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Fever and antibiotic use in maternal urinary tract infections during pregnancy and risk of congenital heart defects: Findings from the National Birth Defects Prevention Study

Jenil Patel[1,2,3], **Maria D. Politis**[2,3,4], **Meredith M. Howley**[5], **Marilyn L. Browne**[5,6], **Elijah H. Bolin**[7], **Elizabeth C. Ailes**[8], **Candice Y. Johnson**[9], **Everett Magann**[10], **Wendy N. Nembhard**[2,3], **The National Birth Defects Prevention Study**

[1]Department of Epidemiology, Human Genetics and Environmental Sciences, University of Texas Health Science Center at Houston (UTHealth) School of Public Health, Dallas, Texas, USA

[2]Department of Epidemiology, Fay W. Boozman College of Public Health, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA

[3]Arkansas Center for Birth Defects Research and Prevention, Fay W. Boozman College of Public Health, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA

[4]Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, New York, USA

[5]Birth Defects Registry, New York State Department of Health, Albany, New York, USA

[6]Department of Epidemiology and Biostatistics, School of Public Health, University at Albany, Rensselaer, New York, USA

[7]Department of Pediatrics, Section of Pediatric Cardiology, University of Arkansas for Medical Sciences and Arkansas Children's Hospital, Little Rock, Arkansas, USA

[8]National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

[9]Department of Family Medicine and Community Health, Duke University, Durham, North Carolina, USA

[10]Department of Obstetrics and Gynecology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA

Abstract

Correspondence: Wendy N. Nembhard, Department of Epidemiology, Fay W. Boozman College of Public Health, University of Arkansas for Medical Sciences, 4301 West Markham Street, Slot #820, Little Rock, AR, 72205-7199, USA. wnembhard@uams.edu.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

This analysis has been replicated by Maria D. Politis, DrPH, also a co-author on the project.

CONFLICT OF INTEREST

The authors report no conflict of interest.

SUPPORTING INFORMATION

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

Background: Previous studies report an association between prenatal maternal urinary tract infections (UTI) and specific congenital heart defects (CHDs); however, the role of fever and antibiotic use on this association is poorly understood. Using data from the National Birth Defects Prevention Study, we examined whether the relationship between maternal UTIs during the periconceptional period and occurrence of CHDs is modified by the presence of fever due to UTI and corresponding antibiotic use among 11,704 CHD case infants and 11,636 live-born control infants.

Methods: Information on UTIs, fever associated with UTI and antibiotic use (sulfonamides, nitrofurantoin, cephalosporins, penicillin, macrolides, and quinolones) during pregnancy were obtained using a computer-assisted telephone interview. Using unconditional multivariable logistic regression, we calculated adjusted odds ratios (ORs) to determine the association between maternal UTIs and subtypes of CHDs. Analyses were stratified by the presence of fever and medication use associated with UTI.

Results: The prevalence of UTIs during the periconceptional period was 7.6% in control mothers, and 8.7% in case mothers. In the absence of fever, UTI was associated with secundum atrial septal defects (ASD) (OR 1.3; 95% confidence interval [CI] 1.1–1.5) and in the absence of antibiotics, UTI was associated with conotruncal defects as a group and for four specific CHDs. When fever and UTI occurred concomitantly, no significantly elevated odds ratios were noticed for any subtypes of CHD. Among women with UTIs who used antibiotics, an elevated but statistically non-significant estimate was observed for secundum ASD (OR 1.4; 95% CI 1.0–2.0).

Conclusion: Findings in the present study suggest that fever due to UTI and corresponding maternal antibiotic use do not substantially modify the association between maternal UTIs and specific CHDs in offspring. Further studies with larger sample sizes are warranted to guide clinical management of UTIs during the periconceptional period.

Keywords

CHDs; congenital heart defects; fever; maternal infections; pregnancy; UTI

1 | INTRODUCTION

Congenital heart defects (CHDs) are the most common group of birth defects, affecting six to 12 of every 1000 infants in the United States (US); they are also associated with significant pediatric morbidity and mortality (Botto et al., 2001; Botto et al., 2007; Christianson et al., 2006; Cleves et al., 2008; Moller et al., 1993). Although some CHDs occur in the setting of genetic syndromes (e.g., trisomy 21) or teratogenic exposures (e.g., anticonvulsants, maternal infections), approximately 80% are of unknown etiology (Caton et al., 2009; Erickson, 1991; Jenkins et al., 2007).

