OBSTETRICS

Antifungal drugs and the risk of selected birth defects

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OBJECTIVE: This study examined whether first-trimester antifungal drug use was associated with the risk of selected birth defects.

STUDY DESIGN: Subjects were participants in a case-control study, the National Birth Defects Prevention Study, with singleton deliveries from 1997 to 2003. Based on maternal interviews, first-trimester antifungal drug use was compared between 7047 cases with isolated defects and 4774 nonmalformed controls using unconditional logistic regression.

RESULTS: Risk was elevated for hypoplastic left heart syndrome (odds ratio, 2.30; 95% confidence interval, 1.04, 5.06) but not for other cardiovascular defects. An increased risk of 1.88 was observed for diaphragmatic hernia but was not statistically significant. Estimates approximated unity for neural tube defects, oral clefts, anorectal atresia, hypospadias, and craniosynostosis.

CONCLUSION: First-trimester antifungal drug exposure was not strongly associated with the risk of most birth defects, but further studies should examine the preliminary results of an association with hypoplastic left heart syndrome.

Key words: antifungal agents, congenital abnormalities, pregnancy, teratogens

Cite this article as: Carter TC, Druschel CM, Romitti PA, et al. Antifungal drugs and the risk of selected birth defects. Am J Obstet Gynecol 2008;198:191.e1-191.e7.

The most common clinical indication for antifungal drug use in women is vulvovaginal candidiasis, and the Centers for Disease Control and Prevention (CDC) have recommended topical azole antifungal medication (butoconazole, clotrimazole, miconazole, tioconazole, terconazole) for the treatment of this condition in pregnancy.[1] In animal studies, birth defects have been associated with exposure to the antifungal drugs 5-fluorocytosine and fluconazole.[2,3] In humans, case-control studies found no increased risk of birth defects with topical clotrimazole or tolnaftate exposure[4,5]; however, oral nystatin use was associated with hypospadias,[6] and topical econazole exposure was associated with cardiovascular defects but not when exposure was restricted to drug prescriptions documented in medical records.[7]

Although previous studies have not established whether antifungal drugs can cause birth defects, their teratogenic potential should be evaluated because of their use in pregnancy to treat a common, and sometimes recurring, vaginal infection. The aim of this study was to determine whether there is an association between first-trimester exposure to antifungal drugs and the risk of selected birth defects using data from a large, population-based study.

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Received Feb. 23, 2007; revised May 24, 2007; accepted Aug. 21, 2007.

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This study was supported by a cooperative agreement with the Centers for Disease Control and Prevention, Grant U50/CCU223184. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

0002-9378/$34.00 • © 2008 Mosby, Inc. All rights reserved. • doi: 10.1016/j.ajog.2007.08.044

MATERIALS AND METHODS

Data were obtained from the National Birth Defects Prevention Study, an ongoing, multisite, case-control study of the causes of birth defects.[8] The study has been approved by the institutional review boards of the study sites and the CDC. Cases and controls were identified by the birth defects surveillance systems in 10 states (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, Texas, North Carolina, Utah). Controls were live births without birth defects that were randomly selected from birth certificates or birth hospitals in the geographic regions monitored by the state surveillance systems. Cases included live births, stillbirths 20 weeks or longer or greater than 500 g, or elective terminations.

Case classification

Medical records, including data on physical exams, clinical tests, surgeries, and autopsies, were obtained for all cases to confirm the presence of birth defects. Clinical geneticists reviewed this information for all cases to classify them as isolated (if all birth defects were confined

to the same organ system or body part) or nonisolated[9]; those with known single-gene disorders or chromosomal abnormalities were excluded. Classification was intended to define case groups that were more likely to be etiologically homogenous; for example, isolated craniosynostosis cases are probably etiologically distinct from cases that have other types of isolated defects or cases with multiple defects including craniosynostosis.

Based on clinical and pathological criteria, cardiovascular defects were additionally classified as simple, associations, or complex. The defects were characterized as simple if no other cardiovascular defects were present, and they were considered to be either specific, single defects (eg, atrial septal defect) or a well-defined pattern of defects recognized as a single diagnostic entity (eg, hypoplastic left heart syndrome, which is composed of a hypoplastic left ventricle and anomalies of the mitral valve, aortic valve, and ascending aorta). Defects were described as associations if there were 2 or 3 simple cardiovascular defects that are known to occur frequently together (eg, atrial septal defect–secundum type with a ventricular septal defect–perimembranous), but no other cardiovascular defects were present. Complex defects were those that occurred in multiple cardiac structures. Associations and complex defects are considered likely to have a different etiology from simple defects.

