High Rates of Persistent and Recurrent Chlamydia in Pregnant Women after Treatment with Azithromycin

Article *in* American Journal of Obstetrics & Gynecology MFM · August 2020

DOI: 10.1016/j.ajogmf.2020.100216

6 authors, including:

Jodie A. Dionne-Odom
University of Alabama at Birmingham
72 PUBLICATIONS **397** CITATIONS
SEE PROFILE

William Geisler
University of Alabama at Birmingham
112 PUBLICATIONS **1,601** CITATIONS
SEE PROFILE

High rates of persistent and recurrent chlamydia in pregnant women after treatment with azithromycin

Jodie Dionne-Odom, MD, MSPH; Akila Subramaniam, MD, MPH; Kristal J. Aaron, DrPH, MPH; William M. Geisler, MD, MPH; Alan T. N. Tita, MD, PhD; Jeanne Marrazzo, MD, MPH

BACKGROUND: *Chlamydia trachomatis* is a common bacterial sexually transmitted infection that can persist or recur after antibiotic treatment. Universal screening for chlamydia in pregnancy is recommended to prevent adverse birth outcomes. Single-dose oral azithromycin has been the first-line therapy for chlamydia in pregnancy since 2006.

OBJECTIVE: In the setting of limited data and rising sexually transmitted infection rates in the United States, our goal was to document rates and risk factors for persistent or recurrent chlamydia after azithromycin treatment in pregnancy.

STUDY DESIGN: This retrospective cohort study included pregnancies with urogenital chlamydia and follow-up testing in women who delivered at an Alabama facility between November 2012 and December 2017. Pregnancies with prescribed azithromycin therapy and repeat chlamydia testing ≥21 days later were included. *Chlamydia trachomatis* nucleic acid amplification testing was performed on genital swab or urine samples. Descriptive characteristics and birth outcomes were compared for categories stratified by repeat test results: persistence (+ +), recurrence (+ − +), or clearance (+ −). Logistic regression models were used to identify demographic and clinical risk factors for persistent or recurrent chlamydia in pregnancy.

RESULTS: Among 810 women with 840 pregnancies with repeat chlamydia testing after azithromycin treatment, 114 (14%) had persistence and an additional 72 (9%) had recurrence later in pregnancy. The median time to repeat testing was 30 days (interquartile range, 24—49 days). Concomitant gonorrhea or syphilis in pregnancy was independently associated with persistent or recurrent chlamydia (adjusted odds ratio, 1.6; 95% confidence interval, 1.1—2.4).

CONCLUSION: Persistent or recurrent chlamydia after azithromycin treatment was detected in nearly 1 in 4 pregnancies with repeat testing in our urban center, highlighting the importance of performing a test of cure and ensuring partner therapy to reduce recurrent chlamydia risk.

Key words: azithromycin, *Chlamydia trachomatis*, infection in pregnancy, recurrent chlamydia

Introduction

Chlamydia trachomatis is an intracellular bacterium that causes cervical infection. More than 1.1 million cases of chlamydia in women were reported to the US Centers for Disease Control and Prevention (CDC) in 2018.[1] Women between the ages of 15 and 24 years and women who reside in the southeastern United States, where the case rate is 744 cases per 100,000 persons, are disproportionally affected by chlamydia.[1−4] Untreated chlamydia in pregnancy has been associated with preterm delivery and low birthweight (LBW) infants.[5−9] Infection in women is usually asymptomatic, and timely screening and treatment in pregnancy can prevent adverse outcomes.[10] Despite rising chlamydia rates in the US, few studies focus on chlamydia treatment outcomes after azithromycin therapy in pregnant women.[1,11]

The American College of Obstetricians and Gynecologists (ACOG) has recommended universal screening for chlamydia in pregnancy since 2007.[12] CDC recommends performing a test of cure for pregnant women with chlamydia at least 21 days after treatment and repeat testing 12 weeks later to screen for reinfection.[13,14] In an observational study from a commercial laboratory database in the United States (2005−2008), 59% of pregnant women had chlamydia testing and 3.5% had a positive result. Among women with chlamydia who underwent repeated testing, 6% had repeat positivity during pregnancy but treatment data were not available.[12] Recurrent chlamydia in nonpregnant women is well documented: a systematic review suggested a 14% recurrence rate during follow-up periods ranging from 2 months to 13 years.[15] Younger age (<26 years) and bacterial sexually transmitted infection (STI) coinfection have been associated with recurrent chlamydia in nonpregnant women.[16−19]

Chlamydia infection that recurs after antibiotic treatment and clearance (defined by a negative test) usually represents reinfection from a sexual partner. The mechanism for repeatedly positive chlamydia testing is more varied. It may represent recurrent infection (after undocumented clearance), false-positive polymerase chain reaction test result owing to residual DNA/RNA, or treatment failure.[16] Unlike gonococcal infection, antimicrobial resistant chlamydial infection is rare.[20−22] Single-dose oral azithromycin (1 g) is the CDC-recommended treatment for chlamydia in pregnancy.[23] Azithromycin has a favorable safety profile in pregnancy, and it is one of the most commonly prescribed antibiotic agents worldwide.[24] Recent reports suggest that clinical treatment failure can occur with azithromycin treatment for rectal chlamydia and nonresponse to azithromycin for urogenital chlamydia in pregnancy has been reported.[21,25−27]

Cite this article as: Dionne-Odom J, Subramaniam A, Aaron KJ, et al. High rates of persistent and recurrent chlamydia in pregnant women after treatment with azithromycin. Am J Obstet Gynecol MFM 2020;XX:x.ex−x.ex.

