsia based on cost considerations. In under-resourced settings, 43 women with pre-eclampsia need to be treated to prevent one case of eclampsia, for a cost (in 2001 US dollars) of $456.
- **Prevention of cerebral palsy in infants born before 34 weeks' gestation**
  $MgSO_4$ decreases the risk of cerebral palsy by 30% when infants are born before 34 weeks' gestation, based on the results of four trials and over 4,000 babies. $MgSO_4$ may be administered before delivery in the same way as for eclampsia prevention.

ACTIONS

Above: An instructional chart showing the procedure of im $MgSO_4$ administration.

© PRE-EMPT Project

- **Standardise MgSO4 concentrations** in order to address complicated dosage preparations and variations in dosing regimens that are among the major barriers to use of $MgSO_4$ according to the Maternal Health Technical Resource Team of the UN Commission on Life-Saving Commodities. The WHO is advocating use of a 50% solution, equivalent to 50 g of $MgSO_4$ in 100mL of solution; as each ampule contains 10mL of solution, each vial contains 5 g of $MgSO_4$. National or institutional essential medicine lists (EMLs) should be updated to include this standardised concentration (50%) of $MgSO_4$.
- **Strengthen supply chains** by offering results-based financing of maternal health commodities that rewards providers when they meet performance standards for $MgSO_4$ administration.
- **Ensure procurement** by providing advanced market commitments or pooled procurements at the regional/central level to incentivise manufacturers to supply $MgSO_4$ and create a more sustainable market
- **Update national protocols** to facilitate education, training and proper use of $MgSO_4$ among health care workers, including community midwives and health care workers. Materials should include a standardised toolkit which includes treatment guidance such as visual record of monitoring and treatment, as well as other drugs needed for women with severe pre-eclampsia/eclampsia.
- **Strengthen the treatment at the community level** where few centres initiate treatment for pre-eclampsia and eclampsia. Ready-to-use packs comprising a loading dose pack, a maintenance dose pack, of appropriate strengths of $MgSO_4$, in addition to critical items such as lidocaine and a 20mL syringe, could enhance the use of MgSO4 at the community level. Taken in the context of the 'three delays' model of maternal mortality, this represents a lost opportunity for improving maternal outcome
- **Dispel myths about the safety of $MgSO_4$**. $MgSO_4$ is a safe drug with a very low incidence of severe side effects (1-2%). These are usually attributable to medication errors that would be addressed by standardising use of 50% $MgSO_4$, as discussed above. Even when adverse effects occur, delaying the next scheduled dose is generally sufficient to mitigate the effect.

Appendix 8.5

Recommendations for fluids, drugs and transfusion from international clinical guidelines*

	QLD 2013	*NICE 2010*	*WHO 2011*
Antihypertensive therapy (antenatally or postnatally)			
Antihypertensive therapy for severe Hypertension (defined)	(≥160/110 mmHg)	(≥160/110 mmHg)	
Treatment recommended	For women with any HDP, treat severe hypertension	For women with any HDP, treat severe hypertension (immediately) during pregnancy or postpartum	For women with any HDP, treat severe hypertension
Target BP level (level at which treatment may be unchanged; level above which treatment should be started; below which treatment should be decreased if on antihypertensive therapy)	For women with any HDP, goal of ≤160/100 mmHg	For women with any HDP (in critical care), goal of <150/80–100 mmHg is recommended	
Initial antihypertensive therapy/first choice	Initial anti-hypertensive therapy can be with one of a variety of antihypertensive drugs	Labetalol (oral or IV, hydralazine (IV) or nifedipine (oral) are recommended for women in a critical care setting Consider administration of up to 500 mL of crystalloid before or with the first dose of hydralazine IV	Should be based on clinician's experience, cost and local availability
Alternative antihypertensives			
Antihypertensives NOT to use			
Other considerations		For women with PET, consider side-effect profiles if giving treatment other than labetalol For women with severe hypertension treated in critical care setting, monitor response to treatment, ensure BP falls, identify adverse effects, and modify treatment according to response	

NVOG 2011	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
(≥160/110 mmHg)	(≥160/110 mmHg)	(≥160/110 mmHg)	(≥160/110 mmHg)
For women with any HDP, treat severe hypertension		For women with any HDP, treat severe hypertension	For women with any HDP, treat severe hypertension
		For women with chronic hypertension, goal of <160/105 mmHg is recommended For women with PET, goal of <160/110 mmHg	For women with any HDP, goal of <160/110 mmHg is recommended
Methyldopa, labetalol and nifedipine			Labetalol (IV), hydralazine (IV) or nifedipine (oral capsules) recommended Nifedipine and $MgSO_4$ can be used contemporaneously
			Alternatives are nitroglycerin (IV) methyldopa (oral), labetalol (oral), clonidine (oral), or captopril (oral) only postpartum Sodium nitroprusside recommended for refractory hypertension
ACE inhibitors, ARBs and direct renin inhibitors during pregnancy			$MgSO_4$ as an antihypertensive
			FHR monitoring (until stable BP) recommended

continued

Appendix 8.5 *continued*

	QLD 2013	*NICE 2010*	*WHO 2011*
For non-severe hypertension			
Target BP level (level at which treatment may be unchanged; level above which treatment should be started or increased; level below which any antihypertensive therapy should be decreased)		For women with uncomplicated chronic hypertension, goal of <150/100 mmHg (without lowering dBP to <80 mmHg) is recommended For women with chronic hypertension and target organ damage, goal of <140/90 mmHg recommended	
Antihypertensives to use		For women with chronic hypertension, choose an agent(s) based on pre-existing treatment, side-effect profiles and teratogenicity For women with GH, offer antihypertensive medication (other than labetalol) ONLY after considering side-effect profiles Alternatives include methyldopa† and nifedipine	
Antihypertensives NOT to use during pregnancy (and should be stopped)		For women with any HDP, ACE, ARBs or chlorothiazide (as they are associated with an increased risk of major malformations) For women with chronic hypertension, stop ACE inhibitors or ARBs in pregnancy (preferably within 2 working days of notification of pregnancy) and offer alternatives Tell women who took ACE inhibitors or ARBs "during pregnancy" that these medications increase the risk of congenital abnormalities Tell women who took chlorothiazide "during pregnancy" that this medication may increase the risk of congenital abnormalities and neonatal complications	

NVOG 2011	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
For any HDP, goal of <160/110 mmHg is recommended		For women with uncomplicated chronic hypertension, goal of 120–159/80–104 mmHg is recommended For women with mild GH or PET, goal of <160/110 mmHg is recommended	For any HDP, goal of 130–155/80–105 mmHg is recommended For women with any HDP and a comorbid condition(s), goal of <140/90 mmHg is recommended
For women with any HDP, methyldopa, labetalol, and nifedipine recommended as agents of first choice		For women with chronic hypertension, methyldopa, labetalol, and nifedipine recommended as agents of first choice	For women with any HDP, the choice of antihypertensive agent should be based on patient characteristics, contraindications and physician and patient preference For women with any HDP, methyldopa, labetalol, nifedipine, other beta-blockers, or other calcium channel blockers are reasonable as agents of first choice Methyldopa, labetalol and nifedipine are acceptable choices in the 1st trimester of pregnancy
For women with any HDP, ACE inhibitors, ARBs, and direct renin inhibitors		For women with uncomplicated chronic hypertension, ACE inhibitors, ARBs, renin inhibitors, and mineralcorticoid receptor antagonists are NOT recommended	For women with any HDP, atenolol and prazosin are not acceptable for use For women with any HDP, ACE inhibitors and ARBs (which should be stopped) – not acceptable for use

continued

Appendix 8.5 *continued*

	QLD 2013	*NICE 2010*	*WHO 2011*
Antenatal corticosteroids			
"≤34 weeks" – FIRST dose		"Between 24 and 34 weeks" For women with PET who are likely to deliver within 7 days	
REPEAT dosing			
"35–36 weeks"		"35–36 weeks" For women with PET who are likely to deliver within 7 days	
≤38^{+6} weeks gestation and elective Caesarean			

NVOG 2011	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
"Before 34 weeks" For women with any HDP who are likely to delivery within 2-10 days		"At ≤34^{+0} weeks" For women with severe PET or superimposed PET who are receiving expectant care "≤$33^{+6/7}$ weeks" For women with severe PET who require delivery, without delivery being delayed NOTE: Listed were: uncontrollable severe hypertension, eclampsia, pulmonary oedema, abruption placentae, disseminated intravascular coagulation, evidence of non-reassuring feta status, intrapartum fetal demise "≤$33^{+6/7}$ weeks" For women with severe PET who are stable enough to have delivery delayed by 48 h NOTE: Criteria specified were: low platelet count (<100,000/mL), persistently abnormal hepatic enzyme concentrations (twice or more the upper normal values), fetal growth restriction (less than the fifth percentile), severe oligohydramnios (amniotic fluid index <5 cm), reversed end-diastolic flow on umbilical artery Doppler studies, new-onset renal dysfunction or increasing renal dysfunction	"At ≤34^{+6} weeks" For women with PET "≤34^{+6} weeks" For women with GH who may deliver within the next 7 days
"Before 33 weeks" For women with any HDP, ONLY if first does were given at <30 weeks and >14 days prior			"≤34^{+6} weeks" For women with any HDP, if first dose ≥7 days prior
			"≤38^{+6} weeks" May consider for women with any HDP who are delivered by elective Caesarean

continued

Appendix 8.5 *continued*

	QLD 2013	*NICE 2010*	*WHO 2011*
Antenatal corticosteroids			
Fluid administration (including management of oliguria)		For women with severe PET, do NOT administer a fixed IV fluid bolus routinely prior to neuraxial analgesia For women with severe PET, limit ongoing fluid administration to 80 mL/h (unless ongoing fluid losses)	
Treatment of oliguria			
Aspects of care for women with pre-existing hypertension			
General considerations		Advice and treatment should be in line with 'Hypertension: the management of hypertension in adults in primary care' (NICE clinical guideline 34), unless it specifically differs from recommendations in this guideline Schedule additional antenatal consultations based on needs of woman and baby	
Specialist referral		(Specialist in hypertensive disorders) For women with secondary chronic hypertension	
Antihypertensive therapy – BEFORE pregnancy	For women with any prior HDP, preconceptional advice should be offered at a formal postnatal review	Tell women of reproductive age who take ACE inhibitors or ARBs that these medications increase the risk of congenital abnormalities if they are taken "during pregnancy" Tell women who take chlorothiazide that this medication may increase the risk of congenital abnormalities and neonatal complications if the drug is taken "during pregnancy" Discuss alternatives to ACE inhibitors, ARBs, and chlorothiazide for women planning pregnancy	

