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Association between Antibiotic Use among Pregnant Women with Urinary Tract Infections in the First Trimester and Birth Defects, National Birth Defects Prevention Study 1997 to 2011

Elizabeth C. Ailes[1,*], **Suzanne M. Gilboa**[1], **Simerpal K. Gill**[2], **Cheryl S. Broussard**[1], **Krista S. Crider**[1], **Robert J. Berry**[1], **Tonia C. Carter**[3], **Charlotte A. Hobbs**[4], **Julia D. Interrante**[1,5], **Jennita Reefhuis**[1], and **The National Birth Defects Prevention Study**

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

[2]Duchesnay Inc, Blainville, Quebec, Canada

[3]Marshfield Clinic, Marshfield, Wisconsin

[4]College of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas

[5]Oak Ridge Institute for Science and Education, Oak Ridge, Tennessee

Abstract

Background—Previous studies noted associations between birth defects and some antibiotics (e.g., nitrofurantoin, sulfonamides) but not others (e.g., penicillins). It is unclear if previous findings were due to antibiotic use, infections, or chance. To control for potential confounding by indication, we examined associations between antibiotic use and birth defects, among women reporting urinary tract infections (UTIs).

Methods—The National Birth Defects Prevention Study is a multi-site, population-based case-control study. Case infants/fetuses have any of over 30 major birth defects and controls are live-born infants without major birth defects. We analyzed pregnancies from 1997 to 2011 to estimate the association between maternally reported periconceptional (month before conception through the third month of pregnancy) use of nitrofurantoin, trimethoprim-sulfamethoxazole, or cephalosporins and specific birth defects, among women with periconceptional UTIs. Women with periconceptional UTIs who reported penicillin use served as the comparator.

Results—Periconceptional UTIs were reported by 7.8% (2029/26,068) of case and 6.7% (686/10,198) of control mothers. Most (68.2% of case, 66.6% of control mothers) also reported antibiotic use. Among 608 case and 231 control mothers reporting at least one periconceptional UTI and certain antibiotic use, compared with penicillin, nitrofurantoin use was associated with oral clefts in the offspring (adjusted odds ratio, 1.97 [95% confidence interval, 1.10–3.53]), trimethoprim-sulfamethoxazole use with esophageal atresia (5.31 [1.39–20.24]) and diaphragmatic

*Correspondence to: Elizabeth Ailes, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, 4770 Buford Hwy NE, MS E-86, Atlanta, GA 30341. eailes@cdc.gov.

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hernia (5.09 [1.20–21.69]), and cephalosporin use with anorectal atresia/stenosis (5.01 [1.34–18.76]).

Conclusion—Periconceptional exposure to some antibiotics might increase the risk for certain birth defects. However, because individual birth defects are rare, absolute risks should drive treatment decisions.

Keywords

birth defects; antibiotic; cephalosporin; nitrofurantoin; penicillin; trimethoprim-sulfamethoxazole; urinary tract infection

Introduction

Urinary tract infections (UTIs) are common bacterial infections in pregnancy; 1 to 4% of pregnant women experience acute cystitis and 4 to 10% have asymptomatic bacteriuria (Foxman, 2002). If left untreated, UTIs can progress to pyelonephritis, which has been associated with preterm labor and low birth weight (Delzell and Lefevre, 2000). Even uncomplicated UTIs have been associated with intrauterine growth restriction and preterm labor, and maternal UTIs have been associated with early onset sepsis and UTIs in the neonate (Schieve et al., 1994; Bhutta and Yusuf, 1997; Delzell and Lefevre, 2000; Emamghorashi et al., 2012). To prevent these adverse pregnancy outcomes, pregnant women are screened for UTIs during early pregnancy while in prenatal care (U.S. Preventive Services Task Force, 2008).

According to Infectious Diseases Society of America guidelines, nonpregnant women with uncomplicated UTIs should be treated with nitrofurantoin or trimethoprim-sulfamethoxazole (Gupta et al., 2011). However, Crider and colleagues' analysis of 1997 to 2003 National Birth Defects Prevention Study (NBDPS) data raised concern that these commonly prescribed antibiotic treatments for UTIs might be associated with specific birth defects (Crider et al., 2009). In 2011, the American College of Obstetricians and Gynecologists (ACOG) issued a Committee Opinion stating that sulfonamides and nitrofurantoin can be prescribed in the first trimester of pregnancy if other antimicrobial therapies are deemed inappropriate (American College of Obstetricians and Gynecologists Committee on Obstetric Practice, 2011).

More recent epidemiologic studies have found trimethoprim to be associated with both miscarriage and birth defects, but trimethoprim-sulfonamides not to be associated with birth defects (Andersen et al., 2013a, 2013b; Hansen et al., 2016). Subsequent studies of nitrofurantoin use in pregnancy have not found it to be associated with birth defects, although these studies may have been underpowered to detect associations with specific birth defect types (Goldberg et al., 2013; Nordeng et al., 2013). Despite rising rates of antibiotic resistance in some geographic areas (Mazzulli, 2012), penicillins are still frequently used to treat UTIs in pregnant women (Car, 2006; Petersen et al., 2010), likely because of their purported relative safety (Crider et al., 2009).