2589-9333

https://doi.org/10.1016/j.ajogmf.2020.100216

AJOG MFM at a Glance

Why was this study conducted?

The study was conducted to assess azithromycin treatment outcomes for chlamydia infection in pregnancy in the midst of rising sexually transmitted infection rates in the United States.

Key findings

Persistent and recurrent chlamydia infection in pregnancy occurred in more than 1 in 5 women who were prescribed azithromycin in our urban academic center.

What does this add to what is known?

The clinical implication of our study findings is that medication adherence and follow-up chlamydia testing after treatment should be ensured.

In this study, we sought to document rates of persistent or recurrent urogenital chlamydia among pregnant women who were prescribed with azithromycin and retested for chlamydia at least 21 days later and to identify risk factors for persistence or recurrence.

Methods

Study design and population

This retrospective cohort study included pregnancies in women who delivered at the University of Alabama at Birmingham (UAB) between November 1, 2012 and December 31, 2017. UAB serves as a primary care facility and a regional referral center with more than 4000 deliveries each year. Women with positive urogenital *C trachomatis* nucleic acid amplification (NAAT) testing, documented azithromycin prescription according to pharmacy records, and repeat chlamydia testing $\geq$ 21 days later were included. Data were extracted from the electronic medical record, and laboratory data were queried to identify pregnancies with chlamydia testing according to inclusion criteria. Once the cohort was identified, associated variables and birth outcomes were also queried. The standard clinical practice at UAB was to order a chlamydia test of cure $\geq$21 days after therapy with repeat chlamydia testing in the third trimester. There were no electronic reminders for repeat testing. Antibiotic treatment was recommended for sexual partners through referral to the local county health department sexually transmitted disease clinic.

Study outcomes

For study outcomes, persistence (group 1) was defined by positive *C trachomatis* NAAT results on follow-up testing performed in pregnancy (+ + or + + +). Recurrence (group 2) was an incident infection defined by negative NAAT results on the first follow-up test followed by a positive NAAT result (+ − +). Clearance (group 3) was defined by negative NAAT results on all follow-up testing in pregnancy (+ − or + − −). Frequent prenatal visits with multiple testing opportunities allowed us to categorize persistence or recurrence separately but many studies of repeated chlamydia infection use a combined outcome of persistent and recurrent infection outcome owing to variable follow-up periods and limited treatment data. For our association model, we used the combined outcome of persistent and recurrent infection given the sample size and for the sake of comparison with previous studies. Birth outcomes included preterm delivery (<37 weeks' gestation), LBW (<2500 g), and intrauterine fetal demise (IUFD) or stillbirth.

Study demographics included age, race, ethnicity, marital status, medical insurance, urban residence (Jefferson County), and year of delivery. Other variables included gestational age at the time of the initial positive test, time in days between the initial positive test and repeat testing, location of testing, and date of azithromycin prescription.[16] HIV/STI coinfection in pregnancy was defined according to the results of gonorrhea NAAT testing on urogenital samples, syphilis serology with confirmatory testing, and HIV antibody screening with confirmatory testing. The timing of gonorrhea or syphilis coinfection during pregnancy in relation to the timing of the initial positive chlamydia test was collected.

Chlamydia diagnostic testing

All testing during the study period used the highly sensitive *C trachomatis* NAAT on urogenital samples. The UAB Obstetrics and Gynecology Diagnostic Laboratory tested outpatient samples using Roche Amplicor (Roche Diagnostics, Indianapolis, IN) in 2011−2012, and Roche COBAS 4800 in 2013−2017. The main UAB laboratory tested samples collected in the emergency room and inpatient setting using BD Viper (BD Diagnostic Systems, Sparks, MD) in 2011−2014 and Hologic Aptima (Hologic, San Diego, CA) in 2014−2017. The sensitivity of various NAAT tests performed for *C trachomatis* in this study ranges from 90% to 98% with specificity of >99% and similar performance characteristics for all sample sites (vaginal, cervical, and urine).[28−31]

Statistical analysis

Characteristics of pregnancies stratified by the chlamydia outcome group were compared using chi-squared test, Fisher exact test, or Kruskal-Wallis test, as indicated. Statistical significance was defined as $P<.05$. Continuous variables were compared using the Wilcoxon rank-sum test. Adverse birth outcomes were compared by group. Given the minimal missing data (<2%), a complete case analysis was performed.

The rate of persistence or recurrence was calculated as the proportion of pregnancies with each outcome among all pregnancies with at least 1 repeat test $\geq$21 days after azithromycin treatment. Logistic regression was used to model risk factors for the combined outcome of persistence or recurrence, and generalized estimating equations was used to account for the few women with 2 births during the study period. Variables that were significant in the univariate model

($P<.1$) or associated with recurrence in previous studies were included in the multivariable (MV) model. In sensitivity analyses, models with shortened testing windows (60 days and 180 days after therapy) and only 2 chlamydia tests in pregnancy were created. Statistical analysis was conducted with SAS v 9.4 (SAS Institute Inc, Cary, NC).

