2018

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This article was originally published as:
Reekie, J., Donovan, B., Guy, R., Hocking, J. S., Kaldor, J. M., Mak, D. B., Pearson, S., Preen, D., Stewart, L., & Liu, J. W. (2018). Risk of pelvic inflammatory disease in relation to chlamydia and gonorrhea testing, repeat testing, and positivity: A population-based cohort study. *Clinical Infectious Diseases, 66* (3), 437-443.

Original article available here:
https://dx.doi.org/10.1093/cid/cix769

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

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Word count 250 abstract; 3500 text

Current count: 237; 3387

Reference max 30

Abstract

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

Methods: A cohort of reproductive-aged women was created by linking Birth Registrations and Electoral Roll records for women in Western Australia born from 1974-1995. This cohort was linked to both chlamydia testing records and the state perinatal registry for data on preterm births and other adverse obstetric outcomes. Associations between chlamydia testing, test positivity and adverse obstetric outcomes were determined using multivariate logistic regression.

Findings: From 2001 to 2013, there were 101,558 women with a singleton birth of which 3921 (3·9%) were classified as having a spontaneous preterm birth, 9762 (9·6%) a small-for-gestational-age baby and 682 (0·7%) a stillbirth. During their pregnancy, 21,267 (20·9%) women had at least one chlamydia test record and 1365 (6·4%) of those tested were positive. Respective numbers of women tested and positive prior to pregnancy were 19,157 (18·9%) and 1595 (8·3%). Among all women with a test record, after adjusting for age, ethnicity, maternal smoking and history of other infections, there was no significant association between a positive chlamydia test and spontaneous preterm birth, small-for-gestational-age or stillbirth (adjusted OR 1·08 (95%CI 0·91-1·28), 0·95 (0·85-1·07), and 0·93 (0·61-1·42) respectively).

Interpretation: A chlamydia infection diagnosed and treated either during or prior to pregnancy does not substantially increase a woman’s risk of adverse obstetric outcomes.

Funding: Australian National Health and Medical Research Council

Introduction

Worldwide, chlamydia is one of the most common sexually transmissible infections (STIs) with an estimated 131 million new cases annually; the majority diagnosed in women of childbearing age.[1] While genital infections are thought to contribute to the incidence of adverse obstetric outcomes such as spontaneous preterm birth and stillbirth,[2] there are limited data regarding the role of chlamydia infections on these outcomes. 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 rates of preterm birth.[4] Findings from observational studies have been inconsistent with most,[5-15] but not all,[16-22] suggesting chlamydia infection increases the risk of preterm birth. There is similar discordance in studies examining the effects of chlamydia infection on birth weight and stillbirth.[9,23]

There are many possible explanations for the discrepancy in findings between published observational studies. These include studies with small numbers of events leading 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 where control populations may 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 use a large cohort of women with laboratory chlamydia testing and positivity records and reliable ascertainment of outcomes to examine the effects of chlamydia infection on the risk of spontaneous preterm birth, and other adverse birth outcomes.

Methods

Study population and linkage

A cohort comprising women of reproductive age residing in the Australian state of Western Australia (WA) was 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, 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 Dataset. The laboratory data included all chlamydia nucleic-acid amplification tests (NAAT) conducted between 1st January 2001 and 31st December 2013 at two large pathology laboratories providing services in the state as well as tests for gonorrhoea and trichomonas. Data included the test type, the date of test, and test result (positive, negative, or equivocal/undetermined). Previous analysis has estimated that these two laboratories cover approximately 50% of all the chlamydia NAAT conducted in the state.[25]

The WA Midwives Notification System is a statutory database which receives information from birth attendants about all births attended in WA where the infant has a gestational age of 20 weeks or more, a birthweight of 400 grams or more, or if gestation is unknown. Information available in this dataset includes details regarding the birth such as labour onset, gestational age (based mostly on ultrasound or date of last menstrual period), birth weight, infant sex, stillbirth, maternal demographics and 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 Dataset includes a record of all public and private hospitalisations in the state. Data include the primary diagnosis (coded

according to the International Classification of Diseases), any procedures and admission and discharge dates.

Data linkage was conducted by the WA Data Linkage Branch 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 conducted independent of the study investigators and only de-identified data were provided to the researchers.

