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Maternal Self-Reported Genital Tract Infections During Pregnancy and the Risk of Selected Birth Defects

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Abstract

BACKGROUND: Genital tract infections are common during pregnancy and can result in adverse outcomes including preterm birth and neonatal infection. This hypothesis-generating study examined whether these infections are associated with selected birth defects.

METHODS: We conducted a case-control study of 5913 children identified as controls and 12,158 cases with birth defects from the National Birth Defects Prevention Study (1997–2004). Maternal interviews provided data on genital tract infections that occurred from one month before pregnancy through the end of the first trimester. Infections were either grouped together as a single overall exposure or were considered as a subgroup that included *chlamydia*/gonorrhea/pelvic inflammatory disease. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using unconditional logistic regression with adjustment for potential confounders.

RESULTS: Genital tract infections were associated with bilateral renal agenesis/hypoplasia (OR, 2.89; 95% CI, 1.11–7.50), cleft lip with or without cleft palate (OR, 1.46; 95% CI, 1.03–2.06), and transverse limb deficiency (OR, 1.84; 95% CI, 1.04–3.26). *Chlamydia*/gonorrhea/pelvic inflammatory disease was associated with cleft lip only (OR, 2.81; 95% CI, 1.39–5.69). These findings were not statistically significant after adjustment for multiple comparisons.

CONCLUSIONS: Caution is needed in interpreting these findings due to the possible misclassification of infection, the limited sample size that constrained consideration of the effects of treatment, and the possibility of chance associations. Although these data do not provide strong

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evidence for an association between genital tract infections and birth defects, additional research on the possible effects of these relatively common infections is needed.

Keywords

Chlamydia; congenital abnormalities; female genital diseases; gonorrhea; herpes genitalis

INTRODUCTION

Maternal genital tract infections occur frequently during pregnancy and prevalence varies by age, race, and geographic location. The prevalence among pregnant women has been estimated to range from 5 to 40% for recto-vaginal colonization with group B streptococcus (*Streptococcus agalactiae*; Valkenberg-van den Berg et al., 2006), 6 to 32% for bacterial vaginosis (Tolosa et al., 2006), 3 to 23% for *Trichomonas vaginalis* (French et al., 2006), 1 to 8% for *Neisseria gonorrhoeae* (Miller Jr et al., 2003; Johnson et al., 2007), 2 to 21% for *Chlamydia trachomatis* (Govender et al., 2009), and 5 to 64% for human papillomavirus (Banura et al., 2008; Castellsague et al., 2009). In pregnancy, approximately 2% of women seroconvert upon infection with herpes simplex virus types 1 and 2 (Brown et al., 1997).

One or more of these infections have been associated with adverse reproductive outcomes. These outcomes include premature rupture of membranes (Minkoff et al., 1984), preterm delivery (Meis et al., 1995; Cotch et al., 1997), intrauterine growth restriction (Investigators of the Johns Hopkins Study of Cervicitis and Adverse Pregnancy Outcome, 1989), miscarriage (Rastogi et al., 2000), stillbirth (Gencay et al., 2000), ectopic pregnancy (Chow et al., 1990), tubal infertility (World Health Organization Task Force on the Prevention and Management of Infertility, 1995), and neonatal morbidity (lesions on the skin, conjunctivitis, pneumonia, sepsis, meningitis, encephalitis, and multi-organ dysfunction), and mortality (Schuchat et al., 1990; Kimberlin et al., 2001).

Case reports have described birth defects purportedly resulting from intrauterine infection with herpes simplex virus early in pregnancy. These defects include microcephaly, microphthalmia, cerebellar hypoplasia, and limb hypoplasia (South et al., 1969; Hutto et al., 1987; Johansson et al., 2004). Ascending infection in the cervical canal and hematogenous transplacental infection have been proposed in these reports as mechanisms by which the infection could reach the fetus in the presence of intact fetal membranes. In addition, a few epidemiologic studies have examined whether structural birth defects could be one of the consequences of maternal genital tract infections during pregnancy (Métneki et al., 2005; Vogt et al., 2005; Norgård et al., 2006; Acs et al., 2008a; Acs et al., 2008b; Feldkemp et al., 2008; Bánhidly et al., 2010). One of these studies reported an association between acute pelvic inflammatory disease and cardiovascular defects overall but did not examine specific types of cardiovascular defects (Acs et al., 2008c). This small body of epidemiologic data does not provide sufficient evidence to support or refute an association between genital tract infections and birth defects; therefore, more studies are needed to determine whether these infections influence the risk of birth defects.

The purpose of this study was to examine whether maternally reported genital tract infections that occurred during the period from one month before conception through the

end of the first trimester are associated with selected major structural birth defects. Because we had no a priori hypotheses about the relationship between specific infections and specific birth defects, we considered this to be a hypothesis-generating study.

