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Original Article

Intrahepatic cholestasis of pregnancy: Is a screening for differential diagnoses necessary?

Agathe Donet[a], Aude Girault[a,b], Anne Pinton[a,*], Jacques Lepercq[a]

[a] Port-Royal Maternity Unit, Department of Obstetrics, Cochin Broca Hôtel-Dieu Hospital, Assistance Publique-Hôpitaux de Paris, France
[b] INSERM UMR 1153, Obstetrical, Perinatal and Paediatric Epidemiology Research Team (Epopé), Centre for Epidemiology and Statistics Sorbonne Paris Cité (CRESS), DHU Risks in Pregnancy, Paris Descartes University, Paris, France

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ABSTRACT

Objective: To evaluate the benefit of performing a screening for differential diagnoses by hepatobiliary ultrasound and viral serologies, in case of suspected intrahepatic cholestasis of pregnancy (ICP).
Methods: Retrospective single-center study in a tertiary maternity unit, including all women with a suspected ICP between January 2012 and September 2018. The primary outcome was the differential diagnosis rate obtained through initial screening. We described women characteristics, symptoms, and blood results that led to ICP suspicion. We evaluated the rate of differential diagnosis established by the initial screening. We described the population of women presenting with an ICP differential diagnosis.
Results: The study included 254 women. Prevalence of differential diagnosis was 2 %. ICP was suspected in more than 50 % of cases in third trimester of pregnancy (79.5 %). Women presented with pruritus in 90.9 % of cases. Bile acid levels were between 20 and 40 μmol/L in 56.3 % of cases and above 40 μmol/L in 12.2 % of cases. The screening to rule out differential diagnosis of ICP was performed in half of the cases. When performed, the screening did not lead to the diagnosis of any differential disease.
Conclusion: In this cohort, among the 254 women, one (0.4 %) would have been wrongly diagnosed with ICP if the initial screening for differential diagnosis had not been performed. Screening for differential diagnosis does not seem to provide any benefit regarding the management of suspected ICP and could therefore only be performed in case of atypical clinical presentation of ICP, resistance to treatment or persisting abnormal liver function tests in the postpartum period.

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is the most frequent hepatic disease occurring during pregnancy [1]. It is defined by the association of a pruritus and an unexplained elevation in liver enzymes and/or bile acid concentrations (>10 μmol/L), resolving after delivery [2]. This disease occurs in 0.3–2 % of pregnancies depending on women's geographic origin [2]. In France, its prevalence during pregnancy is known to be between 0.5 and 0.8 % [3].

The etiology if ICP is multifactorial (hormonal, genetic and environmental factors) and may be related to hormonal factors like estrogens [2–5]. This could explain why this disease occurs more frequently during the last trimester of pregnancy, when the estrogen production is the highest and disappears quickly in the postpartum period. Also family history and ethnic factors in women with ICP suggest a genetic susceptibility. Recent studies have identified mutations of genes involved in bile canaliculus secretion, in particular heterozygous mutations of the ABCB4 gene (also called multidrug resistance protein 3). Several studies have shown mutations in the coding region of ABCB4 in 10 % of the women with ICP [6–8].

The risk of developing an ICP increases with age, parity and multiple pregnancy [9]. Fetal prognosis is related to the risks of preterm birth, stillbirth [10–12] and meconial liquid inhalation [3]. In case of ICP diagnosis, a urso-deoxycholic acid (UDCA) treatment is recommended as it has shown to reduce pruritus, improve hepatic tests, and probably decrease the preterm birth risk [3,13]. However, recent studies, including Chapell et al.'s study, do not show a significative reduction of neonatal mortality in women treated with UDCA [14].

ICP remains a diagnosis of exclusion, which is only suspected after having ruled out other diseases such as dermatologic pruritus (allergic drug reactions, pruritic urticarial papules of pregnancy, eczema, xerosis, pemphigoid gestationis), liver

* Corresponding author.

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diseases (viral and autoimmune hepatitis) and biliary tract obstruction.

Other liver diseases occur in less than 1% of the pregnancies but can produce the same symptoms than ICP [15]. Indeed, a cholestatic syndrome associating pruritus and jaundice can be caused by a biliary tract obstruction or an infectious liver disease. Elevated liver enzymes can also be seen in vascular pathologies such as pre-eclampsia or HELLP syndrome, but pruritus is not present in these situations.