Outcome definitions

A woman was categorised as having a spontaneous preterm birth if she had a delivery at <37 weeks gestation with spontaneous onset of labour. A small-for-gestational-age baby was defined if the infant birth weight was less than the 10th centile for gestational age by infant sex. Stillbirths (>20 weeks gestational age) were identified in the Midwives Notification System.

Exposure to chlamydia testing and infection

Women were initially categorised according to their history of chlamydia testing in relation to the pregnancy. The date of conception was calculated by subtracting the number of weeks gestation from the date of birthing. Women were classified as 'tested during pregnancy' if the women had at least one chlamydia test during the pregnancy, 'tested prior to pregnancy' if there was no record of a test during pregnancy but at least one chlamydia test record dated prior to the pregnancy, and 'no test record' if there was no linked chlamydia test prior to the date of birthing.

As 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' prior to pregnancy, tested 'positive' prior to pregnancy and no test record with priority given to tests that occurred most proximal to the date of birthing. A three category analysis was also investigated examining the association with chlamydia positivity regardless of the timing of the test (during or prior to pregnancy).

Validity of chlamydia test result was assessed by comparing those testing positive from the pathology data with chlamydia notifications from the WA Notifiable Infectious Diseases Database.

Statistical analyses

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 ≥15 years at the time of giving birth.

Spontaneous preterm birth versus term birth, small-for-gestational-age versus not, and stillbirth versus live birth were examined separately, however outcomes were not mutually exclusive (e.g. stillbirths could also be classified as born preterm). Those with missing outcome data were excluded from each analysis.

Multivariate logistic regression was used 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), area of residence (metropolitan, rural and remote, based on a Australian standard statistical classification of postal codes), and socio-economic status (in tertiles based on the Australian Bureau of Statistics Socio-Economic Indexes for Areas). We then adjusted for other covariates based on known predictors of adverse obstetric outcomes. These included: ethnicity (Caucasian, Aboriginal, other), smoking during pregnancy (yes/no), other infections (hepatitis B/C or syphilis notification prior to the delivery date); and based on linked pathology data, gonorrhoea and trichomonas (all test negative, ≥1 test positive, no test record). Analyses were further adjusted for parity (0, 1+), prior adverse obstetric outcomes (for each outcome we included a variable indicating if the woman had an earlier birth record of that outcome), hypertensive disease (yes/no), gestational and pre-existing diabetes (yes/no), antepartum haemorrhage (yes/no), urinary tract infection (yes/no), and use of assisted reproductive technologies (ART) (yes/no). Assessment of ART was based on a hospital record in the year prior to 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.

As during the period of observation, chlamydia screening guidelines in Australia recommended regular testing for young women and Aboriginal women, and chlamydia testing patterns increased substantially after 2005,[25] analyses were repeated stratified by Aboriginality, age (<25 and ≥25 years), and year of giving birth (≤2005, >2005). A sub-analysis was also conducted for preterm birth defined as <34 weeks gestation.

All analyses were performed using SAS software version 9.4 (SAS Institute Inc, Cary, North Carolina). This study was approved by the Government of WA Department of Health Human Research Ethics Committee (Ref #2012/73) and the WA Aboriginal Health Ethics Committee (Ref 470).

Role of funding source

The funding source had no role in the study design, analysis, interpretation; nor in the report writing and decision to submit for publication

Results

We identified 101,558 women with a first record of a singleton birth between 2001 and 2012 in the cohort. Of births that could be classified, 3921/101558 (3·9%) had a spontaneous preterm birth, 9762/101371 (9·6%) births were small-for-gestational-age and 682/101,558 (0·7%) were stillbirths.

Table 1 shows women's characteristics according to birth outcome. Generally, women with each of the adverse obstetric outcomes shared similar characteristics. They were younger, had lower socioeconomic status, were less likely to be resident in a major city, and less likely to identify 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 prior to the pregnancy.