MATERIALS AND METHODS

Cases and Controls

We evaluated data from the National Birth Defects Prevention Study (NBDPS), an ongoing, multicenter, population-based, case-control study of risk factors for birth defects (Yoon et al., 2001). Cases were live births, still-births, or elective terminations identified through the birth defects surveillance systems in 10 states (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah) and were considered eligible if they were diagnosed with at least one of >30 selected major, structural birth defects. Clinical geneticists at each study center reviewed the medical data for each case to ensure that the case definition criteria were attained. Cases with single-gene disorders or chromosome abnormalities were excluded. Control children were live births that had no major birth defects; they were randomly selected from the geographic areas monitored by the surveillance systems through the use of birth hospitals or birth certificates. Each study center completed approximately 100 interviews of mothers of control infants during each year of participation in the NBDPS. Cases and controls with an estimated date of delivery (EDD) from October 1, 1997 through December 31, 2004 were included in the present study. Excluded were mothers who reported preexisting type 1 or 2 diabetes mellitus. Each study center obtained institutional review board approval to conduct the NBDPS.

For each birth defect group, a clinical geneticist classified the cases as isolated or multiple (>1 major unrelated birth defect in separate organ systems) based on knowledge of the embryology and pathogenesis of the defects (Rasmussen et al., 2003). The study included only second-degree and third-degree hypospadias cases. Cardiovascular defects that were categorized as simple defects (single defects or diagnostic entities, e.g., tetralogy of Fallot) or associations (defects that commonly occurred together, e.g., atrial septal defect with ventricular septal defect) were included in this study (Botto et al., 2007).

Exposure

Case and control mothers completed a telephone interview within 24 months of their EDD after providing oral informed consent. The questionnaire pertained to exposures that occurred before or during pregnancy and asked about demographic factors, pregnancy history, illnesses, medications, nutrition, and environmental exposures. Mothers were asked about diabetes, hypertension, seizures, respiratory illnesses, kidney/bladder/urinary tract infections, pelvic inflammatory disease, and any other fevers or illnesses that had not been specifically identified in the interview. Mothers reported genital tract infections in response to questions about pelvic inflammatory disease and any other fevers or illnesses that had not been previously mentioned in the interview. The names of the diseases that the mothers reported in response to questions about other fevers or illnesses were searched for reports of genital tract infections. The reported infections included group B streptococcus, *chlamydia*,

gonorrhea, pelvic inflammatory disease, genital herpes, genital warts, human papillomavirus, trichomoniasis, bacterial vaginosis, unspecified bacterial vaginal infections, and unspecified vaginal infections. All reported medications and their active ingredients were categorized according to the Slone Epidemiology Center Drug Dictionary. Vaginal yeast infections during pregnancy and the medications used for their treatment have been addressed in a previous report (Carter et al., 2008) and, therefore, were not examined in the present study.

Exposure was defined as maternal report of a genital tract infection at any time during the period from one month before conception through the end of the first trimester, hereafter called “first trimester”. Date of conception was calculated from the EDD provided by mothers in the interview; therefore, an exposure period beginning from one month before conception was specified to accommodate possible errors in the EDD reported by mothers. Infections were grouped together as a single overall exposure. Mothers were excluded from the analysis if they reported that they did not know whether they had pelvic inflammatory disease or any other fevers and illnesses not specifically queried in the interview, or if they reported genital tract infections but did not know the time when those infections occurred. Mothers were classified as unexposed if they had no reports of genital tract infections within the first trimester.

Covariates

We selected an a priori group of covariates based on their association with the exposure or with birth defects in the published literature. Those associated with exposure included maternal age (<20, 20–34, 35 years; Hiltunen-Back et al., 2001), race/ethnicity (white, African American, Hispanic, other) (Allsworth et al., 2009), education (<12, 12, >12 years; Allsworth et al., 2009), parity (primiparous, multiparous; Werden et al., 2008), smoking in the first trimester (Yes, No; Thorsen et al., 2006), and alcohol use in the first trimester (Yes, No; Thorsen et al., 2006). Those associated with birth defects include pre-pregnancy body mass index (<30, 30 kg/m²; Waller et al., 2007), family history of a similar birth defect in a first-degree relative (Yes, No; Queisser-Luft et al., 2002), and folic acid supplement use in the first trimester (Yes, No; MRC Vitamin Study Research Group, 1991). To account for subject recruitment at different sites, we also included study center as a covariate.