Previous studies have typically examined the association of antibiotic classes with specific birth defects regardless of indication (Crider et al., 2009; Andersen et al., 2013b; Goldberg et al., 2013; Nordeng et al., 2013). However, a potential confounding factor in these studies is the indication for antibiotic use, as maternal urinary tract, genital, and sexually transmitted infections have been associated with birth defects in previous studies (Cleves et al., 2008; Feldkamp et al., 2008). To minimize confounding by indication, we examined the association between maternally reported periconceptional antibiotic use and birth defects, among women with UTIs, using 1997 to 2011 NBDPS data, by comparing the odds of birth defects among women reporting periconceptional nitrofurantoin, trimethoprim-sulfamethoxazole, or cephalosporin use to women reporting periconceptional penicillin use.

Materials and Methods

NBDPS

The NBDPS is a population-based, multi-site, case–control study of risk factors for select major birth defects (Reefhuis et al., 2015). Our analysis included case and control infants or fetuses born on or after October 1, 1997, with estimated dates of delivery (EDD) on or before December 31, 2011. Cases included infants/fetuses with 1 of more than 30 major birth defects identified through birth defects surveillance systems in the states of Arkansas (1998–2011), Iowa, New Jersey (1998–2002), and Utah (2003–2011), or select counties in California, Georgia, Massachusetts, North Carolina (2003–2011), New York, and Texas. Cases were live-born infants (all sites), stillbirths of ≥20 weeks gestation (nine sites), and elective terminations (eight sites). Infants/fetuses with major chromosomal abnormalities, single-gene disorders, and birth defects with known etiology were excluded. Controls were live-born infants without major birth defects selected annually from vital or hospital discharge records from the same catchment areas as case infants/fetuses.

Case and control mothers were interviewed by telephone in English or Spanish using a computer-based questionnaire 6 weeks to 24 months after the EDD. Information was obtained on maternal demographics; nutritional, behavioral, and occupational exposures; maternal disease including infections; and over-the-counter and prescription medications, vitamins, and supplements. Clinical data regarding the birth defects were abstracted from medical records, and birth defects were classified by clinicians and clinical geneticists using previously described NBDPS classification criteria (Rasmussen et al., 2003; Botto et al., 2007). During 1997 to 2011, the participation rate was 67% for case mothers and 64% for control mothers. All subjects consented to participation and the NBDPS was approved by the Institutional Review Boards at the Centers for Disease Control and Prevention and all participating institutions.

EXPOSURE DEFINITION

During the structured interview, women were asked whether they experienced any of the following: a kidney, bladder, or UTI from 3 months before conception through the end of pregnancy. Subsequent questions ascertained whether the infection was diagnosed by a doctor, when the infection occurred (pregnancy month[s] or trimester[s]), any over-the-counter and prescription medication(s) taken for the infection, and the name, dates taken,

duration, and frequency of medication(s) used. Later in the questionnaire, women were asked if they took any medications not already discussed and to provide the name, dates taken, duration, and frequency of use, although not the specific indication for use.

Exposure was defined as maternal report of any antibiotic use in the periconceptional period (defined as the month before conception through the third month of pregnancy). Medications were coded using the Slone Drug Dictionary (Boston University), collapsing specific antibiotics into their respective antibiotic classes (Werler et al., 2011). We created mutually exclusive categories of antibiotics: penicillin, nitrofurantoin, trimethoprim-sulfamethoxazole, or cephalosporins, as well as other, unknown or use of multiple antibiotics. Women reporting a periconceptional doctor-diagnosed UTI but no periconceptional use of oral antibiotics, including those using only topical antibiotics or another type of oral anti-infective medication (e.g., antivirals, antifungals), were excluded.

ANALYSES

We excluded women with type 1 or type 2 diabetes, multiple or missing number of gestations, pelvic inflammatory disease, fever during the month before conception through the third month of pregnancy, missing UTI information, UTIs not diagnosed by a doctor, and missing antibiotic exposure dates (Fig. 1). We restricted our analysis of the association between specific antibiotics and birth defects to defect types with at least 100 total or at least four exposed and four unexposed cases to the four specific antibiotic classes under investigation (penicillins, nitrofurantoin, trimethoprim-sulfamethoxazole, and cephalosporins). Due to limited sample sizes or interpretability, we did not assess other antibiotics, multiple antibiotics or unknown types of antibiotics and birth defects associations. We selected potential covariates because of their association with birth defects in previous studies. These included: maternal age, race/ethnicity (non-Hispanic white vs. other), education (<high school vs. ≥high school), prepregnancy body mass index (body mass index ≥ 30 kg/m^2 vs. < 30 kg/m^2), use of any folic acid supplements in the month before through the first month of pregnancy, periconceptional smoking, periconceptional alcohol use, EDD year (1997–2003, 2004–2011), time from EDD to interview (≤ 6 months, 7–12 months, 13–24 months), and NBDPS study site.