Ethics

The study was approved by the UAB Institutional Review Board with a waiver for informed consent.

Results

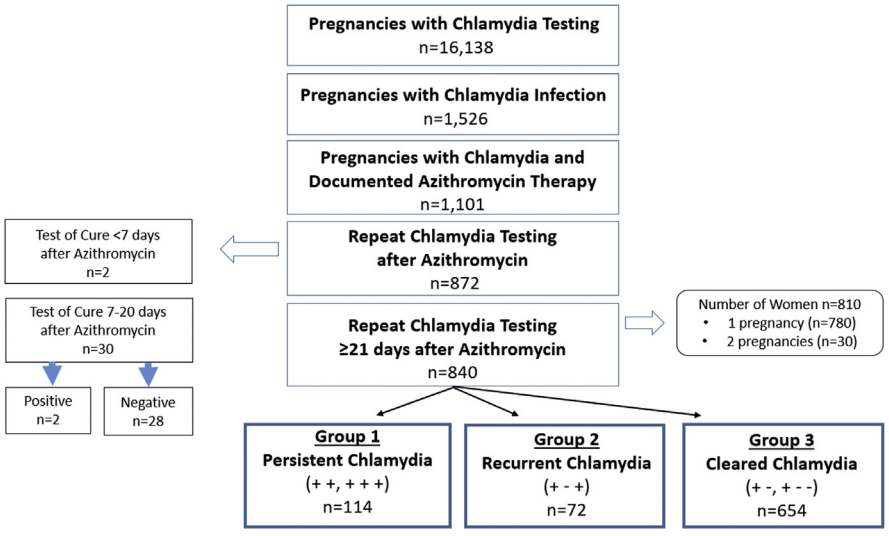
There were 16,138 pregnancies among 13,692 women with urogenital chlamydia NAAT testing performed at our center between November 1, 2012 and December 31, 2017. The overall testing rate for chlamydia in pregnancy at the UAB laboratory was 77% because women were referred to UAB for pregnancy complications after chlamydia testing had been performed at an outside laboratory. Among those who were tested, 9.5% of pregnancies (1526 of 16,138) had a positive result and 1101 (72%) had documented azithromycin therapy. A total of 872 (79%) had repeat chlamydia testing, and 840 pregnancies (in 810 women) comprised the final study cohort with retesting at least 21 days after azithromycin treatment. Pregnancies were categorized into 3 groups according to follow-up test results: persistence (n=114 of 840; 13.6%), recurrence (n=72 of 840; 8.6%), and clearance (n=654 of 840; 77.9%). Among 709 pregnancies with at least 3 chlamydia tests, the outcome categories were similar: persistence, 14.1%; recurrence, 10.2%; and clearance, 75.7%. When the testing window was limited to repeat testing at 21 to 60 days, a similar proportion (13%; 91 of 717) had persistence. Most early tests of cure performed 7 to 20 days after treatment had a negative result (30 of 32; 94%) (Figure 1). No time trends in terms of persistent or recurrent infection during the 5-year study period were noted.

Baseline characteristics according to the treatment outcome group are presented in Table 1. The 3 groups were similar overall. Median age was 21 years, 84% of women were black, 83% had public insurance, and 96% were urban residents of Jefferson County, AL. Most of the initial positive chlamydia testing was from samples collected in the clinic (87%) during the first trimester (53%). Repeat chlamydia testing was performed a median of 30 days after azithromycin treatment (range, 21–211 days). Most (85%) repeat testing occurred within 60 days of treatment. Pregnancies with persistent infection had later repeat testing (median, 37 days) compared with recurrent infection (28 days) or cleared infection groups (30 days; $P<.01$). On chart review, reasons for delayed chlamydia repeat testing included documented clearance before 21 days, missed testing opportunities in the clinic, and patient loss to follow-up. Most pregnancies (82%) had at least 3 chlamydia tests performed; those with persistence or recurrence were tested more frequently than the group with clearance ($P<.001$).

Of note, 19% (22 of 114) of pregnancies in group 1 had a prolonged duration of persistence (≥90 days), with a median of 4 chlamydia tests performed (range, 3–6 tests) and >1 course of treatment prescribed (range, 1–6 courses). Among the 100 women with persistent positivity and ≥3 tests, 88 (88%) had clearance and 12 (12%) had persistent positivity without documented clearance. Coinfection with gonorrhea or syphilis during pregnancy was more common in groups with persistent or recurrent chlamydia than cleared infection ($P=.02$). Among 127 gonococcal infections in pregnancy, 6 (5%) were diagnosed before the initial positive chlamydia test, 99 (78%) had coinfections with chlamydia, and 22 (17%) were diagnosed afterwards. All 7 syphilis infections were diagnosed after the initial positive chlamydia test. Only 1 woman with HIV was included. She had good virologic control and had been diagnosed as having HIV before pregnancy. She was in the group with recurrent chlamydia.

Adverse birth outcomes according to the chlamydia outcome group are presented in Figure 2. Rates of preterm delivery (14%), LBW (13%), and IUFD (2%) were higher in the persistent chlamydia group than the other groups although differences were not statistically significant (preterm delivery, $P=.08$; LBW and IUFD, $P=.41$). These rates are slightly higher than the 2019 state average for Alabama (preterm delivery, 12%; LBW, 10%).[32] In 2018, preterm delivery rates in both Jefferson County and the state of Alabama were

FIGURE 1
Study flow diagram



Dionne-Odom et al. Persistent and recurrent chlamydia in pregnancy after treatment. AJOG MFM 2020.