Statistical Analyses

Pearson’s chi-square test was used to compare characteristics between cases and controls and between mothers with and without a report of genital tract infections in the first trimester. Unconditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between maternal self-reported genital tract infections and each birth defect phenotype. All covariates were included in the regression models. The main analysis included only isolated cases. The association between gastroschisis and sexually transmitted infections in the NBDPS has been reported previously (Feldkemp et al., 2008), therefore, this birth defect is not included in the present study. Subanalyses were performed after restricting the exposed group to mothers who reported *chlamydia*, gonorrhea, or pelvic inflammatory disease. We considered these as clinically-related conditions because the most common pathogens causing pelvic inflammatory disease

are *C. trachomatis* and *N. gonorrhoeae* (Wiesenfeld et al., 2005). We also stratified by treatment status to distinguish whether any observed association with birth defects might be due to the medication used for treatment. Additional subanalyses were performed by restricting the case and control groups to singleton births and interviews completed within one year of the EDD to determine whether any of these factors influenced the results of the regression analysis. Analyses were repeated including cases with multiple defects. Analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC).

RESULTS

Participation in the maternal interview was 71.4% among case mothers and 67.9% among control mothers. A total of 12,422 mothers of cases with birth defect phenotypes included in the present study, and 5958 control mothers, were interviewed. Excluding mothers with pre-existing type 1 or 2 diabetes mellitus (241 cases, 33 controls) and those with missing data on exposure to genital tract infections in the first trimester (23 cases, 12 controls) produced 12,158 cases and 5913 controls for analysis. Compared to control mothers, case mothers were more likely to be 35 years old, obese (body mass index ≥ 30 kg/m²), and to have a multiple birth (Table 1). Case and control mothers also differed by race/ethnicity, parity, smoking in the first trimester, time to interview, and study center.

Genital tract infections during the first trimester were reported by 139 of control mothers (2.35%) and 292 of case mothers (2.40%; Table 2). Few mothers reported having more than one type of genital tract infection or that their infection was accompanied by a fever. Mothers were asked in which month(s) their illness(es) occurred, which permitted us to examine whether mothers reported having infections that occurred in multiple months during this period. Although 53 control mothers and 120 case mothers reported that their infection occurred in more than one month, the small numbers in each case group did not permit subanalyses according to gestational timing of infection. Among the exposed control and case mothers, 71 (51.1%) and 121 (41.4%), respectively, reported also having genital tract infections in the second and/or third trimesters. Most of these mothers reported a recurrence of the same infection; four control mothers and six case mothers reported having another type of infection in the second and/or third trimesters. Compared to case and control mothers who did not report a genital infection in the first trimester, mothers who reported an infection were more likely to be <20 years old and to have smoked in the first trimester (Table 1). Control mothers who reported an infection were also more likely to be primiparous. In addition, case mothers who reported an infection differed by education, race/ethnicity, body mass index, birth plurality, alcohol use, and study center from case mothers who did not report a genital tract infection.

An association was observed between maternal reports of any genital tract infections and bilateral renal agenesis/hypoplasia (OR, 2.89; 95% CI, 1.11–7.50; Table 3). There were borderline associations between all genital tract infections and cleft lip with or without cleft palate (OR, 1.46; 95% CI, 1.03–2.06) and transverse limb deficiency (OR, 1.84; 95% CI, 1.04–3.26). Cleft lip only was not associated with all genital tract infections, but was associated with the subgroup of infections that included *chlamydia*/gonorrhea/pelvic inflammatory disease (OR, 2.81; 95% CI, 1.39–5.69; Table 3). Subanalyses restricted to

singleton births and interviews within one year of the EDD did not produce substantial changes in the results. In addition, there was little change in the results obtained after including cases with multiple defects. Of note, none of the findings was statistically significant after performing a Bonferroni adjustment for the 103 statistical tests in Table 3.

For those defects that showed a positive association with genital tract infections, we performed analyses stratified by treatment status in an attempt to distinguish whether the observed associations could be due to the medications used for treatment rather than to the infection itself. The only case group having adequate numbers of exposed mothers to permit statistical analysis (3 mothers who reported having an infection) in the treated and untreated groups was transverse limb deficiency (7 untreated and 7 treated mothers among the 14 mothers who reported a genital tract infection). Untreated genital tract infections overall were associated with transverse limb deficiency (OR, 2.69; 95% CI, 1.20–6.02) but no association was observed with treated infection (OR, 1.41; 95% CI, 0.65–3.08).

Among case groups with positive associations, there were no suspected teratogens such as methotrexate, isotretinoin, and valproic acid among any medications reported by exposed mothers. Also, these mothers did not report having other infections known to be associated with congenital anomalies including syphilis, cytomegalovirus, rubella, toxoplasmosis, and varicella zoster virus.

DISCUSSION

We observed that maternal genital tract infections were associated with bilateral renal agenesis/hypoplasia, cleft lip with or without cleft palate, and transverse limb deficiency. However, these findings must be interpreted with caution because of the possibility of chance associations. In our large study population, we also did not observe associations with the other birth defects that were examined. Consequently, the results of this hypothesis-generating study do not provide evidence that maternal genital tract infections in early pregnancy play an appreciable role in the etiology of the birth defects that we studied.