NVOG 2011	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
			For women with any HDP, do NOT administer a fixed IV fluid bolus routinely prior to neuraxial anaesthesia For women with PET, minimise IV and oral fluid intake
			For women with any HDP, do NOT routinely administer fluid to treat oligura (<15 mL/h for 6 consecutive hours) For women with any HDP, do NOT treat oliguria with dopamine or furosemide
Discuss alternatives to ACE inhibitors, ARBs and direct renin inhibitors for women planning pregnancy		Women of reproductive age should not be prescribed ACE inhibitors, ARBs, renin inhibitors, and/or mineralocorticoid receptor antagonists unless there is a compelling indication	Pre-conceptional counselling is recommended Discuss alternatives to ACE inhibitors and ARBs for women planning pregnancy Changes to antihypertensive therapy should be made when planning pregnancy

continued

Appendix 8.5 *continued*

	QLD 2013	*NICE 2010*	*WHO 2011*
Aspects of care for women with pre-eclampsia			
$MgSO_4$			
Indications	Eclampsia (drug of first choice)	Eclampsia Previous eclampsia in women with severe hypertension or severe PET in a critical care setting Severe PET in a critical care setting when birth is planned within 24 h Severe PET NOTE: features listed: severe hypertension and proteinuria or mild or moderate hypertension and proteinuria with one or more of the following: symptoms of severe headache, problems with vision, such as blurring or flashing before the eyes, severe pain just below the ribs or vomiting, papilloedema, signs of clonus (≥3 beats), liver tenderness, HELLP syndrome, platelet count falling to below 100×10^9/L, abnormal liver enzymes (ALT or AST rising to above 70 IU/L)	Eclampsia (drug of first choice) Severe PET
Dosage		Loading dose: 4 g IV over 5 min Maintenance dose: 1 g/h for 24 h Recurrent seizure dose: 2–4 g IV over 5 min	"Full IV or IM" regimens When full IV or IM regimens cannot be administered, administer loading dose and transfer immediately to a higher level health care facility
Monitoring			
Alternatives to $MgSO_4$		Do NOT use diazepam, phenytoin or lytic cocktail in preference to $MgSO_4$ in women with eclampsia	Do NOT use diazepam, phenytoin or lytic cocktail in preference to $MgSO_4$ in women with eclampsia or severe PET

NVOG 2011	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
Eclampsia (drug of first choice) Severe PET Mild/moderate PET ("can be considered")		Eclampsia (drug of first choice) Severe PET and superimposed PET with severe features, intrapartum and postpartum for severe PET for superimposed PET with severe features NOT routinely for PET with BP <160/110 mmHg and no symptoms Any PET intraoperatively during Caesarean delivery Postpartum, PET with severe hypertension or new-onset hypertension with headaches/ blurred vision	Eclampsia (drug of first choice) "Severe PET" "Non-severe PET" ("can be considered based on cost considerations") Fetal neuroprotection for women with any HDP when imminent preterm birth at $\leq 31^{+6}$ weeks
			Loading dose: "standard dosing", usually 4 mg IV Maintenance dose: "standard dosing", usually 1 g/h
Monitor mothers according to local protocol			Do NOT routinely monitor serum Mg levels
			Do NOT use diazepam or phenytoin in preference to $MgSO_4$ in women with eclampsia or PET

continued

Appendix 8.5 *continued*

	QLD 2013	*NICE 2010*	*WHO 2011*
Plasma volume expansion			
Pre-eclampsia		NOT recommended for women with severe PET (unless hydralazine is the antenatal antihypertensive)	
Therapies for HELLP			
Platelet transfusion			
Corticosteroids		NOT recommended	NOT recommended
Plasma exchange or plasmapheresis			

* SOMANZ 2014 is included in the chapter text, but not in this table adapted from Gillon[187]
ACOG 2013: American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013 Nov; 122(5):1122–1131
AOM 2012: Salehi P, Association of Ontario Midwives HDP CPG, Working Group. Hypertensive disorders of pregnancy (Clinical Practice Guideline 15). 2012; Available: http://www aom on ca/Health_Care_Professionals/Clinical_Practice_Guidelines/
NICE 2010: National Collaborating Centre for Women's and Children's Health (UK). CG107: Hypertension in pregnancy: The management of hypertensive disorders during pregnancy. NICE: Guidance 2010 Aug

NVOG 2011	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
			NOT recommended for women with PET
			Platelet count $<20\times10^9$/L Platelet count 20–49×10^9/L prior to Caesarean Platelet count 20–49×10^9/L prior to vaginal delivery if there is: excessive active bleeding, known platelet dysfunction, a rapidly falling platelet count, or coagulopathy Platelet count $\geq50\times10^9$/L if there is: excessive active bleeding, known platelet dysfunction, a rapidly falling platelet count, or coagulopathy Every obstetrical centre should be aware of the local delay between ordering and receiving platelets units
		NOT recommended to improve clinical outcomes (footnote) Can be considered if improvement in platelet count would be useful (footnote)	NOT recommended
			NOT recommended

NVOG 2011: Nederlandse Vereniging voor Obstetrie en Gynaecologie. Hypertensieve aandoeningen in de zwangerschap. 2011

QLD 2013: Queensland Maternity and Neonatal Clinical, Guidelines Program. Hypertensive disorders of pregnancy. 2013;MN10.13-V4-R15

SOGC 2014: Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. Pregnancy Hypertens 2014;4(2):105–145

WHO 2011: World Health Organization. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. 2011

Appendix 9.1

GRADE evaluation of best practice points regarding timing and mode of delivery

	*Quality of evidence**	*Strength of recommendation†*
Place of delivery		
1. All women with a HDP of any type require delivery in a centre that can provide EmONC	Low	Strong
2. Women with a HDP and serious maternal complications require delivery in a centre capable of providing CEmONC	Low	Strong
Timing of delivery		
Women with pre-eclampsia		
1. Consultation with an obstetrician is advised in women with pre-eclampsia. (If an obstetrician is not available in under-resourced settings, consultation with at least a physician is recommended.)	Low	Strong
2. All women with severe pre-eclampsia as defined by the SOGC should be delivered immediately (either vaginally or by Caesarean), regardless of gestational age‡	Low	Strong
3. For women with non-severe pre-eclampsia at $<24^{+0}$ weeks' gestation, counselling should include information about delivery within days as an option	Low	Weak
4. For women with non-severe pre-eclampsia at 24^{+0}–33^{+6} weeks' gestation, expectant management should be considered, but only in perinatal centres capable of caring for very preterm infants	Moderate	Weak
5. For women with non-severe pre-eclampsia at 34^{+0}–36^{+6} weeks' gestation, expectant management is advised	High	Strong
6. For women with pre-eclampsia at $\geq 37^{+0}$ weeks' gestation, immediate delivery is recommended	High	Strong
7. For women with non-severe pre-eclampsia complicated by HELLP syndrome at 24^{+0}–34^{+6} weeks' gestation, consider delaying delivery long enough to administer antenatal corticosteroids for acceleration of fetal pulmonary maturity if there is temporary improvement in maternal laboratory testing (II-2B)	Low	Weak
8. All women with HELLP syndrome at $\geq 35^{+0}$ weeks' gestation should be considered for delivery within 24 hours	Moderate	Strong
Women with gestational hypertension without pre-eclampsia		
1. For women with gestational hypertension at $<34^{+0}$ weeks, expectant management is advised	Low	Weak
2. For women with gestational hypertension at 34–36^{+6} weeks, expectant management is advised	Low	Weak
3. For women with gestational hypertension at $\geq 37^{+0}$ weeks', childbirth within days should be discussed	Low	Weak

continued

Appendix 9.1 *continued*

	*Quality of evidence**	*Strength of recommendation†*
Timing of delivery		
Women with pre-existing hypertension		
1. For women with pre-existing hypertension at $<34^{+0}$ weeks, expectant management is advised	Low	Weak
2. For women with pre-existing hypertension at $34–36^{+6}$ weeks, expectant management is advised, even if women require antihypertensive therapy	Low	Weak
3. For women with uncomplicated pre-existing hypertension who are otherwise well at $\geq 37^{+0}$ weeks' gestation, delivery should be considered at $38^{+0}–39^{+6}$ weeks' gestation.	Low	Weak
Mode of delivery		
1. For women with any HDP, vaginal delivery should be considered unless a Caesarean delivery is required for the usual obstetric indications	Low	Strong
2. If vaginal delivery is planned and the cervix is unfavourable, then cervical ripening should be used to increase the chance of a successful vaginal delivery	Moderate	Strong
3. At a gestational age remote from term, women with HDP with evidence of fetal compromise may benefit from delivery by emergent Caesarean	Low	Strong
4. Antihypertensive treatment should be continued throughout labour and delivery to maintain sBP at <160 mmHg and dBP at <110 mmHg	Low	Strong
5. The third stage of labour should be actively managed with oxytocin 5 units IV or 10 units IM, particularly in the presence of thrombocytopaenia or coagulopathy	Moderate	Strong
6. Ergometrine maleate should not be administered to women with any HDP, particularly pre-eclampsia or gestational hypertension; alternative oxytocics should be considered	Low	Strong

CEmONC, comprehensive emergency obstetric and neonatal care; BPP, biophysical profile; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; HELLP, haemolysis, elevated liver enzymes, low platelet; HDP, hypertensive disorder of pregnancy

* The judgements about the quality of evidence are based on the confidence that available evidence reflects the true effect of the intervention or service. Evidence is considered to be of high quality when the true effect is thought to lie close to that of the estimate of the effect (e.g., if there are a wide range of studies included in the analyses with no major limitations, there is little variation between studies, and the summary estimate has a narrow confidence interval). Evidence is considered to be of moderate quality when the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different (e.g., if there are only a few studies and some have limitations but not major flaws, there is some variation between studies, or the confidence interval of the summary estimate is wide). Evidence is considered to be of low quality when the true effect may be substantially different from the estimate of the effect (e.g., the studies have major flaws, there is important variation between studies, or the confidence interval of the summary estimate is very wide).

