Ureaplasma screening for pregnant individuals who are at high risk for preterm birth: a retrospective study.

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Abstract

Objective: To examine gestational age at delivery according to Ureaplasma cervical culture results and whether pregnant individuals received antibiotics. Study Design: A retrospective cohort study Setting: Single academic institution Population: All pregnant individuals with risk factors for preterm birth including those with a history of preterm birth, recurrent pregnancy loss, or pregnancy requiring cervical cerclage. Methods: We plotted Kaplan-Meier curves to investigate the association between the gestational age at delivery and Ureaplasma culture results (negative; positive and treated; or positive but did not receive the treatment). A Cox proportional regression model was used to calculate Hazard ratio (HR) with 95% confidence intervals (95%CI), controlling for confounders. Main outcome: Gestational age at delivery. Results: Of 607 individuals, 258 (42.5%) had a negative Ureaplasma culture, 308 (50.7%) had a positive Ureaplasma culture and received treatment, and 41 (6.8%) had a positive Ureaplasma culture and did not receive treatment. Compared to those who had a positive Ureaplasma culture but did not receive treatment, those who had a negative Ureaplasma culture did not have a decreased risk (HR 1.03; 95%CI 0.74-1.44). Compared to those who had a positive Ureaplasma culture but did not receive treatment, those who had a positive Ureaplasma culture and received treatment did not have a decreased risk (HR 0.91; 95%CI 0.66-1.27). The treatment failure rate of Ureaplasma after treatment was 78.6% (95%CI 72.8-83.7%). Conclusion: Routine Ureaplasma cervical culture is not recommended for pregnant individuals who are at high risk for preterm birth

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The authors report no conflict of interest.

Contribution to authorship

TK and CK conceived the idea for the study. TK and NL wrote the article. TK is the corresponding author of the study. TK and CB planned and carried out the study. JCH conducted the analyses. TK, CK, AA, and NL contributed to the interpretation of the data. TK, JW, TD, CB, MC, and ME conducted data collection. TK, NL, CK, and AA critically revised earlier drafts of the article for important intellectual content and gave final approval of the version to be published.

Details of Ethics Approval

Eastern Virginia Medical School Institutional Review Board

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Methods : We plotted Kaplan-Meier curves to investigate the association between the gestational age at delivery and Ureaplasma culture results (negative; positive and treated; or positive but did not receive the treatment). A Cox proportional regression model was used to calculate Hazard ratio (HR) with 95% confidence intervals (95%CI), controlling for confounders.

Main outcome: Gestational age at delivery.

Results: Of 607 individuals, 258 (42.5%) had a negative Ureaplasma culture, 308 (50.7%) had a positive Ureaplasma culture and received treatment, and 41 (6.8%) had a positive Ureaplasma culture and did not receive treatment. Compared to those who had a positive Ureaplasma culture but did not receive treatment, those who had a negative Ureaplasma culture did not have a decreased risk (HR 1.03; 95%CI 0.74-1.44). Compared to those who had a positive Ureaplasma culture but did not receive treatment, those who had a positive Ureaplasma culture and received treatment did not have a decreased risk (HR 0.91; 95%CI 0.66-1.27). The treatment failure rate of Ureaplasma after treatment was 78.6% (95%CI 72.8-83.7%).

Conclusion: Routine Ureaplasma cervical culture is not recommended for pregnant individuals who are at high risk for preterm birth.

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Keywords:

Antibiotics- Preterm birth- Recurrence - Ureaplasma

Introduction

Preterm birth, defined as birth before 37 weeks' gestation, complicates approximately 10% of all live births and is the leading cause of neonatal mortality and long-term neonatal neurologic sequelae. Pregnant individuals with a previous history of preterm birth or second-trimester loss are especially at a higher risk of preterm birth; the incidence of a subsequent preterm birth is approximately 20-30%. Another well-known risk factor for preterm birth is genital tract infections or colonization such as Chlamydia trachomatis, bacterial vaginosis, Trichomonas vaginalis, and Ureaplasma species. Given these associations, we started a quality improvement study that performs Ureaplasma cervical culture in addition to routine sexually transmitted infection screening for pregnant individuals with high-risk factors for preterm birth.