Stratification by treatment status showed that untreated genital tract infections were associated with transverse limb deficiency. For the other defects that showed a positive association with genital tract infections, the small numbers of mothers who reported an untreated infection constrained our ability to stratify by treatment status. When mothers provided the name of a medication for treatment of a genital tract infection, it was most often an antibiotic, an antiviral, or metronidazole. In a previous report on antibiotics and birth defects in the NBDPS, the only defect that was positively associated with use of antibiotics that was also associated with genital tract infections in the current study was transverse limb deficiency (Crider et al., 2009). Mothers of cases with this defect were more likely to report use of erythromycins or sulfonamides than mothers of control infants. However, treated genital tract infections were not associated with transverse limb deficiency in the current study, therefore, the positive association between genital tract infections and transverse limb deficiency is unlikely to be due to antibiotics used for treatment of the infections. There is no evidence that acyclovir increases the overall risk of birth defects when used at normally prescribed doses (Stone et al., 2004) but there are insufficient data

regarding the safety of valacyclovir and famciclovir in pregnancy (Reiff-Eldridge et al., 2000). A meta-analysis found no association between first-trimester exposure to metronidazole and the overall risk of birth defects (Caro-Patón et al., 1997).

A previous study using NBDPS data, observed an association between genitourinary infections and gastroschisis (Feldkemp et al., 2008), in contrast to the largely null findings that we observed for the other birth defects we examined. Others have observed no association between birth defects and genital herpes, vulvovaginitis/bacterial vaginosis, or genital warts, (Norgård et al., 2006; Acs et al., 2008a, Acs et al., 2008b; Bánhidý et al., 2010), or between acute disorders of the urogenital organs and congenital cataracts (Vogt et al., 2005). In a previous study of oral clefts, infections were categorized as vaginitis, salpingitis, and sexually transmitted diseases; it found no association with oral clefts (Métneki et al., 2005). In our study, we observed modest and only borderline significant associations with cleft lip with or without cleft palate but not with cleft palate only. One study reported an association between acute pelvic inflammatory disease and cardiovascular defects overall and found that the number of offspring with atrial septal defect – secundum born to exposed mothers was greater than expected (Acs et al., 2008c). However, we found no association between genital tract infections and cardiovascular defect subgroups. Dissimilarities in the classification of exposure make it challenging to compare results across studies.

It is uncertain how maternal genital tract infections would result in birth defects in the developing fetus, but one possibility is a mechanism that involves inflammation. These infections induce immune responses in the host and lead to changes in the concentrations of inflammatory mediators such as cytokines (Vats et al., 2007; De Francesco et al., 2008). Common variants in the gene encoding tumor necrosis factor, a cytokine, have been examined for an association with limb deficiency; being heterozygous for the –376G>A variant was associated with a twofold increased odds for limb deficiency compared to GG homozygotes, but this was not statistically significant (Carmichael et al., 2006). The possible role of inflammation in structural birth defects and its dependence on the type and severity of infection should be explored in future studies.

A strength of this study was the robust sample sizes available for case review through use of population-based surveillance systems. The lack of association between maternal genital tract infections and a number of birth defects was convincingly shown in our study using these large sample sizes. Another strength was that the control group is generally representative of the source population from which the cases were identified (Cogswell et al., 2009). Other strengths included the use of systematic case definitions, and, importantly, that clinical data were used to verify diagnostic eligibility of all cases. For example, hydrocephaly cases were excluded if the defect was due to intraventricular hemorrhage, tumors, or meningitis, or if it was secondary to a brain malformation.

The limited information on exposure was a weakness of this study. It is not standard clinical practice to routinely screen for some of these infections (group B *streptococcus*, *T. vaginalis*, herpes simplex virus type 2, bacterial vaginosis) in the first trimester. For those tests recommended in the first trimester (*C. trachomatis*, *N. gonorrhoeae*), information on

infection could still be limited either because the test was not performed at the first prenatal visit or because of false-negative results. In addition, data on genital tract infections during specific months of the second trimester were not available from the maternal interview. Therefore, we could not examine exposure through the fourth month of pregnancy which would be relevant for some birth defects (e.g., hypospadias; because development of the male urethra continues through the 16th week of pregnancy).

Maternal self-report of infections raises concerns about the misclassification of exposure. Although no information was available from medical records, most mothers who reported an infection also reported treatment with medications that were presumably prescribed, suggesting that positive maternal reports were based on a clinical diagnosis. Also, some mothers might have misreported genital tract infections as urinary tract infections; therefore, we could not have identified them as being exposed.