In 2011, the Royal College of Obstetricians and Gynaecologists produced guidelines for the diagnosis and management of ICP. They recommended to sought other causes of pruritus and elevated liver enzymes by performing blood tests to rule out: hepatitis A, hepatitis B, hepatitis C, Cytomegalovirus (CMV), Epstein Barr Virus (EBV), autoimmune hepatitis, primitive biliary cirrhosis, and pre-eclampsia [16]. Other guidelines were published in 2011 by the Society for Maternal and Fetal Medicine and in 2016 by the American College of Gastroenterology and are inconsistent on which tests to perform for differential diagnoses in case of suspected ICP [17–19]. In France, no guidelines have yet been published concerning the diagnosis of ICP. Therefore, there are wide discrepancies in the performed tests for suspected ICP and to our knowledge no assessment of the benefits to women of performing these tests.

The main objective was to evaluate the benefit of performing a screening for differential diagnoses: hepatobiliary ultrasound (biliary tract disorders) and viral serologies (viral hepatitis), by evaluating the number of women who would have been wrongly treated for ICP if the screening had not been performed. The secondary objective of this study was to identify the characteristics of women with differential diagnosis of ICP.

Materials and methods

We performed a retrospective single-center study including all women with a suspected ICP in a tertiary maternity unit in Paris, between January 2012 and September 2018. Women were identified using maternity unit data base, DIAMM® by searching for the following key words: “hepatitis”, “cholestasis”, “liver disease”, “hepatopathy”, “elevated liver enzymes”. Data were collected by reviewing all the paper medical file.

ICP was suspected if women presented with a pruritus during pregnancy associated with abnormal liver function tests (LFT) and/or elevated bile acid concentrations (>10 μmol/L). An ICP could be suspected after multidisciplinary discussion, if the women did not present with pruritus but had abnormal LFT and/or elevated bile acid concentrations (>10 μmol/L). The certainty diagnosis was made only after pregnancy when the clinical and biological abnormalities resolved.

In case of suspicion of ICP, the maternity unit guidelines are the following:

- Performance of an initial screening for differential diagnosis by hepatobiliary ultrasound and viral serologies: hepatitis A, hepatitis B, hepatitis C, hepatitis D, CMV, Herpes Simplex Virus (HSV) and EBV.
- Initiation of an UDCA treatment associated with an antihistaminic treatment in case of disabling pruritus.
- In case of treatment resistance: performance of other blood tests to rule out autoimmune hepatitis.
- When ICP is suspected women are hospitalized until pruritus has diminished and the LFT have improved [20].
- If ICP is suspected at or after 37 weeks, induction of labor was initiated with no treatment of ICP.

The following variables were collected: maternal age, geographic origin, body mass index (kg/m^2), medical history (viral hepatitis, autoimmune hepatitis), and obstetric characteristics, (gravidity, parity, assisted reproductive technology, number of fetuses, gestational hypertension, pre-eclampsia, gestational diabetes). Data on suspicion of ICP were also collected: gestational age at suspicion, blood tests results at suspicion (bile acid, liver enzymes, and bilirubinemia), type of screening for differential diagnosis and results.

The primary outcome was the differential diagnosis rate obtained through initial screening.

First, we described women characteristics, symptoms, and blood results that had led to ICP suspicion. Then, we evaluated the rate of differential diagnosis established by the initial screening. Finally, we described the population of women presenting with an ICP differential diagnosis.

In order to evaluate the number of women to include, we assumed that with the initial screening carried out the certainty diagnosis was made in 90 % of the case. By admitting a delta of 5 % of non-diagnosis in the absence of initial screening, with a prevalence of 1 % of differential diagnosis [21] a 80 % power, and an alpha-risk of 0.05 %, a sample of 253 women suspected of ICP was needed.