Ureaplasma species are normal genital flora, carried by 50-80% of pregnant and non-pregnant individuals. Some studies showed that Ureaplasma species are associated with spontaneous preterm birth whereas others did not confirm this association. A proposed mechanism is the presence of toxins and cytokines from Ureaplasma, which lead to high levels of prostaglandins, and later either induce preterm labor or preterm prelabour rupture of membranes (PPROM). Despite this association, previous studies did not show that antibiotics including Erythromycin and Clindamycin to treat Ureaplasma for asymptomatic individuals actually decrease spontaneous preterm birth. This lack of effectiveness could be due to difficulty eradicating Ureaplasma species. A randomized control trial of 60 pregnant individuals who presented with preterm labor or PPROM showed that 93.3% of individuals still had a positive culture for Ureaplasma after 1 gram of Azithromycin. These studies did not treat sexual partners, nor treat pregnant individuals again if the culture was positive after the initial treatment.

It is not known if treating both pregnant individuals and their sexual partners would result in lower positivity rates after treatment, as well as improvement of gestational age at delivery. Since 2014, our institution has been performing cervical cultures of pregnant individuals who are at high-risk for preterm birth and treating both pregnant individuals and their sexual partners. We sought to examine gestational age at delivery according to Ureaplasma cervical culture results and whether pregnant individuals received appropriate antibiotics. We also sought to examine the Ureaplasma positive rates after treatment of pregnant individuals and their partners. Given the data in the literature, we hypothesized that treatment of Ureaplasma was not associated with improved gestational age at delivery, and the treatment failure rate would be high.

Methods

This was a retrospective study of pregnant individuals who had Ureaplasma cervical culture at an academic institution from January 2014 to December 2020. Our Institutional Review Board approved this study. In 2014, we started a quality improvement project in which we routinely obtained Ureaplasma cervical culture for all pregnant individuals with risk factors for preterm birth (history of preterm births or PPROM, history of recurrent pregnancy loss, pregnancy with multiple gestations, or pregnancy requiring cerclage). The American College of Obstetricians and Gynecologists (ACOG) defined preterm birth as delivery less than 37 weeks' gestation. PPROM was defined as rupture of membranes prior to the onset of labor less than 37 weeks' gestation. Recurrent pregnancy loss is defined as 2 or more consecutive early pregnancy losses. Indications for cerclage included history indication, ultrasound indication due to the short cervix, or physical exam indication. These indications were documented in the medical record.

We excluded individuals who had Ureaplasma cervical culture for preterm contraction, multiple gestation, or unknown indications. Therefore, we only analyzed pregnant individuals with singleton pregnancies who had Ureaplasma cervical culture that was obtained for a history of preterm births, a history of recurrent pregnancy loss, or cervical cerclage. We also limited analyses to pregnant individuals who had Ureaplasma cervical culture at or prior to 20 weeks' gestation, since we wanted to assess the effectiveness of early intervention. In addition, we excluded pregnant individuals if they delivered within two weeks of the initial Ureaplasma cervical culture since these individuals would not have enough time to receive the treatment. Pregnant individuals were categorized according to the initial Ureaplasma cervical culture results and whether they

received appropriate antibiotics (negative; positive and received treatment; and positive but did not receive treatment [including those who did not receive appropriate antibiotics]).