If vaginal yeast infections were to be included among the genital tract infections in this study, there would be 233 of 5913 (3.94%) control mothers with a genital tract infection from one month before pregnancy through the first trimester. This is similar to the proportion (3.9%) of control mothers with any genital infection (including a vaginal yeast infection) in the first trimester in a previous report of NBDPS control mothers with an expected date of delivery between 1997 and 2003 (Collier et al., 2009).

The prevalence of individual genital tract infections observed in this study was much lower than that reported in the literature; these previous reports were based on screening all study participants for genital tract infections (asymptomatic and symptomatic), whereas in this study, mothers most likely reported symptomatic infections. Also, in the absence of a specific question on genital tract infections, many mothers reported unspecified vaginal infections making it impractical to perform subanalyses for individual infections. Different types of pathogens produce different types of host responses to infection, both locally and systemically, suggesting that any observed associations with birth defects are likely to differ according to pathogen type. Because we were constrained to group the infections as an overall exposure, we could not determine how specific infections varied in their associations with birth defects. We were also not able to assess differences according to the persistence of the infection, that is, acute versus chronic infections, because of the small number of mothers who reported infections in multiple months during pregnancy.

It is unknown whether the few observed associations in this hypothesis-generating study represent a causal effect of genital tract infections on birth defects, whether the infections are markers for other etiologic factors, or whether the findings may be due to chance; given that the conservative multiple testing adjustment revealed no significant associations, the last possibility appears the most likely explanation for the few and modest associations identified. Our concerns about multiple comparisons and the small number of exposed subjects in each birth defect group led us to re-analyze the data by logistic regression using a Bayesian approach, as described by Greenland (2007), but there were no substantial changes in the results. There was also no prior reason to expect any of the observed associations to be positive, and the mechanisms by which genital tract infections might cause birth defects are unknown. Finally, the likely underreporting and misclassification of exposure necessitate

further caution when interpreting the few observed associations. However, the issue is of clinical concern because if genital tract infections or their treatments do indeed increase risks for selected birth defects, these infections would represent preventable and treatable risk factors for these outcomes. Additional studies based on clinical diagnoses are needed to explore the possible association between genital tract infections and birth defects.

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Table 1

Characteristics of Mothers According to Case-control Status and Self-report of Genital Tract Infections from One Month before Conception through the End of the First Trimester

Characteristic	Controls (N = 5913)		Cases (N = 12,158)		p value ^{ab}	Controls				Cases			
	N (%)		N (%)			No genital tract infections (N = 5774)	Genital tract infections (N = 139)			No genital tract infections (N = 11,866)	Genital tract infections (N = 292)		
Maternal age (years)													
<20	654 (11.1)		1182 (9.7)		<0.0001	625 (10.8)	29 (20.9)			1126 (9.5)	56 (19.2)		<0.0001
20–24	1339 (22.6)		2685 (22.1)			1300 (22.5)	39 (28.1)			2586 (21.8)	99 (33.9)		
25–29	1555 (26.3)		3134 (25.8)			1527 (26.4)	28 (20.1)			3071 (25.9)	63 (21.6)		
30–34	1548 (26.2)		3183 (26.2)			1516 (26.3)	32 (23.0)			3137 (26.4)	46 (15.7)		
35–39	695 (11.7)		1583 (13.0)			686 (11.9)	9 (6.5)			1559 (13.1)	24 (8.2)		
40	122 (2.1)		391 (3.2)			120 (2.1)	2 (1.4)			387 (3.3)	4 (1.4)		
Maternal education (years)													
<12	984 (16.7)		2016 (16.6)		0.9407	956 (16.6)	28 (20.1)			1939 (16.3)	77 (26.4)		<0.0001
12	1462 (24.7)		3039 (25.0)			1422 (24.6)	40 (28.8)			2949 (24.9)	90 (30.8)		
>12	3388 (57.3)		6957 (57.2)			3318 (57.5)	70 (50.4)			6836 (57.6)	121 (41.4)		
Missing	79 (1.3)		146 (1.2)			78 (1.3)	1 (0.7)			142 (1.2)	4 (1.4)		
Maternal race/ethnicity													
Non-Hispanic white	3517 (59.5)		7491 (61.6)		0.0228	3437 (59.5)	80 (57.6)			7333 (61.8)	158 (54.1)		0.0082
African-American	672 (11.3)		1242 (10.2)			651 (11.3)	21 (15.1)			1197 (10.1)	45 (15.4)		
Hispanic	1323 (22.4)		2606 (21.5)			1291 (22.3)	32 (23.0)			2535 (21.4)	71 (24.3)		
Other	379 (6.4)		779 (6.4)			373 (6.5)	6 (4.3)			761 (6.4)	18 (6.2)		
Missing	22 (0.4)		40 (0.3)			22 (0.4)	0 (0.0)			40 (0.3)	0 (0.0)		
Pre-pregnancy body mass index (kg/m ²)													
<18.5	324 (5.5)		648 (5.3)		<0.0001	314 (5.4)	10 (7.2)			624 (5.3)	24 (8.2)		0.0057
18.5–24.9	3197 (54.1)		6227 (51.2)			3126 (54.1)	71 (51.1)			6088 (51.3)	139 (47.6)		
25.0–29.9	1259 (21.3)		2680 (22.1)			1231 (21.3)	28 (20.1)			2598 (21.9)	82 (28.1)		
30	890 (15.0)		2124 (17.5)			863 (15.0)	27 (19.4)			2084 (17.5)	40 (13.7)		