This study was approved by the National Data Protection Authority (Commission Nationale de l’Informatique et des Libertés, CNIL n° 1755849). Under French regulations, this study is exempt from IRB review because it is an observational study using anonymized data from medical records. Women are informed that their records can be used for the evaluation of medical practices and are provided the option to opt out of these studies

Results

Two hundred and sixty-five women with suspected ICP were identified in the maternity unit data base during the study period. A total of 254 women were included after exclusion of 11 missing medical file. Among the women who gave birth at the maternity unit during the study period, the prevalence of suspected ICP was 0.7 %.

The maternal characteristics of women with suspected ICP are shown in Table 1. More than half of the women were nulliparous (59.4 %). A history of ICP was found in 39.8 % of multiparous women. In 77.2 % of the ICP cases the pregnancy was singleton. No

Table 1
Preexisting and obstetric characteristics of women with suspected intrahepatic cholestasis of pregnancy, n = 254.

	Women with suspected ICP n = 254 n(%)
Nulliparity	151 (**59.4**)
History of ICP in a previous pregnancy	41 (**39.8**)
Assisted reproductive technology use	56 (**22.0**)
Stimulation of ovulation	9 (**16.1**)
Intra uterine insemination	4 (**7.1**)
In vitro fertilization	25 (**44.6**)
Egg donation	18 (**32.1**)
Type of pregnancy	
Singleton pregnancy	196 (**77.2**)
Twin pregnancy	53 (**20.9**)
Triplet pregnancy	5 (**2.0**)
Pregnancy disorders	
Gestational diabetes	46 (**18.1**)
Gestational hypertension	8 (**3.1**)
Preeclampsia	16 (**6.3**)
Severe preeclampsia	7 (**2.8**)

ICP: intrahepatic cholestasis of pregnancy.

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Table 2
Clinical features and biochemical abnormalities at suspicion of intrahepatic cholestasis of pregnancy, n = 254.

	Women with suspected ICP n = 254 n(%)
Mode of suspicion of ICP	
Symptomatic	231 (**90.9**)
Incidental finding	20 (**7.9**)
Symptoms at suspicion of ICP	
Pruritus	231 (**90.9**)
Pruritus and clinical jaundice	2 (**0.8**)
Clinical jaundice	0 (**0.0**)
Asymptomatic	18 (**7.1**)
Gestational age at suspicion, weeks	
<22	7 (**2.8**)
22–27,6	12 (**4.7**)
28–31,6	33 (**13.0**)
32–36,6	131 (**51.8**)
≥37	70 (**27.7**)
Hospitalization during pregnancy	
No hospitalization	53 (**20.9**)
Hospitalization	201 (**79.1**)
Length of stay (days, mean ± DS)	4.2 ± 3.7
Biochemical measurements	
Serum bile acids (μmol/L)	
<10	16 (**6.3**)
10–20	64 (**25.2**)
20–40	143 (**56.3**)
>40	31 (**12.2**)
AST (times the upper limit of normal(N))	
<3 N	177 (**69.7**)
3 N–6N	33 (**13.0**)
>6N	13 (**5.1**)
ALT (times the upper limit of normal(N))	
<3 N	158 (**62.2**)
3 N–6N	61 (**24.0**)
>6N	32 (**12.6**)
Total bilirubin (mg/L)	
0–30	223 (**87.8**)
>30	3 (**1.2**)

ICP: intrahepatic cholestasis of pregnancy; AST: aspartate transaminase; ALT: alanine transaminase.

family history of ICP or others liver diseases were found in our cohort.

ICP was suspected in more than 80 % of cases in the third trimester of pregnancy with 51.8 % of cases between 32 and 36 weeks (Table 2). Women presented with pruritus in 90.9 % of cases. Bile acid levels were between 20 and 40 μmol/L in 56.3 % of cases and above 40 μmol/L in 12.2 % of cases. Moderate elevation of liver enzymes (less than 3 times normal) was observed in more than 60 % of cases, and bilirubinemia was normal in more than 85 % of cases (Table 2).

Additional screening to rule out differential diagnosis of cholestasis was performed in half of the cases (Table 3). One hundred and thirty-three women (52.4 %) had a hepatobiliary ultrasound. It was strictly normal in 78.9 % of cases. An incidental finding anomaly such as uncomplicated vesicular lithiasis or moderate hepatomegaly, which did not explain the cholestasis was found in 26.7 % of cases. One hundred and thirty-six women (53.5 %) underwent blood tests for other differential diagnosis (Table 3). These included viral serologies (hepatitis A virus, hepatitis B virus, hepatitis C virus, and hepatitis D virus) in 97.8 % of cases and CMV, HSV, and EBV serologies in 75.7 %, 61 %, and 52.2 % of cases, respectively. A screening for autoimmune hepatitis was performed in 8.1 % of cases.