Among the cohort, 21,267 (20·9%) were tested for chlamydia during their pregnancy of whom 1365 (6·4%) were positive with the median first chlamydia test date at 14 weeks gestation; (IQR 8-23 weeks). Among the 19,157 (18·9%) women who only had a chlamydia test record prior to their pregnancy, 1595 (8·3%) had a positive result with the majority having their most recent test record over a year prior to

conception (median 1·7 years; IQR 0·6-3·5). The remaining 61,134 (60%) women had no linked record of a chlamydia test prior to their date of delivery. Of women who had a positive chlamydia test prior to delivery, 91.7% had a chlamydia notification in the WA Notifiable Diseases Database during the corresponding period. Whilst of those with only negative tests, and those with no test record, 3.2% and 1.4% respectively had a chlamydia notification in the corresponding period.

Figure 1 shows the association between chlamydia testing and each birth outcome evaluated. These results group those with both positive and negative tests together. Compared to women who were tested for chlamydia during their pregnancy, women who only had a record of testing prior to their pregnancy were significantly more likely to have a spontaneous preterm birth (adjusted odds ratio [aOR] 1·15, 95%CI 1·04-1·27, p=0·008). The opposite was observed for small-for-gestational-age, with women tested for chlamydia prior to pregnancy significantly less likely to have a small-for-gestational-age baby than those who were tested during pregnancy (aOR 0·86, 95%CI 0·81-0·92, p<·0001). Women tested for chlamydia prior to pregnancy were also substantially more likely to have a stillbirth than those tested for chlamydia during pregnancy (aOR 1·71, 95%CI 1·35-2·17, p<·0001). For each of the three 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 women tested for chlamydia during their pregnancy, 864 (4·5%) who were negative for chlamydia and 81 (6·2%) who were positive for chlamydia had a spontaneous preterm birth. For women who only had a chlamydia test record prior to their pregnancy, 696 (4·1%) test-negative women and 84 (5·5%) test-positive women had a spontaneous preterm birth. In models adjusted for age, region of residence and socioeconomic status, the risk of spontaneous preterm birth in women testing positive versus negative for chlamydia approached, but did not reach statistical significance. However, in the fully-adjusted model, there was no significant association between chlamydia positivity and spontaneous preterm birth. This was the case for women tested during pregnancy (aOR 1·00, 95%CI 0·79-1·27, p=0·99) and remained regardless of the trimester during which testing occurred (first trimester aOR 1·13, 95%CI 0·82-1·57, p=0·45; second/third trimester aOR 0·88,

95%CI 0·62-1·25, p=0·48) and in women tested only prior to their pregnancy (aOR 1·12, 95%CI 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 Table 1).

Among women tested during pregnancy, a higher percentage of women with a positive chlamydia test had a small-for-gestational-age baby than those who tested negative (17·1% vs 12·2%). Respective proportions among women only tested for chlamydia prior to their pregnancy were 9·6% vs 8·6%. Similar to results for spontaneous preterm birth, after adjustments, there were no significant differences in the risk of a small-for-gestational-age baby by chlamydia positivity.

There were too few stillbirths to investigate the association with chlamydia positivity stratified by test timing. Twenty-six (0·9%) women with a positive chlamydia test and 277 (0·7%) women who were negative for chlamydia had a stillbirth (Figure 2) and there was no significant association between chlamydia positivity and stillbirth (aOR 0·93, 95%CI 0·61-1·42, p=0·74).

Analyses stratified by Aboriginality, age group and year of giving birth were consistent with the main results for both spontaneous preterm birth and small-for-gestational-age (Table 2). There was also no significant difference in the risk of spontaneous preterm birth at <34 weeks by chlamydia positivity (see Appendix Table 2).

Discussion

This large population-based cohort study analysed more than 20,000 women with laboratory chlamydia testing data during pregnancy. With over 900 cases of spontaneous pre-term birth and over 2500 small-for-gestational-age births, we found no increase in the risk of having a spontaneous preterm birth or a small-for-gestational-age baby among women with a positive chlamydia test. While there were fewer cases, we also found no evidence to suggest a relationship of a positive chlamydia test and stillbirth.

