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Investigation of Metronidazole Use during Pregnancy and Adverse Birth Outcomes

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To assess whether treatment with metronidazole during pregnancy is associated with preterm birth, low birth weight, or major congenital anomalies, we conducted chart reviews and an analysis of electronic data from a cohort of women delivering at an urban New York State hospital. Of 2,829 singleton/mother pairs, 922 (32.6%) mothers were treated with metronidazole for clinical indications, 348 (12.3%) during the first trimester of pregnancy and 553 (19.5%) in the second or third trimester. There were 333 (11.8%) preterm births, 262 (9.3%) infants of low birth weight, and 52 infants (1.8%) with congenital anomalies. In multi-variable analysis, no association was found between metronidazole treatment and preterm birth (odds ratio [OR], 1.02 [95% confidence interval [CI], 0.80 to 1.32]), low birth weight (OR, 1.05 [95% CI, 0.77 to 1.43]), or treatment in the first trimester and congenital anomalies (OR, 0.86 [0.30 to 2.45]). We found no association between metronidazole treatment during the first or later trimesters of pregnancy and preterm birth, low birth weight, or congenital anomalies.

Metronidazole, a nitroimidazole derivative, is a recommended treatment during pregnancy for bacterial vaginosis (BV) and infections with *Trichomonas vaginalis* (8, 9). Preterm birth has been associated with both BV and *T. vaginalis* (10, 20). Some trials among high-risk women suggest that screening for BV and treatment with oral metronidazole may reduce preterm birth (16). However, several trials using metronidazole in pregnant women for other reasons (e.g., asymptomatic *T. vaginalis* infection or elevated fetal fibronectin levels) have shown increased preterm birth rates (1, 18).

There may be concerns among prenatal care providers about the theoretical potential for other adverse effects following metronidazole treatment. Metronidazole is an FDA Pregnancy Category B drug, meaning that animal studies have not revealed evidence of harm to the fetus but that adequate, well-controlled studies among pregnant women have not been conducted. It is mutagenic in bacteria (14) and was carcinogenic in rats that consumed daily dietary doses (25). However, prior studies in humans treated with oral or intravaginal metronidazole have not shown evidence of carcinogenicity (2) or teratogenic effects (3, 13, 23, 24, 26). Nonetheless, concerns may persist about treating pregnant women with metronidazole. A 1999 study of prenatal care providers found that only 12% of providers prescribed oral metronidazole or clindamycin during the first trimester (4).

The objective of this analysis was to assess whether treatment with metronidazole during pregnancy was associated with preterm birth, major congenital anomalies, or low birth weight in a cohort of pregnant women and singleton infants in Syracuse, New York.

MATERIALS AND METHODS

This analysis was conducted using data from a cohort study of treatment for BV in pregnancy to reduce adverse birth outcomes (19). The methods are described in detail in a previous publication (19). In brief, 3,111 pregnant women residing in central Syracuse ZIP codes who presented for delivery between 1 January 2000 and 31 March 2002 at the major birth

hospital for Syracuse, NY, were eligible for the study. Women whose charts were abstracted and had a singleton birth ($n = 2,829$) were included in this analysis.

Prenatal care and hospital records of mothers were reviewed to determine whether metronidazole treatment occurred. If a private provider did not permit access to the office prenatal chart, a summary of the prenatal care chart in the hospital chart was used (30% of mothers). Chart reviewers were clinical staff from the birth hospital who received two 3-h training sessions and were blind to the purpose of the study.

Although women could be treated multiple times during pregnancy, metronidazole treatment was defined as the first documented occurrence of treatment during pregnancy with oral or intravenous metronidazole. Intravaginal doses were excluded, as the peak metronidazole serum concentration after a 5-g intravaginal dose of 0.75% metronidazole gel (37.5 mg metronidazole) is less than 2% of that after a 500-mg oral dose (11). Bacterial vaginosis and abnormal flora were determined by Gram stain, and trichomoniasis was determined by a wet mount or culture. Although BV/abnormal flora were treated with different medications and formulations, metronidazole was the only medication prescribed for trichomoniasis. For the analyses of preterm birth and low birth weight, metronidazole treatment in any trimester was compared to no treatment. Because use associated with congenital anomalies would be expected to occur in the first trimester, for this component of the analysis no metronidazole treatment was compared separately to treatment in the first trimester and in the second or third trimesters combined.