TABLE 1
Characteristics according to CT treatment outcomes after azithromycin (n = 840)

Characteristic	Persistence (group 1) (n=114)	Recurrence (group 2) (n=72)	Clearance (group 3) (n=654)	*P* value
Demographics				
Age, y	21.6 (5.0)	20.9 (4.0)	21.6 (5.4)	.08
Age categories, y				.11
13–24	90 (79.0)	64 (88.9)	499 (76.3)	
25–29	21 (18.4)	5 (6.9)	111 (17.0)	
30–39	3 (2.6)	3 (4.2)	43 (6.6)	
≥40	0 (0)	0 (0)	1 (0.2)	
Race				.10
Black	99 (86.8)	67 (93.1)	537 (82.1)	
White	6 (5.3)	1 (1.4)	56 (8.6)	
Other/declined to provide	9 (7.9)	4 (5.6)	61 (9.3)	
Hispanic ethnicity	5 (4.4)	3 (4.2)	37 (5.7)	.97
Single marital status	107 (93.9)	70 (97.2)	593 (90.7)	.11
Insurance				.27
Public	95 (83.3)	65 (90.3)	538 (82.3)	
Private	10 (8.8)	6 (8.3)	62 (9.5)	
Uninsured	9 (7.9)	1 (1.4)	54 (8.3)	
Year of delivery				.67
2011–2014	35 (30.7)	26 (36.1)	203 (31.0)	
2015–2017	79 (69.3)	46 (63.9)	451 (69.0)	
STI testing and treatment in pregnancyrowhead				
Timing of initial CT+ test, wk				.03
0–13	60 (52.6)	48 (66.7)	339 (51.8)	
14–27	42 (37.8)	22 (30.6)	225 (34.4)	
≥28	12 (10.8)	2 (2.8)	90 (13.8)	
Location of initial CT+ test				.80
Outpatient clinic	98 (86.0)	65 (90.3)	566 (86.5)	
Emergency room	16 (14.0)	7 (9.7)	86 (13.2)	
Inpatient	0 (0)	0 (0)	2 (0.3)	
Days to CT retest, d				.40
21–60	91 (79.8)	65 (90.3)	561 (85.8)	
61–90	13 (11.4)	4 (5.6)	52 (8.0)	
91–211	10 (8.8)	3 (4.2)	41 (6.3)	
Total number of CT tests				<.001
2	14 (12.3)	0 (0)	117 (17.9)	
3	36 (31.6)	26 (36.1)	472 (72.2)	
≥4	64 (56.1)	46 (63.9)	65 (9.9)	

Dionne-Odom et al. Persistent and recurrent chlamydia in pregnancy after treatment. AJOG MFM 2020. *(continued)*

TABLE 1
Characteristics according to CT treatment outcomes after azithromycin (n = 840) *(continued)*

Characteristic	Persistence (group 1) (n=114)	Recurrence (group 2) (n=72)	Clearance (group 3) (n=654)	*P* value
STI coinfection in pregnancy	23 (20.2)	18 (25)	91 (13.9)	.02
Gonorrhea	21 (18.4)	17 (23.6)	89 (13.6)	.05
Syphilis	2 (1.7)	1 (1.4)	4 (0.6)	.23

Values are expressed as number (percentage) unless indicated otherwise.

CT, *Chlamydia trachomatis*; *STI*, sexually transmitted infection.

Dionne-Odom et al. Persistent and recurrent chlamydia in pregnancy after treatment. AJOG MFM 2020.

12%.[33] Cesarean delivery rates averaged 17% and were similar among the 3 groups (*P*=.68).

Risk factors for chlamydia persistence or recurrence in pregnancy compared with clearance (n=840) are presented in Table 2. In unadjusted models, black race (odds ratio [OR], 1.8; 95% confidence interval [CI], 1.1−3.0) and STI coinfection with gonorrhea or syphilis (OR, 1.8; 95% CI, 1.2−2.7) during pregnancy were associated with persistence or recurrence. In an adjusted model incorporating age, race, marital status, and insurance, only STI coinfection was associated (adjusted OR, 1.6; 95% CI, 1.1−2.4; *P*=.03). A separate MV model that included only the first pregnancy per woman had similar results. The independent association between STI coinfection and persistent or recurrent chlamydia persisted in sensitivity analyses that limited the retesting window to within 60 and 180 days and to pregnancies with only 2 tests performed.

Discussion

Principal findings

In this retrospective cohort study of 810 pregnant women with urogenital chlamydia treated with first-line azithromycin, nearly 1 in 4 pregnancies with repeat chlamydia testing had persistence or recurrence. STI coinfection with gonorrhea or syphilis during pregnancy was the only significant risk factor for persistent or recurrent chlamydia in a model that adjusted for age, race, and insurance status.

