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Maternal genitourinary infections and risk of birth defects in the National Birth Defects Prevention Study

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Abstract

Background—Genitourinary infections (GUIs) are common among sexually active women. Yet, little is known about the risk of birth defects associated with GUIs.

Methods—Using data from the National Birth Defects Prevention Study, a multisite, population-based, case-control study, we assessed self-reported maternal GUIs in the month before through the third month of pregnancy (periconception) from 29,316 birth defect cases and 11,545 unaffected controls. We calculated odds ratios (ORs) and 95% confidence intervals to estimate the risk of 52 major structural birth defects associated with GUIs. We also calculated risk of birth defects associated with each type of GUI: urinary tract infection (UTI) and sexually transmitted infection (STI).

Results—In our analysis, 10% ($n = 2,972$) of case and 9% ($n = 1,014$) of control mothers reported a periconceptional GUI. A GUI was significantly associated with 11 of the 52 birth defects examined (ORs ranging from 1.19 to 2.26): encephalocele, cataracts, cleft lip, esophageal atresia, duodenal atresia/stenosis, small intestinal atresia/stenosis, colonic atresia/stenosis, transverse limb deficiency, conoventricular septal defect, atrioventricular septal defect, and secundum atrial septal defect. A periconceptional UTI was significantly associated with nine birth defects (ORs from 1.21 to 2.48), and periconceptional STI was significantly associated with four birth defects (ORs ranging from 1.63 to 3.72).

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CONFLICT OF INTEREST

The authors have no conflicts of interest or financial disclosures relevant to this manuscript.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Conclusions—While misclassification of GUIs in our analysis is likely, our findings suggest GUIs during the periconceptional period may increase the risk for specific birth defects.

Keywords

birth defects; congenital malformations; genitourinary infections; infections; sexually transmitted infections; urinary tract infection

1 | INTRODUCTION

Genitourinary infections (GUIs) include both sexually transmitted infections (STIs) and urinary tract infections (UTIs). These infections are common among sexually active women (Centers for Disease Control and Prevention [CDC], 2017; Sheffield & Cunningham, 2005). Several epidemiological studies reported an association between GUIs and gastroschisis, (Baer et al., 2015; Draper et al., 2008; Elliott et al., 2009; Feldkamp et al., 2008; Feldkamp et al., 2015; Yazdy, Mitchell, & Werler, 2014) including one using data from the National Birth Defects Prevention Study ([NBDPS]; Feldkamp et al., 2008). Few studies have assessed the association of maternal GUIs with other birth defects and those that have done so often present conflicting results. Comparing the existing findings is challenging, because studies have different exposure definitions and include different birth defect phenotypes or groupings.

Prior analyses of NBDPS data examined the association between specific GUIs and birth defects. Analyzing births from 1997 to 2003, Cleves, Malik, Yang, Carter, and Hobbs (2008) identified associations between maternal UTIs and two congenital heart defects (CHDs): left ventricular outflow tract obstructive defects and atrioventricular septal defects. Carter et al. (2011) examined GUIs (defined as STIs, pelvic inflammatory disease [PID], and group B streptococcus), finding associations with three birth defects among NBDPS births from 1997 to 2004: renal agenesis/hypoplasia, cleft lip, and transverse limb deficiency. Both analyses were limited by few numbers of exposed mothers and did not explore all birth defects collected in the NBDPS. We conducted a detailed analysis of the association between GUIs and the risk of major birth defects (excluding gastroschisis) using NBDPS data on births from 1997 to 2011. We sought to use the findings to generate hypotheses for future research.

2 | METHODS

The NBDPS was a large, multisite, population-based, case-control study of birth defects that included pregnancies with estimated delivery dates from October 1997 through December 2011 (Reefhuis et al., 2015). Pregnancies affected by one or more of 30 categories of major structural birth defects (cases), excluding those attributed to a known chromosomal or single-gene abnormality, were ascertained through birth defects surveillance programs in 10 states (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah). Control infants were live born without major birth defects randomly selected from hospital records or birth certificates in the same time period and geographic area as the cases. Each study site and the Centers for Disease Control and Prevention obtained Institutional Review Board approval for the NBDPS, and participants provided informed consent.

Case inclusion criteria have been described previously (Reefhuis et al., 2015). Briefly, case information (abstracted from medical records) was obtained from birth defects surveillance programs. Clinical geneticists reviewed each case to determine eligibility and to classify cases as having isolated (only one defect), multiple (major birth defects in more than one organ system), or complex birth defects (Rasmussen et al., 2003). CHD cases were further classified according to a structured protocol that took into account cardiac phenotype, complexity, and presence of non-cardiac defects (Botto, Lin, Riehle-Colarusso, Malik, & Correa, 2007). Birth defects that were known or strongly suspected to be caused by single-gene disorder or chromosomal anomaly were excluded from the NBDPS.

Trained interviewers conducted computer-assisted telephone interviews in English or Spanish with mothers of case and control infants. Interviews occurred between 6 weeks and 24 months after the estimated date of delivery. Mothers reported demographics, pregnancy history, health conditions, medication use, and other exposures before and during pregnancy. Overall, 66.7% of eligible case and 63.7% of eligible control mothers participated in the interview. The average time between the estimated delivery date and interview was 11 months among case mothers and 9 months among control mothers. We considered mothers exposed if they reported a GUI at any time in the month before conception through the third month of pregnancy (periconceptional period). The first 3 months of pregnancy include the critical period in embryonic development associated with most structural birth defects. We included the month prior to conception in the exposure window as it is often difficult to pinpoint the exact date of conception. Mothers reported GUIs in response to the following three questions: (a) “Did you have any of the following illnesses: a kidney, bladder, or urinary tract infection?”, (b) “Did you have pelvic inflammatory disease or PID?”, and (c) “Did you have any other disease or illnesses that we have not already talked about such as infectious diseases including sexually transmitted diseases or chickenpox?”. Two investigators (MLF, KEA), blinded to case/control status, reviewed all free-text responses to the latter question to identify any mention of a GUI. Mothers were classified into four exposure groups: (a) any GUI (either UTI or STI), (b) UTI only (including bladder and kidney infections), (c) STI only (including *Chlamydia trachomatis*, gonorrhea, genital herpes, human papillomavirus, syphilis, trichomoniasis, bacterial vaginosis, PID, or mention of an unspecified STI), or (d) both a UTI and STI. The unexposed group included infants of mothers who did not report a periconceptional GUI.

We excluded 3,168 infants (2,883 cases/285 controls) from analysis (Figure 1). We excluded mothers with missing information on GUIs and those reporting pre-gestational diabetes. As Feldkamp et al. (2008) published results from NBDPS for the association between maternal GUIs and gastroschisis, we excluded infants with isolated gastroschisis from the current analysis. Lastly, we excluded mothers of infants with isolated birth defects from case groups with 50 cases. Some birth defects (oral clefts, glaucoma, cataracts, ventricular septal defects [VSDs], and pulmonary valve stenosis) were not ascertained by all sites for all years of the NBDPS (Rasmussen et al., 2003; Reefhuis et al., 2015); when analyzing these birth defects, we excluded cases and controls for the sites and years with incomplete data.