In the past decade, studies have indicated that maternal urinary tract infections (UTIs) during the first trimester may increase risk for certain CHDs in offspring (Cleves et al., 2008; Erickson, 1991; Howley et al., 2018; Oster et al., 2011). One of these reported that maternal UTIs were associated with heterotaxies and atrial septal defects (ASDs; Erickson, 1991). Another study from the National Birth Defects Prevention Study (NBDPS), and noted positive associations with conoventricular-type ventricular septal defect (VSD),

atrioventricular septal defect (AVSD), and hypoplastic left heart syndrome (HLHS; Howley et al., 2018).

Moreover, studies reported that maternal fever during pregnancy is associated with CHDs, specifically during 3 months before pregnancy through the first trimester (Ailes et al., 2016; Czeizel et al., 2001; Källén & Olausson, 2003; Waller et al., 2018). Additionally, antibiotics commonly used to treat UTIs have been linked to clefts, diaphragmatic hernia, and CHDs (Acs et al., 2005; Ailes et al., 2016; Ferencz, 1997; Tikkanen & Heinonen, 1991). However, it is essential to highlight that prior studies have not delved into the specific relationship between fever associated with UTIs and the corresponding maternal antibiotic medication usage and their combined impact on CHD risk (Cleves et al., 2008) Furthermore, previous studies have not accounted for the presence of other cardiac/extracardiac defects.

In light of these findings regarding maternal fever, antibiotic usage, and their separate associations with congenital heart defects, there arises a critical need to investigate the interplay between fever due to UTIs and the use of antibiotics during pregnancy. Therefore, the purpose of this study was to determine the role of maternal fever due to UTI and corresponding antibiotic medication use on the relationship between maternal UTIs during pregnancy and the occurrence of CHDs using the complete NBDPS data till 2011.

2 | MATERIALS AND METHODS

The study population included cases with CHDs (livebirths, stillbirths, and elective terminations) and liveborn infants without major birth defects (“controls”) born to women participating in the NBDPS, with pregnancies ending on or after October 1, 1997 through estimated dates of delivery on or before December 31, 2011. The NBDPS is one of the largest population-based, case–control studies in the US that examines risk factors for selected major non-syndromic birth defects. The study methods have been published previously (Reefhuis et al., 2015; Yoon et al., 2001). NBDPS cases were diagnosed with at least one of the approximate 30 eligible birth defect types ascertained from birth defects surveillance systems throughout the US: AR, CA, GA, IA, MA, CA, IA, NJ, NY, NC, TX, and UT. Control infants were live births without major birth defects who were randomly selected from hospital records/birth certificates in the same period and region as case infants. Cases with known/suspected genetic syndrome were excluded. Overall participation in the NBDPS was 67.4% for cases and 64.8% for controls.

2.1 | Data collection

Mothers of case/control infants completed an interview using a computer-assisted telephone interview (CATI) that assessed information regarding multiple exposures before and during pregnancy. Interviews were conducted by trained interviewers in English/Spanish between 6 weeks and 24 months after the estimated date of delivery. Mothers were asked questions regarding pregnancy history, maternal illnesses, tobacco and alcohol use, medication use, vitamin/supplement use and dietary intake. Detailed questions were asked about maternal illnesses including respiratory illnesses, UTIs, sexually transmitted diseases, and other infections. The occurrence of fever, associated medication use, and fever independent of other illness were also ascertained.

2.2 | Urinary tract infections

Mothers were classified as having a UTI if they reported a UTI in response to the following question, “Did you have any of the following illnesses: a kidney, bladder, or urinary tract infection?” Women were asked whether UTI was diagnosed by a doctor, the timing of the UTI during the 3 months before to the end of pregnancy, if they experienced a fever with the UTI, how long the fever lasted, the highest recorded temperature, and use of any UTI medications or remedies. Investigators from four study sites (JP, EA, CJ, and MH) reviewed other sections of the CATI and interviewer notes for free-text responses related to UTIs. To be considered to have a UTI for this analysis, the woman must have specified that the UTI occurred in the periconceptional period (between 1 month prior to conception and the end of the first trimester).

2.3 | Fever associated with UTI

Fever associated with UTI was defined as a self-reported fever specifically associated with the reported UTI at least once during the periconceptional period, based on response to the following question, “When you were sick with infection/PID (pelvic inflammatory disease), did you have a fever?”. Women who did not report a fever associated with their UTI were considered unexposed. Fever not associated with UTI was not examined to avoid bias due to independent effects.