There has been one systematic review of 12 observational studies[14] and a number of other observational studies examining the association between chlamydia infection and preterm birth with equivocal findings reported across studies. As a body of evidence, interpreting these findings collectively is difficult for a number of reasons. Firstly there is a lack of consistent outcome definition. Some studies have not distinguished spontaneous preterm births from all other preterm births[5,6,9,12,13,18,19,21-23] 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 many studies report on low birth weight without taking into account gestational age and therefore do not clearly distinguish this outcome from preterm birth.[7,8,18,23] Secondly, all of the larger studies prior to this one do not have information on those who tested negative for chlamydia.[13,15,21,23] Thirdly some studies 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.[8,9,12,22] Lack of consideration of such factors can lead to false positive results. For example much chlamydia screening has focussed on young women with multiple sexual partners.[3] Younger age is strongly associated with spontaneous preterm birth[15] and young women with multiple sexual partners may be more likely to take part in higher risk activities such as smoking in pregnancy that also increase the risk of adverse obstetric outcomes; hence studies comparing positive women to those not tested for chlamydia can be biased. Other differences that may also contribute to the variation in findings include differences in study populations and timing of testing during the pregnancy and the test type.

This study had well-defined and reliably reported outcomes[27] based on a statutory perinatal birth register. We were able to make comparisons between women who tested positive and negative for chlamydia and stratify by timing of tests in relation to the pregnancy. We also took into account 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 (perinatal register and pathology data respectively), reduced the likelihood of biased reporting. On systematic searching of the literature, we identified only four studies larger than this report to have examined the association between chlamydia infection and preterm birth[13,21,22] including one from our research team.[15] However, three lacked 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)[13,15,21] and one case-control study only assessed chlamydia infection through presence of positive serology (IgG) and found no association of chlamydia with preterm birth.[22]

Our findings of no increase in the risk of preterm birth with a chlamydia infection are plausible and supported by results from some of the 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 may be affected by residual confounding. Further, while 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.

As we did not have treatment data, we assumed that women who tested positive were treated for their chlamydia infection[29] and hence our results should 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*. We found that women who were tested for chlamydia prior to pregnancy, but not during pregnancy, had a greater risk of preterm birth and stillbirth (aOR 1·15 and 1·71 respectively) than women who were tested during pregnancy. It is possible that women who were only tested prior to pregnancy could have undiagnosed and hence untreated chlamydia, or other genital infections, during the pregnancy and that the untreated infection (ie. longer duration) may explain the observed increase in the risk of adverse outcomes. Alternate explanations could be that these women were less likely to access preventative antenatal care (including chlamydia screening), and it is the reduced access to care that accounts for their higher risk.

We identified five observational studies that examined the association between chlamydia and preterm birth and documented that the chlamydia infections were untreated.[5,6,16,17,30] Of these, four suggest an increase in risk of preterm birth but they were all conducted prior to the year 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 conducted after 2000. Future studies of untreated chlamydia infection in pregnancy are unlikely to be ethical however studies where routine post-partum testing for chlamydia (regardless of obstetric outcome) is conducted may identify potentially untreated infections that had been present during pregnancy and assist in establishing whether an untreated infection is itself a risk factor for preterm birth.

While our linked pathology data did not include all tests conducted 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 may have been tested at more than one laboratory but our data from the two labs show this was minimal with no women tested at more than one of the labs during pregnancy and less than 10% tested at more than one of the labs in the three years prior to pregnancy. Other caveats on interpreting our findings include the lack of data on NAAT titres that may correlate with severity of infection, and clinical information on whether infections were symptomatic or not. Therefore we could not investigate whether more severe infections themselves are associated with increased risk of adverse birth outcomes. Nor were we able to examine factors such as effects of host genetic susceptibility.

Overall our results suggest that a chlamydia infection diagnosed and treated either during or prior to pregnancy does not increase a woman's risk of spontaneous preterm birth, small-for-gestational-age birth or stillbirth. These findings support the continued screening of high risk women during pregnancy for chlamydia and they should reassure women who have chlamydia diagnosed during pregnancy and treated that there is no increased risk of serious adverse birth outcomes.

Funding

This work was supported by the National Health and Medical Research Council (NHMRC) [grant number APP1020628]. BL, JH, BD, CR, JW, RG, JK are supported by NHMRC fellowships.

Declaration of Interests

The authors have no conflicts of interest to declare.

Author contributions

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, interpretation of results and contributed to all subsequent iterations of this article.