We analyzed second- and third-degree hypospadias (i.e., subcoronal/penile, scrotal, or perineal meatal opening) and restricted the control group to males.

To assess potential confounding, we used chi-square tests to compare characteristics among control infants whose mothers reported GUIs and those who did not. We used logistic regression to estimate crude odds ratios (cORs) and adjusted odds ratios (aORs) with 95% confidence intervals (CI) for any GUI, UTI only, STI only, both UTI and STI, and specific STI pathogens and the risk of birth defects. We calculated aORs and 95% CIs for birth defects with five or more exposed cases, controlling for the following a priori set of covariates: maternal age at delivery (a continuous variable), race/ethnicity (non-Hispanic white, Non-Hispanic black, Hispanic, other), education (high school or less, more than high school), pre-pregnancy body mass index (BMI; weight in kilograms/height in meters²), periconceptional cigarette smoking, folic acid-containing supplement use in the month before through the first month of pregnancy, and state of residence at the time of the infant's birth. For birth defects with three or four exposed cases, we calculated cORs and Fisher's exact CIs. We did not calculate estimates for birth defects with fewer than three exposed cases. We examined whether the associations between any GUI and birth defects varied by maternal age or smoking by evaluating additive interaction. We calculated the relative excess risk due to interaction along with the 95% CIs for each birth defect using a logistic regression model adjusted for the covariates listed above (Hosmer & Lemeshow, 1992).

We conducted three sub-analyses to determine whether specific changes in the analysis would affect the results. To reduce heterogeneity, we restricted the analysis of noncardiac defects to isolated cases. Similarly, we restricted the analysis of CHDs to cases with only one CHD or a well-recognized combination of defects that are considered a single CHD, referred to as "simple isolated" cases. Lastly, as GUIs can cause inflammation that may persist longer than the underlying infection and could impact embryonic development, we examined the association between reported GUIs and the risk of birth defects in a longer exposure window, the 3 months before conception through the third month of pregnancy. For each of these, we implemented the change and recalculated all ORs and 95% CIs as described above. No adjustment was made for the multiple comparisons performed. We conducted analyses in SAS (9.3; SAS Corporation, Cary, NC).

3 | RESULTS

After exclusions, 29,316 case and 11,545 control infants were included in the analysis (Figure 1). Overall, 2,972 (10.1%) case and 1,014 (8.8%) control mothers reported a GUI in the periconceptional period. By type of GUI, 2,457 (8.4%) case and 836 (7.2%) control mothers reported having only a UTI, 428 (1.5%) case and 151 (1.3%) control mothers reported having only an STI, and 87 (0.3%) case and 27 (0.2%) control mothers reported having both a UTI and STI (Figure 1).

The distributions of selected characteristics stratified by the presence or absence of a GUI among control mothers are shown in Table 1. Mothers of control infants who reported a GUI differed from those who did not report a GUI in terms of age, race/ethnicity, education, pre-pregnancy BMI, smoking status, folic acid-containing supplement use, and study center. The percentage of mothers reporting a GUI decreased with increasing age, and this pattern was consistent across the type of GUI (Supporting Information Figure S1). The proportion of

reported GUIs was consistently lower in control mothers compared to case mothers, regardless of maternal age or type of GUI.

The percentage of mothers who reported a periconceptional GUI varied slightly across the 52 birth defects examined, ranging from 5.8% of mothers who reported a GUI for total anomalous pulmonary venous return (TAPVR) to 20.7% for colonic atresia/stenosis (Tables 2 and 3). Any GUI was associated with statistically significant elevated aORs ranging from 1.19 to 2.26 for 11 of the 52 birth defects were studied: encephalocele, congenital cataracts, cleft lip only, esophageal atresia, duodenal atresia/stenosis, small intestinal atresia/stenosis, colonic atresia/stenosis, transverse limb deficiency, conoventricular VSD, atrioventricular septal defect (AVSD), and secundum atrial septal defect (secundum ASD). UTI only was associated with statistically significant elevated aORs ranging from 1.21 to 2.48 for 9 of the 52 birth defects we examined: congenital cataracts, cleft lip only, duodenal atresia/stenosis, small intestinal atresia/stenosis, colonic atresia/stenosis, conoventricular VSD, AVSD, hypoplastic left heart syndrome, and secundum ASD. STI only was associated with statistically significant aORs ranging from 1.63 to 3.72 for 4 of 52 birth defects in the study: holoprosencephaly, cleft lip, transverse limb deficiency, and Ebstein anomaly. While the analysis of mothers reporting both UTI and STI was limited by the small number of exposed cases, reporting both periconceptional STI and UTI was associated with statistically significant elevated cORs for encephalocele and renal agenesis/hypoplasia.

Among mothers who reported any STI, 434 (84%) case and 148 (83%) control mothers provided the specific pathogen; *Chlamydia* was most common (Table 4). Among the mothers who only reported an STI, *Chlamydia* was associated with statistically significant elevated aOR for cleft lip only and statistically significant elevated cOR for conoventricular VSD (Table 5). Additionally, we found elevated statistically significant aORs for human papillomavirus and transverse limb deficiency and for trichomoniasis and cleft lip with cleft palate. In crude analyses, gonorrhea was significantly associated with anotia/microtia.

We examined whether the associations between any GUI and each birth defect differed across maternal age and smoking status (data not shown). We did not find patterns that suggest additive interaction by either maternal age or smoking status for any of the birth defects examined. When we restricted to isolated noncardiac birth defects and simple isolated CHDs, the point estimates were similar to the estimates in the main analysis for most birth defect phenotypes, with the exception being the estimate for isolated cloacal exstrophy which became elevated and statistically significant (Supporting Information Table S1). When we expanded the exposure window to include the 3 months before conception through the third month of pregnancy, we found point estimates that were similar to our main findings (Supporting Information Table S2).

4 | DISCUSSION

We assessed associations between GUIs and 52 birth defects in the NBDPS. Self-reported periconceptional GUIs were common, and slightly higher in case mothers compared to control mothers. We observed that maternal GUI was significantly associated with increased

risk of 11 of the 52 individual birth defects examined, although the magnitude of these associations varied.

The published literature on this topic mostly comes from three important epidemiologic studies that are large enough to examine GUIs and individual birth defects: the Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA) (Acs, Banhidy, Puho, & Czeizel, 2008a, 2008b, 2008c; Banhidy, Acs, Puho, & Czeizel, 2006, 2010; Metneki, Puho, & Czeizel, 2005; Norgard, Norgard, Czeizel, Puho, & Sorensen, 2006), the Baltimore-Washington Infant Study (Ferencz, Loffredo, Correa-Villasenor, & Wilson, 1997; Wilson, Loffredo, Correa-Villasenor, & Ferencz, 1998), and the NBDPS (Ailes et al., 2016; Carter et al., 2011; Cleves et al., 2008). Comparing the existing findings is challenging (Table 6). Variations in exposure definitions (in terms of both the infections and exposure windows examined) as well as different outcome measures (individual or combinations of birth defects) included in these studies prevent a clear picture from emerging.