2.4 | Antibiotic medication use

During the interview, women who reported having a UTI were asked about the medication used for UTI in the form of a question, “Did you take any medications or remedies for your illness?”. Women were also asked later in the interview if they took specific antibiotic medications possibly used to treat a UTI such as “amoxicillin”, “Bactrim”, ‘Cipro”, “doxycycline”, and “augmentin” and about “any medications” that had not already been covered in the interview. A code was assigned to each medication using Slone Epidemiology Center Drug Dictionary. These codes were used to identify the primary components and class for each medication. In our analysis, women were considered to have taken an antibiotic medication for their reported UTI if they reported taking a medication containing sulfonamides, nitrofurantoin, cephalosporins, penicillin, macrolides, or quinolones during the periconceptional period in any section of the questionnaire during the interview. Women who did not report taking an antibiotic periconceptionally were considered unexposed.

2.5 | Congenital heart defects

Each case was reviewed by clinicians with expertise in cardiology and categorized according to co-occurring cardiac defects and the presence of extracardiac defects (Botto et al., 2007). Simple CHDs were single CHDs or well-defined CHD entities (e.g., tetralogy of Fallot). Associated CHDs were common combinations of two distinct CHDs (e.g., transposition of the great vessels with out-flow tract obstruction). Complex CHDs were single ventricle lesions, and/or three or more major and distinct CHDs. Pregnancies affected by CHDs were also categorized according to the presence or absence (“isolated” phenotype or pattern) of extracardiac malformations. For the present study, main analyses included all CHDs. Additional supplemental analyses were conducted among simple isolated cases.

Specific CHDs were additionally grouped into seven major categories: (1) Conotruncal, including truncus arteriosus, tetralogy of Fallot, transposition of the great arteries, double-outlet right ventricle, and conoventricular VSDs; (2) AVSD; (3) total anomalous pulmonary venous return (TAPVR); (4) Left ventricular outflow tract obstruction (LVOTO) defects, including aortic valve stenosis, HLHS and coarctation of the aorta, (5) Right ventricular outflow tract obstruction (RVOTO) defects, including pulmonary valve stenosis (PVS), pulmonary atresia, and tricuspid atresia; (6) Ebstein anomaly; and (7) Septal, including VSDs and secundum ASDs. ASD not otherwise specified was grouped with ASD secundum based on the assumption that most were ASD secundum.

Muscular and unspecified VSDs were ascertained only during the first year of the study; all other VSDs were ascertained through 2005. For these case groups, we restricted to the appropriate controls (i.e., comparing VSDs from certain years to controls from only those years) for the years during which they were actively ascertained. Cases of mild PVS (defined as a gradient of <15 mmHg on echocardiography or when the adjectives “mild”, “trivial” or “whiff” were used in the echocardiogram’s report) became ineligible as of January 1, 2005. Also, cases with PVS born before January 1, 2002 in California were excluded, as they were not actively ascertained before that date.

2.6 | Covariates

Covariates included infant sex (male, female), prepregnancy body mass index (BMI) (underweight [<18.5 kg/m^2], normal [18.5–24.9 kg/m^2], overweight [25.0–29.9 kg/m^2], obese [≥30 kg/m^2]), season of birth (spring, summer, autumn, winter), maternal race/ethnicity (non-Hispanic [NH] White, NH Black, Hispanic, other), annual household income (<$10,000, $10,000–$50,000, > $50,000), maternal education (<12, 12, 13–15, ≥16 years), maternal age (<20, 20–34, ≥35 years), number of previous livebirths (0, 1, >1), maternal gestational diabetes during index pregnancy (yes/no), type 1 or type 2 diabetes diagnosed before the index pregnancy (yes/no), periconceptional maternal cigarette smoking (yes/no), periconceptional maternal alcohol use (yes/no), periconceptional maternal folic acid supplement use (yes/no), family history of CHDs (yes/no), periconceptional UTI medication use (yes/no for any of the following: sulfonamides, nitrofurantoin, cephalosporins, penicillin, macrolides, and quinolones), periconceptional fever associated with UTI (yes/no), and participating study site. BMI was categorized according to the National Heart, Lung and Blood Institute cutoff points (Health, N.I.o., 1998).