We constructed multivariable conditional logistic regression models to estimate adjusted odds ratios and their corresponding 95% confidence intervals. We matched on NBDPS study site, and among the covariates of interest noted above, adjusted for maternal race/ethnicity and body mass index because these factors varied across antibiotic exposures among control mothers (Table 1). Given the potentially serious consequences of untreated UTIs in pregnancy, a comparison population of women with UTIs unexposed to antibiotics would be inappropriate. Thus, to have a disease-matched comparison group, our comparator was women with penicillin-treated periconceptional UTIs, given the relative lack of associations between penicillin and birth defects (Crider et al., 2009). This approach has been used in other studies (Berkovitch et al., 2000; Hansen et al., 2016). We performed one post hoc sensitivity analysis: we removed any cases or controls with a first degree family member (i.e., mother, father, full sibling, or previous pregnancy) with a type of birth defect ascertained in NBDPS.

Results

Periconceptional UTIs were common: 7.8% (2029/26,068) of case and 6.7% (686/10,198) of control mothers reported having at least one doctor-diagnosed, fever-free UTI in the month before conception through the third month of pregnancy. The majority (68.2% of case, 66.6% of control mothers) also reported taking an antibiotic (Fig. 1). The most commonly reported antibiotics used periconceptionally were penicillins and nitrofurantoin; however, more than one-quarter of women could not recall the specific antibiotic taken (Fig. 2). Comparing the early (1997–2003) and later (2004–2011) eras of the NBDPS, “other” antibiotics accounted for a greater proportion of use in the latter period of the study among both case and control mothers.

To determine which potential confounders were associated with exposure, we compared potential confounders between control mothers with and without the relevant exposure (i.e., compared women with UTIs and use of nitrofurantoin, trimethoprim-sulfamethoxazole, or cephalosporin antibiotics periconceptionally to women with UTIs and penicillin antibiotic use periconceptionally). Factors significantly associated with periconceptional nitrofurantoin, trimethoprim-sulfamethoxazole, or cephalosporin use rather than penicillin use among control mothers with UTIs included maternal race/ethnicity and body mass index (Table 1).

After restricting to phenotypes with at least 100 total, or 4 exposed and 4 “unexposed” (i.e., penicillin-exposed) cases, 608 cases and 231 control mothers with periconceptional UTIs and penicillin, nitrofurantoin, trimethoprim-sulfamethoxazole, or cephalosporin antibiotic use were eligible for analysis (Fig. 1). Compared with women with UTIs and penicillin use periconceptionally, women with periconceptional UTIs and nitrofurantoin use had significantly greater odds of having offspring with oral clefts (adjusted odds ratio, 1.97 [95% confidence interval, 1.10– 3.53]) and borderline significant for the subtype of cleft lip with or without cleft palate (1.90 [1.00–3.63]), in particular (Table 2). Those reporting UTIs and trimethoprim-sulfamethoxazole use periconceptionally had significantly greater odds of having offspring with esophageal atresia (5.31 [1.39–20.24]) and diaphragmatic hernia (5.09 [1.20–21.69]; and those reporting cephalosporin use had significantly greater odds of having offspring with anorectal atresia/stenosis (5.01 [1.34–18.76]). Results from the posthoc analyses were similar to those of the primary analysis. Exclusion of the 23 cases and 7 controls with a first degree family member with a birth defect type ascertained in NBDPS tended to strengthen the associations observed in the primary analysis and the association between cephalosporins and cleft lip with or without cleft palate became significant (5.67 [1.67–18.76]; other data not shown).

Discussion

Reports of UTIs in early pregnancy were common; 8% of case and 7% of control mothers reported at least one UTI from the month before conception through the third month of pregnancy. To minimize potential confounding by indication, we restricted our analysis to women reporting fever-free, doctor-diagnosed UTIs, and antibiotic use periconceptionally. Overall, compared with women reporting penicillin use, we found significant associations

between periconceptional use of nitrofurantoin and cleft lip with or without cleft palate; trimethoprim-sulfamethoxazole and esophageal atresia and diaphragmatic hernia; and cephalosporins and anorectal atresia. These associations persisted in a sensitivity analysis excluding cases and controls with a family history of birth defects.

Among women with UTIs, periconceptional nitrofurantoin exposure was more commonly reported than penicillin use by mothers of infants/fetuses with cleft lip with or without cleft palate. Previous studies have noted associations for nitrofurantoin with cleft palate, rectal/anal atresia/stenosis, NTDs, nonchromosomal heart defects, and a borderline significant association with hypospadias (Czeizel et al., 2001a; Kallen and Otterblad Olausson, 2003). Two previous retrospective cohort studies did not find associations between nitrofurantoin and major malformations, cardiac defects, or cleft lip or palate, although their samples sizes may have limited their ability to detect significant associations (Goldberg et al., 2013; Nordeng et al., 2013).

