Chlamydia trachomatis and the risk of spontaneous preterm birth, babies who are born small for gestational age, and stillbirth: a population-based cohort study

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Summary

Background ***Chlamydia trachomatis*** **is one of the most commonly diagnosed sexually transmitted infections worldwide, but reports in the medical literature of an association between genital chlamydia infection and adverse obstetric outcomes are inconsistent.**

Methods The Western Australia Data Linkage Branch created a cohort of women of reproductive age by linking records of birth registrations with the electoral roll for women in Western Australia who were born from 1974 to 1995. The cohort was then linked to both chlamydia testing records and the state perinatal registry for data on preterm births and other adverse obstetric outcomes. We determined associations between chlamydia testing, test positivity, and adverse obstetric outcomes using multivariate logistic regression analyses.

Findings From 2001 to 2012, 101 558 women aged 15 to 38 years had a singleton birth. Of these women, 3921 (3·9%) had a spontaneous preterm birth, 9762 (9·6% of 101 371 women with available data) had a baby who was small for gestational age, and 682 (0·7%) had a stillbirth. During their pregnancy, 21 267 (20·9%) of these women had at least one chlamydia test record, and 1365 (6·4%) of those tested were positive. Before pregnancy, 19 157 (18·9%) of these women were tested for chlamydia, of whom 1595 (8·3%) tested positive for chlamydia. Among all women with a test record, after adjusting for age, ethnicity, maternal smoking, and history of other infections, we found no significant association between a positive test for chlamydia and spontaneous preterm birth (adjusted odds ratio 1·08 [95% CI 0·91–1·28]; p=0·37), a baby who was small for gestational age (0·95 [0·85–1·07]; p=0·39), or stillbirth (0·93 [0·61–1·42]; p=0·74).

Interpretation A genital chlamydia infection that is diagnosed and, presumably, treated either during or before pregnancy does not substantially increase a woman's risk of having a spontaneous preterm birth, having a baby who is small for gestational age, or having a stillbirth.

Funding Australian National Health and Medical Research Council.

Introduction

Worldwide, chlamydia is one of the most common sexually transmitted infections, with an estimated 131 million new cases annually.[1] Although genital infections are thought to contribute to the incidence of adverse obstetric outcomes such as spontaneous preterm birth and stillbirth,[2] there are insufficient data regarding the role of chlamydia infections in these outcomes. To our knowledge, there are no published randomised controlled trials of the effects of chlamydia screening in pregnancy on obstetric outcomes.[3] Furthermore, randomised placebo-controlled prevention trials of antibiotics (including azithromycin) given during the antenatal period to high-risk women have found no effect on the incidence of preterm birth.[4] Findings from observational studies have been inconsistent: most studies[5–15] but not all[16–22] suggest that chlamydia infection increases the risk of preterm birth. There is similar discordance in studies examining the effects of chlamydia infection on birthweight and stillbirth.[9,23]

There are many possible explanations for the discrepancy in findings between published observational studies. These explanations include small numbers of events in these studies, which might have led to random error; inconsistency in the type of chlamydia test used (serology, culture, or nucleic acid amplification); variations in the outcome definition and ascertainment; use of case-control designs in which control populations might not be well matched; inadequate control of potential confounders, including other genital tract infections or other factors known to result in adverse obstetric outcomes, such as smoking during pregnancy; and the potential for publication bias. In this analysis, we used a large cohort of women with records of laboratory chlamydia tests and test positivity, and we used reliable ascertainment of obstetric outcomes to examine the effects of chlamydia infection on the risk of spontaneous preterm birth and other adverse birth outcomes.

Methods

Study design and population

A cohort comprising women of reproductive age residing in the Australian state of Western Australia (WA) was

Research in context

Evidence before this study

We searched MEDLINE and PubMed using the terms "chlamydia*" and "preterm birth", "premature birth", and "preterm delivery" that were published until September, 2017. We identified one meta-analysis of seven studies that was published in 2011 and another 19 studies investigating the association between genital *Chlamydia trachomatis* infection and preterm birth. The findings from the meta-analysis and most the other studies suggest an association between chlamydia infection and preterm birth; however, all studies were observational and many had varying definitions of preterm birth, different measures of chlamydia infection, and variations in the comparison groups. We aimed to determine the association between independently ascertained chlamydia testing data in pregnancy and before pregnancy and obstetric outcomes in a large cohort of women giving birth, to examine the effects of chlamydia infection on risk of spontaneous preterm birth and other adverse obstetric outcomes.

