NATURAL HISTORY

Pregnancy outcomes in women infected with *Chlamydia trachomatis*: a population-based cohort study in Washington State

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Objectives: To measure the risk of preterm delivery, premature rupture of membranes, infant low birth weight and infant mortality, by a population-based retrospective cohort study using Washington State birth certificate data.

Methods: All women diagnosed with *Chlamydia trachomatis* infection (n = 851), noted with a check box on the birth certificate from 2003, and a randomly selected sample of women not diagnosed with *C trachomatis* (n = 3404) were identified. To assess the RR between chlamydia infection and pregnancy outcomes, multivariable logistic regression analysis was used.

Results: Women with chlamydia infection were younger, more likely to be non-white and had less years of education compared with women without chlamydia. Additionally, they were more likely to have inadequate prenatal care and coinfections with other sexually transmitted infections. After adjusting for age and education, chlamydia-infected women were at an increased risk of preterm delivery (RR 1.46, 95% CI 1.08 to 1.99) and premature rupture of membranes (RR 1.50, 95% CI 1.03 to 2.17) compared with non-infected women. However, no increased risk of infant death (RR 1.02, 95% CI 0.37 to 2.80) or low birth weight (RR 1.12, 95% CI 0.74 to 1.68) associated with chlamydia infection was observed.

Conclusion: This study suggests that *C trachomatis* is associated with an increased risk of preterm delivery and premature rupture of membranes, but not with infant death and low birth weight. Routine screening and opportune treatment for *C trachomatis* should be considered a necessary part of prenatal care to reduce these adverse pregnancy outcomes.

Genital chlamydial infection is recognised as one of the most common sexually transmitted infections (STIs) worldwide. In 1999, 92 of the 340 million new STI cases reported by the World Health Organization were due to this infection.[1] *Chlamydia trachomatis* is also the most commonly reported notifiable disease in the US, and the leading cause of bacterial STI in industrialised countries.[2 3] In the US, there are approximately four million new chlamydia infections per year. It is estimated that <10% of these cases are diagnosed, resulting in an adverse impact, especially in women not treated for this infection.[3 4]

Infection with *C trachomatis* can lead to severe complications of the reproductive tract and adverse pregnancy outcomes. The common clinical manifestations of this infection include cervicitis, pelvic inflammatory disease and tubal factor infertility.[5–7] In pregnant women, chlamydia infection has been associated with an increased risk of ectopic pregnancy, preterm delivery, spontaneous abortions, low birth weight, premature rupture of membranes, perinatal mortality and postpartum endometritis.[5 8–14] Because of these risks, screening of pregnant women at the first prenatal visit is recommended by the Centers for Disease Control and Prevention and US Preventive Services Task Force. Additionally, both organisations suggest testing pregnant women at increased risk a second time during the third trimester.[15 16]

In 2003, information regarding chlamydia infection was added to the Washington State birth certificate, allowing for an opportunity to assess the risks of adverse pregnancy outcomes in women with chlamydia infection. Previous studies in pregnant women infected with *C trachomatis* have demonstrated discordant results regarding risks of adverse pregnancy outcomes,[9–12 17–19] and population-based studies are rare. Increased knowledge in this area may enhance awareness in the public health sector, generate public health interventions targeted at high-risk populations, and improve the counselling and treatment of infected pregnant women.

The aim of this population-based study is to measure the risk of preterm delivery, premature rupture of membranes, infant mortality and infant low birth weight among women diagnosed with *C trachomatis* infection during pregnancy, relative to a randomly chosen control group of women not diagnosed with this infection.

METHODS

We performed a population-based retrospective cohort study, using data obtained from the Washington State birth certificates for 2003 linked with infant hospitalisation records within 12 months of birth. The birth certificates record demographic characteristics as well as medical and clinical information from mothers and newborns at all hospitals and birthing centres in Washington State. Approximately 90% of birth certificates and maternal and neonatal hospital discharge records in Washington State were successfully linked in 2003. Women from hospitals in Washington are routinely screened for chlamydia at the first prenatal visit. Women positive for *C trachomatis* and their partners are treated for this infection.