Results

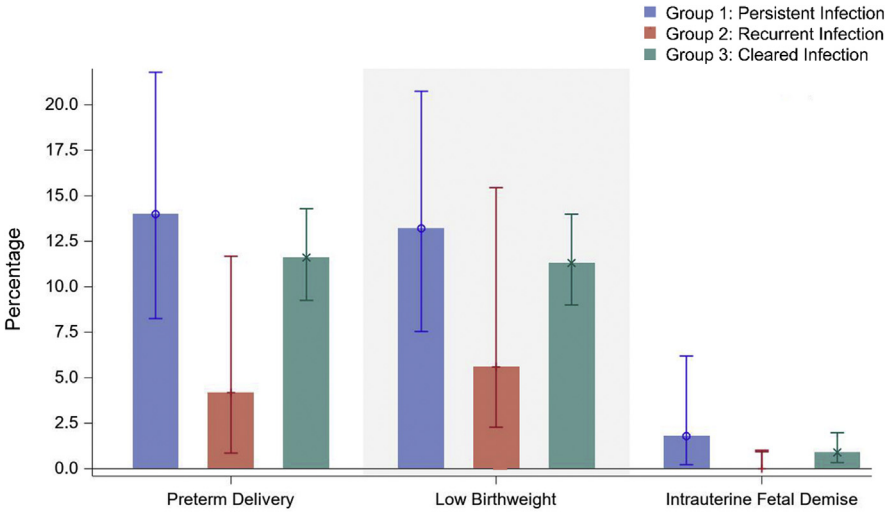
Our analysis adds to the scant information about the outcomes of chlamydia treatment in pregnancy in the midst of an STI epidemic in the United States. Reported rates of chlamydia in women have risen slowly since 2000 with a steeper increase since 2013.[1] The population of young pregnant women included in this study are at increased risk of chlamydia (Alabama has the 15th highest state case rate at 583 cases of 100,000 persons), yet rates are trending upward in all regions in the United States.[1] Rates of chlamydia persistence or recurrence in pregnancy in this study are elevated compared with older published data: 6% repeat positivity in pregnancy was documented in an analysis of laboratory data in the United States collected in 2005−2008, and persistence was 17% among 211 pregnant adolescents with follow-up testing 2 weeks after treatment.[12,34] Rates of recurrent infection in nonpregnant women average 14%, and predictors of recurrence include age of <20 years and black race.[4,15,35] The current study shows that gonorrhea and syphilis coinfection in pregnancy is independently associated with persistent or recurrent chlamydia. This is consistent with studies in nonpregnant women.[16] Sexual networks, regional STI prevalence, biologic susceptibility, and pregnancy status likely affect chlamydia acquisition risk in women but it is challenging to determine the attributable risk for each of these exposures.

The rationale for universal chlamydia screening in pregnant women is to prevent adverse birth outcomes associated with infection. A recent meta-analysis examined the association between untreated chlamydia in pregnancy and preterm delivery and documented a pooled OR of 2.3 (95% CI, 1.6−3.2).[7] Adverse birth outcomes detected in the current study are consistent with these data given the somewhat higher rates of preterm delivery in pregnancies with persistence despite treatment.

Clinical implications

There are 4 explanations that are commonly cited for repeat positive chlamydia tests after treatment: (1) reinfection, (2) medication nonadherence, (3) false-positive NAAT result, and (4) treatment failure. Although we cannot distinguish among these possibilities given our retrospective design, we discuss the likelihood of each. Because the prevalence of chlamydia in pregnancy in our cohort was 10% overall and 9% of women with repeat testing had recurrent infection, we suspect that most cases of repeat positivity were caused by recurrent infection. This study and others emphasize the urgent need to improve access to expedited partner therapy (EPT) for sex partners of pregnant women with chlamydia.[36] ACOG has recommended partner therapy for pregnant women with chlamydia when sex partners are unable or unwilling to seek medical care since 2018.[37−41] Concurrent patient-partner antibiotic therapy reduced recurrent STI in pregnancy in an observational cohort study by Mmeje et al[42] (0% recurrence in the intervention arm vs 18% in the standard referral arm). Alabama is 1 of only 5 states in the United States where EPT is "potentially allowable" instead of "permissible." This restriction may contribute to the high rates of repeat positive testing that we observed.[41]

FIGURE 2
Birth outcomes by chlamydia treatment outcome groups (n = 840)



P=.08 for preterm delivery; *P*=.41 for low birthweight; *P*=.41 for intrauterine fetal demise.

Dionne-Odom et al. Persistent and recurrent chlamydia in pregnancy after treatment. AJOG MFM 2020.

Medication nonadherence may have explained some of our study findings. Nonadherence to electronically prescribed medication is reported but young women and pregnant women generally have higher rates of adherence and single-dose oral azithromycin is a simple regimen.[43,44] On chart review, some women experienced financial barriers while awaiting Medicaid approval. Others had initial evidence of poor tolerance with vomiting, but subsequent azithromycin was well tolerated. Study implications remain relevant with nonadherence because follow-up testing provides critical information.

False-positive chlamydia NAAT result is a third possible explanation for a repeat positive chlamydia test. However, a recent study of 36 pregnant women with chlamydia documented a median of 8 days for clearance (range, 4–29 days) after azithromycin treatment and 94% had a negative NAAT result after 21 days.[14,45] A false-positive test result is unlikely to explain many cases of repeat positive test results because repeat testing was performed 30 days after azithromycin treatment, on average.