Added value of this study

This is the largest study to have compared the risk of spontaneous preterm birth in women with positive and negative tests for genital chlamydia in pregnancy. After accounting for differences in age, ethnicity, and the presence of other infections, we found no increase in the risk of preterm birth in women who tested positive and were treated for chlamydia compared with those who tested negative for chlamydia. We also found no substantive increase in the risk of a baby who was small for gestational age or stillborn.

Implications of all the available evidence

A chlamydia infection that has been identified during pregnancy and treated does not appear to result in a substantial increase in the risk of preterm birth compared with the risk in women tested and shown to not have a chlamydia infection. However, there is insufficient evidence to quantify the effect of untreated chlamydia infections on birth outcomes.

constructed by probabilistically linking two whole-population administrative datasets: birth registrations, which contain a record of all children born and registered in WA from 1974 onwards, and the WA electoral roll. Electoral enrolment is compulsory for Australian citizens, with an estimated 92% of the eligible population included on the roll in WA.[24] Eligible women were all those born between 1974 and 1995, which was derived from birth registrations or the 2014 WA electoral roll.

This cohort was then linked to four datasets: laboratory testing data, the WA Midwives Notification System, the WA Notifiable Infectious Diseases Database, and the WA Hospital Morbidity Data System. The laboratory data included all nucleic acid amplification tests (NAAT) for chlamydia infection conducted between Jan 1, 2001, and Dec 31, 2013, at two large pathology laboratories that provide services in WA (in addition to tests for gonorrhoea and trichomonas infections). Data included the test type, the date of test, and the test result (positive, negative, or equivocal or undetermined). A previous analysis[25] had estimated that these two laboratories cover approximately 50% of all the chlamydia NAAT done in the state.

The WA Midwives Notification System is a statutory database that receives information from birth attendants about all births attended in WA in which the infant has a gestational age of 20 weeks or more, a birthweight of 400 g or more, or if gestation is unknown. Information available in this dataset includes details regarding the birth such as parity, labour onset (spontaneous or not), gestational age (based mostly on ultrasound or date of last menstrual period), birthweight, infant sex, whether the infant was stillborn, maternal demographics, and other aspects of antenatal care and obstetric history. The WA Notifiable Infectious Diseases Database contains a record of all notifiable conditions reported to the WA Department of Health under statute, including chlamydia, gonorrhoea, syphilis, and viral hepatitis. Data obtained included the condition diagnosed and date of onset or diagnosis. The WA Hospital Morbidity Data System includes a record of all public and private hospital admissions in the state. Data obtained included the primary diagnosis (coded according to the International Classification of Diseases; ICD9 until July 1999, and ICD10 afterwards), any procedures done, and admission and discharge dates.

The WA Data Linkage Branch linked data using probabilistic matching of personal identifiers such as name, date of birth, address, and sex. Linkage accuracy using this process is high, with an error rate estimated at 0·11%.[26] All linkage was done independently of the study investigators and only de-identified data were provided for analysis.

Analyses were restricted to women in the cohort who had a first record of a singleton birth (regardless of parity) between 2001 and 2012 in the Midwives Notification System, and were resident in WA and aged at least 15 years at the time of giving birth.

This study was approved by the Government of WA Department of Health Human Research Ethics Committee (no. 2012/73) and the WA Aboriginal Health Ethics Committee (no. 470).

For the **WA Midwives Notification System, the WA Notifiable Infectious Diseases Database, and the WA Hospital Morbidity Data System** see https://www.datalinkage-wa.org.au/data/collections

Outcome definitions and exposure to chlamydia testing

We investigated three obstetric outcomes: spontaneous preterm births, babies who were small for gestational age, and stillbirths. A woman was categorised as having a spontaneous preterm birth if she had a delivery at less than 37 weeks' gestation after spontaneous onset of labour. A baby that was small for gestational age was defined as an infant birthweight of less than the

10th centile for gestational age by infant sex. Stillbirths (>20 weeks' gestation) were identified in the Midwives Notification System.

We initially categorised women according to their history of chlamydia testing relative to the pregnancy. We calculated the date of conception by subtracting the number of weeks of gestation from the date of birth. Women were classified as being tested during pregnancy if they had at least one chlamydia test during the pregnancy, tested before pregnancy if there was no record of a test during pregnancy but at least one chlamydia test record dated before the pregnancy, and no test record if there was no linked chlamydia test before the date of birth.