The exposed cohort consisted of all pregnant women with singleton births who had the check box for maternal chlamydia infection selected in their babies' birth certificates (n = 851). For comparison, the unexposed cohort included randomly selected women (in a 4:1 ratio) from the remaining population who did not have the check box for chlamydia infection marked

Abbreviation: STI, sexually transmitted infection

Table 1 Demographic characteristics, other maternal infections and pregnancy complications of women with and without *Chlamydia trachomatis* infection, Washington State 2003

	Chlamydia infection (n = 851) n* (%)	No chlamydia infection (n = 3404) n* (%)
Maternal age (years)		
13–17	89 (10.5)	99 (2.9)
18–19	155 (18.2)	213 (6.3)
20–24	392 (46.1)	850 (25.0)
25–29	123 (14.5)	913 (26.8)
30–34	61 (7.2)	854 (25.1)
>35	30 (3.5)	474 (13.9)
Maternal race		
White	494 (59.4)	2441 (72.6)
African American	71 (8.5)	149 (4.4)
Native American	69 (8.3)	67 (2.0)
Asian	79 (9.5)	303 (9.0)
Hispanic	116 (14.0)	369 (11.0)
Other	2 (0.2)	35 (1.0)
Unmarried	598 (70.8)	982 (29.0)
Maternal education (years)		
0–8	49 (5.9)	154 (4.6)
9–11	321 (38.5)	493 (14.7)
12–13	405 (48.6)	1581 (47.2)
14–20	59 (7.1)	1122 (33.5)
Maternal smoking during pregnancy (cigarettes/day)		
None	602 (71.1)	3031 (89.7)
1–9	122 (14.4)	158 (4.7)
⩾10	123 (14.5)	189 (5.6)
Number of prenatal care visits (mean)	9.8	10.7
Month prenatal care began (mean)	3.1	2.5
Adequacy of prenatal care†		
Inadequate	184 (26.3)	407 (15.8)
Intermediate	240 (34.3)	941 (36.6)
Adequate	222 (31.7)	994 (38.6)
Intensive	54 (7.7)	232 (9.0)
Other infections and complications		
Gonorrhoea	23 (2.7)	1 (<0.01)
Syphilis	2 (0.2)	0 (0.0)
Genital herpes	45 (5.3)	80 (2.4)
Hepatitis B	7 (0.8)	14 (0.4)
Hepatitis C	4 (0.5)	4 (0.1)
Group B streptococcus	187 (22.0)	536 (15.8)
Chorioamnionitis	18 (2.1)	62 (1.8)
Newborn in NICU	64 (7.6)	158 (4.7)

NICU, neonatal intensive care unit.
*Numbers may not add to the total because of missing data.
†According to Kotelchuck scale.[20]

(n = 3404). Women who had data for chlamydia missing or unknown were excluded from the analysis. The Human Subjects Protection Review Boards at the University of Washington and the Washington State Department of Health approved this study.

Four pregnancy outcomes were of interest: preterm delivery, defined as a gestational period of <37 weeks; premature rupture of membranes, defined as rupture of the amniotic sac before labour begins; low birth weight, defined as a newborn weighing <2500 g; and infant death, defined as death between delivery and the first year of age.

To assess the relative risk (RR) between chlamydia infection and pregnancy outcomes, we used logistic regression analysis, using Stata V.9.1. Potential confounding factors assessed included maternal age, education level, marital status, race, smoking status, herpes infection, streptococcus infection, adequacy of prenatal care, anaemia, body mass index and weight gain during pregnancy. For the evaluation of prenatal care, we used the Adequacy of Prenatal Care Utilization Index, which categorises the adequacy of prenatal care by assessing the gestational age and number of prenatal care visits from the initiation of prenatal care until delivery.[20] When the adjusted risk estimates differed from the crude estimate by ⩾10%, the variable was considered to be a confounder. In final analyses, all risk estimates were adjusted for maternal age and education level, which were found to be confounders.