Ureaplasma cervical culture was obtained at the first prenatal visit by inserting a vaginal speculum and removing the excess mucus from the cervical opening, using a cotton swab. The specimen collection swab was then placed within the external cervical os and gently rotated for 30 seconds for appropriate sampling. The swab was then removed avoiding contact with the vaginal walls and immediately placed into the transport tube which was securely capped. Aptima® swab was commonly utilized for this procedure. This test detects Mycoplasma genitalium, Mycoplasma hominis, and Ureaplasma species through nucleic acid amplification. If Ureaplasma cervical culture was positive, we prescribed Azithromycin for pregnant individuals and Doxycycline for sexual partners (Box 1). If pregnant individuals received antibiotics, we obtained Ureaplasma cervical culture 4 weeks after the initial treatment and treated them again if the second cervical culture was positive. Alternative antibiotics regimens in case of drug allergy are presented in Box 1.

Our primary outcome was gestational age at delivery. The estimated due date (EDD) was based on the date of the last menstrual period confirmed by first-trimester ultrasound. Secondary outcomes included Ureaplasma cervical culture positive 4 weeks after the initial treatment (treatment failure), preterm birth less than 37 weeks' gestation, spontaneous preterm birth less than 37 weeks' gestation, spontaneous preterm birth less than 34 weeks' gestation, chorioamnionitis, PPROM, pregnancy loss less than 22 weeks' gestation, neonatal intensive care unit (NICU) admission, neonatal respiratory distress syndrome (RDS) or transient tachypnea of newborn (TTN), and stillbirth or neonatal demise.

Ureaplasma treatment failure rates were assessed according to the indications for Ureaplasma cervical cultures. For the analysis of the treatment failure rate, we only included pregnant individuals who had a positive Ureaplasma cervical culture, received treatment, and had a repeat Ureaplasma cervical culture after the initial treatment. Because some individuals had several indications for Ureaplasma cervical cultures, we classified mutually exclusive categories for indications using the following hierarchy. First, if individuals had cerclage, the indication was classified as "cerclage." Second, if individuals had a history of preterm births, the indication was classified as "history of preterm birth." Third, if individuals had a history of recurrent pregnancy loss, the indication was classified as "recurrent pregnancy loss." The hierarchy was maintained if individuals had more than one indication, with the highest-order indication prioritized to assign the classification. For example, if an individual had a history of preterm birth and underwent cervical cerclage, this individual was classified as "cerclage" group.

We calculated the sample size based on the following assumptions. We assumed that 90% of individuals with a positive Ureaplasma culture would receive treatment. To obtain an alpha of 0.05 and the power of 80% and detect a Hazard ratio of 0.6, we would need 224 individuals with a positive Ureaplasma culture (201 with appropriate antibiotics and 23 without appropriate antibiotics).

Descriptive statistics were calculated for all study variables. Chi-square test, Fisher's exact test, Student's t-test, Wilcoxon rank sum test, or Kruskal-Wallis tests were performed as appropriate. A P-value <0.05 was considered significant. We plotted the Kaplan-Meier curves to investigate the association between the gestational age at delivery and Ureaplasma culture results (negative; positive and received treatment; or positive but did not receive treatment). Log-rank test was performed to obtain P-value to compare Kaplan-Meier curves. A Cox proportional regression model was used to calculate Hazard ratio (HR) with 95% confidence intervals (95%CI), controlling for variables with a $P<0.05$ based on bivariable analyses. For secondary outcomes, multivariable logistic models were used to calculate adjusted P-value and adjusted odds ratios (aOR) with 95% confidence intervals (95%CI), controlling for variables with a $P<0.05$ based on bivariable analyses (Ureaplasma negative as a referent). A simple logistic regression was used to examine the association between the treatment failure rate and cervical culture indications (history of preterm birth as a referent). All statistical analyses were performed using Stata/SE 17.0 (StataCorp, College Station, TX).

Results

Of 607 pregnant individuals. 258 (42.5%) had a negative Ureaplasma culture, 308 (50.7%) had a positive

Ureaplasma culture and received treatment, and 41 (6.8%) had a positive Ureaplasma culture and did not receive treatment. (Figure 1).