Characteristic	Controls				Cases			
	No genital tract infections (N = 5774)		Genital tract infections (N = 139)		No genital tract infections (N = 11,866)		Genital tract infections (N = 292)	
	N (%)	N (%)	N (%)	p value ^{ab}	N (%)	N (%)	N (%)	p value ^{ad}
Missing	243 (4.1)	479 (3.9)			472 (4.0)	7 (2.4)		
Parity								
Primiparous	2366 (40.0)	5083 (41.8)	0.0179		4945 (41.7)	138 (47.3)	0.0541	
Multiparous	3539 (59.9)	7043 (57.9)			6890 (58.0)	153 (52.4)		
Missing	8 (0.1)	32 (0.3)			31 (0.3)	1 (0.3)		
Birth plurality								
Single birth	5739 (97.1)	11,412 (93.9)	<0.0001		11,129 (93.8)	283 (96.9)	0.0277	
Multiple birth	174 (2.9)	746 (6.1)			737 (6.2)	9 (3.1)		
Folic acid use from 1 month before conception through first trimester								
Yes	5022 (84.9)	10,388 (85.5)	0.3805		10,134 (85.4)	254 (87.0)	0.4409	
No	870 (14.7)	1730 (14.2)			1693 (14.3)	37 (12.7)		
Missing	21 (0.4)	40 (0.3)			39 (0.3)	1 (0.3)		
Smoking from 1 month before conception through first trimester								
Yes	1112 (18.8)	2481 (20.4)	0.0118		2381 (20.1)	100 (34.3)	<0.0001	
No	4740 (80.2)	9557 (78.6)			9368 (78.9)	189 (64.7)		
Missing	61 (1.0)	120 (1.0)			117 (1.0)	3 (1.0)		
Alcohol use from 1 month before conception through first trimester								
Yes	2159 (36.5)	4495 (37.0)	0.5357		4349 (36.6)	146 (50.0)	<0.0001	
No	3668 (62.0)	7482 (61.5)			7340 (61.9)	142 (48.6)		
Missing	86 (1.5)	181 (1.5)			177 (1.5)	4 (1.4)		
Time to interview (months)								
0–12	4570 (77.3)	7445 (61.2)	<0.0001		7274 (61.3)	171 (58.6)	0.3182	
>12	1284 (21.7)	4606 (37.9)			4487 (37.8)	119 (40.7)		
Missing	59 (1.0)	107 (0.9)			105 (0.9)	2 (0.7)		
Study center								
Arkansas	717 (12.1)	1665 (13.7)	<0.0001		1616 (13.6)	49 (16.8)	0.0321	

Characteristic	Controls				Cases			
	No genital tract infections (N = 5774)		Genital tract infections (N = 139)		No genital tract infections (N = 11,866)		Genital tract infections (N = 292)	
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	p value ^{a,d}
California	796 (13.5)	1412 (11.6)	780 (13.5)	16 (11.5)	1372 (11.6)	40 (13.7)		
Georgia	631 (10.7)	1489 (12.2)	610 (10.6)	21 (15.1)	1451 (12.2)	38 (13.0)		
Iowa	662 (11.2)	1231 (10.1)	641 (11.1)	21 (15.1)	1201 (10.1)	30 (10.3)		
Massachusetts	743 (12.6)	1719 (14.1)	726 (12.6)	17 (12.2)	1689 (14.2)	30 (10.3)		
New Jersey	578 (9.8)	1267 (10.4)	568 (9.8)	10 (7.2)	1247 (10.5)	20 (6.9)		
New York	528 (8.9)	936 (7.7)	520 (9.0)	8 (5.7)	919 (7.7)	17 (5.8)		
North Carolina	296 (5.0)	394 (3.2)	292 (5.1)	4 (2.9)	388 (3.3)	6 (2.0)		
Texas	699 (11.8)	1508 (12.4)	681 (11.8)	18 (13.0)	1458 (12.3)	50 (17.1)		
Utah	263 (4.4)	537 (4.4)	259 (4.5)	4 (2.9)	525 (4.4)	12 (4.1)		

^aPearson's chi-square test used for comparing distributions.

^bComparison between cases and controls.