† A strong recommendation should be interpreted as meaning that most people in this situation would want the recommended course of action and only a small number would not. Clinicians should regard the recommendation as applying to most individuals. Policy-makers can adopt the recommendation as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. A weak recommendation should be interpreted as meaning that most people in this situation would want the recommended course of action, but many would not; patients' values and preferences should be considered in reaching a decision. Decision aids may support people in reaching these decisions. Policy-making will require substantial debate and involvement of various stakeholders. An appropriately documented decision making process could be used as a quality indicator.

‡ Severe pre-eclampsia is defined according to Canadian criteria of potentially life-altering complications included within all other definitions of severe pre-eclampsia. There is consensus that these represent indications for delivery: (1) uncontrolled severe maternal hypertension; (2) maternal end-organ complications of the central nervous, cardiorespiratory, haematological, renal, or hepatic systems; or (3) stillbirth or substantial fetal compromise of abruption with maternal/fetal compromise or reversed ductus venosus A wave. Although these conditions are included in the WHO definition of severe pre-eclampsia, WHO also includes other criteria for severe pre-eclampsia that are not clear indications for delivery: heavy proteinuria, gestational age <34 weeks, and evidence of any 'fetal morbidity'.

Appendix 9.2

Timing and mode of delivery according to international clinical practice guidelines*

See next page – this appendix requires a double-page layout

	PRECOG II 2009	*QLD 2013*	*NICE 2010*	*WHO 2011*
Timing of delivery				
General comments			For women with PET at "before 34 weeks", consultant obstetric staff should document maternal and fetal indications for elective birth	
Delivery indicated (indications)			For women with any HDP (regardless of GA) who have refractory severe hypertension after BP has been controlled and a course of antenatal corticosteroids has been completed (if appropriate) For women with PET "before 34 weeks" who have a maternal or fetal indication for delivery (as specified by the care plan), after discussion with neonatal and anaesthetic teams, and after a course of antenatal corticosteroids has been "given" For women with PET "after 37+0 wks" who have mild to moderate hypertension	For women with severe PET before fetal viability (and at a GA at which fetus not viable or unlikely to achieve viability in 1–2 weeks) For women with severe PET "before 34 weeks" or "between 34 and 36 (+6 days) weeks" who cannot be monitored or who have uncontrolled maternal hypertension, increasing maternal organ dysfunction or fetal distress In women with mild GH or mild PET "at term" For women with severe PET "at term"
Expectant care ONLY until steroids have been administered				For women with HELLP syndrome "from fetal viability to $33^{+6/7}$ weeks" with stable maternal and fetal conditions

NVOG 2011	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
For women with any HDP, indications should be based on care provider's own knowledge and experience			For women with "severe PET", consultation must be undertaken (by telephone is necessary) with an obstetrician
For women with severe PET (including HELLP) or any HDP with an abnormal Doppler		For women with severe PET or HELLP syndrome before fetal viability (after maternal stabilisation) for severe PET for HELLP For women with PET or superimposed PET at any GA who have unstable maternal or fetal conditions (after maternal stabilisation) NOTE: Listed were uncontrollable severe hypertension, eclampsia, pulmonary edema, abruption placentae, disseminated intravascular coagulation, non-reassuring fetal status For women with severe PET or HELLP syndrome "≥34 0/7 wks", or superimposed PET with severe features "beyond 34 0/7 wks" (after maternal stabilisation) For women with mild GH or mild PET at "≥37 0/7 wks" who have no severe features	For women with uncomplicated chronic hypertension, consider delivery at $38^{+0/7}$ to $39^{+6/7}$ weeks For women with GH at ≥37 weeks, delivery within days should be discussed For women with PET at $<24^{+0}$ weeks, delivery should be discussed as an option For women with "severe PET" regardless of GA For women with PET at ≥37 weeks For women with HELLP at $≥35^{0}$ wks
			For women with HELLP syndrome at 24^{+0}–34^{+6} weeks If there is temporary improvement in maternal laboratory testing

continued

Appendix 9.2 *continued*

	PRECOG II 2009	*QLD 2013*	*NICE 2010*	*WHO 2011*
Timing of delivery				
Expectant care			For women with PET "until 34 weeks" For women with chronic hypertension at <37 weeks and BP <160/110mmHg For women with GH "before 37 wks" who have BP <160/110 mmHg (even on antihypertensive treatment) For women with PET at 34^{+0} to 36^{+6} weeks who have mild or moderate hypertension, depending on maternal and fetal condition, risk factors and availability of neonatal intensive care	For women with severe PET "before 34 weeks" who have a viable fetus and can be monitored For women with severe PE "between 34 and 36 weeks (+6 days)" who have a viable fetus and can be monitored
Care plan			For women with severe GH or PET, write a care plan that includes: timing and mode of delivery, indications for delivery, timing of antenatal corticosteroids, and when discussion should take place with neonatology and obstetric anaesthesia	
Evidence insufficient to make a recommendation about delivery or expectant care			For women with chronic hypertension at ≥37 weeks and BP <160/110 mmHg ("timing of birth and indications for birth to be agreed upon between woman and specialist") For women with GH "after 37 weeks" who have BP <160/110 mmHg (even on antihypertensive therapy) ("timing of birth, and maternal and fetal indications for birth should be agreed between the woman and the senior obstetrician")	

NVOG 2011	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
		For women with severe PET or severe superimposed PET at $<34^{+0/7}$ weeks who have stable maternal and fetal conditions and who can be monitored at facilities with adequate intensive care resources(Moderate, Strong) for PET For women with superimposed PET "at $<37^{+0/7}$ weeks" who have no severe features and stable maternal and fetal conditions For women with mild GH or PET at "$<37^{+0/7}$ weeks" who have no severe features or indication for delivery, and can be monitored For women with uncomplicated chronic hypertension at <38 weeks For women with PET regardless of the amount or change in proteinuria	For women with non-severe PET at 24^{+0}–33^{+6} weeks, at centres capable of caring for very preterm infants
			For women with non-severe PET at 34^{+0}–36^{+6} weeks For women with GH at <37 weeks

continued

Appendix 9.2 *continued*

	PRECOG II 2009	*QLD 2013*	*NICE 2010*	*WHO 2011*
Labour and delivery				
Intrapartum care			Advice and treatment should be in line with 'Intrapartum care: management and delivery of care to women in labour' (NICE clinical guideline 55), unless it specifically differs from recommendations in this guideline	
BP management			For women with any HDP, continue antihypertensive therapy For women any HDP, monitor BP continuously in women who have severe hypertension, and hourly in women who have non-severe hypertension	
Investigations (for PET)			For women with any HDP and non-severe hypertension, perform haematological and biochemical tests using the same criteria as those used antenatally, whether regional anaesthesia is being considered	
Vaginal or Caesarean delivery		For women with any HDP, Caesarean should be reserved for the usual obstetric indications If vaginal birth is planned and the cervix is unfavourable, cervical ripening is recommended	For women with any HDP and severe hypertenison, severe PET, or eclampsia, choice should be based on clinical circumstances and woman's preference	
Second stage (of labour)			For women with any HDP with severe hypertension whose BP is not meeting treatment targets, recommend operative birth. Otherwise, do NOT limit second stage of labour	
Third stage				

NVOG 2011	*AOM 2012*	*ACOG 2013*	*SOGC 2014*
			For women with any HDP, continue antihypertensive therapy
			For women with PET, platelet count should be done upon admission to delivery suite
		For women with any HDP, Caesarean need not be the mode of delivery, depending on the GA, fetal presentation, cervical status and maternal and fetal conditions	For women with any HDP and evidence of fetal compromise, Caesarean delivery may be beneficial For women with any HDP without fetal compromise, Caesarean should be reserved for the usual obstetric indications If vaginal birth is planned and the cervix is unfavourable, cervical ripening is recommended
	For women with any HDP, active management with oxytocin recommender Ergonovine maleate should NOT be used to prevent/ treat PPH if other suitable uterotonic drugs are available		For women with any HDP, active management with oxytocin (5 units IV or 10 units IM) recommended Ergonovine maleate NOT be used to prevent/treat PPH

continued

Appendix 9.2 *continued*

* SOMANZ 2014 is included in the chapter text, but not in this table adapted from Gillon 2014[80]

