Annals of Epidemiology 110 (2025) 172–177

Contents lists available at ScienceDirect

Annals of Epidemiology

journal homepage: www.sciencedirect.com/journal/annals-of-epidemiology

Association between maternal sexually transmitted diseases and birth defects in the United States: A nationwide population-based study

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ARTICLE INFO

Keywords:
Maternal sexually transmitted infections
Chlamydia
Syphilis
Congenital anomalies
United States

ABSTRACT

Purpose: We estimated the association between maternal sexually transmitted diseases (STDs) and the risk of specific birth defects among live singleton births in the United States (US).
Methods: We conducted a population-based study using data from birth certificates for 14,602,822 live singleton births occurring from 2016 to 2019 in the US. We used logistic regression to estimate the associations between three maternal STDs (chlamydia, gonorrhea, and syphilis) and the risk of four specific birth defects (gastroschisis, cleft lip with or without cleft palate, spina bifida, and hypospadias), adjusting for socio-demographic and pregnancy-related factors.
Results: Maternal chlamydia infection was associated with a higher risk of gastroschisis (adjusted odds ratio [aOR], 1.23; (95 % CI: 1.03, 1.46), cleft lip with or without cleft palate (aOR, 1.26; 95 % CI: 1.08, 1.47), and hypospadias (aOR, 1.26; 95 % CI: 1.08, 1.47). It was not associated with an increased risk of spina bifida. These associations were consistent across subgroups defined by maternal age, race and ethnicity, education, body mass index, and infant sex. We found no evidence of an association between gonorrhea or syphilis infections and the studied birth defects.
Conclusions: Among live singleton births in the US, maternal chlamydia infection may be associated with increased risks of gastroschisis, cleft lip with or without cleft palate, and hypospadias.

Introduction

Birth defects are a significant public health concern, substantially contributing to infant mortality and lifelong morbidity. [1,2] According to the Global Burden of Disease 2021 summary statistics, birth defects accounted for 531,000 deaths, ranking third among 22 causes of disease and injury for children under 5 years old, [3] with a prevalence of 1573 per 100,000. [4]

Birth defects are influenced by various genetic, environmental, and lifestyle factors. For example, nutritional deficiencies and maternal risk behaviors have been linked to the development of specific defects. Neural tube defects are associated with folic acid deficiency, [5] while maternal smoking is related to cleft lip and cardiac defects. [6]

Sexually transmitted diseases (STDs) are common health issues among women of reproductive age, with significant implications for maternal and neonatal outcomes. [7] Despite the availability of effective antimicrobial treatments, bacterial and protozoan STDs remain associated with adverse pregnancy outcomes, such as stillbirth, low birth weight, and premature birth. [8] Congenital syphilis, in particular, can result in severe neonatal complications, including multi-organ failure, skeletal abnormalities, and central nervous system disorders, ultimately leading to poor quality of life and even death. [9]

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https://doi.org/10.1016/j.annepidem.2025.09.004
Received 1 April 2025; Received in revised form 27 August 2025; Accepted 3 September 2025
Available online 4 September 2025
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Previous studies have examined the association between maternal STDs and birth defects. [10–15] For example, data from the US National Vital Statistics System reported a modest association between maternal chlamydia infection and cyanotic congenital heart defects in offspring. [10] The US National Birth Defects Prevention Study identified an increased risk of gastroschisis associated with STDs. [13] A recent case-control study by Feldkamp et al. (2024) also demonstrated an association between chlamydia infection and gastroschisis. [16] However, findings from the Finnish Maternity Cohort found no evidence linking maternal chlamydia infection to gastroschisis. [14] Additionally, a study by Horslev et al. using 2014 US birth certificates also found no evidence of an association between chlamydia infection and gastroschisis. [15]

Accordingly, we aimed to estimate the association between maternal STDs (including chlamydia, gonorrhea, and syphilis) and the risk of specific birth defects using nationwide data from approximately 14 million live singleton births in the US between 2016 and 2019. Additionally, we sought to examine whether these associations varied by maternal age, maternal race and ethnicity, maternal education, body mass index (BMI), and infant sex.