2.7 | Statistical analysis

Descriptive analyses were calculated using Chi-square tests for categorical covariates. The UTI-CHD association was assessed separately among: (i) women with and without fever due to UTI during the periconceptional period and (ii) women who used and did not use any commonly prescribed antibiotics for UTIs during the periconceptional period. All models were computed separately for (i) all CHDs and (ii) simple isolated CHDs alone. Odds ratios (ORs) and 95% confidence intervals (CI) for the association between the occurrence of UTIs and any CHD (or subtypes of CHDs) were adjusted for maternal and infant characteristics and were estimated using unconditional logistic regression. All covariates listed in Table 1 were evaluated for model inclusion using both a priori literature and a

10% change-in-effect method to identify the potential confounders for the study. The final models were adjusted for maternal age, BMI, gestational diabetes during index pregnancy, cigarette smoking, family history of CHDs, study site and UTI medication use or associated fever, as appropriate. Only models with five or more subjects in each comparison group were reported. Due to overall small sample sizes across all models, prior to finalizing the traditional regression models, penalized logistic regression was also run for all the models to check for any changes in estimates (Wang, 2014). All descriptive and statistical analyses were performed using STATA 15 software (StataCorp, L., College Station, TX, 2019). Each study site and the Centers for Disease Control and Prevention obtained Institutional Review Board approval for the NBDPS, and participants provided informed consent. The study was also approved by the University of Arkansas for Medical Sciences Institutional Review Board.

3 | RESULTS

The initial study population included 12,584 cases with CHDs and 11,829 control infants. Of these, all infants with simple or complex VSDs (n = 232), perimembranous VSDs (n = 199) and conoventricular VSDs (n = 42) ascertained during or after 2006 were excluded since these birth defects were not actively ascertained after 2006. Furthermore, both case and control infants whose mothers had missing information on UTIs during the periconceptional period were excluded from the analysis. This resulted in a final sample size of 11,704 cases with CHDs and 11,636 controls.

Table 1 shows the descriptive maternal and infant characteristics of cases with CHDs and controls. Compared to mothers of control infants, mothers of infants with CHDs were more likely to be obese, have gestational diabetes during the index pregnancy, have pre-gestational diabetes, and smoke cigarettes during the periconceptional period. Mothers of infants with CHDs were less likely than mothers of control infants to have household income >$50,000 per year and to have >12 years of education. Among infants, those with a CHD were more likely to be male and have a family history of CHD. The prevalence of UTIs was 7.6% (878/11,636) in mothers of control infants and 8.7% (1022/11,704) in mothers of infants with CHDs.

3.1 | Fever associated with UTI

Among all cases with CHDs and controls, the prevalence of fever was 2.7% (321/11,704) and 2.3% (269/11,636), respectively. Separate ORs stratified by fever for up to 24 CHD phenotypes are reported in Table 2. Among mothers with UTIs and without fever during the periconceptional period, significantly elevated odds ratios were noted for secundum ASD (OR 1.27; 95% CI 1.08–1.51), but not for any other phenotypes.

We also assessed the associations between UTIs and CHDs after restricting to simple isolated CHDs (Table S1). Among mothers with UTIs and without fever during the periconceptional period, elevated odds ratios were observed for HLHS (OR 1.42; 95% CI 1.04–1.93) and secundum ASD (OR 1.39; 95% CI 1.13–1.70).

3.2 | Antibiotic medication use

The prevalence of antibiotic medication use at the time of the UTI was 6.6% (772/11,670) among mothers of infants with CHDs and 6.0% (695/11,621) among mothers of control infants. We assessed associations for women with UTIs who reported using or not using antibiotics among 24 and 17 CHD phenotypes with sufficient sample sizes, respectively. Among women who did not use antibiotic medications, significantly elevated associations were observed for three specific CHDs: AVSD (OR 1.77; 95% CI 1.21–2.60), HLHS (OR 1.39; 95% CI 1.00–1.92), and ASD secundum NOS (OR 1.28; 95% CI 1.07–1.53) (Table 3). Additionally, a significantly protective association was observed for perimembranous VSDs (OR 0.75; 95% CI 0.57–1.00).

When we restricted the analysis to cases with simple isolated CHDs (Table S2), we observed statistically significant associations for UTIs and LVOTO (OR 1.28; 95% CI 1.02–1.61), and two specific CHDs: HLHS (OR 1.51; 95% CI 1.08–2.11), and secundum ASD (OR 1.38; 95% CI 1.11–1.72) in the absence of antibiotic use.

4 | COMMENT/DISCUSSION

4.1 | Principal findings

Using data from a large, multi-center case–control study on risk factors for birth defects, we found that fever due to UTI and corresponding antibiotic medication use did not substantially modify the association of UTIs with certain subtypes of CHDs. We were able to explore the associations between UTIs and CHDs in the presence and absence of fever and antibiotic medication use, and among the subgroup of simple isolated cases. In the absence of fever, UTIs were associated with secundum ASD (OR 1.27). In the absence of antibiotic use, we observed elevated associations for three specific CHDs: AVSD (OR 1.77), HLHS (OR 1.39), and ASD secundum NOS (OR 1.28).