Of the 11 birth defects that were significantly associated with maternal GUI, the estimate for one birth defect, cleft lip, remained elevated and statistically significant among both subgroups of GUIs: mothers who reported UTI only (aOR 1.32) and STI only (aOR 1.63). We found the magnitude of the cleft lip estimate was even higher among infants whose mothers reported *Chlamydia* (aOR 2.76). These findings for cleft lip are consistent with two earlier NBDPS reports (Table 6), one that explored a sub-group of STIs (*Chlamydia*, gonorrhea, and PID) and another that examined maternal nitrofurantoin use for UTI (Ailes et al., 2016; Carter et al., 2011), which is unsurprising given the overlap in study participants. The HCCSCA explored maternal UTIs and cleft lip +/- cleft palate (and not cleft lip only) in two reports: one found an elevated (OR 1.7), but not statistically significant, association with cleft lip +/- palate, while the second observed a significant increased OR for cleft lip +/- palate as well as posterior cleft palate when compared to non-malformed control infants (Banhidy et al., 2006; Metneki et al., 2005). No associations with STIs were identified (Metneki et al., 2005).

Our estimates for 7 of the 11 birth defects significantly associated with maternal GUI remained elevated and statistically significant when we restricted to infants whose mothers reported only a UTI, and UTI only was also associated with an increased risk for hypoplastic left heart syndrome. Our findings regarding UTI and congenital cataracts, AVSD, and hypoplastic left heart syndrome expand on the previous NBDPS findings (Cleves et al., 2008; Prakalapakorn, Rasmussen, Lambert, & Honein, 2010). While the HCCSCA explored a combined outcome of all CHDs and did not identify any association with UTIs, the Baltimore-Washington Infant Study reported an association between UTI and secundum ASD (Banhidy et al., 2006; Ferencz et al., 1997; Wilson et al., 1998). The association between GUI and conoventricular VSDs has not been previously reported.

Three of the birth defects we observed to be associated with GUI, and more specifically with UTI, were related to the gastrointestinal tract: duodenal, small intestinal, and colonic atresia/stenosis. The previous NBDPS analysis that explored antibiotic use for UTIs observed an association with esophageal atresia, but not with other gastrointestinal birth defects (Ailes et al., 2016). The HCCSCA did not find any significant associations between UTI and

gastrointestinal defects, but a nonsignificant elevated risk of diaphragmatic birth defects (congenital diaphragmatic hernia and eventration of the diaphragm) was reported with a wide confidence interval (Banhidy et al., 2006).

Among mothers who reported only an STI, we observed significant associations with three birth defects: holoprosencephaly, transverse limb deficiency, and Ebstein anomaly. The increased risk of holoprosencephaly among mothers who reported only an STI ($n = 5$) was largely driven by three cases exposed to *Chlamydia* (cOR 5.05 [0.99, 16.0]). This finding has not been observed in other studies, although brain anomalies, including holoprosencephaly, have been recently associated with other maternal infections including Zika virus (Hall, Broussard, Evert, & Canfield, 2017; Honein et al., 2017). The magnitude of the significant estimates for transverse limb deficiency increased among mothers who reported only an STI (aOR = 2.06), and increased further among those with maternal reports of HPV (aOR = 4.78). A previous NBDPS report identified an association with STI, however, their STI definition included group B streptococcal infections whereas ours did not (Carter et al., 2011). Using NBDPS data, Ailes et al. (2016) also observed elevated but not significant associations between women who used trimethoprim-sulfamethoxazole for UTI treatment and the risk of transverse limb deficiency in their offspring. Lastly, Ebstein anomaly was significantly associated with mothers reporting only an STI, but we were unable to explore associations by specific STI pathogens given the small number of exposed case mothers. While no other estimate for CHDs reached statistical significance among mothers who reported only an STI, there were elevated crude ORs for STIs and several CHDs, including truncus arteriosus, conoventricular VSDs, atrioventricular VSDs, and secundum ASDs. When we restricted to those reporting *Chlamydia* in the periconceptional period, we found a crude significant association between *Chlamydia* and conoventricular VSDs (cOR 5.65); all three conoventricular VSD case mothers who reported an STI reported having a chlamydial infection. A previous study identified a significant, but weak, association between *Chlamydia* and the grouped outcome of cyanotic CHDs, which includes both Ebstein anomaly and truncus arteriosus (Dong et al., 2016). We were unable to explore the relationship between *Chlamydia* and these two CHDs in more detail, given the lack of exposed infants.

Lastly, we found an elevated significant association between GUI and encephalocele, but the ORs among those exposed to UTI only and STI only were not elevated or statistically significant. Like holoprosencephaly, encephalocele has been with linked with maternal infections including Zika virus (Hall et al., 2017; Honein et al., 2017). However, encephalocele has not been linked to GUIs in previous studies.

The mechanism by which GUIs act to increase the risk of birth defects is unknown, but considerations may include pathogen-mediated damage, the resulting inflammatory response, or treatment-related effects. We explored associations by different STI-related pathogens, but were hindered by small numbers, resulting in crude estimates with wide confidence intervals for several sub-analyses. Additionally, roughly 20% of cases and controls did not report a specific pathogen. Another potential mechanism is through a maternal inflammatory response to a pathogen. Immune response, and the subsequent change in the expression of immune mediators and cytokines in the female reproductive tract

after infection, can result in cell death and changes in gene expression, which could impair embryonic development. (Robertson, Chin, Femia, & Brown, 2018; Robertson, Chin, Schjenken, & Thompson, 2015). If inflammation were an important mediator of birth defects, we would expect that a GUI occurring immediately before conception might also contribute to increased risk of birth defects given that the inflammation from the infection may persist for some time. Finally, GUIs may increase the risk of birth defects through medications used to treat GUIs. The treatments for GUIs vary widely, so it seems unlikely that one medication is responsible for the range of significant associations observed. Studies exploring risk of medications used to treat GUIs, including antibiotics and antiherpetic medications, have been inconsistent (Ahrens et al., 2013; Ailes et al., 2016; Andersen et al., 2013; Hansen et al., 2016; Pasternak & Hviid, 2010; Reiff-Eldridge et al., 2000). We did not explore medications in this analysis.