Among women with a UTI, periconceptional trimethoprim-sulfamethoxazole exposure was more commonly reported than penicillin use by mothers of infants/ fetuses with esophageal atresia and with diaphragmatic hernia. Trimethoprim is a dihydrofolate reductase inhibitor that interferes with DNA synthesis (Schweitzer et al., 1990). A randomized clinical trial found significantly lower levels of serum folate among a sample of healthy men taking a seven day course of trimethoprim compared with those taking placebo (Meidahl Petersen et al., 2016). Dihydrofolate reductase inhibitor use in early pregnancy has also been associated with a variety of reproductive outcomes, including miscarriage and selected birth defects (Andersen et al., 2013a, 2013b; Hernandez-Diaz et al., 2000, 2001). Using data from 1976 to 1998, Hernandez-Diaz et al. (2001) showed that the association between dihydrofolate reductase inhibitors and NTDs diminished with increasing folic acid supplement use (Hernandez-Diaz et al., 2001).

In our study, when compared with women reporting periconceptional penicillin use, women reporting cephalosporin use periconceptionally had significantly elevated odds for anorectal atresia/stenosis. Few published studies describe the associations between cephalosporins and birth defects. An unpublished analysis of Michigan Medicaid data from 1985 to 1992 showed higher than expected numbers of congenital defects, including heart defects, among approximately 4000 women taking cephalosporins during their first trimester (Briggs et al., 2011). A larger Hungarian case–control study again found no association with major malformations overall but did find a significantly elevated association with cardiac defects (Czeizel et al., 2001b).

It is worth noting that we saw several additional elevated but nonsignificant associations. Of the 18 birth defects with calculable odds ratios for nitrofurantoin, there were an additional four elevated (adjusted odds ratio > 1.50) associations: hypoplastic left heart syndrome, cleft palate, esophageal atresia, and craniosynostosis. For trimethoprim-sulfamethoxazole, of the 16 birth defects with calculable odds ratios, there were an additional eight nonsignificantly elevated odds ratios for coarctation of the aorta, neural tube defects, oral clefts overall as well as the specific subtypes of cleft palate and cleft lip with and without cleft palate, anorectal atresia/stenosis, and limb deficiency, including the subtype of transverse limb

deficiency. For cephalosporins, there were nine calculable odds ratio; nonsignificantly elevated odds ratios were observed for pulmonary valve stenosis, perimembranous ventricular septal defects, neural tube defects overall, and the subtype of spina bifida, and oral clefts overall, as well as the subtype of cleft lip with or without cleft palate. Only three "protective" odds ratios (adjusted odds ratio < 0.66) were observed: two for nitrofurantoin (with coarctation of the aorta and gastroschisis) and one for trimethoprim-sulfamethoxazole (with gastroschisis).

A major limitation of our analysis is the potential for exposure misclassification because of maternal self-report of both UTIs and antibiotic exposure, ascertained 6 weeks to 2 years after the EDD, with no verification from other sources (e.g., medical or pharmacy records). To minimize misclassification of UTI status, we restricted our analysis to women reporting doctor-diagnosed infections. Antibiotic information was more problematic; close to one-quarter of women could not recall the name of the antibiotic taken. We included medication exposures reported in the month before conception in addition to those in the first trimester of pregnancy to allow for the potential misclassification of timing of antibiotic use. Recall of medication timing is often better for short-term use, the circumstance for most of our antibiotic exposures, and is also improved when women are prompted with specific medication names, a feature of our study as well (Mitchell et al., 1986; Radin et al., 2013). Finally, while indication for antibiotic use was not available for all women in our study, 96% of case and 97% of control mothers with periconceptional UTIs indicated that their UTI was the indication for their antibiotic use.

There are several considerations in the interpretation of our findings. First, because some birth defects had elevated odds ratios for multiple antibiotic classes, it remains possible that confounding by indication still impacted our results due to lack of additional information on UTI severity, the specific type of infection (as women could have had either a kidney, bladder, or UTI), and the bacterial etiology of the UTI. Second, given the large number (n = 43) of associations examined, multiple comparisons might have impacted our results because approximately two statistically significant associations would be expected by chance alone; however, we do not know which of the four associations we observed are more likely to be due to chance alone. Third, although using conditional logistic regression allowed us to account for differences by NBDPS study site, this modeling method has been shown to potentially lead to biased estimates (Greenland et al., 2000). Fourth, by only including information from women for whom information was available, we assumed the missing information was missing completely at random and, therefore, the impact of informative missingness on our results is unknown.

Strengths of this study include the use of multi-site, population-based data with stringent birth defect classification criteria. Clinical geneticists or pediatric cardiology specialists familiar with the diagnosis of birth defects reviewed all potential NBDPS cases and confirmed that they met study eligibility requirements (Rasmussen et al., 2003; Botto et al., 2007). The study's large size also allowed for the assessment of associations between specific antibiotic exposures and more refined categories of birth defects. Furthermore, our study size and design allowed us to minimize potential confounding by indication, by

restricting our primary analysis to case and control mothers reporting UTIs periconceptionally.