ACOG 2013: American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013 Nov; 122(5):1122–1131

AOM 2012: Salehi P, Association of Ontario Midwives HDP CPG, Working Group. Hypertensive disorders of pregnancy (Clinical Practice Guideline 15). 2012; Available: http://www aom on ca/Health_Care_Professionals/Clinical_Practice_Guidelines/

NICE 2010: National Collaborating Centre for Women's and Children's Health (UK). CG107: Hypertension in pregnancy: The management of hypertensive disorders during pregnancy. NICE: Guidance 2010 Aug

NVOG 2011: Nederlandse Vereniging voor Obstetrie en Gynaecologie. Hypertensieve aandoeningen in de zwangerschap. 2011

QLD 2013: Queensland Maternity and Neonatal Clinical, Guidelines Program. Hypertensive disorders of pregnancy. 2013;MN10.13-V4-R15

PRECOG II: Milne F, Redman C, Walker J, Baker P, Black R, Blincowe J et al. Assessing the onset of pre-eclampsia in the hospital day unit: summary of the pre-eclampsia guideline (PRECOG II). BMJ 2009; 339:b3129

SOGC 2014: Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. Pregnancy Hypertens 2014;4(2):105–145

WHO 2011: World Health Organization. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. 2011

Appendix 10.1

Randomised controlled trials (RCTs) of prevention of the hypertensive response to intubation in women with pre-eclampsia

Author	*Study type*	*Population*	*N*	*Methods (n women)*	*Results*	*Other*
Rout & Rocke 1990[54]	RCT	'Severe' pre-eclampsia	40	Alfentanil 10 μg/kg 3 min before induction (N = 20) Fentanyl 2.5 μg/kg 1 min before induction (N = 20) All induced with lidocaine, etomidate 0.3 mg/kg, succinylcholine	Both groups had ↑ HR after intubation. No significant difference MAP before induction and after intubation	9 fentanyl, 8 alfentanil received magnesium 2 alfentanil group had no treatment for hypertension, rest had various anti-hypertensives
Hood *et al.* 1985[57]	RCT	'Severe' pre-eclampsia	19	Nitroglycerin infusion 200 μg/mL (N = 9) Control (N = 10) Induction: thiopental 4 mg/kg, succinylcholine	Maximum HR occurred 2 min after intubation in both groups Nitroglycerin: MAP ↓ 20% before induction – ↑ 2 min after intubation but significantly more in control group	All received magnesium preoperatively No information re anti-hypertensive medication
Ramanathan *et al.* 1988[58]	RCT	'Mild-moderate' pre-eclampsia	25	Labetalol 20 mg – then 10 mg increments to total 1 mg/kg (N = 15) – administered until DBP<100 or MAP ↓ 20% from baseline Control (N = 10) Induced 10 min after BP stabilised Induction: thiopental 4 mg/kg, succinylcholine	Baseline values similar Labetalol ↓ mean MAP & HR before induction After intubation MAP ↑ significantly both groups but significantly > control Mean HR ↑ significantly more in control group	All received magnesium pre-operatively No antihypertensive medication 3 subjects in labetalol group did not achieve BP goals in spite of maximum dose
Allen *et al.* 1991[53]	RCT	'Moderate' (N = 5) to 'severe' (N = 64) pre-eclampsia	69	Lidocaine 1.5 mg/kg (N = 21) Magnesium 40 mg/kg (N = 24) Alfentanil 10 μg/kg (N = 24) Study drug given after induction with thiopental 5 mg/kg. Succinylcholine given after study drug	↑ SBP, dBP, MAP post intubation > lidocaine group compared to other 2 groups	10 subjects did not receive antihypertensive therapy – various antihypertensives used in other 59 – many in combination Some in other groups received magnesium No control group so difficult to determine effect of lidocaine but authors felt should not be used alone

continued

Appendix 10.1 *continued*

Author	*Study Type*	*Population*	*N*	*Methods (n women)*	*Results*	*Other*
Ashton *et al.* 1991[56]	RCT	'Moderate' and severe pre-eclampsia	38	Magnesium 40 mg/kg (N = 19) Magnesium 30 mg/kg + alfentanil 7.5 μg/kg (N = 19) Study drug given after induction with thiopental 5 mg/kg. Succinylcholine given after study drug	sBP, dBP, MAP ↓ after induction both groups No statistically significant ↑ in BP at intubation – better control sBP in magnesium + alfentanil group	Use of antihypertensives same in both groups
Kumar *et al.* 1993[59]	RCT	Pre-eclampsia	30	Nifedipine 10 mg sublingual (15) Control (15) Study drug given 20 min before induction Induction: thiopental 5 mg/kg, succinylcholine	↓ MAP after nifedipine ↑ MAP during laryngoscopy & intubation both groups but more in control	All patients received antihypertensive medication No information re. magnesium
Yoo *et al.* 2009[50]	RCT	'Severe' pre-eclampsia	42	Remifentanil 1 μg/kg (N = 21) Control (N = 21) Study drug given over 30 s immediately before induction Induction: thiopental 4 mg/kg, succinylcholine Also, looked at BIS	Baseline BP & HR similar Arterial BP ↑ significantly after intubation in both groups but was significantly lower in remifentanil group Transient newborn respiratory depression in remifentanil group	All received magnesium pre-operatively Some received hydralazine 2 in remifentanil group required ephedrine for hypotension
Park 2011[51]	RCT	'Severe' pre-eclampsia	48	Remifentanil 0.5 μg/kg (N = 24) Remifentanil 1.0 μg/kg (N = 24) Study drug prior to induction thiopental 5 mg/kg, succinylcholine	Both effectively attenuated haemodynamic response Transient neonatal respiratory depression	3 subjects in 1.0 μg/kg dose had hypotension
Pournajafian *et al.* 2012[52]	RCT	Pre-eclampsia	38	Fentanyl 50 μg (N = 18) Remifentanil infusion 0.05 μg/kg/min for 3 min (N = 20) Induction: thiopental 5 mg/kg, succinylcholine	Fentanyl group: HR, dBP significantly different pre & post intubation Remifentanil: HR ↑, SBP & DBP ↓ after intubation	Authors suggest study favours remifentanil Nothing about severity of pre-eclampsia or use of magnesium or antihypertensives
Yoo 2013[55]	RCT	'Severe' pre-eclampsia	75	Dose study for remifentanil Doses: 0.25, 0.5, 0.75, 1.0, 1.25 μg/kg before induction with thiopental 5 mg/kg + succinylcholine	Baseline sBP and HR similar among groups ↑ HR & BP attenuated dose-dependent manner ED95 was 1.34 μg/kg Majority of newborns required assisted ventilation	Need to have neonatal resuscitation available.

BIS, bispectral index; dBP, diastolic blood pressure; ED, effective dose; HR, heart rate; MAP, mean arterial pressure; RCT, randomised controlled trial; sBP, systolic blood pressure

Appendix 10.2

Anaesthesia for Caesarean delivery in women with pre-eclampsia

See next page – this appendix requires a double-page layout

Author & date	*Study type*	*Study subjects*	*Number*
Wallace 1995[80]	Prospective, randomised	Severe pre-eclampsia	80
Sharwood-Smith 1999[77]	Prospective, randomised	Severe pre-eclampsia	11 S 10 EA
Dyer 2003[81]	Prospective, randomised	Pre-eclampsia	35 S 35 GA
Visalyaputra 2005[76]	Prospective, randomised	Severe pre-eclampsia	47 EA 53 S
Berends 2005[85]	Prospective, randomised	Severe pre-eclampsia Not in labour	Total 30 10 EA 20 CSE
Aya 2003[73]	Prospective cohort	Severe pre-eclampsia	PE (N = 30) Healthy (N = 30) All had S

Methods	*Results*
3 groups – GA (N = 26), EA (N = 27), CSE (N = 27) All received magnesium, intermittent IV hydralazine as needed IV fluid limited to 60 mL/h but did preload GA: IV hydralazine – dBP 100 mmHg preintubation; lidocaine, NTG; RSI: thiopental 4–5 mg/kg, succinylcholine – nitrous oxide, oxygen, isoflurane EA: preload 1000 mL LR; incremental 2% lidocaine or 3% chloroprocaine CSE: preload 1000 mL LR; hyperbaric 0.75% bupivacaine; epidural supplements 3 mL boluses 0.5% bupivacaine Ephedrine 5 mg doses for hypotension S & EA groups	GA: shortest induction to skin incision time (3 min vs. 25–35 min) Hypotension requiring ephedrine similar in CSE and EA BP ↓ significantly over time in all groups IV fluids > EA & CSE groups than GA group Concluded: all techniques acceptable for CS
All required antihypertensive therapy S: 2.75 mL hyperbaric 0.5% bupivacaine EA: 4 mL + 16 mL 0.5% bupivacaine Preload 250 mL LR, otherwise fluids restricted to 80 mL/h + losses Ephedrine – 6 mg increments if hypotension	Poor anaesthesia in EA group Ephedrine use similar
All had non-reassuring FHR trace Severe PE had magnesium sulphate Dihydralazine IV used for BP control GA: Preload <750 mL LR; thiopental 5 mg/kg then 30–45 mg/kg magnesium sulphate to ablate hypertensive response to intubation, followed by succinylcholine; nitrous oxide, oxygen isoflurane S: Preload <750 mL LR; 1.8 mL hyperbaric 0.5% bupivacaine + 10 μg fentanyl	Groups similar at baseline HR, sBP, dBP, MAP significantly lower in S group > umbilical arterial base deficit & lower median umbilical arterial pH in S group More ephedrine used in S group Questioned the clinical significance of this
EA: 18–23 mL 2% lidocaine with epinephrine S: 2.2 mL 0.5% hyperbaric bupivacaine + morphine Hypothesis MAP 10 mm < S group during delivery	Hypotension > S than EA (51% vs. 23%) Duration short both groups More ephedrine in spinal group
Compared EA vs. CSE with 2 prophylactic regimens EA + fluid preload (N = 10) – preload 10 mL/kg RL CSE + fluid preload (N = 10) – preload 10 mL/kg RL CSE prophylactic ephedrine (N = 10) 15 mg ephedrine in 150 mL LR given over 5 min Primary outcome: incidence hypotension	Shorter time induction to surgery both CSE groups 7 EA group needed supplemental analgesics – only 2 CSE groups MAP similar between groups during surgery More ephedrine, < LR in CSE prophylactic ephedrine group No hypertension
All had magnesium After each PE enrolled the next normotensive was the control Preload 1500–2000 mL LR S: hyperbaric 0.5% bupivacaine 8–12 mg + sufentanil/morphine Hypotension treated with ephedrine	PE group – more nulliparas, younger gestational age, less IV fluid, 12 had magnesium, 11 had nicardipine, 2 urapidil, 8 had both magnesium & nicardipine Bupivacaine > PE group; ↓ in dBP, MAP < PE group; ↓ sBP similar both groups Ephedrine 16.6% PE vs. 53.3% control