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The primary outcome of interest was preterm birth (<37 completed weeks' gestation at birth, with dating based on ultrasound conducted at <24 weeks). Additional outcomes of interest included any major congenital anomalies and low birth weight (<2,500 g). Gestational age and birth weight were identified from mothers' hospital records. Congenital anomalies were ascertained from electronic birth certificates, an electronic Neonatal Intensive Care Unit database, and the local perinatal data system, which contained information gathered at birth. An anomaly that was listed in any of these sources was included in the database. If a listed anomaly was not considered a major congenital anomaly by the authors (e.g., vital signs at birth, Erb's palsy), the anomaly was excluded. Congenital anomalies were recorded in 9 categories: cardiac, central nervous system (CNS), chromosomal, ear/nose/throat (ENT), gastrointestinal (GI), genitourinary (GU), musculoskeletal, respiratory, and miscellaneous. The greatest degree of detail on specific anomalies provided in the database is included in this paper.

Statistical analysis. Bivariate analysis was used to evaluate the relationship between preterm birth, low birth weight, and congenital anomalies and several maternal characteristics: metronidazole treatment, maternal age, maternal race, alcohol consumption, and smoking. For preterm birth and low birth weight, educational status, marital status, prior preterm birth, and prepregnancy body mass index (BMI) were also examined. For congenital anomalies, we also examined preexisting diabetes mellitus, gestational diabetes mellitus, and alcohol consumption. Multivariable analysis was conducted using logistic regression to adjust for variables with *P* values of <0.10 in bivariate analysis. Data were analyzed using SAS statistical software (version 9.2; SAS Institute, Inc., Cary, NC).

RESULTS

Study population. A total of 2,829 singleton/mother pairs had complete information and were included in this analysis. There were 922 (32.6%) mothers treated with metronidazole during pregnancy; overall, 348 (12.3%) were treated in the first trimester, 553 (19.5%) in the second or third trimester. Although 1,067 women were diagnosed with BV/abnormal flora and 162 with trichomoniasis (86 were coinfections) during pregnancy, we found documentation of treatment in 789 and 123 women, respectively. By clinical indication for first treatment, 644 (69.8%) were treated for abnormal vaginal flora or BV, 39 (4.2%) for trichomoniasis, and 194 (21.0%) for BV, abnormal flora, or trichomoniasis identified on the Pap smear. Different doses were used at first treatment: 418 (45.4%) women were prescribed 500 mg twice daily for 7 days, 103 (11.1%) were prescribed 250 mg three times daily for 7 days, 87 (9.4%) of treated women received a 2-g dose, and 245 (26.6%) had no dose recorded. Most of the mothers were aged 18 to 25 (48.2%) or 26 to 35 (35.5%) years and were black (48.7%) or white (40.4%). Overall, the proportion of mothers with prior preterm birth was 11.2%, preexisting diabetes, 1.8%, any reported alcohol consumption, 1.8%, and any reported smoking, 33.4% (Tables 1 and 2).

Preterm birth. There were 333 (11.8%) preterm births among all singletons (Table 1). Among the 922 infants of mothers treated with metronidazole in any trimester, 111 (12.0%) were preterm compared to 222 (11.6%) infants of mothers without metronidazole treatment (odds ratio [OR], 1.04 [95% confidence interval {CI}, 0.82 to 1.32]). Among the 123 women ever treated for trichomoniasis, 18 (14.6%) delivered preterm. Among the 778 women treated in the first trimester or later for abnormal flora or BV with metronidazole, 91 (11.7%) delivered preterm.

In bivariate analysis, preterm birth was significantly associated with maternal history of prior preterm birth (OR, 2.90 [95% CI,

2.18 to 3.87]) and with maternal age less than 18 years (OR, 1.50 [95% CI, 0.99 to 2.26]), 26 to 35 years (OR, 1.33 [95% CI, 1.03 to 1.72]), or 36 years and above (OR, 1.61 [95% CI, 1.10 to 2.41]) compared to women aged 18 to 25 years. Diagnosis with trichomoniasis (OR, 1.54 [95% CI, 1.00 to 2.37]), but not BV/abnormal flora (OR, 0.949 [95% CI, 0.75 to 1.20]), was significantly associated with preterm birth.

Multivariable analysis, adjusting for maternal age, trichomoniasis, and prior preterm birth, also found no association between preterm birth and metronidazole treatment (OR, 0.94 [95% CI, 0.72 to 1.23]). Significant associations remained between preterm birth and maternal age less than 18 years (OR, 1.69 [95% CI, 1.12 to 2.56]), trichomoniasis (OR, 1.64 [95% CI, 1.03 to 2.61]), and prior preterm birth (OR, 2.95 [95% CI, 2.20 to 3.95]).