Data collection

Structured maternal interviews were conducted mainly by telephone in English or Spanish no later than 24 months after the expected date of delivery (EDD) to obtain data on maternal exposures during pregnancy. The proportions of eligible case and control mothers who participated in the interview were 71% and 68%, respectively. Interviews were completed within 6, 12, 18, and 24 months for 19.9%, 42.7%, 24.1%, and 12.7% of participating cases and for 35.9%, 42.0, 15.1, and 6.4% of participating controls. Time of interview completion was missing for 0.6% of cases and controls.

Exposure

Maternal reports of medication use were matched to the active ingredient in the Boston University Slone Epidemiology Center Drug Dictionary (a computerized database of prescription and nonprescription drugs that links drug products to their generic ingredients) to identify subjects who used antifungal drugs in the first trimester. The date of conception was considered to be 266 days before the EDD reported by the mother or obtained from the medical record if no date was provided by the mother. Subjects were classified as exposed if they used at least 1 antifungal drug in the first trimester (the 90-day period that started with the date of conception). Five subjects reported their only fungal infection to be a vaginal yeast infection in the first trimester and also used an antifungal drug but did not recall the date of use; their antifungal drug exposure was assigned as first trimester.

Inclusion and exclusion criteria

The study included 12,733 cases and 4856 controls that were singleton deliveries between October 1997 and December 2003. Mothers who reported a diagnosis of type 1 or 2 diabetes before conception (278 cases, 25 controls), had diabetes of unknown type (18 cases, 0 controls), and did not provide information on ever being diagnosed with diabetes (23 cases, 10 controls) were excluded. Also excluded were 93 cases and 32 controls who did not provide information on medication use in pregnancy as well as 47 cases and 15 controls who reported use of unknown vaginal creams in the first trimester.

To conduct analyses on case groups that were more likely to be etiologically homogenous, only cases with isolated defects were included in multivariable analysis (1654 cases with multiple defects excluded); for cardiovascular defects, only those isolated defects that were also defined as simple were included (925 cases with isolated, nonsimple cardiovascular defects excluded). Case groups were required to have a minimum of 5 cases with first-trimester antifungal drug exposure; these included neural tube defects (anencephaly, craniorachischisis, spina bifida, encephalocele); cleft lip with or without cleft palate; anorectal atresia; hypospadias (second or third degree); craniosynostosis; gastroschisis; diaphragmatic hernia; conotruncal heart defects (truncus arteriosus, interrupted aortic arch type B, d-transposition of the great arteries, double outlet right ventricle, tetralogy of Fallot, pulmonary valve atresia with ventricular septal defect–tetralogy of Fallot anatomy, ventricular septal defect–conoventricular); left ventricular outflow tract obstructive defects (aortic stenosis, coarctation of the aorta, interrupted aortic arch type A, hypoplastic left heart syndrome); right ventricular outflow tract obstructive defects (pulmonary valve stenosis/atresia, tricuspid atresia, Ebstein anomaly); ventricular septal defects (excluding conoventricular type); and atrial septal defects–secundum type or not otherwise specified.

Statistical analysis

Initially, potential confounders were identified based on their association with the exposure or outcomes in the published literature. Those associated with the exposure included urinary tract infections in the first trimester (Yes/No) and use 1 month before conception through the first trimester of the following: antibiotics (Yes/No), hormonal contraceptives (Yes/No), and an intrauterine device (Yes/No). Those related to the outcomes were maternal age-years ($<$20, 20-34, $>$34); maternal education-years ($<$12, 12, $>$12); maternal race (white, African American, Hispanic, other); body mass index-kg/m^2 ($<$18.5, 18.5-$<$25, 25-$<$30, $\geq$30); folic acid supplement use from one month before conception through the first month of pregnancy; fever in the first trimester not caused by a vaginal yeast infection (Yes/No); respiratory illness in the first trimester (Yes/No); maternal cocaine use in the first trimester (Yes/No); maternal occupational exposure to solvents in the first trimester (Yes/No); a history of miscarriage or stillbirth (Yes/No); gestational diabetes affecting the index pregnancy (Yes/No); a family history of birth

defects (Yes/No); consanguineous parental relationship (Yes/No); household income (less than $20,000, $20,000 to less than $50,000, or $50,000 or more). In addition, time to interview completion (within 1 year vs more than 1 year after the EDD) and study center were considered as potential confounders to adjust for differences in interview time and geographic location, respectively.