There are many strengths of the NBDPS, including the use of a multisite, population-based design that used strict inclusion criteria and classification of cases by clinical geneticists (Rasmussen et al., 2003; Reefhuis et al., 2015). Given the large number study population in the NBDPS, we were able to evaluate the associations between GUIs and individual birth defects. Our analysis of NBDPS data, which included births from 1997 to 2011, benefited from the large number of NBDPS participants and included cases and controls analyzed in previous NBDPS publications on GUIs. It is important to acknowledge some of the study limitations. Misclassification of GUIs, and specific types of GUIs, is likely. Maternal self-reported infection during pregnancy is subject to both recognition of the infection and recall of the infection and its timing. GUIs, particularly STIs, are commonly asymptomatic, meaning that a mother may not have symptoms or may be unaware of the infection (Farley, Cohen, & Elkins, 2003; Korenromp et al., 2002). Mothers with an asymptomatic infection would have been classified as unexposed, potentially leading us to underestimate any true associations. The prevalence of GUI in the current analysis (9% of controls and 10% of cases) is lower than expected given the reported prevalence of GUIs during pregnancy and among women of reproductive age in the literature (CDC, 2017; Sheffield & Cunningham, 2005). Mothers were interviewed for NBDPS 6 weeks to 24 months after the estimated date of delivery; relying on retrospective self-reports of infection makes recall bias a concern. Mothers might have misreported or doctors may have misdiagnosed the type of GUI, given the similar symptoms. This would not have impacted our main analysis of GUI, but may have led to misclassification of specific GUI exposure type. Of the 3,407 mothers in our analysis who reported a UTI, 3,221 (95%) reported that the UTI was diagnosed by a doctor. While we do not have similar data from the interview for those mothers reporting an STI, we would expect a large proportion of positive STI reports to have been based on clinical diagnosis.

The number of exposed cases for some birth defects was small, limiting our ability to assess risk, especially in subanalyses by type of infection. Additionally, there may be some uncontrolled confounding by factors not measured, or residual confounding by measured factors. Finally, we conducted many statistical tests, and some of our findings may be due to chance. In our main analysis of 52 birth defects, we would expect to observe approximately two birth defects with a statistically significantly aOR ($52 \times 0.05 = 2.6$) by chance alone. We observed 11 statistically significant associations, and all 11 were elevated aORs. While some

of these associations were reported in other studies (e.g., secundum ASD), the majority of our significant findings have only been identified in our study and therefore should be interpreted cautiously until confirmed in other studies. Probable misclassification and underreporting of exposure lead us to be cautious when interpreting our findings. If GUIs do increase the risk of birth defects, this highlights a potential opportunity for pre-pregnancy prevention, given that GUIs are preventable and treatable.

We sought to identify associations between GUIs and birth defects that may generate future hypotheses. Our findings suggest that maternal GUIs in the month before through the third month of pregnancy may increase the risk of several different types of birth defects. Future research could focus on the larger birth defect phenotypes with more robust results, including cleft lip, or on the findings of associations between GUIs and three gastrointestinal birth defects (duodenal, small intestinal, and colonic atresia/stenosis). Given the limitations of the current analysis, other studies better able to identify infections, and pathogens or measure markers of inflammatory response to infections may help to confirm our findings and improve our understanding of the underlying mechanisms. Based on the findings of this research, women who are planning to or who have recently become pregnant should consider talking to their doctors about GUI prevention and treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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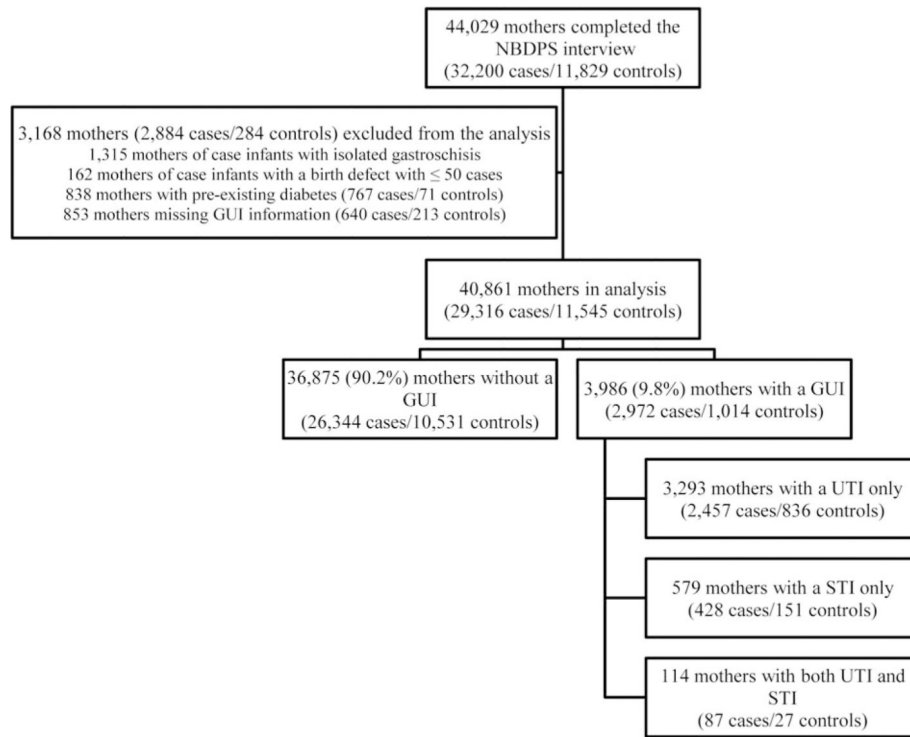


FIGURE 1. Study population, exclusions, and genitourinary infection status in the month before pregnancy through the third month of pregnancy among women in the National Birth Defects Prevention Study, 1997–2011

TABLE 1

Selected characteristics of mothers of controls by reported periconceptional genitourinary infection, National Birth Defects Prevention Study, 1997–2011^a

Maternal characteristic	Genitourinary infection (n = 1,014) n (%) ^b	No genitourinary infection (n = 10,531) n (%) ^b	p value ^c
Age (years)			<.001
<24	489 (48.2)	3,251 (30.9)	
25–29	250 (24.7)	2,940 (27.9)	
30 +	275 (27.1)	4,340 (41.2)	
Race/ethnicity			<.001
Non-Hispanic white	527 (52.0)	6,160 (58.5)	
Non-Hispanic black	130 (12.8)	1,138 (10.8)	
Hispanic	291 (28.7)	2,541 (24.1)	
Other	66 (6.5)	686 (6.5)	
Education			<.001
High school or less	503 (51.0)	4,012 (39.0)	
More than high school	484 (49.0)	6,281 (61.0)	
Pre-pregnancy BMI			<.001
< 18.5	73 (7.5)	515 (5.1)	
18.5–<25.0	472 (48.5)	5,483 (54.4)	
25–<30	223 (22.9)	2,284 (22.7)	
30	205 (21.1)	1,804 (17.9)	
Periconceptional smoking ^a			<.001
Yes	263 (26.6)	1,764 (17.1)	
No	726 (73.4)	8,573 (82.9)	
Periconceptional alcohol use ^a			.655
Yes	375 (38.0)	3,840 (37.3)	
No	612 (62.0)	6,462 (62.7)	
Gestational diabetes			.224
Yes	54 (5.5)	474 (4.6)	
No	931 (94.5)	9,776 (95.4)	
Folic acid-containing supplement use ^d			.006
Yes	489 (48.8)	5,579 (53.3)	
No	514 (51.3)	4,883 (46.7)	
Study Center			<.001
Arkansas	188 (18.5)	1,248 (11.9)	
California	111 (11.0)	1,131 (10.7)	
Georgia	92 (9.1)	1,148 (10.9)	
Iowa	92 (9.1)	1,171 (11.1)	
Massachusetts	79 (7.8)	1,303 (12.4)	
New Jersey	40 (3.9)	534 (5.1)	
New York	74 (7.3)	886 (8.4)	

Maternal characteristic	Genitourinary infection ($n = 1,014$) n (%) ^b	No genitourinary infection ($n = 10,531$) n (%) ^b	p value ^c
North Carolina	84 (8.3)	908 (8.6)	
Texas	165 (16.3)	1,199 (11.4)	
Utah	89 (8.8)	1,003 (9.5)	

Note. BMI = body mass index (weight in kilograms/height in meters²).