Maternal demographics are presented in Table 1. There were statistical differences in distributions and proportions of maternal age, race and ethnicity, smoking, illicit drug, Trichomonas vaginalis co-infection, and reason for Ureaplasma culture. Compared to pregnant individuals who had a negative culture, those who had a positive Ureaplasma and received treatment were more likely to be younger, non-Hispanic black, co-infected with Trichomonas vaginalis, and have Ureaplasma culture indicated for a history of preterm birth (P<0.05). Compared to pregnant individuals who had a negative culture, those who had a positive Ureaplasma and did not receive treatment were more likely to be smokers (P=0.02).

Kaplan Meier curves are presented in Figure 2. There was no difference in gestational age at delivery (Log-rank P=0.40). There was no difference in median gestational age at delivery between groups (negative 37.4 [interquartile 36.0-39.0] weeks vs. positive and received treatment 37.7 [35.6-39.0] weeks vs. positive and did not receive treatment 37.3 [36.0-38.7] weeks; P =0.57). Hazard ratios are presented in Table 2. Compared to those who had a positive Ureaplasma culture but did not receive treatment, those who had a negative Ureaplasma culture did not have decreased a risk (HR 1.02; 95%CI 0.73-1.42). Similarly, compared to those who had a positive Ureaplasma culture but did not receive treatment, those who had a positive Ureaplasma culture and received treatment did not have a decreased risk (HR 0.90; 95%CI 0.65-1.25). Individuals who had Ureaplasma culture for recurrent pregnancy loss compared to those who had Ureaplasma culture for a history of preterm birth had a decreased risk (HR 0.54; 95%CI 0.35-0.85). Secondary outcomes are presented in Table 3. There were no differences in secondary outcomes across the groups.

Of 308 individuals who had a positive Ureaplasma culture and received treatment, 234 (76%) had a follow-up Ureaplasma culture. The overall treatment failure rate after the initial treatment was 78.6% (184/234; 95%CI 72.8-83.7%). Rates of treatment failure according to reasons for Ureaplasma culture are presented in Table 4. Compared to a history of preterm births, cerclage was associated with decreased odds of treatment failure (odds ratio 0.33; 95%CI 0.18-0.61).

Discussion

In our cohort of 607 pregnant individuals who were at high risk for preterm birth, we found that those who had a positive Ureaplasma culture but did not receive treatment had comparable gestational age at delivery compared to those who have negative Ureaplasma culture as well as those who had a positive Ureaplasma culture and received treatment. Further, the rate of treatment failure after the initial treatment was very high (78.6%). We also found that cerclage was associated with lower odds of recurrence compared to a history of preterm birth.

We found that treatment failure of Ureaplasma was very high even after treatment of pregnant individuals and their sexual partners. This finding was consistent with a previous study that showed that treatment of pregnant individuals with preterm labor or PPROM with Azithromycin resulted in a 93.3% treatment failure rate. Interestingly, studies of intra-amniotic Ureaplasma infection showed that treatment of infection resulted in a high rate of clearance of infection (79%). Given that Ureaplasma species are normal genital flora, eradication of Ureaplasma might be challenging. We found that pregnant individuals who had a cervical culture due to cerclage had lower odds of recurrence compared to those who had a cervical culture due to a history of preterm births. We speculate that these lower odds could be due to abstinence from intercourse after cerclage placement. In non-pregnant individuals, sexual intercourse permits the spread of the various Ureaplasma species with their different resistance profiles. In pregnant individuals, those who had sexual intercourse 3 times or greater per week had a Ureaplasma positive rate of 37%, which was much higher than 18% for those who had intercourse less than 3 times per week (P=0.02). It is noteworthy that even though our institution treated all sexual partners with Doxycycline, the treatment failure rate remained high.

We found that giving appropriate antibiotics was not associated with an improvement in gestational age at delivery. Despite the use of different antibiotics, our finding was consistent with previous studies that showed treatment of Ureaplasma was not associated with improvement of adverse pregnancy outcomes compared to

no treatment. For example, a double-blind randomized control trial that randomized pregnant individuals who tested positive for Ureaplasma Urealyticum to either erythromycin treatment or placebo did not show significant differences in gestational age at delivery, PPROM, or neonatal outcomes. Our study is unique, however, since our protocol adopts an Azithromycin regimen and treats their sexual partners.