continued

Appendix 10.2 *continued*

Author & date	*Study type*	*Study subjects*	*Number*
Aya 2005[83]	Case–controlled study	Severe pre-eclampsia Healthy controls	PE 65 Control 71
Tihtonen 2006[75]	Prospective	Pre-eclampsia Healthy	6 severe, 4 mild or moderate PE 10 healthy
Clark 2005[74]	Observational	Normotensive Severe pre-eclampsia	40–20/group
Dyer 2008[65]	Observational	Severe pre-eclampsia	15 S
Hood 1999[78]	Retrospective	Severe pre-eclampsia Not in labour	103 S 35 EA
Chiu 2003[79]	Retrospective	Pre-eclampsia	70 S 51 EA

RCT, randomised controlled trial; GA, general anaesthesia; EA, epidural; CSE, combined spinal-epidural; IV, intravenous; dBP, diastolic BP; NTG, nitroglycerin; RSI, rapid sequence induction; LR, lactated Ringer's; CS, Caesarean delivery; S, spinal; OB, obstetrician; BP, blood pressure; MAP, mean arterial pressure; FHR, fetal heart rate; sBP, systolic BP; CO, cardiac output; HR, heart rate; bpm, beats per minute; SVR, systemic vascular resistance; SVRI, systemic vascular resistance index; SI, stroke index; CI, cardiac index

Methods	*Results*
All subjects were preterm (<35 weeks) patients Consecutive enrollment Pharmacologic treatment of BP before inclusion Nicardipine was 1st line antihypertensive All were on magnesium sulphate Neonatal weight 1100–1900 g Preload 1500–2000 mL LR over 20 min Spinal anaesthesia (8–12 mg hyperbaric bupivacaine, sufentanil, morphine) Primary outcome – 25% difference in hypotension	All had effective anaesthesia PE group: heavier, more nulliparas, 7 had only magnesium, 11 only nicardipine, 18 both drugs Hypotension treated with ephedrine < in PE group Magnitude ↓ sBP, dBP and MAP similar – time to nadir of MAP longer in PE group PE group less ephedrine Risk of hypotension almost 2 times < PE group
PE: 4 received labetalol All had whole-body impedance cardiography S = 2.4–2.7 mL 0.5% hyperbaric bupivacaine Hypotension treated with ephedrine infusion	Baseline: mean MAP and SVRI were significantly ↑ in PE, SI and CI significantly lower in PE S group: SVRI & MAP ↓ Hypotension: 30% PE vs. 80% controls Ephedrine ↑ MAP & SVRI both groups Concluded PE a state of low CO, high SVR. At delivery PE could not increase SI
All spinal anaesthesia: 2.5 mL hyperbaric 0.5% bupivacaine + fentanyl 12.5 μg Preload 250 mL Primary outcome: Difference in ephedrine use of 11 mg with more used in normotensives	All PE subjects were stabilised on antihypertensive drugs before study Mean ephedrine in normotensives 27.9 ± 11.6 mg vs. PE group 16.35 ± 15.0 mg ($p < 0.01$)
All received magnesium sulphate IV-300–500 mL hydroxyethyl starch before IV dihydralazine then crystalloid 120 mL/h Measured cardiac output with LiDCOplus S: co-hydration 10 mL/kg LR; 2.0 mL hyperbaric 0.5% bupivacaine + fentanyl 10 μg Hypotension: 50 μg phenylephrine every minute until within 20% baseline; if MAP ↓ 30% from baseline 100 μg phenylephrine given If CO didn't respond with target MAP then ephedrine 5 or 10 mg was given If HR ↓ <55 bpm + hypotension then 0.5 mg atropine and 10 mg ephedrine were given	All patients were haemodynamically stable Mean baseline SVR was above normal in spite of antihypertensive therapy Mean baseline CO was normal CO changes intraoperatively were clinically insignificant Induction of S was followed by significant ↓ in MAP and SVR Main effect of S was modest afterload reduction 7 did not require phenylephrine before delivery; only 1 required 100 μg before delivery, 7 received 50 μg Of the 8 who had phenylephrine pre-delivery, 4 also required it after delivery 5 required ephedrine pre-delivery
Database reviewed Ephedrine, IV fluids at discretion of anaesthetist Antihypertensive therapy discretion of OB or anaesthetist	EA more likely to receive antihypertensive therapy More IV fluids S group Ephedrine use similar BP ↓ similar both groups
5 year review: Mild, moderate, severe PE Not in labor having CS S = 1.7–2.5 mL 0.5% hyperbaric bupivacaine EA: Incremental boluses 3–10 mL 0.5% bupivacaine with 50–100 μg fentanyl	Labetalol most commonly used antihypertensive, then hydralazine No magnesium in mild or moderate group BP ↓ similarly S and EA Ephedrine use similar EA & S groups & in mild/moderate or severe PE

Appendix 10.3

GRADE evaluation of best practice points for anaesthesia

Recommendation	*Quality of evidence**	*Strength of recommendation†*
1. The anaesthetist should be informed when a woman with pre-eclampsia is admitted to the delivery suite (II-3B).	Low	Strong
2. Women with pre-eclampsia should have a platelet count on admission to the delivery suite. (III-C).	Low	Strong
3. Planning for the care of women with pre-eclampsia should include members of the multi-disciplinary team.	Low	Strong
4. The anaesthetist should assess the woman with pre-eclampsia from the standpoint of possible anaesthetic care and as her status may change, she should be reassessed.	Low	Strong
5. Arterial line insertion may be used for continuous arterial blood pressure monitoring when blood pressure control is difficult or there is severe bleeding. An arterial line also is useful when repetitive blood sampling is required e.g. in women with HELLP syndrome.	Very low	Strong
6. Central venous pressure monitoring is not routinely recommended and, if a central venous catheter is inserted, it should be used to monitor trends and not absolute values.	Very low/ low	Strong
7. Pulmonary artery catheterisation is not recommended unless there is a specific associated indication and then only in an intensive care setting.	Very low	Strong
8. Early insertion of an epidural catheter (in the absence of contraindications) is recommended for control of labour pain.	Moderate/ strong	Strong
9. In the absence of contraindications, all of the following are acceptable methods of anaesthesia for women undergoing Caesarean section: epidural, spinal, continuous spinal, combined spinal epidural and general anaesthesia.	Moderate/ strong	Strong
10. A routine, fixed intravenous fluid bolus should not be administered prior to neuraxial anaesthesia.	Low	Strong
11. Neuraxial analgesia and/or anaesthesia are appropriate in women with any hypertensive disorder of pregnancy provided there are no associated coagulation concerns (Table 6.6) or other specific contraindications.	Very low	Weak

continued

Appendix 10.3 *continued*

aPTT, activated partial thromboplastin time; ASA, aspirin; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; HELLP, Haemolysis, Elevated Liver enzyme, Low Platelet syndrome; LMWH, low-molecular weight heparin; UFH, unfractionated heparin

* The judgements about the quality of evidence is based on the confidence that available evidence reflects the true effect of the intervention or service. Evidence is considered to be of *high quality* when the true effect is thought to lie close to that of the estimate of the effect (e.g., if there is a wide range of studies included in the analyses with no major limitations, there is little variation between studies, and the summary estimate has a narrow confidence interval). Evidence is considered to be of *moderate quality* when the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different (e.g., if there are only a few studies and some have limitations but not major flaws, there is some variation between studies, or the confidence interval of the summary estimate is wide). Evidence is considered to be of *low quality* when the true effect may be substantially different from the estimate of the effect (e.g., the studies have major flaws, there is important variation between studies, or the confidence interval of the summary estimate is very wide).

† A *strong recommendation* should be interpreted as meaning that most people in this situation would want the recommended course of action and only a small number would not. Clinicians should regard the recommendation as applying to most individuals. Policy-makers can adopt the recommendation as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. A *weak recommendation* should be interpreted as meaning that most people in this situation would want the recommended course of action, but many would not; patients' values and preferences should be considered in reaching a decision. Decision aids may support people in reaching these decisions. Policy-making will require substantial debate and involvement of various stakeholders. An appropriately documented decision making process could be used as a quality indicator.