Since the risk of adverse outcomes could vary according to when a woman was tested, analyses were then conducted to determine associations between chlamydia positivity and each of the three outcomes taking test timing into account. Women were classified into five categories: tested negative during pregnancy, tested positive during pregnancy, tested negative before pregnancy, tested positive before pregnancy, and no test record, with priority given to tests that occurred most proximal to the date of birth. We also did a three-category analysis to examine the association with chlamydia positivity regardless of the timing of the test (during or before pregnancy).

We assessed the validity of the results of the chlamydia tests by comparing women testing positive in the pathology data with chlamydia notifications from the WA Notifiable Infectious Diseases Database.

Statistical analysis

Spontaneous preterm birth versus term birth, small for gestational age versus not, and stillbirth versus livebirth were examined separately; however, outcomes were not mutually exclusive (eg, stillbirths could also be classified as being born preterm). Women with missing outcome data were excluded from each analysis.

We used multivariate logistic regression analyses to determine the associations between chlamydia testing and positivity and each of the three outcomes. All regression analyses were initially adjusted for maternal age at delivery (in 5-year age groups), health area of residence (metropolitan, rural, and remote, based on residential postal codes), and socioeconomic status (in tertiles, based on the Australian Bureau of Statistics Socio-Economic Indexes for Areas). We then adjusted for other covariates on the basis of known predictors of adverse obstetric outcomes. These included ethnicity ("Caucasian", "Aboriginal", other), smoking during pregnancy (yes or no), and other infections (notification of hepatitis B or C or syphilis before the delivery date and, based on linked pathology data, gonorrhoea and trichomoniasis in the categories: all tests negative, ≥1 test positive, no test record). Analyses were further adjusted for parity (0 or ≥1), previous adverse obstetric outcomes (for each outcome, we included a variable indicating whether the woman had an earlier birth record of that outcome), hypertensive disease (yes or no), gestational and pre-existing diabetes (yes or no), antepartum haemorrhage (yes or no), urinary tract infection (yes or no), and use of assisted reproductive technologies (yes or no). Assessment of use of assisted reproductive technologies was based on a hospital record in the year before conception, with a code for procreative management or assisted reproductive technologies in the diagnosis or procedure fields. The most parsimonious model was reported in the results.

During the period of observation, chlamydia screening guidelines in Australia recommended regular testing for young women and Aboriginal women, and chlamydia testing increased substantially after 2005,[25] so analyses were repeated stratified by whether the mother was Aboriginal, age (<25 and ≥25 years), and year of giving birth (before or during 2005 or after 2005). A sub-analysis was also done for spontaneous preterm birth occurring before 34 weeks' gestation.

All analyses were performed using SAS software version 9.4 (SAS Institute Inc, Cary, NC, USA).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. JR and BL had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 101 558 women aged 15 to 38 years in the cohort with a first record of a singleton birth between 2001 and 2012. Of births that could be classified, 3921 (3·9%) of 101 558 women had a spontaneous preterm birth, 9762 (9·6%) of 101 371 births were small for gestational age, and 682 (0·7%) of 101 558 infants were stillborn (table 1).

Table 1 shows the characteristics of the mothers, grouped according to obstetric outcomes. Generally, women with each of the adverse obstetric outcomes shared similar characteristics. They were typically younger, had lower socioeconomic status, were less likely to be resident in a major city, and were less likely to be classified as Caucasian than those without the three adverse outcomes. They were also more likely to have smoked during the pregnancy and to have been diagnosed with hepatitis C, syphilis, gonorrhoea, and trichomoniasis during or before the pregnancy.

Of the 101 558 women included, 40 424 (39·8%) were tested for chlamydia and 61 134 (60·2%) had no linked record of a test before giving birth. 21 267 (20·9%) were tested during pregnancy and 19 157 (18·9%) were tested before pregnancy.