4.2 | Results in the context of what is known

Only a few studies have explored the associations of UTI and CHDs, with one exploring the association in the setting of fever and antibiotic use associated with UTI (StataCorp, L., College Station, TX, 2019; Bánhidy et al., 2006; Cleves et al., 2008; Howley et al., 2018; Wilson et al., 1998). A recent NBDPS study by Howley et al. showed positive associations of UTI with conoventricular VSDs and HLHS (Howley et al., 2018). We observed that UTI-CHD associations vary by the absence or presence of fever; the previously observed increased risk of conoventricular VSDs was observed in the absence of fever in our study (Howley et al., 2018). Furthermore, a previous NBDPS study by Cleves et al. on UTI-CHD associations that explored stratification of fever with pregnancies from 1997 to 2003 showed significantly stronger associations between UTI and RVOTO defects, primarily PVS, but only in the presence of fever (Cleves et al., 2008). We did not observe these associations, which might have been due to chance as a result of smaller sample size in the earlier study.

4.3 | Clinical implications

While not directly assessed in this study, previous studies have found associations between fever or antibiotic use and CHDs. One animal study suggests that hyperthermia leads to

vascular abnormalities in chick embryos (Nilsen, 1984). Epidemiologic studies have also found associations between fever and CHDs (Mohan Dass et al., 2022; Oster et al., 2011; Shi et al., 2014). A systematic review by Shi et al. indicated that maternal fever in the first trimester is the risk factor of congenital heart diseases in offspring (pooled OR for meta-analysis 1.53 (95% CI 1.36–1.73), with a particular indication on VSD and right obstructive defects (Shi et al., 2014). With regard to antibiotic use, a recent NBDPS study by Ailes et al. showed an elevated non-significant association of nitrofurantoin use with HLHS, compared to our findings being non-significant and not elevated (Ailes et al., 2016). A study by Huang et al. reported an association between the use of sulfonamides in the first trimester and CHDs (Huang & Stafford, 2002). Furthermore, Cleves et al., in their previous NBDPS study, reported some evidence suggesting that the risk of LVOTO and anomalous pulmonary venous return (total/partial) may be greater among women who used sulfonamide antibiotics (Cleves et al., 2008). In our study, we did not observe any positive associations in the presence of fever or antibiotics. However, in the absence of fever, UTIs were associated with secundum ASD and in the absence of antibiotic use, positive associations were observed for truncus arteriosus, HLHS, ASD-secundum NOS, and AVSDs. The cause of CHDs is likely multifactorial (Simeone et al., 2016).

4.4 | Research implications

Mechanisms underlying the association between maternal fever, antibiotic use, and/or UTIs and CHDs remain unclear and need further exploration using larger sample sizes.

4.5 | Strengths and limitations

Our study should be considered in light of several limitations. First, we observed a total of eight significant odds ratios (seven among women with UTIs and no antibiotic use and one among women with UTIs and no fever). In our primary analysis, at maximum we had 25 models conducted across the two fever and two antibiotic strata each, and thus we expected five significant results due to chance alone. Second, we anticipate presence of misclassification bias as the mothers with asymptomatic infection would likely have been classified as unexposed, increasing the likelihood of spurious associations. Also, we did not account for fever from conditions other than the UTI, so the non-exposed group could have included women who had a fever periconceptionally due to other conditions, such as influenza. Additionally, we did not account for multiple UTIs during pregnancy. Third, mothers were interviewed 6 weeks to 24 months after the estimated date of delivery, which might lead to potential recall bias. However, case–control studies are the preferred way of studying rare outcomes and a previous NBDPS analysis showed that UTIs were equally likely to be reported regardless of time to interview (Tinker et al., 2013). Additionally, if there were recall bias, we would have expected to find associations between UTI and a wider range of birth defects than we observed. Fourth, we could not perform analyses by categories of UTI (asymptomatic UTI, acute cystitis, pyelonephritis) because women were not asked about the specific type of infection in the interview. Finally, the current evidence on confounding by indication for UTI-related antibiotic use and its association with congenital heart defects (CHDs) in the existing literature is somewhat limited. While numerous studies have explored the relationship between UTIs during pregnancy, antibiotic usage, and CHDs, the specific consideration of confounding by indication, which addresses

the potential bias introduced when antibiotics are prescribed for UTIs due to underlying health conditions, was not assessed.