Finally, in terms of treatment failure, azithromycin is the only CDC-recommended therapy for chlamydia in

TABLE 2
Model for persistent or recurrent chlamydia in pregnancy after azithromycin (n = 840)

Characteristic	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Demographics				
Age categories, y		.06		.21
13–24	1.49 (0.98–2.29)		1.31 (0.86–2.02)	
≥25	Ref		Ref	
Race		.02		.12
Black	1.80 (1.09–3.01)		1.51 (0.90–2.54)	
White/other/declined to provide	Ref		Ref	
Marital status		.06		.24
Single	2.02 (0.98–4.16)		1.56 (0.75–3.24)	
Partnered	Ref		Ref	
Insurance		.72		.95
Public/none	1.11 (0.62–1.98)		0.98 (0.55–1.76)	
Private	Ref		Ref	
Location of chlamydia test		.70		
Emergency room	1.10 (0.68–1.80)		N/A	
Outpatient clinic	Ref			
STI coinfection (gonorrhea or syphilis)	1.75 (1.16–2.65)	.01	1.60 (1.05–2.43)	.03

CI, confidence interval; *N/A*, not available; *OR*, odds ratio; *STI*, sexually transmitted infection.

Dionne-Odom et al. Persistent and recurrent chlamydia in pregnancy after treatment. AJOG MFM 2020.

pregnancy with high levels of efficacy in published studies to date.[11,13,46–48] A recent Cochrane review that focused on chlamydia treatment in pregnancy included 6 randomized controlled trials (n=191) and showed cure rates of 94% with azithromycin.[11] CDC uses a threshold of 95% efficacy to determine which antibiotic agents to recommend for STI because antimicrobial testing is rarely performed.[49,50] Antimicrobial resistance is unlikely to explain the elevated rates of repeat positive tests demonstrated in the current study but further study is needed.

Research implications

The importance of STI coinfection, genital tract immunity, rectal infection, genetic and microbiome factors that predispose to recurrent chlamydia, and the mechanism of prolonged chlamydia persistence in pregnancy warrant additional study.[16,51,52] Pregnant women diagnosed as having syphilis or gonorrhea may benefit from more frequent chlamydia screening with test of cure and enhanced efforts to ensure partner therapy.

Strengths and limitations

The study's limitations include a lack of information about sexual partners, which can contribute to a potential misclassification of persistence vs recurrence. We also assumed that women were adherent to single-dose azithromycin, as prescribed. The timing of repeat testing varied and chlamydia testing and treatment at outside facilities was not captured; this could have biased our estimates in either direction. Misclassification owing to the number of tests performed during pregnancy is possible but most women were tested at least 3 times and study outcomes were similar in this subgroup. Finally, our diverse urban population in a region with high STI rates may not be representative of all pregnant women in the United States. Strengths include the cohort size, the use of sensitive diagnostic testing, and the linkage of pharmacy, clinical, and testing data to outcomes in pregnant women who access care.

Conclusion

Persistent or recurrent chlamydia infection in pregnancy after azithromycin treatment was detected in nearly 1 in 4 pregnancies in our single-center cohort. Universal screening for chlamydia in pregnancy and follow-up testing should be ensured. ■

References

1. Sexually transmitted disease surveillance 2018. Centers for Disease Control and Prevention. 2019. Available at: https://www.cdc.gov/std/stats18/STDSurveillance2018-full-report.pdf. Accessed May 29, 2020.

2. Williams CL, Harrison LL, Llata E, Smith RA, Meites E. Sexually transmitted diseases among pregnant women: 5 states, United States, 2009-2011. Matern Child Health J 2018;22:538–45.

3. Torrone E, Papp J, Weinstock H; Centers for Disease Control and Prevention (CDC). Prevalence of Chlamydia trachomatis genital infection among persons aged 14-39 years–United States, 2007-2012. MMWR Morb Mortal Wkly Rep 2014;63:834–8.

4. Cha S, Newman DR, Rahman M, Peterman TA. High rates of repeat chlamydial infections among young women-Louisiana, 2000-2015. Sex Transm Dis 2019;46:52–7.

5. Martin DH, Koutsky L, Eschenbach DA, et al. Prematurity and perinatal mortality in pregnancies complicated by maternal Chlamydia trachomatis infections. JAMA 1982;247:1585–8.

6. Voskakis I, Tsekoura C, Keramitsoglou T, et al. Chlamydia trachomatis infection and Vγ9Vδ2 T cells in women with recurrent spontaneous abortions. Am J Reprod Immunol 2016;76:358–63.

7. Ahmadi A, Ramazanzadeh R, Sayehmiri K, Sayehmiri F, Amirmozafari N. Association of Chlamydia trachomatis infections with preterm delivery; a systematic review and meta-analysis. BMC Pregnancy Childbirth 2018;18:240.

8. Olson-Chen C, Balaram K, Hackney DN. Chlamydia trachomatis and adverse pregnancy outcomes: meta-analysis of patients with and without infection. Matern Child Health J 2018;22:812–21.

9. Hill AV, Perez-Patron M, Tekwe CD, Menon R, Hairrell D, Taylor BD. Chlamydia trachomatis is associated with medically indicated preterm birth and preeclampsia in young pregnant women. Sex Transm Dis 2020;47:246–52.