1365 of the women tested during pregnancy were positive, with a median first chlamydia test date of 14 weeks before gestation (IQR 8–26). 1595 of the women

	All births	Term	Preterm		Small-for-gestational-age baby		Stillbirth
			Planned*	Spontaneous	No	Yes	
Number of births	101 558	94 276	3361	3921	91 609	9762	682
Percentage of all births	100·0%	92·8%	3·3%	3·9%	90·4%	9·6%	0·7%
Maternal demographics							
Median age (IQR), years	26·8 (23·0–29·8)	26·8 (23·0–29·8)	26·8 (23·0–30·0)	26·2 (21·7–29·7)	26·9 (23·1–29·9)	26·1 (21·7–29·5)	25·7 (22·2–29·3)
Socioeconomic status in the lower third	35 722 (35·2%)	33 023 (35·0%)	1187 (35·3%)	1513 (38·6%)	31 755 (34·7%)	3885 (39·8%)	256 (37·6%)
Resident of a major city	75 240 (74·1%)	69 917 (74·2%)	2549 (75·8%)	2774 (70·7%)	68 427 (74·7%)	6687 (68·5%)	463 (67·9%)
Caucasian	84 385 (83·1%)	78 785 (83·6%)	2630 (78·3%)	2970 (75·7%)	77 288 (84·4%)	6962 (71·3%)	506 (74·2%)
Aboriginal	8087 (8·0%)	7062 (7·5%)	392 (11·7%)	633 (16·1%)	6493 (7·1%)	1556 (15·9%)	105 (15·4%)
Other ethnicity	9086 (8·9%)	8429 (8·9%)	339 (10·1%)	318 (8·1%)	7828 (8·5%)	1244 (12·7%)	71 (10·4%)
Antenatal factors							
Smoked cigarettes during pregnancy	17 673 (17·4%)	16 024 (17·0%)	664 (19·8%)	985 (25·1%)	14 617 (16·0%)	3010 (30·8%)	175 (25·7%)
Nulliparous	60 184 (59·3%)	55 941 (59·3%)	1922 (57·2%)	2321 (59·2%)	54 189 (59·2%)	5889 (60·3%)	402 (58·9%)
Used ART before conception†	1282 (1·3%)	1136 (1·2%)	82 (2·4%)	64 (1·6%)	1179 (1·3%)	98 (1·0%)	16 (2·3%)
Infections‡							
Hepatitis C	754 (0·7%)	658 (0·7%)	37 (1·1%)	59 (1·5%)	626 (0·7%)	125 (1·3%)	NA (1·2%)
Hepatitis B	370 (0·4%)	342 (0·4%)	12 (0·4%)	16 (0·4%)	301 (0·3%)	67 (0·7%)	NA (0·3%)
Syphilis	122 (0·1%)	107 (0·1%)	NA (0·2%)	NA (0·2%)	90 (0·1%)	32 (0·3%)	NA (0·4%)
Gonorrhoea	1200 (1·2%)	1032 (1·1%)	72 (2·1%)	96 (2·5%)	901 (1·0%)	293 (3·0%)	17 (2·5%)
Trichomoniasis	348 (0·3%)	294 (0·3%)	26 (0·8%)	28 (0·7%)	261 (0·3%)	85 (0·9%)	NA (0·3%)

Data are number of participants (percentage of the total births in the group, as stated at the top of each column), excluding those with missing values, unless otherwise indicated. ART=assisted reproductive technology. NA=data not available because small cell numbers have been suppressed. *Including labour inductions and prelabour caesarean sections. †Hospital records show access to ART in the year before conception. ‡Diagnosed during or before pregnancy.

Table 1: **Participant characteristics in Western Australian women who were born from 1974 to 1995 and gave birth from 2001 to 2012, grouped by obstetric outcome**

tested before pregnancy were positive, with a median time before conception of 1·7 years (IQR 0·6–3·5). Of the women who had a positive chlamydia test before delivery, 91·7% had a chlamydia notification in the WA Notifiable Diseases Database during the corresponding period. 3·2% of those with only negative tests and 1·4% of those with no test record had a chlamydia notification in the corresponding period.

For regression analyses of spontanous preterm birth we did the analyses in 98 197 women (all women, excluding those with planned preterm birth). For analyses of babies who were small for gestational age, we included 101 371 women and, for analyses of stillbirths, we included 101 558 women.

Figure 1 shows the association between chlamydia testing (grouping those with both positive and negative tests together) and each birth outcome evaluated. Compared with women who were tested for chlamydia during their pregnancy, women who only had a chlamydia test before their pregnancy were significantly more likely to have a spontaneous preterm birth (fully adjusted odds ratio [aOR] 1·15, 95% CI 1·04–1·27; p=0·008). The opposite was observed for babies who were small for gestational age: mothers who were only tested for chlamydia before pregnancy were significantly less likely to have a baby that was small for gestational age than those who were tested during pregnancy (0·86, 0·81–0·92; p<0·0001). Women who were only tested for chlamydia before pregnancy were also substantially more likely to have a stillbirth than those tested for chlamydia during pregnancy (1·71, 1·35–2·17; p<0·0001). For each of the three obstetric outcomes, there was no significant difference in risk between women with no test record and women tested for chlamydia during their pregnancy in the fully adjusted models.