Our study also had several strengths. We were able to update previous estimates from the NBDPS study by Cleves et al. to explore independent effects of fever and antibiotic use on UTI-CHD associations using data on pregnancies from 1997 to 2011 (Cleves et al., 2008). Second, the NBDPS was a multisite, population-based study with strict inclusion criteria and CHD case classification by pediatric cardiologists and clinical geneticists (Reefhuis et al., 2015; Yoon et al., 2001). Finally, we consider this study to be a comprehensive follow-up to previous NBDPS studies that directly measured UTI-CHD associations using similar data, giving us an opportunity to compare our results to those without stratification of fever and medication use (Ailes et al., 2016; Cleves et al., 2008; Howley et al., 2018).

4.6 | Conclusions

To summarize, the presence and absence of fever associated with UTI and corresponding antibiotic use did not substantially modify the risk of different subtypes of CHDs in offspring of mothers with UTIs, despite some minor differences observed. Further studies with larger sample sizes are warranted to guide clinical management of UTIs during the periconceptional period.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY STATEMENT

Data from the National Birth Defects Prevention Study (NBDPS) are not released to the public. Qualified researchers can be granted access to NBDPS for analysis through collaboration with one of the Centers for Birth Defects Research and Prevention (CBDRP). Detailed information on application for accessing the NBDPS can be found at https://www.cdc.gov/ncbddd/birthdefects/nbdps-public-access-procedures.html.

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TABLE 1

Sociodemographic and birth characteristics of mothers of infants with (cases) and without (controls) congenital heart defects (CHDs), National Birth Defects Prevention Study, 1997–2011.

	Cases	Controls	
	n **= 11,704 *n* (%)**	***n*** **= 11,636 *n* (%)**	**Chi-Square *p* value**
Infant sex			<0.001
Male	6281 (53.7)	5932 (51.0)	
Female	5413 (46.3)	5694 (49.0)	
Body mass index			<0.001
Underweight (<18.5 kg/m^2)	592 (5.3)	591 (5.3)	
Normal (18.5–24.9 kg/m^2)	5500 (49.0)	5983 (53.7)	
Overweight (25.0–29.9 kg/m^2)	2675 (23.9)	2524 (22.6)	
Obese (30 kg/m^2)	2444 (21.8)	2046 (18.4)	
Season of birth			0.36
Spring	2838 (24.2)	2882 (24.8)	
Summer	3064 (26.2)	3015 (25.9)	
Autumn	3020 (25.8)	2906 (25.0)	
Winter	2782 (23.8)	2833 (24.3)	
Maternal race/ethnicity			0.18
Non-Hispanic White	6825 (58.3)	6731 (57.9)	
Non-Hispanic Black	1344 (11.5)	1280 (11.0)	
Hispanic	2744 (23.5)	2858 (24.6)	
Other	788 (6.7)	761 (6.5)	
Annual household income			<0.001
<$10,000	2072 (19.2)	1980 (18.8)	
$10,000–$50,000	5079 (47.2)	4714 (44.7)	
>$50,000	3619 (33.6)	3860 (36.5)	
Maternal education (in years)			<0.001
<12	1947 (17.0)	1876 (16.5)	
12	2925 (25.5)	2685 (23.6)	
13–15	2751 (24.0)	2606 (22.9)	

	Cases	Controls	
	***n* = 11,704 *n* (%)**	***n* = 11,636 *n* (%)**	**Chi-Square *p* value**
≥16	3850 (33.5)	4200 (37.0)	
Maternal age (in years)			<0.001
<20	1034 (8.8)	1149 (9.9)	
20–34	8823 (75.4)	8836 (75.9)	
≥35	1847 (15.8)	1651 (14.2)	
Number of previous livebirths			0.42
0	4676 (39.9)	4609 (39.6)	
1	3718 (31.8)	3789 (32.6)	
>1	3310 (28.3)	3238 (27.8)	
Maternal gestational diabetes during index pregnancy			<0.001
No	10,246 (94.0)	10,727 (95.3)	
Yes	656 (6.0)	528 (4.7)	
Pre-gestational diabetes			<0.001
No	11,089 (96.9)	11,374 (99.4)	
Yes	359 (3.1)	64 (0.6)	
Periconceptional maternal smoking[a]			0.001
No	9223 (78.8)	9370 (80.5)	
Yes	2481 (21.2)	2266 (19.5)	
Periconceptional maternal alcohol use			0.002
No	7414 (64.7)	7138 (62.7)	
Yes	4047 (35.3)	4239 (37.3)	
Periconceptional maternal folic acid supplement use			0.09
No	1712 (14.7)	1611 (14.0)	
Yes	9911 (85.3)	9934 (86.0)	
Family history of CHD			<0.001
No	11,255 (96.2)	11,497 (98.8)	
Yes	449 (3.8)	139 (1.2)	
Periconceptional UTI			0.001
No	10,682 (91.3)	10,758 (92.4)	
Yes	1022 (8.7)	878 (7.6)	