Materials and methods

Study population

We obtained data on live births in the United States (US) from the Centers for Disease Control and Prevention (CDC) National Center for Health Statistics (NCHS) [17]. For our analysis, we focused on live singleton births (n = 14,859,956), delivered to mothers aged between 18 and 49 years (n = 14,663,019). We restricted the analysis to this age range to focus on the typical reproductive ages and minimize potential confounding from pregnancies at extremely young or advanced maternal ages. We excluded births with missing or unknown responses for the birth defect variable (n = 30,129, 2.05 %) and those born to mothers with unknown or missing information on STDs (n = 30,068, 2.05 %). The final analytical sample included 14,602,822 singleton live births (Fig. 1).

Birth defect assessment

Birth defects were identified using birth certificate data, with each defect recorded using a checkbox [18]. The dataset included 11 specific types of birth defects: any birth defect, anencephaly, Meningomyelocele/spina bifida, cyanotic congenital heart disease, congenital diaphragmatic hernia, omphalocele, gastroschisis, limb reduction defect, cleft lip with or without cleft palate (which may present unilaterally, bilaterally, or in the midline), cleft palate alone, Down syndrome, hypospadias, and suspected chromosomal disorder. Birth certificate data have been widely used to estimate the prevalence of birth defects in the US, [19–21] and their reliability for accurately identifying birth defects has been validated in a prior study. [22]

For the analysis, we included only those birth defects with a positive predictive value greater than 70 %, as validated in the prior study, [22] and excluded defects that were genetically inherited. The defects included in our analysis were gastroschisis, hypospadias, cleft lip with or without cleft palate, and spina bifida.

Gastroschisis is defined as an abnormality of the anterior abdominal wall, lateral to the umbilicus, resulting in herniation of abdominal contents directly into the amniotic cavity. Hypospadias is defined as incomplete closure of the male urethra, resulting in the urethral meatus opening on the ventral surface of the penis. Cleft lip with or without cleft palate is characterized by incomplete closure of the lip, which may present unilaterally, bilaterally, or in the midline. Spina bifida is defined as a gap in the fetal spinal vertebrae, which usually includes herniation of the fetal meninges and/or spinal cord.

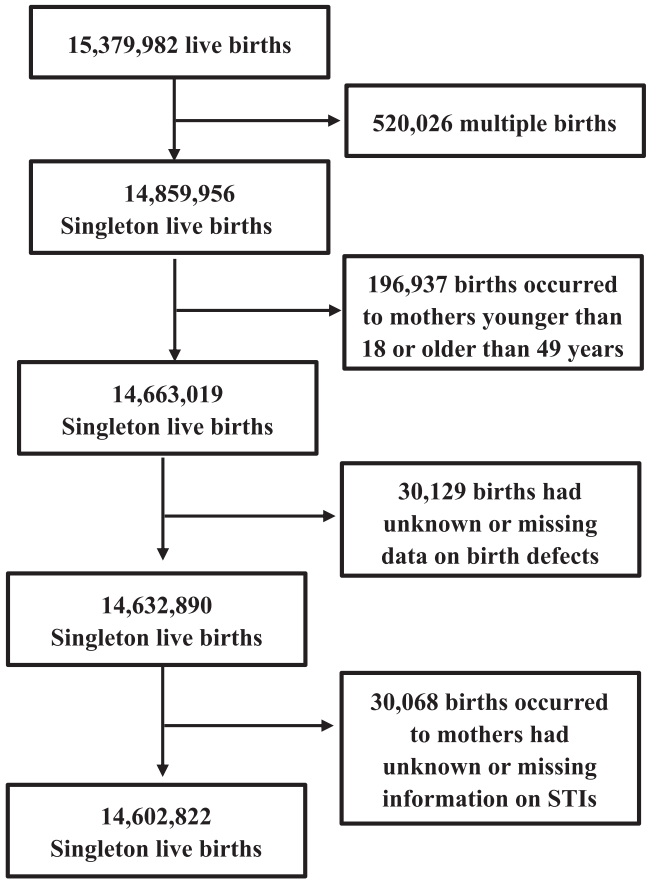

Fig. 1. Flowchart of the study participants.