In the evaluation of the risk of premature rupture of membranes associated with maternal chlamydia infection, we additionally conducted a subanalysis restricting subjects to women who did not undergo caesarean section.

RESULTS

Women with chlamydia infection were more likely to be young, non-white, non-married, and were less educated than women without chlamydia infection. They were also more likely to smoke and have inadequate prenatal care than women without the infection; women with chlamydia started prenatal care later and had fewer prenatal care visits compared with women without chlamydia. Additionally, coinfection with gonorrhoea, syphilis, genital herpes, hepatitis C, group B streptococcus and complications such as chorioamnionitis or hospitalisation in a neonatal care intensive unit were significantly more frequent in the exposed cohort with chlamydia infection (table 1).

In multivariable logistic regression analysis, adjusting for maternal age and education, there was a significantly increased risk of preterm delivery (RR 1.46, 95% CI 1.08 to 1.99) and premature rupture of membranes (RR 1.50, 95% CI 1.03 to 2.17) in women with *C trachomatis* infection compared with those without infection (table 2). A similar increased risk of premature rupture of membranes was also observed when we restricted this analysis to women without caesarean section (RR 1.53, 95% CI 0.99 to 2.38), although this did not attain statistical significance. We did not observe an increased risk of low birth weight (RR 1.12, 95% CI 0.74 to 1.68) or death (RR 1.02, 95% CI 0.37 to 2.80) in infants of women with chlamydia infection relative to infants of women without infection.

DISCUSSION

In the current population-based retrospective cohort study of mothers and infants in Washington State, we found that *C trachomatis* infection, as recorded on birth certificates, was associated with increased risk for premature rupture of membranes and preterm delivery, but not with low birth weight or infant death. These associations were present even after adjusting for the confounding effects of maternal age and education, and were unaffected by further potential confounding due to other maternal infections, including group B streptococcus, herpes, gonorrhoea, hepatitis B or hepatitis C.

Our finding that *C trachomatis* was associated with preterm delivery (RR 1.46, 95% CI 1.08 to 1.99) is consistent with previous studies that have assessed this relationship. In a case–control study, Andrews *et al*[17] found that genitourinary *C trachomatis* infection at 24 weeks' gestation was associated with a two- to threefold increased risk of subsequent spontaneous preterm birth. In a similar study design, Gencay *et al*[21] found a higher prevalence of *C trachomatis* IgM antibodies in sera from mothers with preterm delivery. Martius *et al*,[8] in a case–control study, found that both chlamydia infection (OR 3.9) and bacterial vaginosis (OR 2.3) were associated with preterm delivery. Similar results were observed by Martin *et al*[22] in a prospective cohort study, which detected a fourfold increase

Table 2 Risk of adverse pregnancy outcomes among women with chlamydia infection relative to those without the infection, Washington State 2003

	Chlamydia infection (n = 851) n (%)	No chlamydia infection (n = 3404) n (%)	RR*	95% CI
Birth weight (g)				
<2500	40 (4.7)	114 (3.4)	1.12	0.74 to 1.68
2500–3999	734 (86.6)	2857 (84.1)	Ref	
>3999	74 (8.7)	425 (12.5)	0.81	0.61 to 1.07
Premature rupture of membranes				
Yes	49 (5.8)	130 (3.8)	1.50	1.03 to 2.17
No	800 (94.2)	3248 (96.2)	Ref	
Gestational length (weeks)				
<37	76 (10.3)	181 (6.1)	1.46	1.08 to 1.99
37–41	542 (73.7)	2426 (81.6)	Ref	
⩾42	117 (15.9)	365 (12.3)	1.25	0.98 to 1.60
Infant death				
Yes	7 (0.8)	15 (0.4)	1.02	0.37 to 2.80
No	844 (99.2)	3389 (99.6)	Ref	

*Adjusted for maternal age and education.

in the risk of preterm delivery among chlamydia-infected women compared with non-infected women (RR 4.40).