	Cases	Controls	
	***n* = 11,704 *n* (%)**	***n* = 11,636 *n* (%)**	**Chi-Square *p* value**
Periconceptional fever associated with UTI			0.04
No	11,383 (97.3)	11,367 (97.7)	
Yes	321 (2.7)	269 (2.3)	
Periconceptional antibiotic use[b] at the time of the UTI			0.04
No	10,898 (93.4)	10,926 (94.0)	
Yes	772 (6.6)	695 (6.0)	

Abbreviation: UTI, urinary tract infection.

[a] Mother reported any smoking between 1 month prior to conception to end of first trimester.

[b] Sulfonamides, nitrofurantoin, cephalosporins, penicillin, macrolides, and quinolones.

TABLE 2

Association between urinary tract infections (UTIs) during the periconceptional period and occurrence of all congenital heart defects (CHDs)[a] stratified by maternal fever associated with UTI, National Birth Defects Prevention Study, 1997–2011.

	No maternal fever			Maternal fever		
	No UTI	UTI		No UTI	UTI	
	n	*n*	Adjusted OR[b] (95% CI)	*n*	*n*	Adjusted OR[b] (95% CI)
Any CHD	10499[c]	884	1.11 (1.00–1.24)	183	138	1.31 (0.91–1.87)
Conotruncal	2335	193	1.06 (0.88–1.27)	32	24	1.44 (0.74–2.82)
Truncus arteriosus	118	14	1.71 (0.92–3.19)	<5	<5	–
Tetralogy of Fallot	1100	73	0.86 (0.66–1.14)	18	14	1.25 (0.53–2.94)
d-TGA[d]	695	64	1.07 (0.79–1.46)	6	<5	1.11 (0.24–5.02)
DORV-TGA[e]	178	15	1.24 (0.69–2.22)	<5	<5	–
Other DORV	107	12	1.27 (0.63–2.57)	<5	<5	–
Conoventricular VSD[f]	99	12	1.76 (0.92–3.38)	<5	<5	–
AVSD [g]	320	38	1.40 (0.95–2.06)	5	8	3.33 (0.92–12.11)
TAPVR [h]	277	13	0.70 (0.39–1.26)	7	5	1.58 (0.32–7.72)
LVOTO [i]	1847	157	1.15 (0.95–1.40)	24	19	1.37 (0.68–2.79)
HLHS[j]	573	59	1.34 (0.99–1.82)	10	7	1.13 (0.37–3.50)
Coarctation of aorta	899	75	1.10 (0.84–1.44)	7	9	2.16 (0.73–6.43)
Aortic stenosis	470	27	0.83 (0.54–1.30)	8	<5	–
RVOTO [k]	1711	127	1.01 (0.82–1.23)	31	29	1.38 (0.76–2.52)
Pulmonary atresia	236	16	0.87 (0.55–1.54)	5	<5	–
PVS[l]	1351	104	1.09 (0.86–1.36)	25	20	1.40 (0.70–2.82)
Tricuspid atresia	162	9	0.59 (0.25–1.35)	<5	<5	–
Ebstein	166	11	0.85 (0.44–1.65)	<5	<5	–
Septal	3826	326	1.12 (0.96–1.29)	80	57	1.18 (0.74–1.88)
Perimembranous VSD	1324	81	0.82 (0.64–1.07)	28	11	0.44 (0.18–1.08)
Muscular VSD	146	8	0.87 (0.39–1.94)	<5	<5	–
ASD secundumNOS[m,n]	2450	240	1.27 (1.08–1.51)	55	45	1.44 (0.86–2.42)

	No maternal fever			Maternal fever		
	No UTI	UTI		No UTI	UTI	
	n	*n*	Adjusted OR[b] (95% CI)	*n*	*n*	Adjusted OR[b] (95% CI)
Single ventricle	155	16	1.41 (0.79–2.51)	<5	<5	–
Heterotaxy	306	31	1.38 (0.91–2.10)	5	6	1.62 (0.40–6.50)

Note: Bold font indicates a statistically significant finding ($p < 0.05$). Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Simple, associated and complex.