^aPericonceptional defined as the month before through the third month of pregnancy.

^bTotals vary because of missing values.

^cChi-square test for difference in the distribution within each covariate.

^dIn the month before pregnancy through the first month of pregnancy.

Associations between periconceptional genitourinary infections and noncardiac birth defects, by type of infection, National Birth Defects Prevention Study 1997–2011

TABLE 2

Birth defect	% with GUI	Any GUI		UTI Only		STI Only		Both STI & UTI		
		Unexp	Exp	OR (95% CI) ^a	Exp	OR (95% CI) ^a	Exp	OR (95% CI) ^a	Exp	OR (95% CI) ^a
Controls ^b	8.8	10,531	1,014		836		151		27	
Amniotic band sequence	11.4	289	37	1.16 (0.81, 1.66)	32	1.23 (0.84, 1.81)	2	NC	3	4.05 (0.78, 13.3)
Anencephaly	12.3	548	77	1.31 (1.00, 1.72)	65	1.32 (0.99, 1.77)	9	1.23 (0.62, 2.44)	3	2.14 (0.41, 6.97)
Spina bifida	10.0	1,134	126	1.07 (0.86, 1.32)	112	1.18 (0.95, 1.48)	11	0.55 (0.28, 1.10)	3	1.03 (0.20, 3.36)
Encephalocele	13.2	190	29	1.53 (1.01, 2.32)	22	1.41 (0.88, 2.26)	4	1.47 (0.39, 3.90)	3	6.16 (1.19, 20.3)
Holoprosencephaly	13.1	133	20	1.55 (0.95, 2.51)	14	1.32 (0.75, 2.32)	5	2.66 (1.06, 6.70)	1	NC
Dandy-Walker malformation	9.0	162	16	1.06 (0.62, 1.79)	12	0.99 (0.54, 1.80)	4	1.72 (0.46, 4.59)	0	NC
Hydrocephaly	11.0	430	53	1.14 (0.83, 1.56)	41	1.07 (0.75, 1.52)	11	1.56 (0.81, 3.01)	1	NC
Cerebellar hypoplasia ^c	11.5	54	7	1.35 (0.52, 2.98)	7	1.63 (0.62, 3.61)	0	NC	0	NC
Anophthalmia/microphthalmia	12.7	192	28	1.42 (0.94, 2.16)	25	1.55 (1.00, 2.41)	2	NC	1	NC
Congenital cataracts	11.9	305	41	1.53 (1.09, 2.15)	33	1.48 (1.02, 2.16)	6	1.48 (0.64, 3.42)	2	NC
Glaucoma	11.0	162	20	1.34 (0.81, 2.22)	17	1.35 (0.78, 2.32)	3	1.37 (0.28, 4.18)	0	NC
Anotia/microtia	10.6	592	70	1.15 (0.87, 1.52)	59	1.15 (0.85, 1.56)	11	1.41 (0.75, 2.66)	0	NC
Choanal atresia	10.2	141	16	1.32 (0.75, 2.32)	12	1.14 (0.59, 2.20)	4	1.98 (0.52, 5.28)	0	NC
Cleft palate only	8.6	1,424	134	1.01 (0.83, 1.23)	112	1.05 (0.85, 1.30)	18	0.85 (0.51, 1.41)	4	1.08 (0.27, 3.11)
Cleft lip only	11.2	955	120	1.36 (1.10, 1.67)	96	1.32 (1.05, 1.66)	22	1.63 (1.02, 2.60)	2	NC
Cleft lip with cleft palate	10.7	1,771	211	1.15 (0.98, 1.36)	168	1.11 (0.93, 1.34)	33	1.24 (0.84, 1.83)	10	1.80 (0.83, 3.90)
Esophageal atresia	10.3	665	76	1.31 (1.01, 1.69)	62	1.28 (0.97, 1.70)	10	1.19 (0.62, 2.29)	4	2.35 (0.59, 6.76)
Duodenal atresia/stenosis	14.8	201	35	1.89 (1.29, 2.75)	27	1.80 (1.18, 2.75)	6	2.02 (0.88, 4.67)	2	NC
Small intestinal atresia/stenosis	12.7	414	60	1.51 (1.12, 2.01)	52	1.61 (1.18, 2.20)	7	1.11 (0.51, 2.40)	1	NC
Colonic atresia/stenosis	20.7	46	12	2.17 (1.10, 4.29)	11	2.48 (1.22, 5.03)	1	NC	0	NC
Anorectal atresia/stenosis	10.5	928	109	1.10 (0.87, 1.37)	89	1.16 (0.91, 1.48)	15	0.74 (0.39, 1.41)	5	1.11 (0.33, 3.69)
Biliary atresia	7.3	179	14	0.83 (0.47, 1.48)	11	0.87 (0.47, 1.61)	2	NC	1	NC
Hypospadias	8.4	2,320	213	1.07 (0.89, 1.28)	184	1.10 (0.91, 1.34)	25	0.81 (0.49, 1.34)	4	0.93 (0.21, 3.21)
Renal agenesis/hypoplasia	13.9	155	25	1.31 (0.82, 2.10)	18	1.23 (0.72, 2.08)	4	1.80 (0.48, 4.80)	3	7.55 (1.45, 24.9)

Birth defect	% with GUI	Any GUI		UTI Only		STI Only		Both STI & UTI		
		Unexp	Exp	OR (95% CI) ^a	Exp	OR (95% CI) ^a	Exp	OR (95% CI) ^a	Exp	OR (95% CI) ^a
Bladder exstrophy	6.9	67	5	0.82 (0.33, 2.06)	4	0.75 (0.20, 2.02)	0	NC	1	NC
Cloacal exstrophy	11.1	88	11	1.40 (0.74, 2.66)	10	1.57 (0.80, 3.06)	1	NC	0	NC
Longitudinal limb deficiency	11.4	443	57	1.20 (0.89, 1.62)	45	1.17 (0.84, 1.63)	11	1.48 (0.77, 2.84)	1	NC
Transverse limb deficiency	11.5	623	81	1.33 (1.03, 1.72)	58	1.17 (0.87, 1.57)	20	2.06 (1.24, 3.40)	3	1.88 (0.36, 6.13)
Craniosynostosis	8.5	1,440	133	1.03 (0.85, 1.26)	120	1.12 (0.91, 1.39)	12	0.59 (0.31, 1.14)	1	NC
Diaphragmatic hernia	10.7	763	91	1.23 (0.97, 1.56)	73	1.20 (0.92, 1.56)	15	1.32(0.75, 2.30)	3	1.53 (0.30, 5.00)
Omphalocele	8.4	393	36	0.94 (0.65, 1.34)	33	1.05 (0.72, 1.53)	3	0.53 (0.11, 1.60)	0	NC
Sacral agenesis	14.7	64	11	1.82 (0.94, 3.53)	9	1.78 (0.87, 3.66)	1	NC	1	NC

Note: GUI = genitourinary infection, UTI = urinary tract infection, STI = sexually transmitted infection, Unexp = unexposed, Exp = exposed, OR = odds ratio, CI = confidence interval, NC = not calculated. Bold font indicates a statistically significant finding.