No differential diagnosis was detected with the viral serologies or hepatobiliary ultrasound.

In our cohort, five women had an underlying disease known before pregnancy and causing the ICP symptoms (2 %) : two (0.8 %) had an active viral hepatitis C, two (0.8 %) a primary sclerosing cholangitis and one a pemphigoid gestationis (0.4 %). The women with chronic active hepatitis C had both an early onset of cholestasis (19 and 20 weeks), marked by an important generalized pruritus and moderate elevated bile acid levels (18 μmol/L and 28 μmol/L, respectively) without elevation of liver enzymes. Hepatobiliary ultrasound was subnormal in both cases. The women with primary sclerosing cholangitis presented with generalized pruritus and elevated bile acid levels (above 100 μmol/L) in the third trimester of pregnancy (30 weeks and 32 weeks).

Drugs, mainly anti-hypertensive, anticoagulant or antiplatelet, tocolytic, antibiotic, or endocrinological (insulin, L-thyroxin) treatments were introduced during pregnancy in 33.9 % of the cases. None of them had a demonstrated hepatotoxicity [22].

In the postpartum period, a LFT was performed in all women and was normal or subnormal but improving, in all except one case. In this one case, a diagnosis of acute cholecystitis was made at day 13 postpartum. This woman had an ICP suspicion at 36.5 weeks and the screening did not include a hepatobiliary ultrasound. Therefore, in our cohort, one woman of the 254 (0.4 %) was wrongly diagnosed with ICP. The five women with an underlying disease (primary sclerosing cholangitis, active viral hepatitis C, and pregnant pemphigoid) had normal LFT in the postpartum period.

Discussion

In the absence of initial screening for differential diagnosis, one woman, out of the 254 (0.4 %) women with suspected ICP would have been wrongly diagnosed with ICP. Indeed, one differential diagnosis, obstructed biliary tract, was not made in our cohort. The woman had not had the complete screening, as she did not have a hepatobiliary ultrasound.

Our study was performed in a tertiary center where the number of high-risk pregnancies is important. Thus, our sample concerns

Table 3
Screening for differential diagnoses at suspicion of intrahepatic cholestasis of pregnancy, n = 254.

	Women with suspected ICP n(%)
Hepatobiliary ultrasound performed in the cohort (n = 133 (52.4 %))	
Normal	105 (**78.9**)
Incidental finding anomaly	28 (**26.7**)
Uncomplicated vesicular lithiasis	12 (**42.9**)
Bile duct dilation	1 (**3.6**)
Biological tests performed in the cohort (n = 136 (53.5 %))	
Hepatitis serologies	133 (**97.8**)
CMV serology	103 (**75.7**)
EBV serology	71 (**52.2**)
HSV serology	83 (**61.0**)
Autoimmune tests	11 (**8.1**)

ICP: intrahepatic cholestasis of pregnancy; CMV: cytomegalovirus; EBV: Epstein-Barr virus; HSV: herpes simplex virus.

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Table 4
Clinical elements for differential diagnosis of confounding diseases [15,18].

	Clinical elements						
	Pruritus	Hyper thermia	Hyper algesia	Jaundice	Skin lesions	High blood pressure	Resolving after delivery
Pregnancy specific diseases							
Pemphigoid gestationis	X				X		X
Pruritic urticarial papules and plaques of pregnancy (PUPP)	X				X		X
Preeclampsia						X	X
Acute fatty liver of pregnancy	X						X
Non pregnancy specific diseases							
Viral hepatitis	X			X			
Alcoholic hepatitis	X			X			
Obstructive cholelithiasis	X	X	X	X			
Primary biliary cirrhosis	X			X			
Primary sclerosing cholangitis	X			X			
Renal disease	X						
Hematologic disease	X					X	

women with high risks of developing an ICP and of having differential diagnosis of ICP. Our large sample of women with suspected ICP, allows us to answer our objective as it matches the prior to study calculation. However, this study is retrospective and single-centered which limits its external validity. Although meticulous recording of data on the paper medical files, the exhaustivity issue needs to be addressed. Indeed, a selection bias cannot be excluded as the identification of women with suspicion of ICP depended on the coding in the medical software. However, the key words used for identifying women with suspected ICP were broad: “hepatitis”, “cholestasis”, “liver disease”, “hepatopathy”, “elevated liver enzymes” and each paper medical record of the identify women was read limiting this bias. Moreover, the ICP rate is consistent with that in literature [3].