Odds ratios and 95% confidence intervals were estimated using unconditional logistic regression. Any potential confounders that were associated with both exposure and outcome in bivariate analysis with a $P < .2$ based on Fisher's exact test were included in the initial regression model. Potential confounders were retained in the final model if they were related to the outcome at a $P < .1$ and also caused a change of more than 10% in the coefficient estimate for antifungal drug use when they were dropped from the model. The data were too sparse to reliably determine effect modification. Analyses were performed using SAS 9.1 statistical software (SAS Institute, Cary, NC).

RESULTS

Antifungal drugs

The antifungal drugs used in the first trimester are listed in Table 1. Mothers reported using these drugs for vulvovaginal candidiasis except for 3 case mothers who reported ringworm, an unspecified fungal skin infection, or oral thrush. The most commonly used drugs were miconazole, terconazole, and clotrimazole. Among specifically named antifungal drugs, these 3 drugs accounted for 52 of 59 exposures to controls (88.1%) and 62 of 84 exposures to cases (73.8%). Use of an unknown antifungal drug was reported by the mothers of 29 controls and 55 cases. Most drugs were used 1-2 times/day for periods between 1 and 30 days, but 10 controls and 20 cases reported the duration of use to be between 31 and 90 days for miconazole, terconazole, clotrimazole, and unknown antifungal drugs. All 5 subjects who used ketoconazole reported that exposure was between 31 and 90 days at a frequency of 1-2 times/day. Mothers reported use for more than 30 days when infections lasted for multiple months during gestation, suggesting the presence of recurring infections.

Apart from antifungal drugs, mothers also reported use of other medications. Among exposed subjects, 83.3% of controls (70 of 84) and 84.1% of cases (111 of 132) reported using multiple medications in the first trimester (excluding vitamins). Among all study subjects, 42.1% of controls (2012 of 4774) and 45.4% of cases (3198 of 7047) reported use of more than 1 medication in the same period. The most frequently used medications were acetaminophen, ibuprofen, pseudoephedrine, amoxicillin, naproxen, and aspirin.

Birth defect risk

Estimates of the risk of selected birth defects associated with first-trimester exposure to any antifungal drugs are shown in Table 2. The crude and adjusted estimates were similar; therefore, only the adjusted estimates are presented. A statistically significant increased risk was observed for hypoplastic left heart syndrome, based on 7 exposed cases: 3 used miconazole, 1 used terconazole, 1 used ketoconazole, and 2 used an unknown antifungal drug. Risk increased almost 2-fold for diaphragmatic hernia, although the effect was not statistically significant. The 9 exposed diaphragmatic hernia cases used miconazole, fluconazole, and unknown antifungal drugs (Table 1). No increase in crude or adjusted risk was observed for the other case groups. There was little difference in the results obtained when the analyses were repeated for live births only or for subjects with no family history of birth defects.

COMMENT

First-trimester exposure to antifungal drugs was associated with a modestly increased risk of isolated hypoplastic left heart syndrome and diaphragmatic hernia, although only the increase in risk for hypoplastic left heart syndrome was statistically significant. Hypoplastic left heart syndrome is a rare birth defect with an estimated prevalence of 1-4 cases per 10,000 births[10,11]; therefore, if our findings reflect a real association, an approximate 2-fold increase in risk will result in 2-8 cases per 10,000 births. It is unknown whether the observed increase in risk of these birth defects was directly related to the use of antifungal drugs or whether the drugs might be a marker for other exposures or diseases related to the risk of birth defects. Another explanation is that the estimates were due to chance because of the small number of exposed subjects and should be conservatively interpreted as suggesting the possibility of an effect until these results can be confirmed in another study.