Low birth weight. Metronidazole treatment was also examined in relation to birth weight; there were 262 infants of low birth weight. Of the treated women, 93 (10.1%) had a low-birth-weight infant compared to 169 (8.9%) of untreated women. There was no significant association between metronidazole treatment and low birth weight in bivariate analysis (OR, 1.15 [95% CI, 0.88 to 1.51]). The significant risk factors for low birth weight in bivariate analyses (age, race, marital status, prior preterm birth, trichomoniasis, BMI, smoking, and consumption of alcohol [data not shown]) were combined with metronidazole treatment in multivariable analysis; metronidazole treatment remained unassociated with low birth weight (OR, 0.96 [95% CI, 0.69 to 1.34]), although maternal age less than 18 years (OR, 1.75 [95% CI, 1.06 to 2.91]), maternal age greater than 35 years (OR, 1.73 [95% CI, 1.05 to 2.86]), black race (OR, 1.50 [95% CI, 1.08 to 2.09]), prior preterm birth (OR, 3.34 [95% CI, 2.37 to 4.71]), and smoking (OR, 1.54 [95% CI, 1.15 to 2.07]) remained significantly associated with low birth weight.

Congenital anomalies. There were 52 (1.8%) singletons with one or more congenital anomalies (Tables 2 and 3). Of the 1,907 infants of women with no metronidazole treatment, 38 (2.0%) had anomalies. Out of the 348 infants of women with first trimester maternal treatment, 4 (1.2%) had anomalies (OR, 0.58 [95% CI, 0.21 to 1.63]), and of the 553 infants with second or third trimester maternal treatment, 10 (1.3%) had anomalies (OR, 0.92 [95% CI, 0.45 to 1.85]).

In bivariate analysis, infants had significantly greater odds of congenital anomalies if they were born to white mothers (OR, 2.69 [95% CI, 1.86 to 7.34]) or nonwhite, nonblack mothers (OR, 2.89 [95% CI, 1.11 to 7.50]) compared to black mothers or mothers with preexisting diabetes (OR, 3.46 [95% CI, 1.04 to 11.48]). Congenital anomalies were also significantly associated with maternal age above 35 years (OR, 2.64 [95% CI, 1.24 to 5.61]), compared to maternal age of 18 to 25 years.

In multivariable analysis, after adjusting for maternal age, maternal race, and preexisting diabetes, no association was found between congenital anomalies and metronidazole treatment in the first trimester compared to treatment in the second or third trimesters or none (OR, 0.86 [95% CI, 0.30 to 2.45]), or when first trimester metronidazole treatment (OR, 0.81 [95% CI, 0.28 to 2.36]) was compared to second or third trimester (OR, 0.94 [95% CI, 0.42 to 2.10]) treatment. In both models, congenital anomalies remained significantly associated with maternal age above 35 years (OR, 2.41 [95% CI, 1.08 to 5.34]), white race (OR, 2.30 [95%

TABLE 1 Preterm births (delivery at <37 weeks of gestation) and association with selected risk factors among mothers in the cohort, Syracuse, NY, 2000–2002