10. Reekie J, Roberts C, Preen D, et al. Chlamydia trachomatis and the risk of spontaneous preterm birth, babies who are born small for gestational age, and stillbirth: a population-based cohort study. Lancet Infect Dis 2018;18:452–60.

11. Cluver C, Novikova N, Eriksson DO, Bengtsson K, Lingman GK. Interventions for treating genital Chlamydia trachomatis infection in pregnancy. Cochrane Database Syst Rev 2017;9:CD010485.

12. Blatt AJ, Lieberman JM, Hoover DR, Kaufman HW. Chlamydial and gonococcal testing during pregnancy in the United States. Am J Obstet Gynecol 2012;207:55.e1–8.

13. Workowski KA. Centers for Disease Control and Prevention sexually transmitted diseases treatment guidelines. Clin Infect Dis 2015;61(Suppl 8):S759–62.

14. Lazenby GB, Korte JE, Tillman S, Brown FK, Soper DE. A recommendation for timing of repeat Chlamydia trachomatis test following infection and treatment in pregnant and nonpregnant women. Int J STD AIDS 2017;28:902–9.

15. Hosenfeld CB, Workowski KA, Berman S, et al. Repeat infection with Chlamydia and gonorrhea among females: a systematic review of the literature. Sex Transm Dis 2009;36:478–89.

16. Khosropour CM, Bell TR, Hughes JP, Manhart LE, Golden MR. A population-based study to compare treatment outcomes among women with urogenital chlamydial infection in Washington State, 1992 to 2015. Sex Transm Dis 2018;45:319–24.

17. Owings AJ, Clark LL, Rohrbeck P. Incident and recurrent Chlamydia trachomatis and Neisseria gonorrhoeae infections, active component, U.S. Armed Forces, 2010-2014. MSMR 2016;23:20–8.

18. van der Helm JJ, Koekenbier RH, van Rooijen MS, Schim van der Loeff MF, de Vries HJC. What is the optimal time to retest patients with a urogenital Chlamydia infection? A randomized controlled trial. Sex Transm Dis 2018;45:132–7.

19. Berggren EK, Patchen L. Prevalence of Chlamydia trachomatis and Neisseria gonorrhoeae and repeat infection among pregnant urban adolescents. Sex Transm Dis 2011;38:172–4.

20. Mestrovic T, Ljubin-Sternak S. Molecular mechanisms of *Chlamydia trachomatis* resistance to antimicrobial drugs. Front Biosci (Landmark Ed) 2018;23:656–70.

21. Somani J, Bhullar VB, Workowski KA, Farshy CE, Black CM. Multiple drug-resistant Chlamydia trachomatis associated with clinical treatment failure. J Infect Dis 2000;181:1421–7.

22. Kirkcaldy RD, Soge O, Papp JR, et al. Analysis of Neisseria gonorrhoeae azithromycin susceptibility in the United States by the Gonococcal Isolate Surveillance Project, 2005 to 2013. Antimicrob Agents Chemother 2015;59:998–1003.

23. 2015 sexually transmitted diseases treatment guidelines. Centers for Disease Control and Prevention. 2019. Available at: https://www.cdc.gov/std/tg2015/default.htm. Accessed May 29, 2020.

24. Salman S, Rogerson SJ, Kose K, et al. Pharmacokinetic properties of azithromycin in pregnancy. Antimicrob Agents Chemother 2010;54:360–6.

25. Kong FYS, Horner P, Unemo M, Hocking JS. Pharmacokinetic considerations regarding the

treatment of bacterial sexually transmitted infections with azithromycin: a review. J Antimicrob Chemother 2019;74:1157–66.

26. Kong FY, Tabrizi SN, Fairley CK, et al. Higher organism load associated with failure of azithromycin to treat rectal chlamydia. Epidemiol Infect 2016;144:2587–96.

27. Dukers-Muijrers NH, Speksnijder AG, Morré SA, et al. Detection of anorectal and cervicovaginal Chlamydia trachomatis infections following azithromycin treatment: prospective cohort study with multiple time-sequential measures of rRNA, DNA, quantitative load and symptoms. PLoS One 2013;8:e81236.

28. Zakher B, Cantor AG, Pappas M, Daeges M, Nelson HD. Screening for gonorrhea and Chlamydia: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2014;161:884–93.

29. Centers for Disease Control and Prevention. Recommendations for the laboratory-based detection of Chlamydia trachomatis and Neisseria gonorrhoeae–2014. MMWR Recomm Rep 2014;63(RR-02):1–19.

30. Van Der Pol B, Taylor SN, Liesenfeld O, Williams JA, Hook EW 3rd. Vaginal swabs are the optimal specimen for detection of genital Chlamydia trachomatis or Neisseria gonorrhoeae using the Cobas 4800 CT/NG test. Sex Transm Dis 2013;40:247–50.

31. Rönn MM, Mc Grath-Lone L, Davies B, Wilson JD, Ward H. Evaluation of the performance of nucleic acid amplification tests (NAATs) in detection of chlamydia and gonorrhoea infection in vaginal specimens relative to patient infection status: a systematic review. BMJ Open 2019;9:e022510.

32. 2019 Annual Report. America's Health Rankings. 2019. Available at: https://www.americashealthrankings.org/learn/reports/2019-annual-report. Accessed July 28, 2020.