It is important to note that giving antibiotics to pregnant individuals could change bacterial flora and could have unknown consequences. Even though Azithromycin is not associated with short-term neonatal adverse outcomes, little is known regarding the long-term outcomes. A previous study has indicated that antibiotics may be associated with an infant gut microbiota imbalance during the first year of life. Future studies that examine long-term neonatal and infants' outcomes associated with prenatal Azithromycin exposure would be useful.

Our study has many strengths. In 2014, our institution started a quality improvement project that tests and treats pregnant individuals with a positive Ureaplasma cervical culture as well as their sexual partners. Our protocol was to repeat Ureaplasma cervical culture after the initial treatment and treat again if treatment failure is noted. Though previous studies treated pregnant individuals only once, we thought repeating Ureaplasma cervical culture was important due to the high treatment failure rate. We believe the quality of our data is high: data were obtained from a chart review of outpatient, inpatient, and anesthesia records. We think that this study sets a good example of a quality improvement project; given the high rate of treatment failure despite treatment of pregnant individuals and sexual partners, our institution decided to stop routine Ureaplasma cervical culture for pregnant individuals who were at high risk for preterm birth. Our study underscores the importance of assessing the effects of a quality improvement project and changing our practice based on study findings.

Our study is not without limitations. Given the retrospective nature of the study, we were not able to assess the compliance rates of treatment for pregnant individuals and their sexual partners. We tried to adjust for covariates using cox or multivariable logistic regression models. However, there could be residual confounding. Since this was a retrospective cohort study, we were only able to assess association but not causation. Our study was from a single academic center. Therefore, our findings may not be generalizable in other clinical settings. Unfortunately, due to our protocol of treating all pregnant individuals who had positive Ureaplasma culture, the sample size of pregnant individuals who had a positive Ureaplasma culture and did not receive treatment was low. Since our study was powered to examine gestational age at delivery, other analyses were exploratory. Lastly, we did not differentiate the Ureaplasma species. It is possible that some species of Ureaplasma such as Ureaplasma parvum but not Ureaplasma Urealyticum are associated with spontaneous preterm birth.

Conclusion

Ureaplasma species are commonly isolated from pregnant individuals who are at high-risk for preterm birth. The treatment failure rate was very high even after treating pregnant individuals and their sexual partners. There were no statistical differences in gestational age at delivery as well as adverse pregnancy outcomes regardless of Ureaplasma culture results and whether pregnant individuals received treatment. Routine Ureaplasma cervical culture is not recommended for pregnant individuals who are at high risk for preterm birth.

Figure legend:

Figure 1. Cohort diagram

Figure 2. Kaplan-Meier curve

Box 1. Institution management of Ureaplasma and Mycoplasma infection in pregnancy:

Screening Criteria	All pregnant individuals at increased risk for preterm delivery, including: Individuals with a history of prior pre-term delivery or PPROM Individuals with a history of two or more unexplained first-trimester SABs Individuals with multiple gestations Individuals who are receiving a cerclage	
Antibiotics Regimen	**1st Line Regimen**	**Alternative Regimen**
Ureaplasma	Azithromycin 500mg PO x 1 then 250mg PO daily for a total of 7 days	Clindamycin 300mg PO BID x 7 days
Mycoplasma	Clindamycin 300mg PO BID x 7 days	
Ureaplasma + Mycoplasma	Azithromycin 500mg PO x 1 then 250mg PO daily for a total of 7 days And Clindamycin 300mg PO BID x 7 days	
Partner Treatment	Doxycycline	
Rescreening	Test-of-cure can be offered 3-4 weeks following completion of antibiotic therapy with re-treatment x 1 if still positive	Treatment with more than two courses of antibiotics is not recommended

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