Risk factor	No. (%) of mothers	No. (%) of preterm births	Bivariate analysis (OR [95% CI]) ^a	Multivariable analysis (OR [95% CI]) ^a
Metronidazole treatment				
None	1,974 (66.9)	226 (11.9)	1.00 (ref)	1.00 (ref)
Any trimester	978 (33.1)	107 (11.6)	0.97 (0.76–1.24)	0.94 (0.72–1.23)
Maternal age (yr)				
<18	231 (8.2)	33 (14.3)	1.50 (0.99–2.26)	1.69 (1.12–2.56)
18–25	1,363 (48.2)	136 (10.0)	1.00 (ref)	1.00 (ref)
26–35	1,004 (35.5)	129 (12.9)	1.33 (1.03–1.72)	1.28 (0.99–1.67)
36+	231 (8.2)	35 (15.2)	1.61 (1.10–2.41)	1.47 (0.97–2.21)
Maternal race				
White	1,120 (40.4)	123 (11.0)	1.00 (ref)	
Black	1,349 (48.7)	173 (12.8)	1.19 (0.93–1.53)	
Other	302 (10.2)	37 (10.3)	0.93 (0.61–1.41)	
Missing	181 (6.1)			
Educational status				
<High school	1,033 (36.5)	124 (12.0)	1.09 (0.82–1.45)	
High school graduate	944 (33.4)	106 (11.2)	1.00 (ref)	
>High school	852 (30.1)	103 (12.1)	1.08 (0.82–1.42)	
Married				
Yes	864 (30.5)	94 (10.9)	1.00 (ref)	
No	1,965 (69.5)	239 (12.2)	1.13 (0.88–1.46)	
Prior preterm birth				
No	2,513 (88.8)	255 (10.2)	1.00 (ref)	1.00 (ref)
Yes	316 (11.2)	78 (24.7)	2.90 (2.18–3.87)	2.94 (2.20–3.94)
Pre-pregnancy BMI^b				
<19	219 (7.9)	32 (14.6)	1.31 (0.86–1.97)	
19–24.9	1,268 (45.6)	147 (11.6)	1.00 (ref)	
25–29.9	644 (23.2)	63 (9.8)	0.83 (0.61–1.13)	
30+	649 (23.4)	78 (12.0)	1.04 (0.78–1.40)	
Missing	49	13		
Smoking				
No	1,875 (66.7)	203 (10.8)	1.00 (ref)	
Yes	938 (33.3)	121 (12.9)	1.22 (0.96–1.56)	
Missing	16	9		
Trichomoniasis				
No	2,667 (94.3)	306 (11.5)	1.00 (ref)	1.00 (ref)
Yes	162 (5.7)	27 (16.7)	1.54 (1.00–2.37)	1.64 (1.03–2.61)
Bacterial vaginosis/abnormal flora				
No	1,762 (62.3)	211 (12.0)	1.00 (ref)	
Yes	1,067 (37.7)	122 (11.4)	0.95 (0.749–1.20)	

^a Ref indicates reference.^b BMI refers to body mass index (kg/m²).

CI, 1.15 to 4.63]), and races other than white or black (OR, 3.15 [95% CI, 1.33 to 7.51]).

Table 3 describes each known anomaly among the 52 infants with congenital anomalies. There were 4 infants with anomalies whose mothers had first trimester metronidazole treatment. The mothers of two infants took metronidazole at 8 weeks 5 days of gestation. These infants did not have the same anomalies; one had hydrocephalus, the other had an unspecified GI anomaly. The mothers of the other two infants were treated at 5 weeks 3 days and

12 weeks 2 days of gestation. Both infants had congenital heart disease; the infant with maternal treatment at 5 weeks 3 days also had unspecified ENT and CNS anomalies.

DISCUSSION

No association was found between metronidazole treatment during pregnancy and preterm birth, low birth weight, or congenital anomalies among the 2,829 singleton/mother pairs in this cohort. Metronidazole is recommended for treatment of BV and *T. vagi-*

TABLE 2 Association between congenital anomalies in infants and possible risk factors among mothers in the cohort, Syracuse, NY, 2000–2002

Risk factor	No. (%) of mothers	No. (%) of infants with anomalies	Bivariate analysis (OR [95% CI]) ^a	Multivariable analysis (OR [95% CI]) ^a
Metronidazole treatment				
None	1,907 (67.4)	38 (2.0)	1.00 (ref)	1.00 (ref)
1st trimester	348 (12.3)	4 (1.2)	0.58 (0.21–1.63)	0.88 (0.30–2.56)
2nd or 3rd trimester	553 (19.5)	10 (1.8)	0.92 (0.45–1.85)	1.10 (0.51–2.37)
Maternal age (yr)				
<18	231 (8.2)	6 (2.6)	1.55 (0.63–3.86)	1.79 (0.71–4.49)
18–25	1,363 (48.2)	23 (1.7)	1.00 (ref)	1.00 (ref)
26–35	1,004 (35.5)	13 (1.3)	0.76 (0.39–1.52)	0.67 (0.33–4.49)
36+	231 (8.2)	10 (4.3)	2.64 (1.24–5.61)	2.15 (0.97–4.75)
Maternal race				
Black	1,120 (40.4)	11 (1.0)	1.00 (ref)	1.00 (ref)
White	1,349 (48.7)	33 (2.4)	3.69 (1.86–7.34)	3.67 (1.79–7.53)
Other	360 (12.7)	7 (1.9)	2.89 (1.11–7.50)	2.97 (1.13–7.78)
Pre-existing diabetes				
No	2,776 (98.2)	49 (1.8)	1.00 (ref)	1.00 (ref)
Yes	51 (1.8)	3 (5.9)	3.46 (1.04–11.48)	2.93 (0.86–10.00)
Gestational diabetes				
No	2,685 (95.0)	47 (1.8)	1.00 (ref)	
Yes	142 (5.0)	5 (3.5)	2.05 (0.80–5.24)	
Alcohol consumption				
No	2,355 (83.3)	41 (1.7)	1.00 (ref)	
Yes	44 (1.6)	1 (2.3)	1.32 (0.18–9.77)	
Missing	428 (15.1)	10 (2.3)		
Smoking				
No	1,873 (66.3)	32 (1.7)	1.00 (ref)	
Yes	938 (33.2)	20 (2.1)	1.26 (0.71–2.21)	
Missing	16 (0.6)	0 (0)		