Assessment of maternal sexually transmitted diseases

Information on the presence of STDs during pregnancy was obtained from birth certificates. [23] Maternal STD status was recorded on the birth certificate by hospital personnel who extracted this information from records of prenatal care, labor and delivery, and the newborn exam. [23] This method for ascertaining syphilis has been validated for studying trends and characteristics of maternal STDs in the US. [24] STDs, including gonorrhea, syphilis, and chlamydia, were recorded if they were either present at the time of pregnancy diagnosis or confirmed during pregnancy, regardless of whether treatment was documented. [23]

Covariates

Covariates were obtained from birth certificate data and included maternal age, race and ethnicity, marital status, educational level, insurance type, parity, initiation month of prenatal care, smoking before pregnancy, pre-pregnancy body mass index (BMI), infant sex, and pre-pregnancy health conditions such as pregestational diabetes and essential hypertension. Race and ethnicity were categorized following the 1997 Office of Management and Budget standards. [25] We classified race and ethnicity into non-Hispanic white, non-Hispanic black, non-Hispanic American Indian or Alaska Native (AIAN), non-Hispanic Asian, non-Hispanic Native Hawaiian or Other Pacific Islander (NHOPI), non-Hispanic more than one race, and Hispanic. To ensure a sufficient sample size for comparisons, individuals identified as non-Hispanic AIAN, non-Hispanic NHOPI, non-Hispanic more than one race, or those with missing race information were grouped into an “other race” category. [26] Pre-pregnancy body mass index (BMI) was categorized into six groups: underweight (<18.5 kg/m^2), normal weight

(18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), obesity I (30.0–34.9 kg/m^2), obesity II (35.0–39.9 kg/m^2), and obesity III (≥40 kg/m^2),

Statistical analysis

We used logistic regression models to estimate the association between maternal STDs and the risk of specific birth defects, adjusting covariates in a stepwise manner. Model 1 was adjusted for maternal age (18–24, 25–29, 30–34, 35–40, 40–49 years), race and ethnicity (non-Hispanic White, non-Hispanic Black, non-Hispanic Asian, Hispanic, and Other), and mutually adjusted for the presence of STDs. Model 2 was further adjusted for marital status (married versus unmarried), maternal educational level (lower than high school, high school, or higher than high school), insurance type (Medicaid, private insurance, self-pay, or other), parity (0,1, and ≥2), initiation month of prenatal care (no

Table 1
Characteristics of the study population by the presence of maternal sexually transmitted diseases.