We found that the initial screening for differential diagnosis was not systematically carried out unlike what is notified in the unit’s protocol. This could have biased our sample by underestimating the number of differential diagnoses, nevertheless, these diagnoses would have been made in the postpartum period which was not the case in this study. Two hypotheses may explain this finding. First, most women of the cohort had a reassuring clinico-biological presentation: pruritus without associated jaundice, moderately elevated LFT, and normal bilirubinemia. Second, in 90 % of women with incomplete initial screening, labor was induced within 3 days of the ICP suspicion (109 women out of 121).

This study suggests that the initial screening for differential diagnosis does not modify women management, when carried out in a population of women with suspected ICP. When hepatobiliary ultrasound was performed, it was normal in 78.9 % of cases, and found irrelevant abnormalities in 21.1 % of cases. Interestingly, a previous study showed that biliary lithiasis were more frequent in women with ICP compared with an age-matched control population [9]. In cases of suspected ICP, the objective of ultrasound is to rule out biliary tract obstruction requiring emergency surgical procedures. However, in most cases, women requiring these procedures present with a clinical presentation contrasting with the of ICP: abdominal pain, hyperthermia or marked jaundice. In the case of the woman diagnosed with acute cholecystitis at day 13 postpartum, it should be noted that these signs were not present before delivery or in the first days postpartum. We therefore can assume that a pre-partum biliary lithiasis migration was complicated by acute cholecystitis in the postpartum period. Hepatobiliary ultrasound at the time of suspicion of ICP may not have changed the woman’s management.

Prevalence of underlying disease associated with ICP in our cohort was 2 %. These results are consistent with literature [15].

To this date, there is no French guidelines concerning the initial screening in case of suspicion of ICP. The English and Western Australian guidelines suggest screening for differential diagnosis by performing viral serologies, and other blood test to rule out auto-immune hepatitis and preeclampsia, in women suspected with ICP [16,23]. The American College and the Western Australia guidelines recommend performing an ultrasound to exclude hepatobiliary diseases [18,23]. But the European Association for the study of the liver does not recommend any type of tests [24].

This study allows us to suggest a new diagnostic strategy for women with suspected ICP, in order to standardize medical practices and optimize the time to treatment. ICP diagnosis could be discussed after clinical evaluation and ruling out of preeclampsia and pruritus gestationis, and could be based on the association of pruritus with abnormal LFT and increase in bile acid levels (>10 μmol/L) with normal platelets after 24 weeks. Additional investigations such as hepatobiliary ultrasound, viral serologies, screening for auto-immune hepatitis and ACBC4 (ATP binding cassette subfamily B member 4) genetic mutation could be performed only for women with atypical clinical presentation (hyperalgesia, hyperthermia, jaundice) (Table 4) and/or in case of resistance to treatment and/or a persistence of signs after childbirth. ABCB4 mutation was not tested in this study as it is not recommended in our center. It is known that approximately 10 % of women with ICP have a mutated ABCB4 allele [6,7] and could reveal a Low Phospholipid-Associated Cholelithiasis. The search for this mutation is therefore relevant in case of atypical ICP presentations in order to discuss ursodesoxycholic acid continuation after delivery.

Conclusion

In this cohort, one woman would have been wrongly diagnosed with ICP if the initial screening for differential diagnosis had not been performed. These results support the need of regularly evaluating protocols, in particular when they are applied in only 50 % of the cases. Screening for differential diagnosis could only be performed in case of atypical clinical presentation of ICP, resistance to treatment or persisting abnormal LFT in the postpartum period.

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Declaration of Competing Interest

The authors report no declarations of interest.

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