^a Ref indicates reference.

nal (8, 9). These conditions have been associated with preterm birth (10, 20). While it is widely recognized that symptomatic BV and *T. vaginalis* should be treated in pregnant women, the American Academy of Pediatrics also notes that some experts recommend screening and oral treatment of BV in asymptomatic pregnant women at high risk for preterm delivery (9). In this cohort, compared to women who were screened but untreated for BV/abnormal flora, women who were treated experienced reduced preterm delivery (19).

Several trials have suggested that there may be an increased risk for preterm birth among women given metronidazole during pregnancy. In one study of 617 women, there were more preterm deliveries among women given two 2-g doses of oral metronidazole for asymptomatic *T. vaginalis* infection than among women in the placebo group (RR, 1.8 [95% CI, 1.2 to 2.7]) (18). In a separate study, asymptomatic pregnant women with a positive cervical or vaginal fetal fibronectin test were given metronidazole (250 mg 3 times daily) and erythromycin (250 mg orally 4 times daily) or placebo. Among the 76 women with a previous spontaneous preterm delivery, there was an increased risk of repeat preterm birth among women who were given metronidazole without a currently accepted clinical indication. In other U.S. trials and studies in which women were treated with metronidazole for a currently accepted clinical indication such as BV, no increased risk

of preterm birth has been found (6). Women in the cohort described in this study were not randomized to treatment; they also received metronidazole for laboratory-confirmed clinical indications.

Two trials in Africa have also shown an increased risk of adverse events among infants of mothers given metronidazole during pregnancy. In one South African trial, primigravida or women with a previous mid-trimester abortion or preterm delivery diagnosed with BV by clinical criteria (pH > 4.7, amine odor, gray discharge, greater than 20% clue cells, and fewer than 2+ lactobacilli by microscopic examination) who were treated with 400 mg oral metronidazole twice daily for 2 days had a significantly increased risk of preterm birth compared to women who took vitamin C ($P = 0.03$) (22). In a subanalysis of a trial of presumptive sexually transmitted disease (STD) treatment in Rakai, Uganda, women with *T. vaginalis* who were randomized to receive orally 1 g azithromycin, 400 mg cefixime, and 2 g metronidazole had more low-birth-weight infants than women who took multivitamins (RR, 2.5 [95% CI, 1.1 to 5.5]), but did not have significantly increased rates of preterm birth (RR, 1.3 [95% CI, 0.8 to 2.0]) (17).

Although studies have not shown metronidazole to be carcinogenic in humans (2), it has been documented as a bacterial mutagen and carcinogen in animals (14, 25). In humans, metronidazole crosses the placenta. Therefore, there is a theoretical risk to

TABLE 3 Descriptions of major congenital anomalies among infants, by metronidazole treatment status of mother

Congenital anomaly(ies) among infants of mothers:	
With metronidazole treatment (<i>n</i> = 14)	Without metronidazole treatment (<i>n</i> = 38)
Gastroschisis	Bilateral club feet, perineal hypospadias
Congenital heart defect (2 infants)	Diaphragmatic hernia
Congenital heart defect, central nervous system defect, ear/nose/throat anomalies	Trisomy 13, polydactyly, omphalocele, fused fingers
Congenital hydrocephalus	Congenital heart defect (4 infants)
Congenital heart defect, bilateral hydronephrosis	Inguinal hernia
Gastrointestinal	Gastrointestinal anomaly (4 infants)
Rhabdomyoma	Abnormal appearing
Polydactyly	Hypospadias
Congenital heart defect, partial situs inversus, balanced translocation	Type III congenital cystic adenomatoid malformation
Central nervous system defect	Right testicular torsion
Weaver syndrome, bilateral club feet	Vocal cord lesion
Unbalanced partial trisomy 5	DiGeorge syndrome
Congenital hydrocephalus	Cleft lip and palate (2 infants)
	Polydactyly
	Bilateral congenital hydronephrosis (2 infants)
	Gastroschisis
	Posterior urethral valves, hydronephrosis, pulmonary hypoplasia
	Ureterocele
	Omphalocele
	Hand abnormality
	Congenital heart defect, hypospadias
	Cleft lip
	Velocardiofacial syndrome
	Congenital hydrocephalus
	Congenital hydrocephalus, holoprosencephaly
	Choanal stenosis, vertebral and rib anomalies
	47, XXY Klinefelter's syndrome
	Congenital hip dislocation
	Central nervous system defect
	Cornelia De Lange syndrome