Characteristics	Total(n=14,602,822)	Chlamydia(n=258,461)	Gonorrhea(n=41,690)	Syphilis(n=16478)
Age, years, n (%)				
< 25	3477,376 (23.8)	154,689 (59.9)	22,887 (54.9)	5324 (32.3)
25–29	4305,955 (29.5)	65,319 (25.3)	11,349 (27.2)	5103 (31.0)
30–34	4211,468 (28.8)	27,333 (10.6)	5227 (12.5)	3574 (21.7)
35–39	2136,916 (14.6)	9397 (3.6)	1896 (4.5)	1914 (11.6)
≥ 40	471,107 (3.2)	1723 (0.7)	331 (0.8)	563 (3.4)
Race and ethnicity, n (%)				
Hispanic	3435,786 (23.5)	69,845 (27.0)	6691 (16.0)	4358 (26.4)
Non-Hispanic White	7552,616 (51.7)	83,306 (32.2)	11,887 (28.5)	3818 (23.2)
Non-Hispanic Black	2074,374 (14.2)	83,845 (32.4)	19,546 (46.9)	6860 (41.6)
Non-Hispanic Asian	952,081 (6.5)	4082 (1.6)	327 (0.8)	403 (2.4)
Other*	587,965 (4.0)	17,383 (6.7)	3239 (7.8)	1039 (6.3)
Educational attainment				
Lower than high school	1752,974 (12.0)	59,722 (23.1)	11,070 (26.6)	4701 (28.5)
High school	3737,758 (25.6)	113,274 (43.8)	18,538 (44.5)	6270 (38.1)
Higher than high school	8923,390 (61.1)	82,969 (32.1)	11,634 (27.9)	5179 (31.4)
Unknown	188,700 (1.3)	2496 (1.0)	448 (1.1)	328 (2.0)
Marital status				
Married	8050,019 (55.1)	45,025 (17.4)	5276 (12.7)	3710 (22.5)
Unmarried	5234,710 (35.8)	204,097 (79.0)	34,841 (83.6)	10,975 (66.6)
Unknown	1318,093 (9.0)	9339 (3.6)	1573 (3.8)	1793 (10.9)
Parity, n (%)				
0	5544,229 (38.0)	115,564 (44.7)	15,132 (36.3)	4929 (29.9)
1	4735,758 (32.4)	73,032 (28.3)	11,936 (28.6)	4366 (26.5)
2	2501,871 (17.1)	38,978 (15.1)	7524 (18.0)	3326 (20.2)
≥ 3	1797,965 (12.3)	30,528 (11.8)	7030 (16.9)	3816 (23.2)
Unknown	22,999 (0.2)	359 (0.1)	68 (0.2)	41 (0.2)
Initiation month of prenatal care, n (%)				
No prenatal care	239,687 (1.6)	5444 (2.1)	1502 (3.6)	807 (4.9)
1st−3rd month	11,048,548 (75.7)	160,477 (62.1)	24,414 (58.6)	9518 (57.8)
4th−6th month	2309,746 (15.8)	65,559 (25.4)	10,966 (26.3)	4122 (25.0)
7th-final month	644,332 (4.4)	20,728 (8.0)	3485 (8.4)	1457 (8.8)
Unknown	360,509 (2.5)	6253 (2.4)	1323 (3.2)	574 (3.5)
Insurance type				
Medicaid	6110,935 (41.8)	189,940 (73.5)	33,400 (80.1)	12,414 (75.3)
Private insurance	7223,086 (49.5)	48,737 (18.9)	5829 (14.0)	2650 (16.1)
Self-pay	628,762 (4.3)	9070 (3.5)	1029 (2.5)	685 (4.2)
Other	551,932 (3.8)	9086 (3.5)	1203 (2.9)	620 (3.8)
Unknown	88,107 (0.6)	1628 (0.6)	229 (0.5)	109 (0.7)
Smoking before pregnancy, n (%)				
Yes	1257,259 (8.6)	46,182 (17.9)	10,524 (25.2)	3063 (18.6)
No	13,276,473 (90.9)	210,304 (81.4)	30,714 (73.7)	13,180 (80.0)
Unknown	69,090 (0.5)	1975 (0.8)	452 (1.1)	235 (1.4)
Pre-pregnancy BMI, kg/m^2, n (%)				
Underweight: < 18.5	462,707 (3.2)	11,771 (4.6)	1845 (4.4)	527 (3.2)
Normal weight: 18.5–24.9	6087,568 (41.7)	101,550 (39.3)	15,845 (38.0)	5697 (34.6)
Overweight: 25.0–29.9	3777,752 (25.9)	64,944 (25.1)	10,082 (24.2)	4121 (25.0)
Obesity: ≥ 30	3924,696 (26.9)	74,035 (28.6)	12,810 (30.8)	5540 (33.7)
Unknown	350,099 (2.4)	6161 (2.4)	1108 (2.7)	593 (3.6)
Pre-pregnancy diabetes				
Yes	134,927 (0.9)	2253 (0.9)	433 (1.0)	296 (1.8)
No	14,463,302 (99.0)	256,053 (99.1)	41,225 (98.9)	16,175 (98.2)
Unknown	4593 (<0.001)	155 (0.1)	32 (0.1)	7 (<0.001)
Pre-pregnancy hypertension				
Yes	284,354 (1.9)	5570 (2.2)	1282 (3.1)	728 (4.4)
No	14,313,875 (98.0)	252,736 (97.8)	40,376 (96.8)	15,743 (95.5)
Unknown	4593 (<0.001)	155 (0.1)	32 (0.1)	7 (<0.001)
Infant sex				
Male	7473,349 (51.2)	131,415 (50.8)	21,276 (51.0)	8410 (51.0)
Female	7129,473 (48.8)	127,046 (49.2)	20,414 (49.0)	8068 (49.0)