Acknowledgements

The authors wish to thank the staff at the Western Australian Data Linkage Branch, WA Department of Health Data Collections, WA Registry of Births, Deaths and Marriages, WA Electoral Commission. Chlamydia and Reproductive Health Outcome

Investigators: B Liu, D Preen, J Hocking, B Donovan, C Roberts, J Ward, D Mak, R Guy, J Kaldor, S Pearson, L Stewart, H Wand, J Reekie.

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Table 1 Participant characteristics according to birth outcome in Western Australian women born 1974-1995

	All births	Term	Preterm		Small-for-gestational-age		Stillbirth
			Planned∞	Spontaneous	No	Yes	
N	101558	94276	3361	3921	91609	9762	682
% of all births	100.0	92.8	3.3	3.9	90.4	9.6	0.7
Demographics							
Median age, years	26.8	26.8	26.8	26.2	26.9	26.1	25.7
(IQR)	(23.0-29.8)	(23.0-29.8)	(23.0-30.0)	(21.7-29.7)	(23.1-29.9)	(21.7-29.5)	(22.2-29.3)
% lower third socioeconomic status (N)	35.2 (35722)	35.0 (33023)	35.3 (1187)	38.6 (1513)	34.7(31755)	39.8 (3885)	37.6 (256)
% resident in major city (N)	74.1 (75240)	74.2 (69917)	75.8 (2549)	70.7 (2774)	74.7 (68427)	68.5 (6687)	67.9 (463)
% Caucasian (N)	83.1 (84385)	83.6 (78785)	78.3 (2630)	75.7 (2970)	84.4 (77288)	71.3 (6962)	74.2 (506)
% Aboriginal (N)	8.0 (8087)	7.5 (7062)	11.7 (392)	16.1 (633)	7.1 (6493)	15.9 (1556)	15.4 (105)
% other ethnicity (N)	8.9 (9086)	8.9 (8429)	10.1 (339)	8.1 (318)	8.5 (7828)	12.7 (1244)	10.4 (71)
Antenatal factors							
% smoked cigarettes during pregnancy (N)	17.4 (17673)	17.0 (16024)	19.8 (664)	25.1 (985)	16.0 (14617)	30.8 (3010)	25.7 (175)
% nulliparous (N)	59.3 (60184)	59.3 (55941)	57.2 (1922)	59.2 (2321)	59.2 (54189)	60.3 (5889)	58.9 (402)
% ART¥ prior to conception (N)	1.3 (1282)	1.2 (1136)	2.4 (82)	1.6 (64)	1.3 (1179)	1.0 (98)	1.3 (16)
Infections†							
% hepatitis C (N)	0.7 (754)	0.7 (658)	1.1 (37)	1.5 (59)	0.7 (626)	1.3 (125)	1.2 (*)
% hepatitis B (N)	0.4 (370)	0.4 (342)	0.4 (12)	0.4 (16)	0.3 (301)	0.7 (67)	0.3 (*)
% syphilis (N)	0.1(122)	0.1 (107)	0.2 (*)	0.2(*)	0.1 (90)	0.3 (32)	0.4 (*)
% gonorrhoea (N)	1.2(1200)	1.1 (1032)	2.1(72)	2.5(96)	1.0(901)	3.0(293)	1.4 (17)
% trichomoniasis (N)	0.3 (348)	0.3 (294)	0.8 (26)	0.7 (28)	0.3 (261)	0.9 (85)	0.3 (*)

*small cell numbers suppressed

∞including labour inductions and prelabour caesarean sections

†diagnosed during or prior to pregnancy

¥Hospital record of access to assisted reproductive technology in year prior to conception (see methods)

Table 2 Association between chlamydia positivity and adverse obstetric outcomes by Aboriginality, age and year of giving birth