Appendix 10.4

Recommendations for anaesthesia from international guidelines[127]

	PRECOG II 2009	*QLD 2013*	*NICE 2010*	*WHO 2011*	*NVOG 2011*
General principles					

AOM 2012	*ACOG 2013*	*SOGC 2014*
	For women with PET, neuraxial analgesia or anaesthesia (spinal or epidural) is recommended (Moderate, Strong)	For women with PET who are admitted to delivery suite, the anaesthesiologist should be informed (Low, Strong)
		Early insertion of an epidural catheter for analgesia is recommended (Moderate, Strong)
		Acceptable methods of anaesthesia include epidural, spinal, combined spinal-epidural and general anaesthesia (Moderate, Strong)
		For women with any HDP, neuraxial analgesia and/or anaesthesia are appropriate:
		a) With PET, provided there are no associated coagulation concerns. (Low, Strong);
		b) With a platelet count $\geq 75 \times 10^9$/L (Very low, Weak);
		c) Taking low-dose ASA in the presence of an adequate platelet count. (Moderate/High, Strong);
		d) Receiving UFH in a dose of ≤10,000 IU/d subcutaneously, 4 h after the last dose and possibly IV after the last dose without any delay (Very low, Weak);
		e) Receiving UFH in a dose of 10,000 IU/d subcutaneously if they have a normal aPTT 4 h after the last dose (Very low, Weak);
		f) Receiving IV heparin in a therapeutic dose if they have a normal aPTT 4 h after the last dose (Very low, Weak); or
		g) Receiving low-molecular weight heparin (LMWH) a minimum of 10–12 h after a prophylactic dose, or 24 h after a therapeutic dose (Very low, Weak)
		For women with any HDP, phenylephrine or ephedrine may be used to treat hypotension during neuraxial anaesthesia (Moderate, Strong)

continued

Appendix 10.4 *continued*

	PRECOG II 2009	*QLD 2013*	*NICE 2010*	*WHO 2011*	*NVOG 2011*
General principles					
Fluid administration (including management of oliguria)			For women with severe PET, do NOT administer a fixed IV fluid bolus routinely prior to neuraxial analgesia For women with severe PET, limit ongoing fluid administration to 80 mL/h (unless ongoing fluid losses)		
Treatment of oliguria					
Anesthesia – monitoring					
Invasive haemodynamic monitoring					

ACOG, American College of Obstetricians and Gynecologists; ASA, aspirin; BP, blood pressure; GA, gestational age; GH, gestational hypertension; BPP, good practice point; HDP, hypertensive disorders of pregnancy; HELLP, haemolysis, elevated liver enzyme, low platelet syndrome; LMWH, low molecular weight heparin; $MgSO_4$, magnesium sulphate; NICE, National Institute for Health and Clinical Excellence; NVOG, Nederlandse Vereniging voor Obstetrie en Gynaecologie; PET, pre-eclampsia; PRECOG, pre-eclampsia community guideline; QLD, Queensland Maternity and Neonatal Clinical Guidelines Program; SOGC, Society of Obstetricians and Gynaecologists of Canada; UFH, unfractionated heparin; WHO, World Health Organization

ACOG 2013: American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013 Nov; 122(5):1122–1131

AOM 2012: Salehi P, Association of Ontario Midwives HDP CPG, Working Group. Hypertensive disorders of pregnancy (Clinical Practice Guideline 15). 2012; Available: http://www aom on ca/Health_Care_Professionals/Clinical_Practice_Guidelines/

AOM 2012	*ACOG 2013*	*SOGC 2014*
		For women with any HDP, do NOT administer a fixed IV fluid bolus routinely prior to neuraxial anaesthesia (Low, Strong)
		For women with PET, minimize iv and oral fluid intake (Low, Strong)
		For women with any HDP, do NOT routinely administer fluid to treat oligura (<15 mL/h for 6 consecutive hours) (Very low, Weak)
		For women with any HDP, do NOT treat oliguria with dopamine or furosemide (Moderate, Strong)
	For women with severe PET, do NOT routinely use invasive haemodynamic monitoring (Low, Qualified)	For women with any HDP, do NOT routinely use central venous pressure monitoring (Very low/Low, Strong)
		If a central venous monitoring is used, trends (and not absolute values) should be monitored (Very low/Low, Strong)
		For women with any HDP, an arterial line may be used when BP is difficult to control or there is severe bleeding (Very low, Strong)
		For women with any HDP, pulmonary artery catheterisation is NOT recommended unless there is a specific indication (Very low, Strong)
		If used, a pulmonary catheter should be used only in a critical care setting (Very low, Strong)

NICE 2010: National Collaborating Centre for Women's and Children's Health (UK). CG107: Hypertension in pregnancy: The management of hypertensive disorders during pregnancy. NICE: Guidance 2010 Aug
NVOG 2011: Nederlandse Vereniging voor Obstetrie en Gynaecologie. Hypertensieve aandoeningen in de zwangerschap. 2011
QLD 2013: Queensland Maternity and Neonatal Clinical, Guidelines Program. Hypertensive disorders of pregnancy. 2013;MN10.13-V4-R15
PRECOG II: Milne F, Redman C, Walker J, Baker P, Black R, Blincowe J et al. Assessing the onset of pre-eclampsia in the hospital day unit: summary of the pre-eclampsia guideline (PRECOG II). BMJ 2009; 339:b3129
SOGC 2014: Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. Pregnancy Hypertens 2014;4(2):105–145
WHO 2011: World Health Organization. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. 2011

Appendix 11.1

Training material for health care providers

MULTIPLE CHOICE QUESTIONS

1. When does blood pressure reach its peak during the postpartum period?
   a. Immediately after delivery
   b. Within the first 24 hours after delivery
   c. Days 3–6 postpartum
   d. Within 14 days postpartum
   e. Blood pressure remains the same throughout the postpartum period

2. Which of the following are acceptable antihypertensive choices during breastfeeding?
   a. Enalapril
   b. Labetalol
   c. Nifedipine
   d. Methyldopa
   e. All of the above

3. Of the following groups of women, which one has the highest risk for premature cardiovascular disease?
   a. A woman who develops gestational hypertension
   b. A woman who develops pre-eclampsia at 36 weeks' gestational age
   c. A woman who develops severe pre-eclampsia at 38 weeks' gestational age
   d. A woman who develops mild pre-eclampsia at 38 weeks' gestational age
   e. A woman with pre-existing hypertension who does not develop a hypertensive disorder of pregnancy

4. In which of the following scenarios, should a woman who developed pre-eclampsia be investigated for underlying renal disease?
   a. Persistent proteinuria at 6 months postpartum
   b. Urine analysis persistently showing leukocytes
   c. Hypertension at 4 weeks requiring 2 agents
   d. Ongoing hypertension at 6 weeks postpartum
   e. Delivery at 37 weeks' gestational age

5. In the postpartum cardiovascular evaluation of a woman with a history of pre-eclampsia, which of the following should be undertaken:
   a. Screening for traditional cardiovascular risk factors
   b. Counselling about a heart-healthy lifestyle
   c. Treating blood pressure, dyslipidaemia and blood sugar according to locally accepted guidelines
   d. Discussion about postpartum weight loss
   e. All of the above

Answers

1) c 2) e 3) b 4)a 5) e

CASE STUDY

A 34 year-old G1P1 previously healthy woman developed pre-eclampsia at 33 weeks' gestation. She developed severe hypertension, elevated liver enzymes and proteinuria with a protein to creatinine ratio of 257. She is now 3 months postpartum and has been referred for evaluation of ongoing postpartum hypertension. Her blood pressure is 135/85 mmHg on labetalol 200 mg TID.

1. The patient has been having difficulty taking antihypertensives three times a day and asks about other options that are dosed once daily and acceptable in breastfeeding.

Adalat and Enapril are two antihypertensives that are dosed daily and are acceptable in breastfeeding.

2. What would prompt you to screen this patient for underlying renal disease?

This patient should be screened for renal disease given that she developed severe pre-eclampsia and delivered before 34 weeks. Other factors that should prompt evaluation for underlying renal disease include proteinuria that persists beyond 3–6 months postpartum, glomerular filtration rate (GFR) <60 or abnormal urinary sediment.

3. How would you confirm that end organ dysfunction related to pre-eclampsia has resolved?

The patient had three manifestations of end organ dysfunction: hypertension, proteinuria and elevated liver enzymes. In women with severe pre-eclampsia, blood pressure may take about 3–6 months to resolves. Liver enzymes should normalise by 6 weeks. Proteinuria should resolve by 3–6 months postpartum and can be evaluated using albumin to creatinine ratio (ACR).

4. What are the long-term risks of pre-eclampsia?

Pre-eclampsia is associated with a number of long-term risks. These include cardiovascular disease (hypertension, ischaemic heart disease, stroke), end stage renal disease and diabetes.

5. What is her risk of developing ischaemic heart disease in the future?

Women who develop early onset pre-eclampsia are at the greatest risk of developing ischaemic heart disease in the future. The risk is almost 8 times higher than in women who developed pre-eclampsia after 37 weeks. She is at risk of developing premature disease as disease occurred as early as 12 years after the index pregnancy.

6. When should be screened and how should she be managed?

There are no specific guidelines for timing and type of screening for this group of high risk women. She should be screened for traditional cardiovascular risk factors according to local guidelines. There is also no evidence to suggest preventive therapies at an earlier age than usual. However, a heart-healthy lifestyle should be prescribed, as we know that there is evidence for lifestyle intervention for the prevention of cardiovascular disease. The postpartum period provides a unique window of opportunity to begin this important discussion.