Our findings support continued caution with periconceptional use of trimethoprim-sulfamethoxazole, cephalosporins, and nitrofurantoin. However, the body of literature on the topic of maternal antibiotic use and birth defects is limited and has not produced consistent findings. Furthermore, the birth defects found to be associated with antibiotics in this study (cleft lip with or without cleft palate, esophageal atresia, diaphragmatic hernia, and anorectal atresia/stenosis) are rare, with a birth prevalence of approximately 0.99%, 0.22%, 0.27%, and 0.41%, respectively, reported by active birth defects surveillance programs during the period 2008 to 2012 (Mai et al., 2015). By comparison, nearly 1 in 10 women experience a UTI during early pregnancy and as the maternal and fetal complications associated with untreated UTIs are common and serious, women should seek treatment if they suspect they might have a UTI. Therefore, although some of the associations observed in this study were relatively strong, it is important to note that individual birth defects are rare, and potential absolute risks of birth defects associated with antibiotic use remain small (~ 1%) compared with the risks of complications due to untreated UTIs in pregnancy.

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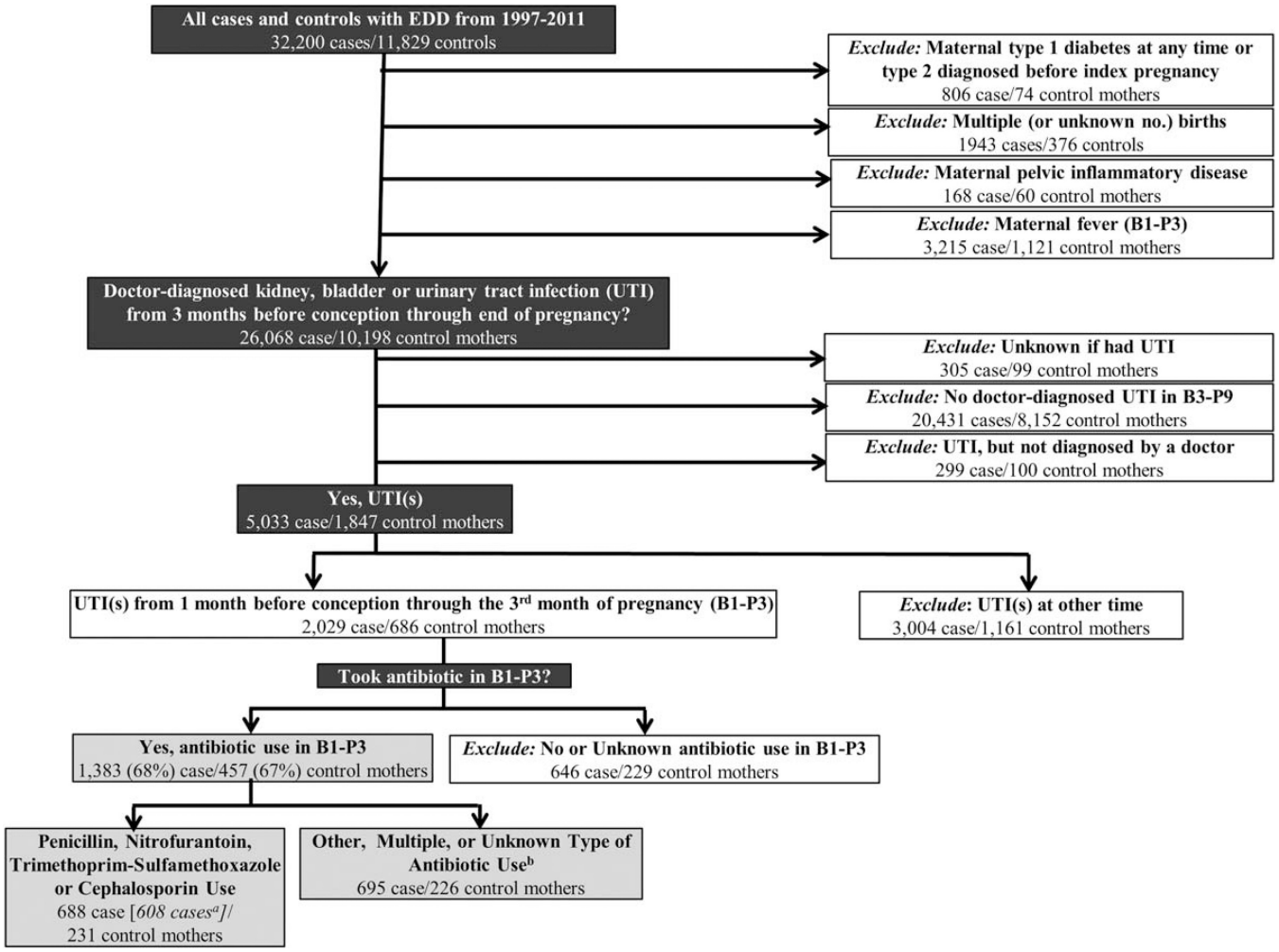

FIGURE 1.