In our study, *C trachomatis* was associated with premature rupture of membranes (RR 1.50, 95% CI 1.03 to 2.17), a relationship that was maintained when we restricted the analysis to women without caesarean section (RR 1.53). Harrison *et al*[23] also demonstrated a positive association between IgM-positive women and premature rupture of the membranes. In a large prospective study, Gravett *et al*[10] found a large increased risk of premature rupture of membranes among women with chlamydia infection compared with those without the infection (OR 2.4). In a cohort study, Ryan *et al*[24] showed an increased risk in the incidence of premature rupture of membranes in patients with positive chlamydia cultures who did not receive treatment, compared with patients with negative cultures for chlamydia (OR 2.12). Similarly, Cohen *et al*[25] showed a decreased risk in premature rupture of membranes in patients positive for chlamydia who were successfully treated for the infection, compared with patients who were treated but who had either persistent or recurrent chlamydia infection at the end of pregnancy (OR 0.31).

A possible explanation for the less strong increased risk of premature rupture of membranes in our study compared with the studies of Gravett and Ryan is the implementation of screening and treatment for *C trachomatis* in Washington State. In the present study, we were unable to assess whether women diagnosed with *C trachomatis* were successfully treated for the infection. However, presumably, the majority of women identified as *C trachomatis* positive during pregnancy were treated appropriately before delivery. The mechanism by which chlamydia causes premature rupture of membranes has not been well established.[26] However, there is some evidence that it operates through the production of choriodecidual inflammation and through histological chorioamnionitis.[9]

In contrast to the results of other studies, in the present study, *C trachomatis* was not found to be associated with low birth weight. Gravett *et al*[10] found an increased risk in low birth weight infants among chlamydia-infected women relative to uninfected women (OR 2.7). Ryan *et al*[24] found an increased risk in the incidence of low birth weight in patients with positive chlamydia cultures who did not receive treatment, compared with patients whose culture for chlamydia was negative. By contrast, Nyari *et al*[27] did not find an increased risk of low birth weight in chlamydia-infected women relative to those not infected.

Additionally, we did not find an association between chlamydia infection and infant death. However, owing to the small number of infant deaths in chlamydia-infected and non-infected women, we had adequate power to identify only very large risk estimates for this outcome. In the present study, deaths among infants born to women with chlamydia infection (n = 7) were caused by a variety of factors: congenital heart malformations, epileptic syndromes, chorioamnionitis, extreme immaturity and birth asphyxia; our study did not include microbiological and histopathological analysis of the infants or the placenta and therefore cannot directly attribute any of these deaths to chlamydia infection.

Ryan *et al*[24] found that infants born to untreated chlamydia-infected mothers did not differ in perinatal survival compared with those born to mothers who had chlamydia and were treated, and to mothers who did not have chlamydia. By contrast, Martin *et al*[22] found a 10-fold increase in the risk of perinatal death among chlamydia-positive patients compared with chlamydia-negative patients. However, the pathological studies that were done in the fetuses and neonates of chlamydia-infected mothers did not provide evidence that this infection was responsible for the perinatal mortality.

A possible explanation for these discrepancies in findings regarding low birth weight and infant death is that the provision of treatment for *C trachomatis* could have lowered the impact of this infection on the frequency and severity of these outcomes, as has been reported in previous studies.[24 25]

Our study has many potential limitations. One potential limitation is the possibility of exposure misclassification. Exposure was not assessed by laboratory methods, but was based on a check box on the birth certificate. Ascertainment of this exposure could have been incomplete. Women who were found to be chlamydia negative early in pregnancy could have been infected and become positive later, before delivery, and so have been erroneously classified as non-infected. Furthermore, if screening was inconsistent, infected but unscreened women could have been misclassified as negative. Additionally, there may be inconsistencies in the recording of a positive or a negative diagnosis if a woman was positive at the beginning and negative at the end of her pregnancy, and vice versa. These instances of exposure misclassification would most probably

have biased our estimates towards the null. The timing of infection during pregnancy, as well as whether a woman had a positive diagnosis at the beginning or at the end of the pregnancy, is not recorded on the birth certificate. Although the initiation of prenatal care may have been a proxy for the initial time of screening, testing may also have been performed later in the pregnancy. In addition, the check box for *C trachomatis* was implemented in the birth certificate for the first time in 2003, and healthcare personnel may have overlooked this new item and under-reported the presence of this infection.