Mothers in this study most often used topical antifungal agents in pregnancy, but some were exposed to ketoconazole and fluconazole, which are available for systemic use. Topical antifungal drugs applied at usual therapeutic doses have low systemic absorption (0-15%) with a concentration in serum of 1-100 ng/mL at 12-72 hours after dose.[12-14] In contrast, oral antifungal drugs administered at usual therapeutic doses have a concentration in plasma of 1-100 μg/mL (10-1000 times greater than for topical drugs) at 2-48 hours after dose,[15,16] and their higher systemic concentration raises concern if they are potential teratogens.

We could not perform analyses based on categories of duration and frequency of use, topical vs systemic drugs, or use of over-the-counter vs prescription drugs. Most drugs were used for no more than 14 days at a frequency of 1-2 times/day and the variation in duration and frequency of use was not sufficient to form categories for comparison. In addition, topical/systemic status could not be determined for unknown antifungal drugs, and mothers were not asked in the interview whether drugs were obtained over the counter or by prescription. These limitations did not allow us to be more specific about the type of antifungal drug use in pregnancy that could be most relevant to the risk of birth defects.

The antifungal drugs used by exposed cases of hypoplastic left heart syndrome and diaphragmatic hernia were miconazole, terconazole, fluconazole, and ke-

TABLE 1

First-trimester antifungal drug use among cases and controls, National Birth Defects Prevention Study (1997-2003)

Antifungal drug	Controls, (n = 4774)	Neural tube defects, (n = 750)	Cleft lip with or without cleft palate, (n = 1086)	Anorectal atresia, (n = 209)	Hypospadias, (n = 776)	Craniosynostosis, (n = 447)	Gastroschisis, (n = 455)	Diaphragmatic hernia, (n = 275)	Cardiovascular defects, (n = 3049)[a]
Miconazole	39	10	9	3	3	2	1	2	13
Clotrimazole	7	2	0	1	2	2	0	0	5
Terconazole	6	0	2	0	1	0	0	0	4
Fluconazole	0	2	2	0	2	1	0	1	4
Tioconazole	4	0	1	0	0	1	0	0	0
Ketoconazole	1	1	0	0	1	0	0	0	2
Econazole	1	0	1	0	0	0	0	0	0
Butoconazole	1	0	0	0	0	0	0	0	0
Ciclopirox olamine	0	0	1	0	0	0	0	0	0
Propionic acid	0	1	0	0	0	0	0	0	0
Terbinafine	0	0	1	0	0	0	0	0	0
Unknown antifungal drug	29	4	8	1	4	5	4	6	23
Any antifungal drug	84[b]	18[c]	23[d]	5	13	10[e]	5	9	49[f]

[a] Cardiovascular defect case groups have been combined to present data on drug use.

[b] Four control mothers used more than 1 drug: 1 used miconazole and clotrimazole; 1 used miconazole and terconazole; 2 used miconazole and an unknown antifungal drug.

[c] Two neural tube defect case mothers used more than 1 drug: 1 (encephalocele) used ketoconazole and an unknown antifungal drug; 1 (anencephaly) used fluconazole and miconazole.

[d] One cleft lip with cleft palate case mother used econazole, ciclopirox olamine, and terbinafine.

[e] One craniosynostosis case mother used fluconazole and an unknown antifungal drug.

[f] Two cardiovascular defect case mothers used more than 1 drug: 1 (aortic stenosis) used clotrimazole and an unknown antifungal drug; 1 (perimembranous ventricular septal defect) used miconazole and an unknown antifungal drug.

Carter. Antifungal drugs and the risk of selected birth defects. Am J Obstet Gynecol 2008.