[b] Adjusted for maternal age, BMI, gestational diabetes during index pregnancy, cigarette smoking, family history of CHDs, fever associated with UTI, and participating study site.

[c] Number of controls for any CHD (in order of columns): 10,253; 673; 198; 497.

[d] Dextro-transposition of Greater Arteries.

[e] Double outlet right ventricle—TGA.

[f] Ventricular septal defect.

[g] Atrioventricular septal defects.

[h] Total anomalous pulmonary venous return.

[i] Left ventricular outflow tract obstruction defects.

[j] Hypoplastic left heart syndrome.

[k] Right ventricular outflow tract obstruction defects.

[l] Pulmonary valve stenosis.

[m] Atrial septal defects.

[n] Not otherwise specified.

TABLE 3

Association between urinary tract infections (UTIs) during the periconceptional period and occurrence of all congenital heart defects (CHDs)[a] stratified by corresponding maternal antibiotic use, National Birth Defects Prevention Study, 1997–2011.

	No antibiotic medication use			Antibiotic medication use		
	No UTI	UTI		No UTI	UTI	
	n	*n*	Adjusted OR (95% CI)[b]	*n*	*n*	Adjusted OR (95% CI)[b]
Any CHD	10123[c]	775	**1.15 (1.02–1.29)**	236	536	1.07 (0.84–1.36)
Conotruncal	2231	174	1.17 (0.97–1.41)	129	40	0.77 (0.50–1.18)
Truncus arteriosus	114	13	1.88 (0.99–3.57)	8	<5	–
Tetralogy of Fallot	1045	69	1.00 (0.75–1.31)	70	17	0.60 (0.32–1.11)
d-TGA[d]	659	57	1.24 (0.91–1.70)	39	8	0.43 (0.18–1.06)
DORV-TGA[e]	173	14	1.28 (0.70–2.33)	5	<5	–
DORV-Other	106	11	1.24 (0.59–2.60)	<5	<5	–
VSD-Conoventricular[f]	96	8	1.51 (0.72–3.17)	<5	6	–
AVSD [g]	300	38	**1.77 (1.21–2.60)**	24	7	0.70 (0.27–1.77)
TAPVR [h]	274	12	0.69 (0.37–1.28)	10	6	1.27 (0.39–4.12)
LVOTO [i]	1771	128	1.12 (0.91–1.38)	96	48	1.33 (0.88–2.01)
HLHS[j]	544	49	**1.39 (1.00–1.92)**	39	17	1.14 (0.60–2.15)
Coarctation of Aorta	862	60	1.06 (0.78–1.42)	42	24	1.51 (0.85–2.70)
Aortic stenosis	458	25	0.85 (0.55–1.32)	17	6	0.87 (0.31–2.48)
RVOTO [k]	1666	125	1.08 (0.88–1.33)	70	29	0.89 (0.55–1.45)
Pulmonary Atresia	228	17	1.04 (0.59–1.81)	12	<5	–
PVS[l]	1320	97	1.11 (0.88–1.41)	52	26	1.14 (0.66–1.97)
Tricuspid Atresia	152	10	0.92 (0.44–1.93)	9	<5	–
Ebstein	160	9	0.83 (0.40–1.72)	10	<5	–
Septal	3713	282	1.10 (0.94–1.28)	189	96	1.25 (0.90–1.72)
VSD-perimembranous	1295	69	**0.75 (0.57–1.00)**	54	22	0.90 (0.51–1.60)
VSD muscular	142	5	0.68 (0.26–1.78)	7	<5	–
ASD secundum-NOS[m,n]	2371	210	**1.28 (1.07–1.53)**	131	70	1.37 (0.95–1.98)

	No antibiotic medication use			Antibiotic medication use		
	No UTI	UTI		No UTI	UTI	
	n	*n*	Adjusted OR (95% CI)[b]	*n*	*n*	Adjusted OR (95% CI)[b]
Single ventricle	277	23	1.51 (0.95–2.40)	20	11	1.60 (0.68–3.76)
Heterotaxy	298	28	1.37 (0.89–2.12)	12	9	1.52 (0.53–4.36)

Note: Bold font indicates a statistically significant finding ($p < 0.05$). Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Simple, associated and complex.

[b] Adjusted for maternal age, BMI, gestational diabetes during index pregnancy, cigarette smoking, family history of CHDs, fever associated with UTI, and participating study site.

[c] Number of controls for any CHD (in order of columns): 10,253; 673; 198; 497.

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