Figure 2 shows the association between chlamydia positivity and each adverse obstetric outcome. Among the 20 492 women tested for chlamydia during their pregnancy who were included in analyses for spontaneous preterm birth, 864 (4·5%) who were negative for chlamydia and 81 (6·2%) who were positive for chlamydia had a spontaneous preterm birth. For 18 439 women who only had a chlamydia test record before their pregnancy, 696 (4·1%) women who tested negative for chlamydia and 84 (5·5%) women who tested positive for chlamydia had a spontaneous preterm birth. In minimally adjusted models (adjusted for age, region of residence, and socioeconomic status) and fully adjusted models, the risk of spontaneous preterm birth in women testing positive versus negative for chlamydia was not significant. The absence of effect of chlamydia positivity on risk of spontaneous preterm birth was true

for women tested during pregnancy (aOR 1·00, 95% CI 0·79–1·27; p=0·99), regardless of trimester during which testing occurred (first trimester 1·13, 0·82–1·57; p=0·45; second or third trimester 0·88, 0·62–1·25; p=0·48), and for women only tested before their pregnancy (1·12, 0·89–1·42; p=0·33). The main factors resulting in attenuation of the risks included adjustment for ethnicity, age, and other infections (appendix).

See Online for appendix

	Population	Cases	Minimally adjusted OR (95% CI)	Fully adjusted OR (95% CI)	p value
Spontaneous preterm birth					
Tested during pregnancy	20492	945 (4·6%)	1·00	1·00	
Tested before pregnancy	18439	780 (4·2%)	1·05 (0·95–1·16)	1·15 (1·04–1·27)	0·008
No test record	59266	2196 (3·7%)	0·91 (0·84–0·99)	1·07 (0·90–1·27)	0·43
Small for gestational age					
Tested during pregnancy	21233	2650 (12·5%)	1·00	1·00	
Tested before pregnancy	19109	1666 (8·7%)	0·77 (0·72–0·82)	0·86 (0·81–0·92)	<0·0001
No test record	61029	5446 (8·9%)	0·79 (0·75–0·84)	0·95 (0·85–1·06)	0·37
Stillbirth					
Tested during pregnancy	21267	136 (0·6%)	1·00	1·00	
Tested before pregnancy	19157	167 (0·9%)	1·57 (1·24–1·99)	1·71 (1·35–2·17)	<0·0001
No test record	61134	379 (0·6%)	1·11 (0·91–1·37)	1·12 (0·76–1·65)	0·57

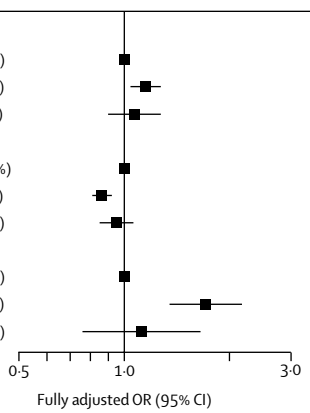

Figure 1: **Association between chlamydia testing history and adverse obstetric outcomes**
Populations are the number of women with available data for each obstetric outcome in each category. The minimally adjusted model was adjusted for age, area of residence, and socioeconomic status. The fully adjusted model was adjusted for age, area of residence, socioeconomic status, smoked during pregnancy, other infections, and ethnicity; p values relate to fully adjusted OR. OR=odds ratio.