^aFor defects with 5+ exposed cases, estimates were adjusted for maternal age (continuous), race/ethnicity, education, BMI, smoking, folic acid supplement use, and state of residence at the time of birth. Counts in the adjusted analysis were slightly lower than presented due to missing values for some covariates. Crude ORs and exact 95% CIs are presented for defects groups with 3–4 exposed cases. Estimates are not presented for analyses based on <3 exposed cases.

^bThe number of controls differed for the following birth defect analyses: congenital cataracts and glaucoma (865 exposed and 8,971 unexposed controls), clefts (1,001 exposed and 10,409 unexposed controls), and hypospadias (521 exposed and 5,366 unexposed male controls).

^cAdjusted logistic model did not converge; estimates presented are crude OR and exact 95% CIs.

TABLE 3

Associations between periconceptional genitourinary infections and congenital heart defects, by type of infection, National Birth Defects Prevention Study 1997–2011

Birth Defect	% with GUI	Any GUI		UTI Only		STI Only		Both STI & UTI		
		Unexp	Exp	OR (95% CI) ^a	Exp	OR (95% CI) ^a	Exp	OR (95% CI) ^a	Exp	OR (95% CI) ^a
Controls ^b	8.8	10,531	1,014		836		151		27	
Conotruncal defects										
Truncus arteriosus	13.8	106	17	1.63 (0.95, 2.79)	14	1.62 (0.90, 2.93)	3	1.97 (0.40, 6.04)	0	NC
Tetralogy of Fallot	9.0	1,057	105	1.09 (0.88, 1.36)	77	1.00 (0.78, 1.28)	24	1.53 (0.97, 2.42)	4	1.48(0.37, 4.25)
D-TGA	9.1	683	68	0.99 (0.75, 1.31)	61	1.09 (0.82, 1.47)	5	0.43 (0.16, 1.16)	2	NC
DORV-TGA	9.8	166	18	1.17 (0.71, 1.93)	16	1.28 (0.75, 2.16)	2	NC	0	NC
Other DORV	12.7	103	15	1.34 (0.74, 2.42)	13	1.42 (0.75, 2.67)	2	NC	0	NC
Conoventricular VSD	15.5	93	17	2.26 (1.32, 3.89)	14	2.48 (1.38, 4.45)	3	1.72 (0.34, 5.31)	0	NC
Atrioventricular septal defect	14.8	299	52	1.82 (1.33, 2.49)	43	1.86 (1.33, 2.61)	7	1.64 (0.76, 3.55)	2	NC
TAPVR	5.8	277	17	0.62 (0.37, 1.04)	17	0.76 (0.46, 1.28)	0	NC	0	NC
Left ventricular outflow tract obstruction defects										
Hypoplastic left heart syndrome	10.7	568	68	1.26 (0.96, 1.65)	61	1.37 (1.03, 1.82)	5	0.67 (0.27, 1.65)	2	NC
Coarctation of the aorta	8.9	1,036	101	1.08 (0.86, 1.35)	89	1.13 (0.89, 1.44)	10	0.78 (0.41, 1.50)	2	NC
Aortic valve stenosis	7.2	463	36	0.79 (0.54, 1.14)	32	0.83 (0.56, 1.23)	4	0.60 (0.16, 1.59)	0	NC
Right ventricular outflow tract obstruction defects										
Pulmonary atresia	9.0	232	23	0.97 (0.62, 1.54)	18	0.91 (0.54, 1.53)	4	1.20 (0.32, 3.18)	1	NC
Pulmonary valve stenosis	9.9	1,375	151	1.13 (0.93, 1.37)	122	1.09 (0.88, 1.35)	26	1.37 (0.88, 2.13)	3	0.88 (0.17, 2.90)
Tricuspid atresia	7.7	156	13	0.79 (0.42, 1.47)	12	0.89 (0.46, 1.71)	1	NC	0	NC
Ebstein anomaly	10.6	160	19	1.23 (0.75, 2.02)	10	0.75 (0.38, 1.47)	8	3.72 (1.77, 7.81)	1	NC
Septal defects										
Perimembranous VSD	8.2	1,233	110	0.94 (0.75, 1.18)	78	0.87 (0.67, 1.13)	26	1.13 (0.73, 1.75)	6	1.52(0.59, 3.92)
Muscular VSD	8.7	167	16	1.01 (0.54, 1.86)	12	0.90 (0.45, 1.80)	3	0.97 (0.17, 3.65)	1	NC
Secundum atrial septal defect	11.3	2,611	332	1.19 (1.04, 1.37)	274	1.21 (1.04, 1.41)	47	1.06 (0.74, 1.51)	11	1.36(0.65, 2.82)
Single ventricle defects	11.5	139	18	1.39 (0.83, 2.34)	16	1.48 (0.86, 2.56)	2	NC	0	NC
Heterotaxy	12.5	281	40	1.35 (0.94, 1.93)	30	1.25 (0.83, 1.88)	7	1.40 (0.61, 3.22)	3	4.16 (0.80, 13.65)

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Note. GUI = genitourinary infection, UTI = urinary tract infection, STI = sexually transmitted infection, Unexp = unexposed, Exp = exposed, OR = odds ratio, CI = confidence interval, NC = not calculated, TGA = transposition of the great arteries, DORV = double outlet right ventricle, VSD = ventricular septal defect, TAPVR = total anomalous pulmonary venous return. Bold font indicates a statistically significant finding.

^aFor defects with 5+ exposed cases, estimates were adjusted for maternal age (continuous), race/ethnicity, education, BMI, smoking, folic acid supplement use, and state of residence at the time of birth. Counts in the adjusted analysis were slightly lower than presented due to missing values for some covariates. Crude ORs and exact 95% CIs are presented for defects groups with 3–4 exposed cases. Estimates are not presented for analyses based on < 3 exposed cases.

^bThe number of controls differed for the following birth defects analyses: pulmonary valve stenosis (964 exposed and 10,116 unexposed controls) conoventricular and perimembranous VSDs (568 exposed and 6,130 unexposed controls), and muscular VSDs (63 exposed and 648 unexposed controls).