Selection of subjects with UTIs and antibiotic use, National Birth Defects Prevention Study, 1997 to 2011. B1, month before conception; B3, 3 months before conception; EDD, estimated date of delivery; P3, third month of pregnancy; P9, ninth month of pregnancy. [a]After restricting to defects with 100 total or at least 4 cases exposed to and unexposed to a specific antibiotic group (see the Materials and Methods section). [b]Only included in descriptive analysis.

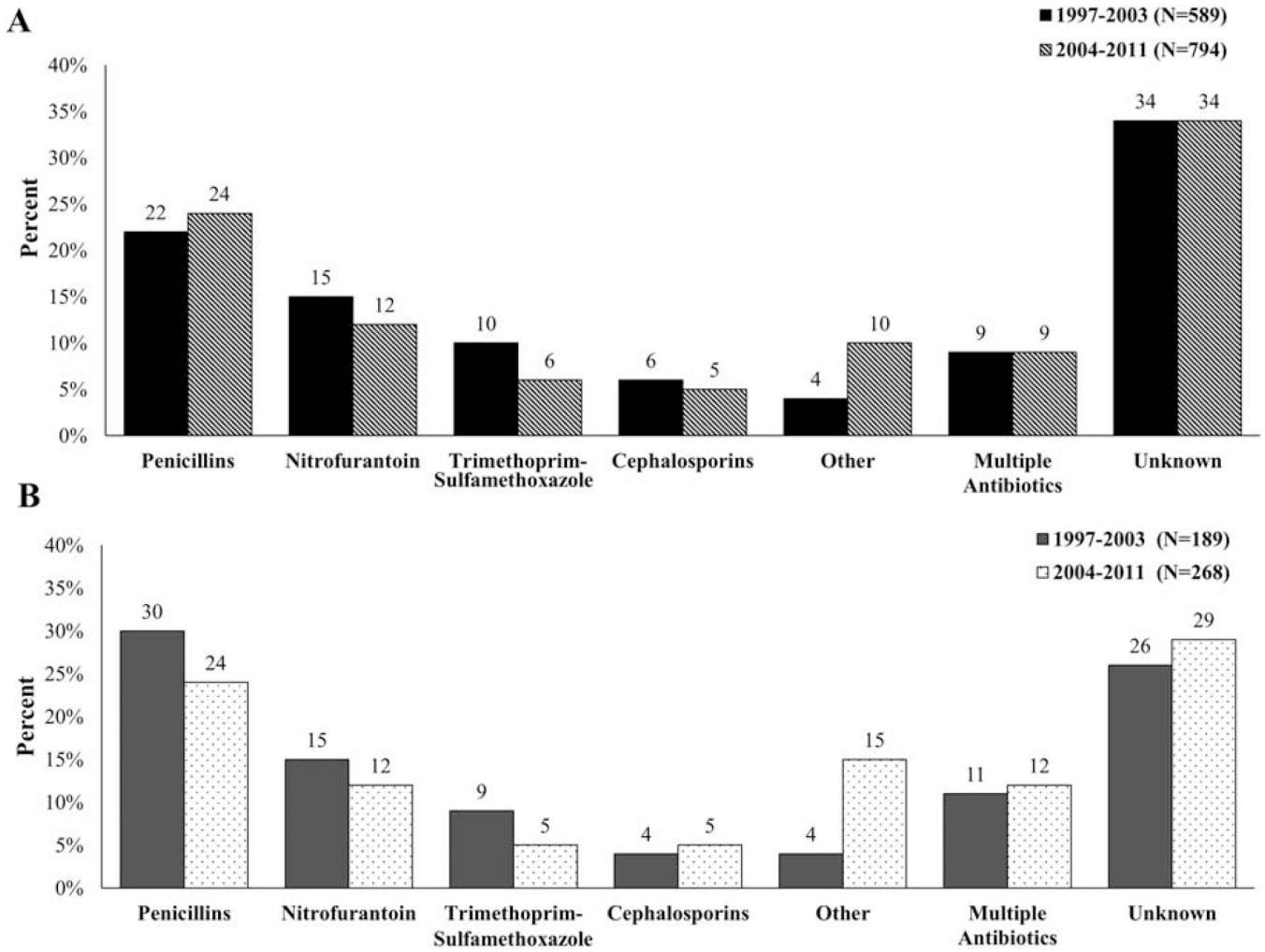

FIGURE 2.

Proportion of women reporting each type of antibiotic, among women with UTIs and antibiotic use in the month before conception through the third month of pregnancy, by Era, Among Mothers of Cases (**A**), and Controls (**B**), National Birth Defects Prevention Study, 1997 to 2011.