	Population	Cases	Minimally adjusted OR (95% CI)	Fully adjusted OR (95% CI)	p value
Spontaneous preterm birth					
Tested during pregnancy					
Negative	19184	864 (4·5%)	1·00	1·00	
Positive	1308	81 (6·2%)	1·17 (0·93–1·49)	1·00 (0·79–1·27)	0·99
Tested before pregnancy					
Negative	16909	696 (4·1%)	1·00	1·00	
Positive	1530	84 (5·5%)	1·26 (1·00–1·60)	1·12 (0·89–1·43)	0·33
Combined tests before and during pregnancy					
Negative	36093	1560 (4·3%)	1·00	1·00	
Positive	2838	165 (5·8%)	1·22 (1·04–1·45)	1·08 (0·91–1·28)	0·37
Small for gestational age					
Tested during pregnancy					
Negative	19876	2418 (12·2%)	1·00	1·00	
Positive	1357	232 (17·1%)	1·25 (1·07–1·45)	1·05 (0·90–1·22)	0·58
Tested before pregnancy					
Negative	17523	1515 (8·6%)	1·00	1·00	
Positive	1586	151 (9·5%)	1·02 (0·85–1·21)	0·88 (0·73–1·05)	0·15
Combined tests before and during pregnancy					
Negative	37399	3933 (10·5%)	1·00	1·00	
Positive	2943	383 (13·0%)	1·11 (0·99–1·25)	0·95 (0·85–1·07)	0·39
Stillbirth					
Combined tests before and during pregnancy					
Negative	37470	277 (0·7%)	1·00	1·00	
Positive	2954	26 (0·9%)	1·06 (0·70–1·59)	0·93 (0·61–1·42)	0·74

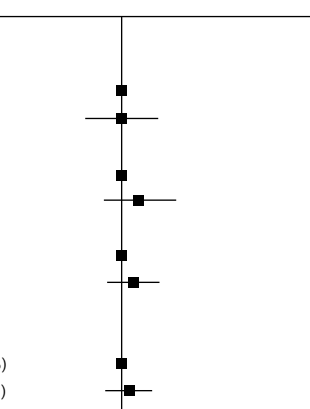

Figure 2: **Association between chlamydia positivity and adverse obstetric outcomes**
Women with no test record were included in the analysis but these data are not shown. Populations are the number of women with available data for each obstetric outcome in each category. The minimally adjusted model was adjusted for age, area of residence, and socioeconomic status. The fully adjusted model was adjusted for age, area of residence, socioeconomic status, smoked during pregnancy, other infections, and ethnicity; p values relate to the fully adjusted OR. OR=odds ratio.

	Negative for chlamydia*, n/N (%)	Positive for chlamydia, n/N (%)	Minimally adjusted odds ratio† (95% CI)	Fully adjusted odds ratio‡ (95% CI)	p value heterogeneity
Spontaneous preterm birth					
Mother is Aboriginal					0·74
No	1191/31 535 (3·8%)	83/1939 (4·3%)	1·11 (0·89–1·40)	1·09 (0·87–1·38)	..
Yes	369/4558 (8·1%)	82/899 (9·1%)	1·10 (0·86–1·42)	1·10 (0·85–1·42)	..
Age of mother, years					0·71
<25	689/14 212 (4·8%)	121/1881 (6·4%)	1·31 (1·07–1·60)	1·12 (0·92–1·37)	..
≥25	871/21 881 (4·0%)	44/957 (4·6%)	1·17 (0·85–1·59)	1·09 (0·80–1·49)	..
Year of giving birth					0·45
2001–05	307/5827 (5·3%)	38/533 (7·1%)	1·24 (0·87–1·76)	1·06 (0·74–1·51)	..
2006–12	1253/30 266 (4·1%)	127/2305 (5·5%)	1·22 (1·00–1·47)	1·10 (0·90–1·33)	..
Small for gestational age					
Mother is Aboriginal					0·23
No	2938/32 614 (9·0%)	203/2000 (10·1%)	1·09 (0·94–1·27)	1·04 (0·90–1·21)	..
Yes	995/4785 (20·8%)	180/943 (19·1%)	0·87 (0·73–1·05)	0·83 (0·69–1·00)	..
Age of mother, years					0·73
<25	1874/14 706 (12·7%)	285/1956 (14·6%)	1·12 (0·98–1·29)	0·94 (0·81–1·08)	..
≥25	2059/22 693 (9·1%)	98/987 (9·9%)	1·09 (0·88–1·35)	0·98 (0·79–1·22)	..
Year of giving birth					0·76
2001–05	817/6047 (13·5%)	93/550 (16·9%)	1·12 (0·89–1·42)	0·93 (0·73–1·19)	..
2006–12	3116/31 352 (9·9%)	290/2393 (12·1%)	1·12 (0·98–1·27)	0·96 (0·84–1·10)	..

N=the total number of women with available data for each obstetric outcome in each category. n=the number of women in each demographic category who are positive for each obstetric outcome. *Reference group (odds ratio=1·00). †Adjusted for age, area of residence, and socioeconomic status. ‡Adjusted for age, area of residence, socioeconomic status, smoking during pregnancy, other infections, and ethnicity. Women with no test record were included in the analysis but these data are not shown.