Appendix 11.2

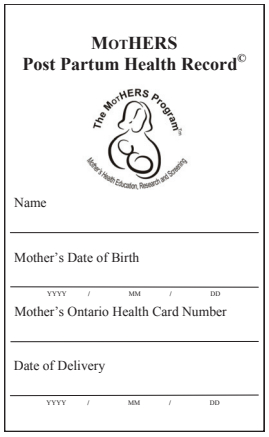
Knowledge translation tools

Patient resources

HH4M (Heart Health 4 Moms): a research study, designed for women with a recent pregnancy complicated by pre-eclampsia, to learn more about the best ways o reduce their risk of heart disease. [http://www.hh4m.org/]

Pre-eclampsia Registry: the first patient registry to focus on the HDPs and bring together those affected, their family members, and researchers to advance knowledge, and discover preventative approaches and treatments for the HDPs. Affected women can share their health and pregnancy histories and pose research questions. [http://preeclampsiaregistry.org/]

The Postpartum Mother's Health Record (see below): a record for the mother's use where the collection of information coincides with the baby's scheduled visits and immunisations. The card can help mothers to set goals and keep track of weight loss. [http://www.themothersprogram.ca/after-delivery/postpartum-health/maternal-health-clinic]


MOTHERS
Post Partum Health Record©
Name
Mother's Date of Birth
YYYY / MM / DD
Mother's Ontario Health Card Number
Date of Delivery
YYYY / MM / DD

Maternelle: an obstetrician-designed mobile application that focuses on the health of new mothers and their babies. Women can track weight, activity level, blood pressure and breast feeding. [http://www.mothersprogram.ca/apps/maternelle]

Virtual Care Program: online interactive health communication portal that will help women take control and manage their heart disease risk factors. This web-based platform will give women the latest medical information and lifestyle advice. It will encourage women to share information and experiences and help them navigate the spectrum of medical care for various aspects of heart disease. [http://cwhhc.ottawaheart.ca/changing-things/care]

Women@Heart Program: a peer support programme led by women with heart disease, for women with heart disease that aims to create a caring environment for women to learn from each other. The Women@Heart Program provides women with heart disease, with access to emotional support, educational support and a caring environment for a better recovery after a cardiac event. [http://cwhhc.ottawaheart.ca/changing-things/care]

Health care providers

The Maternal Health Follow Up Form: a form to record postpartum information and calculate a woman's lifetime risk for heart disease and stroke in order to help them improve their patients' long-term health. [http://www.themothersprogram.ca/after-delivery/postpartum-health/maternal-health-clinic]

The Postpartum Maternal Health Clinic Handbook: the handbook provides guidance on how to set up a postpartum cardiovascular health clinic. It provides information on the day-to-day management of the clinic including documents and the protocol followed by the Maternal Health Clinic at Kingston General Hospital. [http://www.themothersprogram.ca/after-delivery/postpartum-health/postpartum-maternal-health-clinic-handbook]

Appendix 11.3

GRADE evaluation of best practice points for postpartum care

	*Quality of evidence**	*Strength of recommendation†*
Care in the 6 weeks after birth		
1. Blood pressure should be measured during the time of peak postpartum blood pressure, at days 3–6 after delivery.	Low	Strong
2. Women with postpartum hypertension should be evaluated for pre-eclampsia (either arising de novo or worsening from the antenatal period).	Low	Weak
3. Antihypertensive therapy may be continued postpartum, particularly in women with antenatal pre-eclampsia and those who delivered preterm.	Low	Weak
4. Severe postpartum hypertension must be treated with antihypertensive therapy, to keep systolic blood pressure <160 mmHg and diastolic blood pressure <110 mmHg.	Moderate	Strong
5. Antihypertensive therapy may be used to treat non-severe postpartum hypertension, to keep blood pressure at <140/90 mmHg for all but women with pre-gestational diabetes mellitus among whom the target should be <130/80 mmHg.	Very low	Weak
6. Antihypertensive agents acceptable for use in breastfeeding include nifedipine XL (slow-release), labetalol, methyldopa, captopril and enalapril.	Moderate	Weak
7. There should be confirmation that end-organ dysfunction of pre-eclampsia has resolved.	Very low	Strong
8. Non-steroidal anti-inflammatory drugs should not be given postpartum if hypertension is difficult to control, there is evidence of kidney injury (oliguria and/or an elevated creatinine) (≥90 μmol/L) or platelets are $<50 \times 10^9$/L.	Low	Weak
9. Postpartum thromboprophylaxis should be considered in women with pre-eclampsia who have other risk factors for thromboembolism.	Low	Weak
Care beyond the first 6 weeks after birth		
1. Women with a history of severe pre-eclampsia (particularly those who presented or delivered at <34 weeks) should be screened for pre-existing hypertension and underlying renal disease.	Low	Weak
2. Referral for internal medicine or nephrology consultation should be considered for women with postpartum hypertension that is difficult to control, or women who had pre-eclampsia and have at 3–6 months postpartum ongoing proteinuria, decreased eGFR (<60 mL/min), or another indication of renal disease (such as abnormal urinary sediment).	Low	Weak
3. Women who are overweight should be encouraged to attain a healthy body mass index to decrease risk in future and for long-term health.	Low/ moderate	Strong
4. Women with pre-existing hypertension or persistent postpartum hypertension should undergo the following investigations (if not done previously): urinalysis; serum sodium, potassium and creatinine; fasting glucose; fasting lipid profile; and standard 12-lead electrocardiography.	Low	Weak

continued

Appendix 11.3 *continued*

	*Quality of evidence**	*Strength of recommendation†*
Care beyond the first 6 weeks after birth		
5. Women who are normotensive but who have had a hypertensive disorder of pregnancy, may benefit from assessment of traditional cardiovascular risk markers.	Low/ moderate	Weak
6. All women who have had a hypertensive disorder of pregnancy should pursue a healthy diet and lifestyle.	Low	Strong

eGFR, estimated glomerular filtration rate

* The judgements about the quality of evidence is based on the confidence that available evidence reflects the true effect of the intervention or service. Evidence is considered to be of *high quality* when the true effect is thought to lie close to that of the estimate of the effect (e.g., if there is a wide range of studies included in the analyses with no major limitations, there is little variation between studies, and the summary estimate has a narrow confidence interval). Evidence is considered to be of *moderate quality* when the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different (e.g., if there are only a few studies and some have limitations but not major flaws, there is some variation between studies, or the confidence interval of the summary estimate is wide). Evidence is considered to be of *low quality* when the true effect may be substantially different from the estimate of the effect (e.g., the studies have major flaws, there is important variation between studies, or the confidence interval of the summary estimate is very wide)

† A *strong recommendation* should be interpreted as meaning that most people in this situation would want the recommended course of action and only a small number would not. Clinicians should regard the recommendation as applying to most individuals. Policy-makers can adopt the recommendation as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. A *weak recommendation* should be interpreted as meaning that most people in this situation would want the recommended course of action, but many would not; patients' values and preferences should be considered in reaching a decision. Decision aids may support people in reaching these decisions. Policy-making will require substantial debate and involvement of various stakeholders. An appropriately documented decision making process could be used as a quality indicator

Appendix 11.4

Postnatal care care – Policy brief

Postnatal care (PNC) is considered to be an essential intervention for reducing maternal mortality. In LMICs, almost 40% of women experience complications after delivery and in 15% of women, those complications are life-threatening. A 2013 WHO systematic analysis of the causes of maternal deaths (2003–09) determined that 480,000 or 19.7% of maternal deaths worldwide occurred postpartum. Most of those deaths occur in the first week postpartum.

Postpartum care has the potential to optimise future pregnancy outcomes and the long-term health of the mother. PNC affords the opportunity to counsel women about birth spacing and contraception. Also, the HDPs, and pre-eclampsia in particular, are associated with an increase in many adverse maternal health conditions, including hypertension, heart disease, stroke, renal disease, and diabetes mellitus. Postpartum care offers care providers the opportunity to educate women about these risks as well as changes in diet, lifestyle, and medical management that may modify them.

Postnatal period remains the most neglected period for provision of critical care for mothers and babies. In low-income countries, an estimated 70% of women do not receive any postnatal care.

Literature suggests that in sub Saharan Africa, 15.2% maternal deaths occurred in the postnatal period.

ACTIONS

Advancing PNC policy and implementing evidence-based programmatic changes in the national and state level health policies is crucial to improving access to care and reducing maternal mortality and morbidity.

- **Increase demand** for PNC care by engagement with women and communities
- **Engage relevant stakeholders** at the community and state levels in order to establish leadership for integration of a PNC package at the community level
- Develop a **local PNC package** adapted that includes all of the STRONG recommendations from the WHO 2013 Postnatal Care guidelines' recommendations (see Table S11.1 below), as follows:
  - PNC care beginning within 24 h of birth, consisting of at least three visits, and occurring ideally at home
  - Exclusive breastfeeding
  - Assessments of the mother that include physical and mental health evaluations, as well as targeted approaches for family planning needs. Providers need to be trained about the mental health implications of the HDPs, such as anxiety, depression, and post-traumatic stress disorder
- Engage **traditional birth attendants** in delivery of PNC

Table S11.1 Recommendations graded as STRONG in the WHO Postnatal Care Guidelines 2013[95]

Nature of recommendation	*Details*
Postnatal contact	
	Timing (as early as possible within 24 h)
	Number (3 visits)
	Place (home visits are recommended)
Exclusive breastfeeding of baby	
	Maternal counselling to encourage and support
Maternal assessment	
Physical	
Within 24 h of birth	*Starting shortly after birth and taken again at 6 h:* Blood pressure
	Starting from the first hour after birth and continuing routinely during the first 24 h: Assessment for vaginal bleeding, uterine contraction, fundal height, temperature and heart rate (pulse) routinely during the first 24 hours
Beyond 24 h of birth	*Ongoing assessment of:* general symptoms (headache, fatigue, back pain); uterine tenderness and lochia; voiding (i.e., micturition and urinary incontinence, bowel function); healing of any perineal wound, perineal pain, and perineal hygiene; breast pain and breastfeeding progress
	Counselling of mother on: warning signs and symptoms of PPH, infection, and pre-eclampsia/eclampsia; good nutrition, hygiene, especially hand washing; birth spacing and family planning; gentle exercise, iron and folic acid supplementation
Mental health	Emotional well-being
Psychosocial support	For women who have lost her baby
	Accounting for experiences in hospital