The Washington birth certificates also lack information regarding treatment history and treatment compliance among pregnant women infected with *C trachomatis* and their partners. Additionally, we do not have information about the number of women who were re-screened, and whether a test of cure was performed in women who were treated for the infection. A recent cohort study conducted by Miller *et al*[28] found that retesting for chlamydia at 34 weeks of gestation identified 29 additional infections out of the 139 (21.6%) total infections of that cohort. Also, the repeated testing to verify cure in pregnant women treated for chlamydia identified that 14 of the 105 (13.3%) women who were treated for the infection had a treatment failure and/or re-infection. Treatment efficacy in pregnant women may differ by treatment regimen, as azithromycin and amoxicillin may be associated with higher cure rates compared with erythromycin.[29] Effective treatment for chlamydia has been shown to decrease the risk of some adverse pregnancy outcomes.[24 25] Therefore, re-infection or non-curative treatment of some women in our study is a possible explanation of the increased risk of some adverse pregnancy outcomes.

Although we were able to assess the potential confounding effects of a number of other infections, including group B streptococcus, gonorrhoea, syphilis, herpes, hepatitis B and hepatitis C, some of the increased risk associated with *C trachomatis* infection in our study could also be due to unmeasured confounding by other genital infections present during pregnancy. For instance, *Mycoplasma hominis*, bacterial vaginosis and ureaplasma urealyticum have been associated with adverse pregnancy outcomes,[8 30 31] but, as they are not recorded on the Washington State birth certificate, we were unable to assess the effect of these infections.

The recently issued 2003 US Standard Certificates of Live Birth and Death added new items such as infections during pregnancy, which were crucial for the ability to conduct our study.[32] Additionally, the linkage of Washington State birth certificate data with infant hospitalisation records gave us a unique opportunity to perform a population-based study assessing *C trachomatis* infection and adverse pregnancy outcomes. This rich database allowed us to assess a number of other maternal factors and known risk factors, including young age, lack of prenatal care, and other maternal infections and complications, as potential confounders in the relationship between chlamydia infection and birth outcomes. However, as chlamydia infection was denoted by a single check box on the Washington State birth certificate, without information regarding time of infection, treatment regimens, test of cure or potential re-infection with chlamydia, the results represent a weighted average of risk of poor outcomes associated with chlamydia infection identified during pregnancy across a variety of unknown screening times and treatments. The addition of information regarding the timing and treatment of infections during pregnancy to the Washington State birth certificate could facilitate changes that might help reduce the impact of chlamydia infection on adverse pregnancy outcomes.

In conclusion, these results raise the possibility that *C trachomatis* is still an important agent associated with premature rupture of membranes and preterm delivery even in settings such as Washington State, where screening and treatment for *C trachomatis* have been implemented.

Key messages

- *Chlamydia trachomatis* infection is associated with increased risk for premature rupture of membranes and preterm delivery in Washington State, a setting where screening and treatment for *C trachomatis* has been implemented.
- In contrast with previous studies, *C trachomatis* infection was not associated with low birth weight or infant death.
- The linkage of Washington State birth certificate data with infant hospitalisation records provides a unique opportunity to perform population-based studies that assess the effect of certain infections on adverse pregnancy outcomes.
- The addition of information regarding the timing and treatment of infections during pregnancy to the Washington State birth certificate could facilitate changes which might help reduce the impact of these infections on adverse pregnancy outcomes.

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