^cComparison between groups with and without self-reported genital tract infections from one month before pregnancy through the first trimester among controls.

^dComparison between groups with and without self-reported genital tract infections from one month before pregnancy through the first trimester among cases.

Table 2

Maternal Self-reported Genital Tract Infections from One Month before Conception through the End of the First Trimester

Exposure	Controls (N = 5913)	Cases (N = 12,158)
	N (%)	N (%)
Group B <i>streptococcus</i>	10 (0.17)	10 (0.08)
<i>Chlamydia</i>	34 (0.58)	88 (0.72)
Gonorrhea	6 (0.10)	13 (0.11)
Pelvic inflammatory disease	14 (0.24)	35 (0.29)
Genital herpes	37 (0.63)	62 (0.51)
Genital warts	5 (0.08)	14 (0.12)
Human papillomavirus	12 (0.20)	29 (0.24)
Trichomoniasis	5 (0.08)	11 (0.09)
Unspecified bacterial vaginal infections/bacterial vaginosis	15 (0.25)	22 (0.18)
Unspecified vaginal infections	7 (0.12)	19 (0.16)
Any genital tract infection	139 (2.35)	292 (2.40)
>1 type of genital tract infection	6 (0.10)	11 (0.09)
Genital tract infections with fever	3 (0.05)	3 (0.02)
Genital tract infections in multiple gestation months in exposure period	53 (0.90)	120 (0.99)
Treated genital tract infections	93 (1.57)	196 (1.61)

Table 3

Association between Maternal Self-reported Genital Tract Infections and Selected Birth Defects

Birth defect	N	All genital tract infections		Chlamydia/Gonorrhea/Pelvic inflammatory disease	
		Exposed, N	aOR (95% CI) ^a	Exposed, N	aOR (95% CI) ^a
Neural tube defects	923	18	0.80 (0.48–1.33)	11	1.22 (0.62–2.37)
Anencephaly	272	8	1.33 (0.64–2.76)	6	2.46 (0.92–5.94)
Spina bifida	564	8	0.55 (0.27–1.15)	4	0.72 (0.26–2.02)
Encephalocele	87	2	0.94 (0.23–3.91)	1	1.00 (0.13–7.51)
Holoprosencephaly	50	2	1.79 (0.42–7.56)	1	1.99 (0.26–15.19)
Hydrocephaly	184	7	1.58 (0.72–3.46)	4	2.43 (0.85–6.97)
Dandy Walker malformation	53	2	1.75 (0.42–7.39)	0	—
Cerebellar hypoplasia	10	1	4.96 (0.58–42.49)	0	—
Anophthalmia/microphthalmia	69	1	0.56 (0.08–4.08)	0	—
Congenital cataracts	142	7	1.93 (0.85–4.37)	1	0.72 (0.10–5.32)
Glaucoma/anterior chamber defects	64	3	1.46 (0.42–6.51)	2	2.56 (0.46–8.66)
Anotia/microtia	264	6	0.94 (0.39–2.26)	2	0.75 (0.18–3.18)
Choanal atresia	45	3	3.62 (0.75–12.06)	1	6.21 (0.77–50.25)
Cleft lip with or without cleft palate	1359	46	1.46 (1.03–2.06)	24	2.16 (1.30–3.58)
Cleft lip only	498	16	1.42 (0.83–2.41)	10	2.81 (1.39–5.69)
Cleft lip with cleft palate	861	30	1.45 (0.96–2.19)	14	1.80 (0.98–3.32)
Cleft palate only	509	8	0.66 (0.32–1.37)	3	0.71 (0.22–2.32)
Esophageal atresia	159	1	0.27 (0.04–1.98)	0	—
Small intestinal atresia or stenosis	288	4	0.55 (0.20–1.52)	2	0.61 (0.15–2.53)
Jejunal/ileal/multiple atresias	199	2	0.41 (0.10–1.66)	1	0.43 (0.06–3.17)
Duodenal atresia or stenosis	66	1	0.61 (0.08–4.45)	0	—
Colonic atresia or stenosis	23	1	1.92 (0.25–14.91)	1	4.22 (0.49–36.26)
Biliary atresia	82	1	0.47 (0.06–3.39)	0	—
Anorectal atresia	256	7	1.17 (0.54–2.54)	4	1.55 (0.55–4.39)
Hypospadias	1042	20	0.90 (0.54–1.49)	10	1.48 (0.71–3.09)
Renal agenesis/hypoplasia, bilateral	66	5	2.89 (1.11–7.50)	2	2.67 (0.60–11.92)
Bladder exstrophy	36	0	—	0	—
Cloacal exstrophy	1	0	—	0	—
Limb deficiency	469	19	1.70 (0.47–2.78)	6	1.37 (0.58–3.25)
Transverse limb deficiency	320	14	1.84 (1.04–3.26)	5	1.63 (0.63–4.21)
Longitudinal limb deficiency	123	3	0.94 (0.29–3.00)	1	0.82 (0.11–6.11)
Intercalary limb deficiency	21	1	1.90 (0.24–14.74)	0	—
Craniosynostosis	605	9	0.65 (0.32–1.31)	3	0.83 (0.25–2.70)
Diaphragmatic hernia	348	9	1.09 (0.55–2.18)	3	1.04 (0.32–3.38)
Omphalocele	139	0	—	0	—
Sacral agenesis	3	0	—	0	—
Conotruncal defects	927	18	0.85 (0.51–1.40)	8	1.07 (0.50–2.28)
Truncus arteriosus	40	1	1.02 (0.14–7.68)	0	—