Appendix 11.5

Recommendations for partartum care of women with hypertensive disorders of pregnancy from international clinical guidelines*

	QLD	*NICE 2010*	*WHO 2011*
BP monitoring		For women with chronic hypertension or GH, measure BP daily for first 2 days, once/day on days 3–5, and as indicated if antihypertensive therapy is changed For women with PET, measure BP 4x/day in hospital, once/day on days 3–5, and if abnormal then, on alternate days (until normal) In women with PET who took antihypertensive therapy, measure BP 4x/day in hospital, then every 1–2 days for 2 weeks until off treatment and normotensive	
PET may appear or worsen	For women with pre-eclampsia, serial surveillance of maternal well-being is recommended	For women with severe PET, ask about severe headache and epigastric pain when BP is measured For women with PET with non-severe hypertension or those who have received critical care, measuring creatinine transaminases within 48–72 h If creatinine and transaminases are normal at 48–72 h after birth, they do NOT need to be retested For women with PET, repeat platelet count, transaminases and serum creatinine "as clinically indicated" and at the 6–8 weeks postnatal review For women with PET who have stepped down from critical care (level 2), do NOT measure fluid balance if creatinine is normal	
Continuation of antenatal antihypertensive therapy		For women with chronic hypertension, continue antenatal antihypertensive therapy In women with GH or PET who were taking antenatal antihypertensive therapy, continue therapy If methyldopa was the antenatal antihypertensive, stop it within 2 days of birth. For women with chronic hypertension, restart the antihypertensive agent that was taken before planning pregnancy	For women with any HDP, continue antenatal antihypertensive therapy
Treatment of severe hypertension		For women with any HDP, treat severe hypertension	For women with any HDP, treat severe hypertension with antihypertensive drugs

AOM 2012	*ACOG 2013*	*SOGC 2014*
Inform women with any HDP that elevated BP may take time to resolve Inform women with GH that hypertension may worsen "during the postpartum period"	For women with GH, PET, or superimposed PET, measure BP in hospital (or equivalent setting) for ≥72 h and at some point on days 7–10 or earlier if PET symptoms occur	For women with any HDP, measure BP at some point on days 3–6 postpartum
Inform women with any HDP to report any symptoms or signs of PET	Inform women with any HDP about symptoms and signs of PET which they should report immediately if they arise	Women with new/worsening postpartum hypertension should be evaluated for PET For women with PET, there should be confirmation that end-organ dysfunction has resolved
		For women with any HDP, especially with PET or preterm delivery, continue antihypertensive therapy
	For women with any HDP, treat severe hypertension (BP ≥160/110 mmHg) within 1 hour	For women with any HDP, treat severe hypertension with antihypertensive drugs For women with any HDP, goal of <160/110 mmHg

continued

Appendix 11.5 *continued*

QLD	*NICE 2010*	*WHO 2011*
Treatment of non-severe hypertension	For women with "chronic hypertension", goal of <140/90 mmHg In women with GH or PET goal of <150/100 mmHg In women with GH or PET consider a reduced dose if BP <140/90 mmHg. Reduce the dose if BP is <130/80 mmHg	
Antihypertensive agents and breastfeeding	Acceptable agents are nifedipine, labetalol, captopril, enalapril, atenolol and metoprolol Do NOT prescribe diuretics to women who are breastfeeding or expressing milk Insufficient evidence to comment on the neonatal safety of the following during breastfeeding: ACE inhibitors (other than enalapril and captopril), ARBs and amlodipine	
Discharge planning for community care	For women with chronic hypertension, review long-term antihypertensive treatment 2 weeks after the birth Offer women with PET transfer to community care if they have no symptoms, BP <150/100 mmHg, and laboratory abnormalities are stable/improving For women with GH or PET, write a detailed care plan before transfer to community care A care plan should include the following details: who will provide follow-up care, including medical review if needed, frequency of BP monitoring needed, thresholds for reducing or stopping treatment, indications for referral to primary care for BP review, and self-monitoring for symptoms	
At midwifery visits between discharge and formal 6–8 weeks postnatal review	Offer medical review (with the pre-pregnancy team) at the 6–8 weeks postnatal review for women with chronic hypertension Offer medical review at the 6–8 weeks postnatal review for women with GH or PET, especially if they are still on antihypertensive treatment 2 weeks after transfer to community care	
Formal medical postnatal review at 6–8 weeks after delivery	In women with PET, perform urinary reagent-strip testing. If proteinuria ≥1+, offer further review at 3 months postpartum If women with PET had improving but still abnormal haematological or biochemical indices at hospital discharge, repeat testing For women with PET, do NOT routinely perform thrombophilia screening	

AOM 2012	*ACOG 2013*	*SOGC 2014*
	For women with any HDP goal of <150/100 mmHg	For women with uncomplicated chronic hypertension, consider goal of <140/90 mmHg For women with chronic hypertension and comorbidities other than pre-gestational diabetes mellitus, consider goal of <140/90 mmHg For women with chronic hypertension and pre-gestational diabetes mellitus, goal of <130/80 mmHg
		Acceptable agents are nifedipine XL, labetalol, captopril and enalapril, and methyldopa For women with any HDP postpartum, captopril, enalapril or quinapril may be used
For women with any HDP, monitor BP at "all regular postpartum visits" in first 2 weeks postpartum, or until normal BP measured twice For women with any HDP who has an elevated BP upon discharge from hospital, ensure plan is in place for physician follow-up in the event that BP remains elevated (or increases further) Upon discharge from midwifery care, communicate information about any HDP to the primary care provider		For women with PET, there should be confirmation that end-organ dysfunction has resolved
		For women with chronic hypertension or any HDP with persistent postpartum hypertension, perform the following (if not done previously): urinalysis, serum Na/K and creatinine, fasting glucose and lipid profile and standard ECG recommended For women with severe PET (particularly with presentation at <34 weeks), screen for chronic hypertension and underlying renal disease) For women with any HDP, consider screening for traditional cardiovascular risk markers

continued

Appendix 11.5 *continued*

	QLD	*NICE 2010*	*WHO 2011*
Counselling about future pregnancy risks	For women with any HDP, offer preconceptual advice		
Counselling about long-term health risks	For women with any HDP, offer "screening" and lifestyle counselling	Advise women with GH or PET (and their primary care physicians) that they are at increased risk of future hypertension and cardiovascular disease in later life Advise women with PET with proteinuria (that has resolved) that they are still at increased risk kidney disease but the absolute risk is very low and follow-up is not necessary Advise women with PET to keep their BMI within healthy range (18.5–24.8 kg/m^2, NICE clinical guideline 43)	
Specialist referral (e.g., renal, etc.)		Hypertension specialist – for women with GH or PET who still need antihypertensive therapy 6–8 weeks after delivery Kidney specialist – for women with PET who have proteinuria ≥1+ at 6–8 weeks after delivery (although clinicians can reassess at 3 months post-delivery to confirm)	
NSAIDs			
Thromboprophylaxis			

* SOMANZ 2014 is included in the chapter text, but not in this table adapted from Gillon 2014[98]. PRECOG II (2009) and NVOG (2011) did not provide postpartum guidance and are not included in this table

ACOG 2013: American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013 Nov; 122(5):1122–1131

AOM 2012: Salehi P, Association of Ontario Midwives HDP CPG, Working Group. Hypertensive disorders of pregnancy (Clinical Practice Guideline 15). 2012; Available: http://www aom on ca/Health_Care_Professionals/Clinical_Practice_Guidelines/

AOM 2012	*ACOG 2013*	*SOGC 2014*
		Advise women with any HDP to keep their BMI within healthy range to decrease risk in future pregnancy
Advise women with any HDP that they may be at increased risk of future hypertension and cardiovascular disease in later life Advise women with any HDP of the benefits of a heart healthy diet and lifestyle	For women with PET and preterm birth (<37 0/7 weeks) or recurrent PET, consider yearly assessment of BP, lipids, fasting blood glucose and BMI	Advise women with any HDP to pursue a healthy diet and lifestyle Advise women with any HDP to keep their BMI within healthy range for long-term health
		Offer in hospital specialist assessment with internal medicine – for women with any HDP when postpartum hypertension is difficult to control Offer outpatient renal assessment – for women who had PET who have proteinuiria, decreased eGFR (<60 mL/min) or another indication of renal disease at 3–6 months after delivery
For women with any HDP, limit use of NSAIDs and offer acetaminophen as an effective alternative (albeit with limited information about side-effects)		For women with any HDP, NSAIDs are NOT recommended if BP is difficult to control, there is kidney injury (oliguria and/or an elevated creatinine) (≥90 μM), or platelets are $<50 \times 10^9$/L
		Consider for women with PET, especially when there are other risk factors

NICE 2010: National Collaborating Centre for Women's and Children's Health (UK). CG107: Hypertension in pregnancy: The management of hypertensive disorders during pregnancy. NICE: Guidance 2010 Aug
QLD 2013: Queensland Maternity and Neonatal Clinical, Guidelines Program. Hypertensive disorders of pregnancy. 2013;MN10.13-V4-R15
SOGC 2014: Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. Pregnancy Hypertens 2014;4(2):105–145
WHO 2011: World Health Organization. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. 2011

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