TABLE 1

Maternal Characteristics of Controls Mothers Reporting Urinary Tract Infections and Antibiotic Use Periconceptionally[a] National Birth Defects Prevention Study, 1997 to 2011

	Exposed (UTIs and nitrofurantoin, trimethoprim-sulfamethoxazole or cephalosporin use, periconceptionally) (*N* = 111)	Comparator (UTIs and penicillin use, periconceptionally) (*N* = 120)	*p*-Value
Maternal age (years)			
<20	13 (12%)	17 (14%)	0.632
20–24	36 (32%)	37 (31%)	
25–29	27 (24%)	36 (30%)	
30–34	21 (19%)	21 (18%)	
> = 35	14 (13%)	9 (8%)	
Maternal non-Hispanic white race/ethnicity			
Yes	76 (68%)	57 (48%)	0.001
No	35 (32%)	63 (53%)	
Maternal pre-pregnancy body mass index > = 30 (kg/m^2)			
Yes	18 (16%)	33 (28%)	0.027
No	92 (83%)	82 (68%)	
Missing	1 (1%)	5 (4%)	
Maternal education >high school			
Yes	67 (60%)	66 (55%)	0.440
No	42 (38%)	51 (43%)	
Unknown	2 (2%)	3 (3%)	
Any maternal smoking[a]			
Yes	28 (25%)	35 (29%)	0.453
No	82 (74%)	82 (68%)	
Unknown	1 (1%)	3 (3%)	
Any maternal alcohol[a]			
Yes	46 (41%)	49 (41%)	0.992
No	64 (58%)	68 (57%)	
Unknown	1 (1%)	3 (3%)	
Any maternal folic acid use[b]			
Yes	65 (59%)	58 (48%)	0.136
No	46 (41%)	61 (51%)	
Unknown	0 (0%)	1 (1%)	
Time from estimated date of delivery to interview (months)			
≤ 6	55 (50%)	57 (48%)	0.836
7–12	38 (34%)	37 (31%)	

	Exposed (UTIs and nitrofurantoin, trimethoprim-sulfamethoxazole or cephalosporin use, periconceptionally) (*N* = 111)	Comparator (UTIs and penicillin use, periconceptionally) (*N* = 120)	*p*-Value
13–24	17 (15%)	21 (18%)	
Missing	1 (1%)	5 (4%)	
Estimated date of delivery year			
1997–2003	54 (49%)	57 (48%)	0.861
2004–2011	57 (51%)	63 (53%)	
NBDPS study site			
Arkansas	27 (24%)	30 (25%)	0.388
California	15 (14%)	12 (10%)	
Georgia	11 (10%)	12 (10%)	
Iowa	11 (10%)	11 (9%)	
Massachusetts	9 (8%)	9 (8%)	
New Jersey	2 (2%)	4 (3%)	
New York	5 (5%)	17 (14%)	
North Carolina	8 (7%)	9 (8%)	
Texas	14 (13%)	12 (10%)	
Utah	9 (8%)	4 (3%)	

[a] From the month before conception through the third month of pregnancy.

[b] From the month before conception through the first month of pregnancy.

B1, month before conception; UTI, urinary tract infection; P3, third month of pregnancy.

TABLE 2

Associations between Antibiotic Use and Birth Defects[a], among Women Reporting Urinary Tract Infections and Antibiotic Use Periconceptionally[b]: National Birth Defects Prevention Study, 1997 to 2011

	Women with periconceptional[b] UTIs and … use									
	Penicillin	Nitrofurantoin			Trimethoprim-sulfamethoxazole			Cephalosporins		
Defect[a] (*N*)	*N*	*N*	cOR (95% CI)	aOR(95% CI)	*N*	cOR (95% CI)	aOR(95% CI)	*N*	cOR (95% CI)	aOR(95% CI)
Controls[c]	*120*	*60*			*30*			*21*		
Heart Defects										
Conotruncal defects										
Tetralogy of Fallot (21)	10	6	1.20 (0.42,3.46)	1.12 (0.36,3.51)	3			2		
Left ventricular outflow tract obstructions										
Hypoplastic left heart syndrome (17)	6	6	2.00 (0.62,6.46)	1.95 (0.55,6.86)	2			3		
Coarctation of the aorta (23)	12	4	0.67 (0.21,2.15)	0.48 (0.13,1.78)	5	1.67 (0.55,5.09)	1.82 (0.53,6.27)	2		
Right ventricular outflow tract obstructions										
Pulmonary valve stenosis (31)	15	7	0.91 (0.35,2.35)	0.99 (0.34,2.87)	4	1.10 (0.34,3.56)	0.83 (0.20,3.46)	5	1.92 (0.63,5.86)	1.66 (0.46,6.00)
Septal defects										
Ventricular septal defect (perimembranous) (33)	18	6	0.67 (0.25,1.77)	0.67 (0.24,1.85)	4	0.89 (0.28,2.82)	0.78 (0.23,2.62)	5	1.59 (0.53,4.74)	1.63 (0.49,5.43)
Atrial septal defect (secundum or NOS) (84)	40	21	1.05 (0.57,1.94)	0.84 (0.43,1.62)	13	1.30 (0.62,2.73)	1.34 (0.60,2.99)	10	1.43 (0.62,3.29)	1.15 (0.47,2.83)
Non-heart defects										
Neural tube defects (49)	23	13	1.13 (0.54,2.39)	1.23 (0.54,2.84)	7	1.22 (0.48,3.10)	1.78 (0.61,5.22)	6	1.49 (0.54,4.10)	2.16 (0.71,6.61)
Anencephaly and craniorachischisis (15)	6	4	1.33 (0.36,4.91)	1.30 (0.29,5.75)	3			2		