Birth defect	All genital tract infections			Chlamydia/Gonorrhea/Pelvic inflammatory disease	
	N	Exposed, N	aOR (95% CI) ^a	Exposed, N	aOR (95% CI) ^a
Dextro-transposition of the great arteries ^b	325	4	0.53 (0.19–1.45)	0	—
Tetralogy of Fallot	331	9	1.20 (0.60–2.39)	4	1.60 (0.56–4.57)
Double outlet right ventricle	57	1	0.70 (0.10–5.19)	1	1.51 (0.20–11.75)
Ventricular septal defect, conoventricular	46	0	—	0	—
Pulmonary artery atresia with ventricular septal defect (Tetralogy of Fallot type)	91	1	0.46 (0.06–3.32)	1	1.29 (0.17–9.70)
Left ventricular outflow tract obstruction	882	18	0.91 (0.55–1.51)	7	1.15 (0.51–2.58)
Hypoplastic left heart syndrome	274	5	0.72 (0.29–1.79)	4	1.72 (0.59–4.95)
Coarctation of the aorta	273	8	1.34 (0.64–2.79)	2	1.09 (0.26–4.62)
Aortic stenosis	157	1	0.27 (0.04–1.98)	0	—
Left ventricular outflow tract obstruction associations ^c	164	3	0.82 (0.26–2.60)	1	0.86 (0.12–6.39)
Right ventricular outflow tract obstruction	901	20	0.93 (0.57–1.50)	7	0.88 (0.37–1.88)
Pulmonary atresia	84	1	0.51 (0.07–3.71)	1	1.61 (0.21–12.15)
Tricuspid atresia	37	1	1.06 (0.14–7.93)	1	2.51 (0.31–20.05)
Ebstein anomaly	58	4	3.23 (0.86–9.27)	1	1.68 (0.22–13.02)
Pulmonary valve stenosis	514	9	0.73 (0.37–1.45)	3	0.66 (0.20–2.16)
Right ventricular outflow tract obstruction associations ^d	208	5	0.94 (0.37–2.39)	1	0.39 (0.05–3.05)
Septal defects	2,118	53	0.99 (0.71–1.38)	30	1.37 (0.85–2.20)
Ventricular septal defect, perimembranous	707	22	1.20 (0.75–1.92)	11	1.37 (0.69–2.73)
Ventricular septal defect, muscular	141	2	0.61 (0.15–2.53)	1	0.99 (0.13–7.42)
Atrial septal defect, secundum	637	14	0.86 (0.48–1.53)	9	1.40 (0.66–2.98)
Atrial septal defect, not otherwise specified	210	5	0.98 (0.38–2.49)	4	1.80 (0.61–5.29)
Septal associations ^e	345	8	0.91 (0.44–1.90)	5	1.56 (0.60–4.03)
Total anomalous pulmonary venous return	127	1	0.32 (0.04–2.34)	0	—
Atrioventricular septal defects	82	3	1.43 (0.44–4.64)	1	1.35 (0.18–10.33)

^aUnconditional logistic regression used to generate adjusted odds ratios (aORs) and 95% confidence intervals (95% CIs). All regression models adjusted for maternal age, race/ethnicity, education, parity, pre-pregnancy obesity, family history of a similar birth defect in a first-degree relative, use of folic acid supplements, smoking, alcohol use, and study center.

^bWith intact ventricular septum or with ventricular septal defect.

^cLeft ventricular outflow tract obstruction associations include coarctation of aorta that co-occurred with a ventricular septal defect or aortic stenosis; and hypoplastic left heart syndrome that co-occurred with anomalous pulmonary venous return.

^dRight ventricular outflow tract obstruction associations include pulmonary valve stenosis that co-occurred with an atrial or ventricular septal defect; tricuspid atresia that co-occurred with a ventricular septal defect or with pulmonary atresia -- intact ventricular septum; and Ebstein anomaly that co-occurred with pulmonary atresia.

^eSeptal associations include an atrial septal defect that co-occurred with a ventricular septal defect.