Abbreviation: BMI=body mass index.

* Other included non-Hispanic American Indian or Alaskan Native, non-Hispanic Native Hawaiian or Other Pacific Islander, non-Hispanic more than one race, and origin unknown or not stated.

prenatal care, 1st-3rd month, 4th-6th month, or 7th-final month), smoking before pregnancy (yes, no, or unknown), pre-pregnancy BMI (underweight, normal weight, overweight, obesity I, obesity II, and obesity III), and infant sex (male versus female). Model 3 was additionally adjusted for pre-pregnancy diabetes (yes versus no) and hypertension (yes versus no).

To identify potentially susceptible subpopulations, we performed subgroup analysis to assess whether the associations varied by maternal age, race and ethnicity, education, BMI, and infant sex, as suggested in existing literature. [10] We tested the differences in the ORs between subgroups (e.g., male versus female) using the following formula:

$$(\widehat{Q_{male}} - \widehat{Q_{female}}) \Big/ \sqrt{(\widehat{SE_{male}})^2 + (\widehat{SE_{female}})^2}$$

Where $\widehat{Q_{male}}$ and $\widehat{Q_{female}}$ are the point estimates of OR for male and female, and $\widehat{SE_{male}}$ and $\widehat{SE_{female}}$ are their corresponding standard errors. [27]

In sensitivity analyses, we excluded women who lack access to prenatal care or had no health insurance, as these individuals might have limited opportunities to screen for maternal STDs during pregnancy.

We reported results as odds ratio (OR) and corresponding 95 % confidence interval (CI). All statistical analyses were performed in R software version 4.2.1. All analyses were two-sided, and a p-value < 0.05 was considered statistically significant.

Results

Among the 14,602,822 live singleton births included in the study, 258,461 (1.77 %) were born to mothers diagnosed with chlamydia infection, 41,690 (0.29 %) to mothers with gonorrhea infection, and 16,478 (0.11 %) to mothers with syphilis infection (Table 1). Mothers with STDs were more likely to be younger, non-Hispanic Black, have lower education levels, be unmarried, and have Medicaid as their insurance type.

A total of 21,019 births were identified with any of the four birth defects, corresponding to a prevalence of 1.4 per 1000 births. Hypospadias had the highest rate at 0.6 per 1000 births, followed by cleft lip with or without cleft palate at 0.5 per 1000 births, gastroschisis at 0.2 per 1000 births, and spina bifida at 0.1 per 1000 births (Table 2).

[insert table 2 here]

Maternal chlamydia infection was associated with a higher risk of gastroschisis, hypospadias, and cleft lip with or without cleft palate (Table 3). In the fully adjusted models, the ORs associated with maternal chlamydia infection were 1.21 (95 % CI: 1.11, 1.33) for any included defect, 1.23 (95 % CI: 1.03, 1.46) for gastroschisis, 1.26 (95 % CI: 1.08, 1.47) for hypospadias, and 1.26 (95 % CI: 1.08, 1.47) for cleft lip with or without cleft palate.

Maternal gonorrhea or syphilis infection was not found to be associated with any of the four birth defects. For example, in the fully adjusted models, the ORs linked to maternal gonorrhea infection were 1.17 (95 % CI: 0.75, 1.81) for gastroschisis, 1.00 (95 % CI: 0.67, 1.50) for hypospadias, 0.93 (95 % CI: 0.61, 1.41) for cleft lip with or without cleft palate, and 0.73 (95 % CI: 0.27, 1.98) for spina bifida (Table 3).