Sexually transmitted infection pathogen reported by mothers of cases and controls, National Birth Defects Prevention Study 1997–2011^a

TABLE 4

Type of STI	Among mothers reporting only STI (<i>n</i> = 579) ^d		Among mothers reporting UTI and STI (<i>n</i> = 114) ^c	
	Case mothers (<i>n</i> = 428) <i>n</i> (%) ^b	Control mothers (<i>n</i> = 151) <i>n</i> (%) ^b	Case mothers (<i>n</i> = 87) <i>n</i> (%) ^b	Control mothers (<i>n</i> = 27) <i>n</i> (%) ^b
Chlamydia trachomatis	132 (31)	47 (31)	28 (32)	7 (26)
Bacterial vaginosis	87 (20)	38 (25)	16 (18)	5 (19)
Human papillomavirus	74 (17)	23 (15)	14 (16)	3 (11)
Herpes simplex virus	42 (10)	14 (9)	3 (3)	1 (4)
Trichomoniasis	23 (5)	7 (5)	7 (8)	3 (11)
Gonorrhea	20 (5)	6 (4)	2 (2)	2 (7)
Syphilis	5 (1)	0	1 (1)	0
Unknown pathogen	61 (14)	23 (15)	20 (23)	7 (26)

Note. UTI = urinary tract infection, STI = sexually transmitted infection.

^aTwenty-one mothers reported two STIs (14 case/7 control), and one case mother reported three STIs.

^bPercentages do not total 100.

^cFive mothers reported two STIs (4 case mothers/1 control mother).

Associations between specific periconceptual sexually transmitted infection pathogens and birth defects, National Birth Defects Prevention Study 1997–2011^a

TABLE 5

Birth defect	Chlamydia		Bacterial vaginosis		HPV		Herpes virus		Trichomoniasis		Gonorrhea	
	Exp	OR (95% CI)	Exp	OR (95% CI)	Exp	OR (95% CI)	Exp	OR (95% CI)	Exp	OR (95% CI)	Exp	OR (95% CI)
Controls ^b	47		38		23		14		7		6	
Anencephaly	6	2.39 (0.99, 5.72)	2	NC	0	NC	0	NC	0	NC	1	NC
Spina bifida	4	0.79 (0.21, 2.17)	4	0.98 (0.25, 2.72)	0	NC	0	NC	1	NC	0	NC
Holoprosencephaly	3	5.05 (0.99, 16.0)	1	NC	1	NC	1	NC	0	NC	1	NC
Hydrocephaly	3	1.56 (0.31, 4.89)	1	NC	2	NC	1	NC	0	NC	2	NC
Anotia/microtia	2	NC	2	NC	2	NC	2	NC	0	NC	4	11.9 (2.45, 50.1)
Cleft palate only	5	0.87 (0.34, 2.21)	4	0.77 (0.20, 2.14)	0	NC	1	NC	2	NC	0	NC
Cleft lip only	11	2.76 (1.36, 5.60)	4	1.15 (0.30, 3.20)	4	1.98 (0.50, 5.85)	2	NC	0	NC	0	NC
Cleft lip with cleft palate	14	1.63 (0.88, 3.01)	4	0.62 (0.16, 1.72)	5	1.30 (0.49, 3.50)	1	NC	5	4.73 (1.46, 15.3)	3	2.94 (0.48, 13.8)
Esophageal atresia	2	NC	1	NC	3	2.07 (0.40, 6.86)	1	NC	2	NC	1	NC
Duodenal atresia/stenosis	3	3.34 (0.66, 10.5)	2	NC	0	NC	0	NC	1	NC	0	NC
Small intestinal atresia/stenosis	1	NC	3	2.01 (0.39, 6.37)	0	NC	2	NC	0	NC	0	NC
Anorectal atresia/stenosis	4	0.97 (0.25, 2.65)	5	0.65 (0.15, 2.69)	0	NC	1	NC	0	NC	0	NC
Hypospadias	8	1.11 (0.46, 2.71)	4	0.51 (0.13, 1.56)	5	1.07 (0.27, 4.20)	5	1.84 (0.50, 6.76)	0	NC	1	NC
Longitudinal limb deficiency	3	1.52 (0.30, 4.74)	5	1.33 (0.41, 4.35)	1	NC	0	NC	0	NC	2	NC
Transverse limb deficiency	4	1.44 (0.38, 3.95)	5	2.23 (0.87, 5.74)	6	4.78 (1.90, 12.0)	1	NC	0	NC	1	NC
Craniosynostosis	2	NC	2	NC	6	1.27 (0.43, 3.74)	0	NC	0	NC	0	NC
Diaphragmatic hernia	4	1.17 (0.31, 3.23)	4	1.45 (0.38, 4.05)	3	1.80 (0.35, 5.98)	3	2.96 (0.54, 10.6)	0	NC	0	NC
Tetralogy of Fallot	8	1.59 (0.71, 3.58)	5	1.12 (0.40, 3.15)	2	NC	4	2.85 (0.68, 9.08)	3	4.27 (0.71, 18.7)	1	NC
D-TGA	0	NC	4	1.62 (0.42, 4.53)	0	NC	0	NC	0	NC	0	NC
Conoventricular VSD	3	5.65 (1.09, 18.4)	0	NC	0	NC	0	NC	0	NC	0	NC
Pulmonary valve stenosis	7	1.16 (0.51, 2.64)	8	1.78 (0.77, 4.11)	5	1.51 (0.56, 4.10)	1	NC	1	NC	0	NC
Perimembranous VSD	9	1.35 (0.64, 2.87)	2	NC	6	1.48 (0.59, 3.72)	4	1.81 (0.42, 6.11)	2	NC	2	NC
Secundum atrial septal defect	18	1.20 (0.67, 2.13)	8	0.66 (0.28, 1.59)	6	0.99 (0.39, 2.52)	4	1.15 (0.28, 3.67)	3	1.73 (0.29, 7.58)	0	NC
Heterotaxy	4	3.19 (0.83, 8.81)	0	NC	1	NC	1	NC	0	NC	0	NC

Note. STI = sexually transmitted infection, HPV = human papillomavirus, Exp = exposed, OR = odds ratio, CI = confidence interval, NC = not calculated, TGA = transposition of the great arteries, VSD = ventricular septal defect. Bold font indicates a statistically significant finding.

^aNot presented in table are birth defects for which there were less than three exposed cases for each STI pathogen: amniotic band sequence, encephalocele, Dandy-Walker malformation, cerebellar hypoplasia, anophthalmia/microphthalmia, congenital cataracts, glaucoma, choanal atresia, colonic atresia/stenosis, biliary atresia, renal agenesis/hypoplasia, bladder exstrophy, cloacal exstrophy, omphalocele, sacral agenesis, truncus arteriosus, double outlet right ventricle-TGA, other double outlet right ventricle, atrioventricular septal defect, total anomalous pulmonary venous return, hypoplastic left heart syndrome, coarctation of the aorta, aortic valve stenosis, pulmonary atresia, tricuspid atresia, Ebstein anomaly, muscular VSD, and single ventricle defects. For defects with 5+ exposed cases, estimates were adjusted for maternal age (continuous), race/ethnicity, education, BMI, smoking, folic acid supplement use, and state of residence at the time of birth. Counts in the adjusted analysis were slightly lower than presented due to missing values for some covariates. Crude ORs and exact 95% CIs are presented for defects groups with 3–4 exposed cases. Estimates are not presented for analyses based on <3 exposed cases.