		N	n	Minimally adjusted* OR (95%CI)	Fully adjusted+ OR (95%CI)	Heterogeneity P value
Spontaneous preterm birth	Chlamydia					
Aboriginality						
Non-Aboriginal	negative	31535	1191	1.00	1.00	0.74
	positive	1939	83	1.11 (0.89-1.40)	1.09 (0.87-1.38)	
Aboriginal	negative	4558	369	1.00	1.00	
	positive	899	82	1.10 (0.86-1.42)	1.10 (0.85-1.42)	
Age group (years)						
<25	negative	14212	689	1.00	1.00	0.71
	positive	1881	121	1.31 (1.07-1.60)	1.12 (0.92-1.37)	
≥25	negative	21881	871	1.00	1.00	
	positive	957	44	1.17 (0.85-1.59)	1.09 (0.80-1.49)	
Year of giving birth						
2001-2005	negative	5827	307	1.00	1.00	0.45
	positive	533	38	1.24 (0.87-1.76)	1.06 (0.74-1.51)	
2006-2012	negative	30266	1253	1.00	1.00	
	positive	2305	127	1.22 (1.00-1.47)	1.10 (0.90-1.33)	
Small-for-gestational-age						
Aboriginality						
Non-Aboriginal	negative	32614	2938	1.00	1.00	
	positive	2000	203	1.09 (0.94-1.27)	1.04 (0.90-1.21)	0.23
Aboriginal	negative	4785	995	1.00	1.00	
	positive	943	180	0.87 (0.73-1.05)	0.83 (0.69-1.00)	
Age group (years)						
<25	negative	14706	1874	1.00	1. 00	
	positive	1956	285	1.12 (0.98-1.29)	0.94 (0.81-1.08)	0.73

≥25	negative	22693	2059	1.00	1.00		
	positive	987	98	1.09 (0.88-1.35)	0.98 (0.79-1.22)		
Year of giving birth							
2001-2005	negative	6047	817	1.00	1.00	0.76	
	positive	550	93	1.12 (0.89-1.42)	0.93 (0.73-1.19)		
2006-2012	negative	31352	3116	1.00	1.00		
	positive	2393	290	1.12 (0.98-1.27)	0.96 (0.84-1.10)		

*Adjusted for age, area of residence, and socioeconomic status;

[+]Adjusted for age, area of residence, socioeconomic status, smoked during pregnancy, other infections listed in table 1 and ethnicity

Appendix Table 1 Association between chlamydia positivity (combining tested during and prior to pregnancy) and adverse obstetric outcomes

	a	b	c	**d**	e	f	**g**	**h**
	OR (95%CI)	OR (95%CI)	OR (95%CI)	**OR (95%CI)**	OR (95%CI)	OR (95%CI)	**OR (95%CI)**	OR (95%CI)
Spontaneous preterm birth								
negative	1.00	1.00	1.00	**1.00**	1.00	1.00	**1.00**	1.00
positive	1.37 (1.16-1.61)	1.24 (1.05-1.47)	1.23 (1.04-1.45)	**1.22 (1.04-1.45)**	1.20 (1.01-1.41)	1.15 (0.97-1.36)	**1.08 (0.91-1.28)**	1.08 (0.91-1.28)
Small for gestational age								
negative	1.00	1.00	1.00	**1.00**	1.00	1.00	**1.00**	1.00
positive	1.27 (1.14-1.43)	1.14 (1.02-1.28)	1.12 (1.00-1.25)	**1.11 (0.99-1.25)**	1.06 (0.95-1.19)	1.00 (0.89-1.13)	**0.95 (0.85-1.07)**	0.95 (0.85-1.07)
Stillbirth								
negative	1.00	1.00	1.00	**1.00**	1.00	1.00	**1.00**	1.00
positive	1.19 (0.80-1.79)	1.08 (0.72-1.62)	1.06 (0.70-1.59)	**1.05 (0.70-1.59)**	1.03 (0.69-1.54)	0.98 (0.65-1.49)	**0.93 (0.61-1.42)**	0.93 (0.62-1.42)