Table 2: **Association between chlamydia positivity and adverse obstetric outcomes by whether the mother is Aboriginal, maternal age, and year of giving birth**

Among women tested during pregnancy, a higher proportion of women with a positive chlamydia test had a baby who was small for gestational age (232 [17·1%] of 1357 women) than those with a negative test (2418 [12·2%] of 19 876). The proportions of babies that were small for gestational age in women who were only tested for chlamydia before their pregnancy were 9·5% (151 of 1586 women) for those testing positive and 8·6% (1515 of 17 523 women) for those testing negative. Like the results for spontaneous preterm birth, after adjustments, there were no significant differences in the risk of a baby who was small for gestational age by chlamydia positivity (figure 2).

There were too few stillbirths to investigate the association with chlamydia positivity stratified by test timing. 26 (0·9%) of 2954 women with a positive chlamydia test and 277 (0·7%) of 37 470 women with a negative test had a stillbirth, and there was no significant association between chlamydia positivity and stillbirth (aOR 0·93, 95% CI 0·61–1·42; p=0·74; figure 2).

Analyses stratified by whether the mother is Aboriginal, maternal age, and year of giving birth were consistent with the main regression analyses for spontaneous preterm birth and babies who were small for gestational age (table 2). There was no increased risk of these outcomes when comparing women testing positive for chlamydia with those testing negative. There was also no significant difference in the risk of spontaneous preterm birth at less than 34 weeks' gestation between mothers who were positive for chlamydia and those who were negative (appendix).

Discussion

This large population-based cohort study analysed more than 20 000 women with laboratory testing data on chlamydia positivity during pregnancy. In more than 900 spontaneous preterm births and more than 2500 babies who were small for gestational age, we found no increase in the risk of having a spontaneous preterm birth or a baby that was small for gestational age among women with a positive chlamydia test during pregnancy. Although there were fewer cases, we also found no evidence to suggest an association between a positive chlamydia test and stillbirth.

There has been one systematic review[14] of seven observational studies and several other observational studies examining the association between genital chlamydia infection and preterm birth, with ambiguous findings reported across studies. As a body of evidence, interpreting these findings collectively is difficult for several reasons. First, there is a lack of consistent definition of outcomes. Many studies[5,6,9,12,13,18,19,21–23] have not distinguished spontaneous preterm births from all other preterm births and, in many high-income countries, a substantial proportion of preterm births are planned (by labour induction or prelabour caesarean

section) to manage obstetric conditions such as hypertensive diseases.[2] Similarly, several studies[7,8,18,23] report on low birthweight without accounting for gestational age and, therefore, do not clearly distinguish this outcome from preterm birth. Second, all the larger reports[13,15,21,23] before this Article do not have information on women who tested negative for chlamydia. Third, some studies[8,9,12,22] do not consider potential confounders, such as the presence of other genital infections, maternal smoking, and ethnicity, and therefore have been unable to account for these factors when quantifying associations. Inadequate consideration of such factors can lead to false-positive results. For example, much chlamydia screening has focused on young women with several sexual partners.[3] Younger age is strongly associated with spontaneous preterm birth,[15] and young women with several sexual partners might be more likely to participate in high-risk activities, such as smoking in pregnancy, that also increase the risk of adverse obstetric outcomes. Therefore, studies comparing outcomes in women who are positive for chlamydia to those not tested for chlamydia can be biased. Finally, other differences that could also contribute to the variation in findings include differences in study populations, timing of testing during the pregnancy, and the test type.

This study had well defined and reliably reported outcomes[27] that were based on a statutory perinatal birth register. We could make comparisons between women who tested positive and negative for chlamydia and stratify by timing of tests in relation to the pregnancy. We also considered other important factors, such as ethnicity, maternal smoking, and other infections. Furthermore, the cohort design, with ascertainment of outcomes and exposures (chlamydia testing information) from independent sources (namely, the perinatal register for outcomes and pathology data for exposures), reduced the likelihood of biased reporting. On systematic searching of the medical literature, we identified four studies[13,15,21,22] larger than this report that have examined the association between chlamydia infection and preterm birth, including one from our research team.[15] However, three studies[13,15,21] did not have information on actual testing for chlamydia (ie, they compared those with a positive chlamydia test to the rest of the population, regardless of whether they had been tested for chlamydia) and one case-control study[22] assessed chlamydia infection through presence of positive serology and found no association of chlamydia with preterm birth.