Defect[a] (*N*)	Penicillin *N*	Women with periconceptional[b] UTIs and … use: Nitrofurantoin *N*	Nitrofurantoin cOR (95% CI)	Nitrofurantoin aOR(95% CI)	Trimethoprim-sulfamethoxazole *N*	Trimethoprim-sulfamethoxazole cOR (95% CI)	Trimethoprim-sulfamethoxazole aOR(95% CI)	Cephalosporins *N*	Cephalosporins cOR (95% CI)	Cephalosporins aOR(95% CI)
Spina bifida (31)	15	9	1.20 (0.50,2.90)	1.26 (0.46,3.42)	3			4	1.52 (0.46,5.04)	2.84 (0.73,11.14)
Oral clefts (100)	37	37	**2.03 (1.17,3.53)**	**1.97 (1.10,3.53)**	14	1.57 (0.75,3.27)	1.71 (0.74,3.94)	12	1.85 (0.83,4.12)	1.63 (0.70,3.81)
Cleft palate (27)	11	10	1.85 (0.74,4.60)	1.93 (0.73,5.10)	4	1.50 (0.45,5.07)	1.59 (0.40,6.30)	2		
Cleft lip +/− cleft palate (73)	26	27	**2.11 (1.13,3.93)**	1.90 (1.00,3.63)	10	1.59 (0.69,3.67)	1.61 (0.64,4.02)	10	2.20 (0.93,5.22)	1.72 (0.70,4.23)
Esophageal atresia (22)	6	7	2.33 (0.75,7.25)	2.57 (0.71,9.22)	7	**4.67 (1.46,14.91)**	**5.31 (1.39,20.24)**	2		
Anorectal atresia/stenosis (19)	6	2			5	3.33 (0.95,11.66)	3.33 (0.95,11.66)	6	**5.71 (1.68,19.41)**	**5.01 (1.34,18.76)**
Hypospadias 2nd/3rd degree (50)	25	16	1.07 (0.51,2.24)	1.29 (0.52,3.20)	7	1.14 (0.42,3.09)	1.24 (0.40,3.87)	2		
Limb deficiency (27)	12	9	1.50 (0.60,3.76)	1.11 (0.39,3.15)	4	1.33 (0.40,4.43)	1.64 (0.45,5.96)	2		
Transverse limb deficiency (21)	10	6	1.20 (0.42,3.46)	0.78 (0.23,2.60)	4	1.60 (0.47,5.46)	1.93 (0.51,7.31)	1		
Craniosynostosis (37)	15	13	1.73 (0.78,3.88)	1.72 (0.70,4.22)	5	1.33 (0.45,3.96)	1.18 (0.36,3.84)	4	1.52 (0.46,5.04)	0.83 (0.21,3.29)
Diaphragmatic hernia (16)	6	3			6	**4.00 (1.20,13.28)**	**5.09 (1.20,21.69)**	1		
Gastroschisis (45)	28	10	0.71 (0.33,1.57)	0.53 (0.22,1.25)	4	0.57 (0.19,1.75)	0.43 (0.13,1.44)	3		

Data in boldface type are significant at $p < 0.05$.

[a] Restricted to birth defect types with at least 4 exposed cases and 4 unexposed cases or 100 total cases.

[b] In the month before conception through the third month of pregnancy.

[c] As pulmonary valve stenosis, and oral cleft cases were only ascertained by a subset of study sites in certain years, and hypospadias cases were only male fetus/infants, controls for these analyses were similarly restricted. For pulmonary valve stenosis, there were a total of 222 controls, of which 115 reported penicillin exposure in the month before conception through the third month of pregnancy, 59 nitrofurantoin, 28 trimethoprim-sulfamethoxazole, and 20 cephalosporins. For oral clefts, there were a total of 229 controls, of which 120 reported penicillin exposure in the month before conception through the third month of pregnancy, 59 nitrofurantoin, 29 trimethoprim-sulfamethoxazole, and 21 cephalosporins. For hypospadias, there were a total of 131 controls, of which 65 reported penicillin exposure in the month before conception through the third month of pregnancy, 39 nitrofurantoin, 16 trimethoprim-sulfamethoxazole, and 11 cephalosporins.

aOR, odds ratio after conditioning on NBDPS study site and adjusting for maternal body mass index and race/ethnicity; cOR, crude (unadjusted) odds ratio; NOS, not otherwise specified; UTI, urinary tract infection.