To identify susceptible subpopulations, we conducted subgroup analyses. The associations were generally consistent across subgroups defined by maternal age, race and ethnicity, maternal education, pre-pregnancy BMI, and infant sex (Table 4). For example, the OR for any included defects associated with chlamydia infection was 1.30 (95 % CI: 1.08, 1.56) among Hispanic mothers compared to 1.01 (95 % CI: 0.81, 1.25) among non-Hispanic black mothers (p for heterogeneity=0.21).

After excluding women who may have limited opportunities for maternal STDs screening during pregnancy (n = 437,779), the results remained largely unchanged (Table S1). For example, in the sensitivity analysis, the OR for gastroschisis associated with chlamydia infection was 1.26 (95 % CI: 1.05, 1.50), compared to 1.23 (95 % CI: 1.03, 1.46) in the main analysis.

Discussion

In this nationwide study of over 14 million live singleton births in the US, we found that maternal chlamydia infection was associated with an increased risk of gastroschisis, hypospadias, and cleft lip with or without cleft palate. However, no evidence of an association was observed between gonorrhea or syphilis infections and any of the four specific birth defects studied.

Our findings of the link between maternal chlamydia infection and the increased risk of gastroschisis, hypospadias, and cleft lip with or without cleft palate align with those of several previous studies. [10,13,28] Chlamydia remains the most frequently reported bacterial sexually transmitted infection in the US. If left untreated, it can lead to adverse pregnancy outcomes such as preterm delivery, ophthalmia neonatorum, and neonatal pneumonia. [29] Prospective studies have showed that 18–44 % of infants born to mothers with chlamydia develop chlamydial conjunctivitis, [30] while 3–16 % may experience chlamydial pneumonia. [30]

In contrast, we found no evidence of an association between gonorrhea or syphilis infection and the risk of birth defects. A prior study by Carter et al. using data from the National Birth Defects Prevention Study (1997–2004), grouped chlamydia, gonorrhea, and pelvic inflammatory disease into a single infection exposure and identified an

Table 2
Specific birth defects among singleton live births (n = 14,602,822) in the United States, 2016–2019.

Birth defects	No.	No. per 1000 births
Any included defect*	21,019	1.4
Gastroschisis	3252	0.2
Hypospadias	8387	0.6
Cleft lip with or without cleft palate	7387	0.5
Spina bifida	2082	0.1
Multiple defects	87	0.006

* Include gastroschisis, hypospadias, cleft lip with or without cleft palate, and spina bifida.

Table 3
The association between maternal sexually transmitted diseases during pregnancy and birth defects in the US.

Birth defects	Chlamydia	Gonorrhea	Syphilis
Gastroschisis			
Model 1*	1.50 (1.25, 1.79)	1.33 (0.86, 2.07)	0.49 (0.12, 1.95)
Model 2†	1.23 (1.03, 1.46)	1.17 (0.75, 1.81)	0.44 (0.11, 1.74)
Model 3‡	1.23 (1.03, 1.46)	1.17 (0.75, 1.81)	0.43 (0.11, 1.74)
Hypospadias			
Model 1*	1.29 (1.11, 1.51)	0.99 (0.66, 1.49)	0.94 (0.47, 1.88)
Model 2†	1.26 (1.08, 1.47)	1.00 (0.67, 1.50)	0.99 (0.49, 1.98)
Model 3‡	1.26 (1.08, 1.47)	1.00 (0.67, 1.50)	0.97 (0.48, 1.95)
Cleft lip with or without cleft palate			
Model 1*	1.37 (1.17, 1.60)	1.03 (0.68, 1.57)	0.91 (0.43, 1.92)
Model 2†	1.26 (1.08, 1.47)	0.93 (0.61, 1.41)	0.81 (0.39, 1.70)
Model 3‡	1.26 (1.08, 1.47)	0.93 (0.61, 1.41)	0.80 (0.38, 1.68)
Spina bifida			
Model 1*	0.82 (0.57, 1.20)	0.79 (0.29, 2.15)	1.51 (0.49, 4.71)
Model 2†	0.78 (0.53, 1.13)	0.73 (0.27, 1.99)	1.35 (0.43, 4.20)
Model 3‡	0.78 (0.53, 1.13)	0.73 (0.27, 1.98)	1.33 (0.43, 4.13)