33. A profile of prematurity in Alabama. Peristats. March of Dimes Foundation. 2018. Available at: https://www.marchofdimes.org/peristats/tools/prematurityprofile.aspx?reg=01. Accessed July 28, 2020.

34. Aggarwal A, Spitzer RF, Caccia N, Stephens D, Johnstone J, Allen L. Repeat screening for sexually transmitted infection in adolescent obstetric patients. J Obstet Gynaecol Can 2010;32:956–61.

35. Newman LM, Warner L, Weinstock HS. Predicting subsequent infection in patients attending sexually transmitted disease clinics. Sex Transm Dis 2006;33:737–42.

36. Jamison CD, Coleman JS, Mmeje O. Improving women's health and combatting sexually transmitted infections through expedited partner therapy. Obstet Gynecol 2019;133:416–22.

37. Unger JA, Matemo D, Pintye J, et al. Patient-delivered partner treatment for Chlamydia, Gonorrhea, and Trichomonas infection among pregnant and postpartum women in Kenya. Sex Transm Dis 2015;42:637–42.

38. Cramer R, Leichliter JS, Stenger MR, Loosier PS, Slive L; SSuN Working Group. The legal aspects of expedited partner therapy practice: do state laws and policies really matter? Sex Transm Dis 2013;40:657–62.

39. Oliver A, Rogers M, Schillinger JA. The impact of prescriptions on sex partner treatment using expedited partner therapy for Chlamydia trachomatis infection, New York City, 2014-2015. Sex Transm Dis 2016;43:673–8.

40. ACOG Committee Opinion no. 737: expedited partner therapy. Obstet Gynecol 2018;131:e190–3.

41. Mmeje O, Wallett S, Kolenic G, Bell J. Impact of expedited partner therapy (EPT) implementation on chlamydia incidence in the USA. Sex Transm Infect 2018;94:545–7.

42. Mmeje O, Coleman JS. Concurrent patient-partner treatment in pregnancy: an alternative to expedited partner therapy? Sex Transm Dis 2012;39:665–70.

43. Fischer MA, Stedman MR, Lii J, et al. Primary medication non-adherence: analysis of 195,930 electronic prescriptions. J Gen Intern Med 2010;25:284–90.

44. Wehbeh H, Fleisher JM, Coasino M, Ayoub A, Margossian H, Zarou D. Erythromycin for chlamydiasis in pregnant women. Assessing adherence to a standard multiday, multidose course. J Reprod Med 2000;45:465–8.

45. Williams JA, Ofner S, Batteiger BE, Fortenberry JD, Van Der Pol B. Duration of polymerase chain reaction-detectable DNA after treatment of Chlamydia trachomatis, Neisseria gonorrhoeae, and Trichomonas vaginalis infections in women. Sex Transm Dis 2014;41:215–9.

46. Cross R, Ling C, Day NPJ, McGready R, Paris DH. Revisiting doxycycline in pregnancy and early childhood–time to rebuild its reputation? Expert Opin Drug Saf 2016;15:367–82.

47. Kacmar J, Cheh E, Montagno A, Peipert JF. A randomized trial of azithromycin versus amoxicillin for the treatment of Chlamydia trachomatis in pregnancy. Infect Dis Obstet Gynecol 2001;9:197–202.

48. Pitsouni E, Iavazzo C, Athanasiou S, Falagas ME. Single-dose azithromycin versus erythromycin or amoxicillin for Chlamydia trachomatis infection during pregnancy: a meta-analysis of randomised controlled trials. Int J Antimicrob Agents 2007;30:213–21.

49. Geisler WM. Diagnosis and management of uncomplicated Chlamydia trachomatis infections in adolescents and adults: summary of evidence reviewed for the 2015 Centers for Disease Control and Prevention sexually transmitted diseases treatment guidelines. Clin Infect Dis 2015;61(Suppl 8):S774–84.

50. Hook EW, Newman L, Drusano G, et al. Development of new antimicrobials for urogenital gonorrhea therapy: clinical trial design considerations. Clin Infect Dis 2020;70:1495–500.

51. Olson KM, Tang J, Brown L, Press CG, Geisler WM. HLA-DQB1*06 is a risk marker for chlamydia reinfection in African American women. Genes Immun 2019;20:69–73.

52. Tamarelle J, Ma B, Gajer P, et al. Nonoptimal vaginal microbiota after azithromycin treatment for Chlamydia trachomatis infection. J Infect Dis 2020;221:627–35.

Author and article information

From the Division of Infectious Diseases, Department of Medicine (Drs Dionne-Odom, Aaron, Geisler, and Marrazzo), Center for Women's Reproductive Health (Drs Dionne-Odom, Subramaniam, Tita, and Marrazzo), and Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology (Drs Subramaniam and Tita), University of Alabama at Birmingham, Birmingham, Alabama.

Received June 8, 2020; revised Aug. 1, 2020; accepted Aug. 13, 2020.

The authors report no conflict of interest.

This work was supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (K23 HD090993 to JD) of the National Institutes of Health.

This work was presented, in part, at the 39th Annual Pregnancy Meeting of the Society for Maternal-Fetal Medicine, Las Vegas, NV, February 11—16, 2019.

Corresponding author: Jodie Dionne-Odom, MD, MSPH. jdionne@uabmc.edu