Models in bold type were reported in Figure 2 in main report

Model a: Unadjusted

Model b: Adjusted for age

Model c: Adjusted for age, and area of residence

Model d: Adjusted for age, area of residence, and socioeconomic status

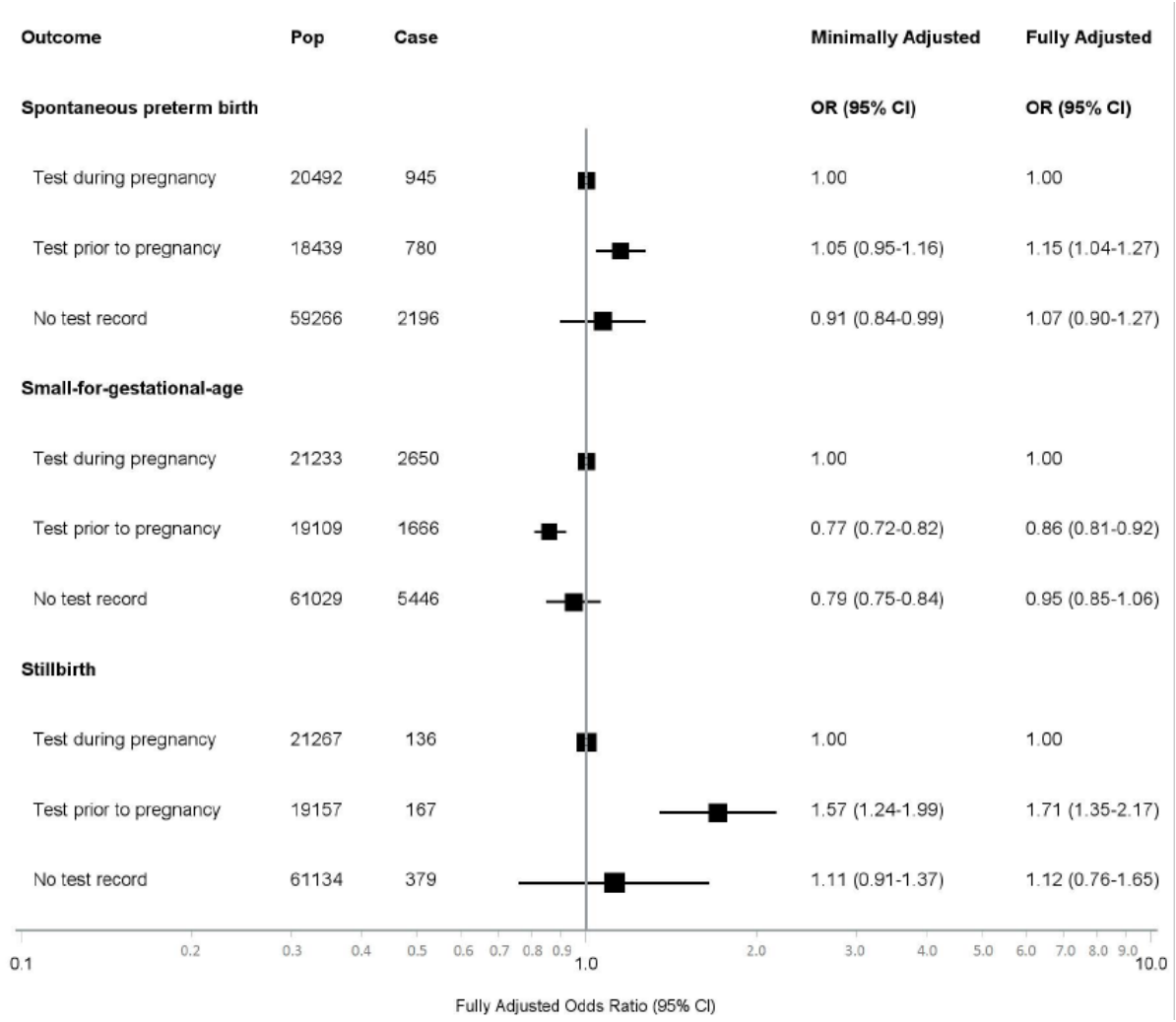
Model e: Adjusted for age, area of residence, socioeconomic status, and smoked during pregnancy

Model f: Adjusted for age, area of residence, socioeconomic status, smoked during pregnancy, and other infections listed in table 1

Model g: Adjusted for age, area of residence, socioeconomic status, smoked during pregnancy, other infections listed in table 1 and ethnicity