Results are presented as odds ratio and corresponding 95 % confidence interval.
* Models were adjusted for maternal age, race and ethnicity, and mutually adjusted for sexually transmitted diseases.
† Models were additionally adjusted for marital status, education, insurance type, parity, initiation month of prenatal care, smoking before pregnancy, pre-pregnancy BMI, and infant sex.
‡ Models were additionally adjusted for pre-pregnancy diabetes and hypertension.

Table 4
The association between maternal chlamydia infections and specific type of birth defects by individual characteristics.

Characteristics	Gastroschisis		Hypospadias		Cleft lip with or without cleft palate	
	OR	P for heterogeneity	OR	P for heterogeneity	OR	P for heterogeneity
Age, years						
< 25	1.18 (0.97, 1.45)	Reference	1.35 (1.11, 1.64)	Reference	1.22 (0.99, 1.49)	Reference
25–29	1.46 (0.97, 2.22)	0.36	1.21 (0.88, 1.66)	0.56	1.24 (0.90, 1.71)	0.93
30–34	1.99 (0.92, 4.30)	0.20	1.07 (0.65, 1.77)	0.40	1.75 (1.16, 2.63)	0.12
35–39	0.77 (0.10, 6.10)	0.69	0.86 (0.32, 2.30)	0.38	1.24 (0.57, 2.70)	0.97
≥ 40	NA	NA	0.80 (0.10, 6.13)	0.62	NA	NA
Race and ethnicity						
Non-Hispanic White	1.22 (0.94, 1.58)	Reference	1.21 (0.96, 1.52)	Reference	1.20 (0.95, 1.53)	Reference
Hispanic	1.44 (1.03, 1.99)	0.44	1.36 (0.94, 1.97)	0.60	1.30 (0.97, 1.75)	0.68
Non-Hispanic Black	0.94 (0.58, 1.51)	0.35	1.05 (0.76, 1.45)	0.48	1.05 (0.71, 1.55)	0.57
Non-Hispanic Asian	1.55 (0.21, 11.42)	0.82	1.22 (0.30, 4.95)	0.99	1.91 (0.61, 5.99)	0.43
Other	1.21 (0.69, 2.11)	0.98	2.23 (1.41, 3.53)	0.02	1.72 (1.08, 2.74)	0.18
Pre-pregnancy BMI, kg/m^2						
Normal weight: 18.5–24.9	0.65 (0.28, 1.54)	Reference	1.99 (1.12, 3.56)	Reference	1.31 (0.66, 2.62)	Reference
Underweight: < 18.5	1.21 (0.95, 1.54)	0.17	1.15 (0.88, 1.49)	0.09	1.13 (0.87, 1.46)	0.69
Overweight: 25.0–29.9	1.70 (1.23, 2.36)	0.05	1.22 (0.88, 1.68)	0.15	1.90 (1.45, 2.50)	0.33
Obesity: ≥ 30	0.91 (0.51, 1.60)	0.52	0.68 (0.21, 2.15)	0.11	0.95 (0.69, 1.31)	0.41
Unknown	0.83 (0.25, 2.78)	0.75	1.38 (1.05, 1.80)	0.26	1.08 (0.40, 2.92)	0.75
Educational attainment						
High school	1.20 (0.93, 1.55)	Reference	1.12 (0.88, 1.43)	Reference	1.11 (0.86, 1.42)	Reference
Lower than high school	1.47 (1.04, 2.08)	0.36	1.37 (0.97, 1.94)	0.35	1.29 (0.95, 1.75)	0.46
Higher than high school	1.08 (0.75, 1.54)	0.64	1.32 (1.02, 1.71)	0.36	1.44 (1.10, 1.88)	0.16
Unknown	1.96 (0.46, 8.34)	0.51	3.20 (0.97, 10.6)	0.09	1.61 (0.39, 6.67)	0.61
Infant sex						
Male	1.20 (0.94, 1.54)	Reference	1.26 (1.08, 1.47)	Reference	1.18 (0.96, 1.45)	Reference
Female	1.26 (0.98, 1.61)	0.78	NA	NA	1.38 (1.09, 1.75)	0.33