the fetus that prenatal care providers may consider when making therapeutic choices for pregnant women. A survey of obstetricians and gynecologists from the mid-1990s revealed that only 1.5% of providers prescribed oral metronidazole during the first trimester (21). A 1999 survey found that 95% of prenatal care providers used oral metronidazole to treat nonpregnant patients with symptomatic BV, but 56% prescribed it for pregnant patients with symptomatic BV. Furthermore, only 12% of providers prescribed oral metronidazole or clindamycin for treatment of BV during the first trimester (4). These studies suggest that providers still have theoretical concerns about oral metronidazole use. Providers now have the option of choosing topical metronidazole, although no surveys have been published recently to allow for comparison with current practices.

Multiple epidemiologic studies and meta-analyses have not shown an association between metronidazole treatment during pregnancy and congenital anomalies in infants. Case reports from the 1980s document midline facial defects (cleft lip/palate and holotelencephaly) in three infants whose mothers took metronidazole during pregnancy (5, 15). These defects usually arise in months 2 to 3 of gestation. A Hungarian case-control study of 30,000 pregnant women who had healthy infants and 17,000 women who had infants with congenital anomalies did not find increased odds of any congenital anomaly except cleft lip/palate after metronidazole treatment in the second or third month of pregnancy (OR, 8.54 [95% CI, 1.06 to 68.86]) (12). The authors

note that this represents an increase of 0.03 cases per 1,000 above the expected number (1 per 1,000) of cleft lip/palate cases in Hungary without metronidazole treatment. In this cohort, we did not find any infants with cleft lip/palate whose mothers were treated with metronidazole; two infants whose mothers were not treated with metronidazole had cleft lip/palate.

Two other large studies found no association between metronidazole exposure and congenital anomalies. A retrospective cohort study of Medicaid records of 104,339 Michigan births found 63 congenital anomalies among 1,083 infants of mothers with first trimester metronidazole treatment (RR, 0.92 [95% CI, 0.7 to 1.2]) (24). A Danish population-based retrospective cohort study found no association with congenital anomalies (OR, 0.44 [95% CI, 0.11 to 1.81]) among infants of metronidazole-treated mothers (26). Two smaller studies also found no association; a retrospective cohort study of 1,387 pregnant women from Tennessee found no excess of congenital anomalies (RR, 1.2 [95% CI, 0.9 to 1.6]) among infants of women who filled a prescription for metronidazole between 30 days before and 120 days after their last menstrual period, (23) and a cohort study in Israel found 3 anomalies among 190 infants of mothers with first trimester metronidazole treatment and 8 anomalies among 575 infants whose mothers did not take metronidazole (RR, 1.13 [95% CI, 0.30 to 4.23]) (13).

In addition to these studies, meta-analyses have evaluated first trimester metronidazole treatment. None of them found an asso-

ciation between first trimester metronidazole treatment and congenital anomalies (weighted OR, 0.93 [95% CI, 0.73 to 1.18] [3] and OR, 1.08 [95% CI, 0.90 to 1.29] [7]).

This study has several limitations. First, instances of metronidazole treatment that were not recorded in the prenatal chart could have occurred, leading to misclassification. Pregnancy outcomes are not known for all women who could have potentially been included in this cohort. For example, data were not available on spontaneous or elective abortions or stillbirths that could have occurred subsequent to the development of a congenital anomaly. This study only reports congenital anomalies that were evident shortly after birth. Each of these limitations would lead to a bias toward the null. Finally, because of the small sample size, there is limited power to detect a change in the proportion of infants with congenital anomalies.

The results of this study in combination with others suggest that metronidazole treatment during pregnancy, given for currently accepted clinical indications at recommended doses, is not associated with an elevated risk of the adverse outcomes examined. There may still be a need to offer information to prenatal care providers about clear indications for metronidazole use in pregnancy. We suggest that providers follow the current recommendations of the CDC STD treatment guidelines regarding metronidazole use in pregnancy (8).

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