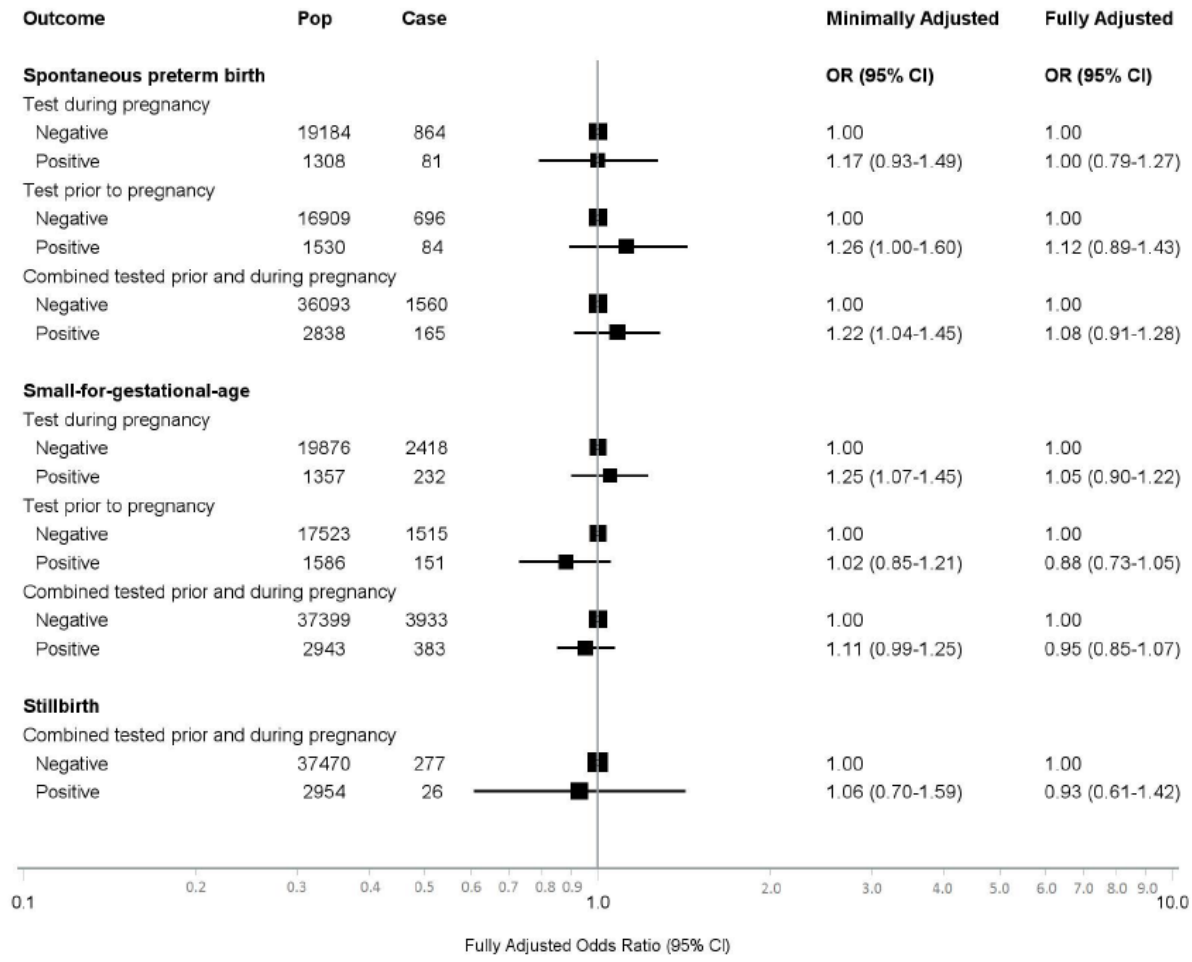
Model h: Adjusted for age, area of residence, socioeconomic status, smoked during pregnancy, other infections listed in table 1, ethnicity and use of assisted reproductive technologies.

Figure 1: Association between chlamydia testing history an adverse obstetric outcomes



Minimally adjusted model adjusted for age, area of residence, and socioeconomic status
Fully adjusted model adjusted for age, area of residence, socioeconomic status, smoked during pregnancy, other infections listed in table 1 and ethnicity

Figure 2: Association between chlamydia positivity and adverse obstetric outcomes



Women with no test record were included in the analysis but data not shown
Minimally adjusted model adjusted for age, area of residence, and socioeconomic status
Fully adjusted model adjusted for age, area of residence, socioeconomic status, smoked during pregnancy, other infections listed in table 1 and ethnicity