Abbreviation: BMI=body mass index.
NA=not applicable.
Models were adjusted for maternal age, race and ethnicity, educational attainment, marital status, parity, smoking before pregnancy, smoking during pregnancy, timing of initiation of prenatal care, pre-pregnancy BMI, insurance type, pre-pregnancy diabetes, pre-pregnancy hypertension, and infant sex, and mutually adjusted for gonorrhea and syphilis infections.

association with cleft lip with or without cleft palate (OR, 2.81; 95 % CI, 1.39–5.69), but not with other birth defects. [31] Similarly, Bornstein et al. conducted a retrospective analysis of the CDC Natality Live Birth database (2016–2018) and reported a marginal association between gonorrhea and birth defects. [32] The association between gonorrhea infection and birth defects may depend on disease severity and treatment status. Gonorrhea is typically curable with single-dose antibiotic regiment; however, the rapid rise in antimicrobial resistance has significantly limited treatment options. This growing concern has prompted the World Health Organization to support national initiatives aimed at monitoring and addressing antimicrobial resistance in gonorrhea, such as the Gonococcal Antimicrobial Surveillance Programme.

Several limitations must be considered in this study. First, there is a potential for misclassification of maternal STD status, as exposures were assessed using a simple yes/no checkbox on the birth certificate. Among chlamydial infections, 70 %-80 % are asymptomatic. [33] This suggests that unless laboratory testing is performed many cases may go undetected. Reliance on birth certificate data will underestimate the true rates of infection, especially chlamydia, gonorrhea, and syphilis. [34] Variation in prenatal screening practices may also contribute to missed cases, particularly if the pathogen has already cleared from the cervix but was vertically transmitted. [35] s, birth certificate data lack information on the timing of STD diagnoses during pregnancy and whether treatment was received. It is therefore possible that an STD was acquired after the development of the birth defect, which may bias our findings toward a null association. Third, we used birth certificates rather than State-Based Birth Defects Tracking Systems to identify birth defects, which may have led to some defects being missed. However, the four specific birth defects studied in our analysis were identified through birth certificates with a positive predictive value greater than 70 %, indicating that most cases are likely true. [22] Nonetheless, under-ascertainment could attenuate the observed associations between maternal STDs and birth defects. Fourth, we included all types of hypospadias and cleft lip with or without cleft palate in our analysis; however, we did not have information on their sub-categories. Future studies should obtain data to analyze each type separately. Fifth, although we adjusted for a range of potential confounders, not all factors could be accounted for, such as parental medical history, environmental exposures, and maternal folic acid intake. [36] Despite these limitations, to our knowledge, this study is one of the few nationwide investigations in the US that examines the association between maternal STDs and specific types of birth defects.

Conclusions

Among over 14 million live singleton births in the US, maternal chlamydia infection was associated with an increased risk of gastroschisis, hypospadias, and cleft lip with or without cleft palate. These birth defects develop during early embryologic windows (weeks 5–14 of gestation), often before many women begin prenatal care. These findings highlight the importance of standardizing and strengthening STD screening and treatment protocols as integral parts of routine prenatal care. To facilitate prompt treatment of STDs and effectively mitigate potential risks to fetal health, women should be routinely screened for STDs before pregnancy and at the first prenatal visit.

Funding

None

CRediT authorship contribution statement

Chunrong Li: Writing – original draft, Resources. **Wangnan Cao:** Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Valery A Danilack:** Writing – review & editing. **Feng Sun:** Writing – review &

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.annepidem.2025.09.004.

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