^bAs in Tables 2 and 3, 10,531 unexposed controls were included in all sub-analyses except: clefts (46 exposed and 10,409 unexposed controls), hypospadias (19 exposed and 5,366 unexposed male controls), pulmonary valve stenosis (44 exposed and 10,116 unexposed controls), and conoventricular/perimembranous VSDs (35 exposed and 6,130 unexposed controls).

TABLE 6
Epidemiologic studies of genitourinary infections and birth defects (except gastroschisis)

Author, year	Study design, setting	Exposure	Outcomes	Main findings
Carter et al., 2011	NBDPS; case-control study of births from 1997 to 2004 from 10 states	Self-reported STIs, PED, or group B streptococcus infection in the month before through the third month of pregnancy; 290 case mothers and 139 control mothers were exposed	Individual birth defects and larger birth defect groupings (e.g., NTDs.)	OR (95% CI) for (a) bilateral renal agenesis/hyposplasia: 2.89 (1.11, 7.50); CL ± CP: 1.46 (1.03, 2.06); transverse limb deficiency: 1.84 (1.04, 3.26)
Cleves et al., 2008	NBDPS; case-control study of births from 1997 to 2003 from 10 states	Self-reported UTI in the first trimester; 247 case mothers and 290 control mothers were exposed	Individual CHDs, larger CHD groupings, and any CHD	OR (95% CI) for (a) LVOTO: 1.41 (1.04, 1.93); (b) HLHS: 1.61 (1.01, 2.59); (c) AVSD: 2.29 (1.11, 4.73)
Ailes et al., 2016	NBDPS; case-control study of births from 1997 to 2016 from 10 states	Self-reported use of nitrofurantoin, trimethoprim-sulfamethoxazole, or cephalosporine to treat fever-free, doctor-diagnosed UTIs in the month before through the third month of pregnancy compared to penicillin; 608 case mothers and 231 control mothers were exposed	Individual birth defects and larger birth defect groupings (e.g., NTDs)	OR (95% CI) for nitrofurantoin and clefts: 1.97 (1.10, 3.53). OR (95% CI) for trimethoprim-sulfamethoxazole for esophageal atresia: 5.31 (1.39, 20.24); diaphragmatic hernia: 5.09 (1.20, 21.69) OR (95% CI) for cephalosporine and anorectal atresia/stenosis: 5.01 (1.34, 18.76)
Ferencz et al., 1997	BWIS; case-control study of births from 1981 to 1989 in the Baltimore-Washington area	Self-reported UTIs in the 3 months before through the third month of pregnancy; 38 ASD case mothers and 467 control mothers were exposed	Individual CHDs, larger CHD groupings, and any CHD	OR (95% CI) for ASD: 1.6 (1.1, 2.3).
Wilson et al., 1998	BWIS; case-control study of births from 1981 to 1989 in the Baltimore-Washington area	Self-reported UTIs in the 3 months before through the third month of pregnancy; 38 ASD case mothers and 467 control mothers were exposed	Individual CHDs, larger CHD groupings, and any CHD	Attributable fraction for UTIs and ASD (95% CI): 6.4 (2.2, 10.7).
Acs et al., 2008a	HCCSCA; case-control study births from 1980 to 1996 in Hungary	Recurrent genital herpes in the first trimester and any time during pregnancy collected from antenatal care logbook, medical records, and self-report; 160 case mothers and 228 control mothers were exposed	Individual birth defects, larger birth defect groupings, and any birth defect	No significant ORs
Acs et al., 2008b	HCCSCA; case-control study births from 1980 to 1996 in Hungary	Acute PED during the second and third month of pregnancy that was prospectively collected and recorded in antenatal care logbook or medical record; 67 case mothers and 128 control mothers were exposed	Individual birth defects, larger birth defect groupings, and any birth defect	OR (95% CI) for any CHD: 2.6 (1.2, 5.4)
Acs et al., 2008c	HCCSCA; case-control study births from 1980 to 1996 in Hungary	Vulvovaginitis and bacterial vaginosis during the second and third month of pregnancy that was prospectively collected and recorded in antenatal care logbook or medical record; 1,556 case mothers and 2,698 control mothers were exposed	Individual birth defects, larger birth defect groupings, and any birth defect	No significant elevated ORs Protective ORs (95% CI) for (a) limb deficiencies: 0.6 (0.4, 0.9); (b) musculo-skeletal birth defects: 0.4 (0.2, 0.9)
Banhidy et al., 2006	HCCSCA; case-control study births from 1980 to 1996 in Hungary	UTI during the second and third months of pregnancy was collected from antenatal care logbook, medical records, and self-report; 1,542 case mothers and 2,188 control mothers were exposed	Individual birth defects, larger birth defect groupings, and any birth defect	No significant ORs
Banhidy et al., 2010	HCCSCA; case-control study of birth from 1980 to 1996 Hungary	Genital warts (caused by HPV) during the second and third months of pregnancy was collected from antenatal care	17 case infants: 4 CHDs, 7 NTDs, 2 hypospadias, 2	No significant ORs

Author, year	Study design, setting	Exposure	Outcomes	Main findings
Metneki et al., 2005	HCCSCA; case-control study births from 1980 to 1996 in Hungary	logbook, medical records, and self-report; 17 case mothers and 25 control mothers were exposed UTIs and STIs during the second, third, and fourth month of pregnancy was collected from antenatal care logbook, medical records, and self-report; 14 NTD case mothers and 182 non-NTD case mothers (the comparison group) were exposed	syndactyly, and 7 with other birth defects Isolated CL \pm CP and PCP	OR (95% CI) for UTI and (a) CL \pm CP: 1.7 (1.1, 2.5); (b) PCP: 2.1 (1.2, 3.5) No significant ORs for STI and CL \pm CP or PCP
Norgard et al., 2006	HCCSCA; case-control study births from 1980 to 1996 in Hungary	Herpes labialis during the first trimester and any time during pregnancy was collected from antenatal care logbook, medical records, and self-report; 14 NTD case mothers and 182 non-NTD case mothers (the comparison group) were exposed	Isolated NTDs	No significant ORs for NTDs
Dong, Binongo, & Kancherla, 2016	Case-control study of live singleton births in the United States during 2012	<i>Chlamydia</i> any time during pregnancy as reported on the birth certificate; 43 (1.7%) case mothers and 55,834 (1.7%) control mothers were exposed	Any cyanotic CHD as reported on the birth certificate	OR (95% CI) for cyanotic CHDs: 1.39 (1.02, 1.90)

Note. NBDFS = National Birth Defects Prevention Study, BWIS = Baltimore-Washington Infant Study, HCCSCA = Hungarian Case-Control Surveillance of Congenital Abnormalities; STI = sexually transmitted infection., PID = pelvic inflammatory disease, UTI = urinary tract infection, HPV = human papillomavirus, NTDs = neural tube defects, CHD = congenital heart defect, ASD = atrial septal defect, CL \pm CP = cleft lip with or without cleft palate, PCP = posterior cleft palate, LVOTO = left ventricular outflow tract obstruction defects; HLHS = hypoplastic left heart syndrome; AVSD = atrioventricular septal defect, OR = odds ratio, CI = confidence interval.