Our finding that there is no significant increase in the risk of spontaneous preterm birth with a genital chlamydia infection is plausible and is supported by other observational studies.[11,17,19–22] The substantial attenuation of the risk of any adverse obstetric outcome (including preterm birth) that we found after adjusting for other infections and ethnicity support the notion that studies that reported positive associations between chlamydia infection and preterm birth might be affected by residual confounding. Furthermore, although there are no reported trials of chlamydia screening of women in pregnancy to reduce preterm birth,[3] placebo-controlled trials of prophylactic antibiotics (including azithromycin or erythromycin, which are both effective against chlamydia) given to women during the antenatal[4] and preconception period[28] have shown no significant reduction in preterm birth rates. These trial findings suggest that chlamydia is not a major causative organism in preterm birth.

We did not have treatment data; however, an audit of general practitioner-notified chlamydia cases in WA in 2008 found that 92% were prescribed either azithromycin (83%) or doxycycline (9%)[29] and, thus, we assumed that most women who tested positive were treated for their chlamydia infection. Our results should therefore be interpreted in this light. That is, the risk of spontaneous preterm birth is similar between women who tested negative and those who tested positive who were treated. However, a substantial proportion of the chlamydia diagnosed in our cohort is likely to have been detected through asymptomatic screening[29] and, therefore, the duration of infection before testing and treatment could vary substantially. We found that women who were tested for chlamydia before pregnancy, but not during pregnancy, had a greater risk of preterm birth (aOR 1·15, 95% CI 1·04–1·27) and stillbirth (1·71, 1·35–2·17; figure 1) than women who were tested during pregnancy. It is possible that women who were only tested before pregnancy could have undiagnosed and, hence, untreated chlamydia (or other genital infections) during the pregnancy and that the untreated infection (ie, of a longer duration) might explain the observed increase in the risk of adverse outcomes. Alternative explanations could be that these women were less likely to access preventive antenatal care (including chlamydia screening), and it is the reduced access to care that accounts for their higher risk.

Only some observational studies examining the association between chlamydia and preterm birth have reported on treatment. Of those reporting or assuming treatment, two studies[18,23] showed significant associations between chlamydia infection and preterm birth, but others were equivocal.[14,19] Of studies[5,6,16,17,30] documenting that the chlamydia infections were untreated, four[5,6,16,30] suggested an increase in risk of preterm birth from chlamydia infection but they were all done before 2000, when nucleic acid testing for chlamydia became widespread. The only study[17] that showed no increase in risk was also the only one to have been done after 2000. Studies of untreated chlamydia infection in pregnancy would be unlikely to be ethical; however, studies where routine post-partum testing for chlamydia (regardless of obstetric outcome) is done might identify untreated infections that had been present during pregnancy and could assist in establishing whether an untreated infection is a risk factor for spontaneous preterm birth.

Although our linked pathology data did not include all tests done in the state,[25] our main comparisons are between women who tested positive for chlamydia and those who tested negative. It is conceivable that some women might have been tested at more than one laboratory, but our data from the two laboratories show that this co-testing was minimal: no women were tested at more than one of the laboratories during pregnancy and less than 10% of women were tested at more than one of the laboratories in the 3 years preceding pregnancy. Other caveats on interpreting our findings include the lack of data on NAAT titres, which might correlate with severity of infection, and of clinical information on whether infections were symptomatic or not. Therefore, we could not investigate whether more severe infections are associated with an increased risk of adverse birth outcomes, nor were we able to examine factors such as effects of host genetic susceptibility.

This is the largest study, in the era of widespread nucleic acid testing, to compare the risk of adverse birth outcomes in women with positive and negative chlamydia tests. Our results suggest that a chlamydia infection diagnosed and, presumably, treated either during or before pregnancy does not increase a woman's risk of spontaneous preterm birth, a baby that is small for gestational age, or stillbirth. These findings support the continued screening of high-risk women during pregnancy for chlamydia and should reassure women who have chlamydia diagnosed and treated during pregnancy that there is no increased risk of these serious adverse birth outcomes.

Contributors

BL instigated the study and obtained the data for the study. JR conducted the analyses. JR and BL wrote the initial draft. All authors advised on the analyses and interpretation of results and contributed to all subsequent iterations of this Article.

Chlamydia and Reproductive Health Outcome Investigators

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Declaration of interests

BD and BL report grants from the Australian National Health and Medical Research Council during the conduct of the study. All other authors declare no competing interests.

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