TABLE 2

Odds ratios for the association between first-trimester use of antifungal drugs and the risk of selected birth defects, National Birth Defects Prevention Study (1997-2003)

Case group	Cases, n[a]	Controls, n[a]	Cases exposed, n (%)	Controls exposed, n (%)	Covariates included in the regression model	Adjusted odds ratio (95% confidence interval)
Neural tube defects	699	4526	16 (2.3)	81 (1.8)	Periconceptional folic acid use, urinary tract infections in the first trimester, prepregnancy body mass index, maternal education	1.25 (0.72, 2.15)
Spina bifida	441	4581	11 (2.5)	81 (1.8)	Periconceptional folic acid use, prepregnancy body mass index	1.40 (0.74, 2.66)
Cleft lip with or without cleft palate[b]	1040	4415	23 (2.2)	78 (1.8)	Urinary tract infections in the first trimester, prepregnancy body mass index	1.24 (0.78, 1.99)
Anorectal atresia	199	4565	5 (2.5)	81 (1.8)	Prepregnancy body mass index, maternal education	1.42 (0.66, 3.06)
Hypospadias (second and third degree)[c]	775	2397	13 (1.7)	44 (1.8)	Maternal education	0.86 (0.46, 1.61)
Craniosynostosis	440	4581	8 (1.8)	81 (1.8)	Prepregnancy body mass index	1.02 (0.49, 2.13)
Gastroschisis	450	4733	5 (1.1)	84 (1.8)	Urinary tract infections in the first trimester, maternal age	0.64 (0.25, 1.62)
Diaphragmatic hernia	274	4717	9 (3.3)	84 (1.8)	Hormonal contraceptives use in the month before conception through the first trimester	1.88 (0.93, 3.78)
Conotruncal heart defects	707	4581	15 (2.1)	81 (1.8)	Prepregnancy body mass index	1.20 (0.69, 2.10)
Tetralogy of Fallot	250	4581	5 (2.0)	81 (1.8)	Prepregnancy body mass index	1.11 (0.45, 2.77)
Left ventricular outflow tract obstructive heart defects	513	4698	8 (1.6)	84 (1.8)	Antibiotics use in the month before conception through the first trimester	0.84 (0.40, 1.74)
Hypoplastic left heart syndrome with intact ventricular septum	176	4581	7 (4.0)	81 (1.8)	Prepregnancy body mass index	2.30 (1.04, 5.06)
Right ventricular outflow tract obstructive heart defects	507	4581	9 (1.8)	81 (1.8)	Prepregnancy body mass index	1.00 (0.50, 1.99)
Ventricular septal defects	709	4698	9 (1.3)	84 (1.8)	Antibiotics use in the month before conception through the first trimester	0.70 (0.35, 1.39)
Perimembranous ventricular septal defects	531	4698	7 (1.3)	84 (1.8)	Antibiotics use in the month before conception through the first trimester	0.72 (0.33, 1.57)
Atrial septal defects (secundum type or not otherwise specified)	529	4733	5 (1.0)	84 (1.8)	Urinary tract infections in the first trimester	0.52 (0.21, 1.28)

[a] Number after excluding subjects with missing values for covariates in unconditional logistic regression analysis.

[b] Subjects from the Utah study center were excluded from the control group in analyses with oral cleft cases because these cases were ascertained in all study centers except Utah.

[c] Hypospadias cases were compared with male controls.

Carter. Antifungal drugs and the risk of selected birth defects. Am J Obstet Gynecol 2008.

toconazole. Previous reports indicate that miconazole use does not increase the risk of birth defects,[17] but the evidence is less consistent for ketoconazole and fluconazole. A Hungarian study found an increased risk of cardiovascular defects after oral ketoconazole exposure, but this was based on only 2 exposed cases and was not statistically significant.[18] Case reports have described a pattern of craniofacial and skeletal malformations after fluconazole exposure,[19-21] but these findings were not observed in the current study. Studies that have used computerized medical or prescription databases to identify women exposed during pregnancy to fluconazole, miconazole, ketoconazole, econazole, itraconazole, clotrimazole, and nystatin found no increased risk of birth defects overall after first-trimester exposure.[22,23] No published reports relating to topical terconazole use and the risk of birth defects in humans were found.

One of the limitations of our study was probable underreporting of exposure. Approximately 10-20% of women have vulvovaginal candidiasis during pregnancy[24,25]; however, in this study, only 1.8% of control mothers reported first-trimester antifungal use. Therefore, it was estimated that at least 80% of affected women did not report their yeast infection and associated antifungal use. Missing from the interview was an item that asked specifically about use of antifungal drugs based on drug name or clinical indication. Instead, reports of antifungal drug use were provided in response to a question about the occurrence of fever or to a general question about the presence of diseases such as chronic, infectious, or sexually transmitted diseases during pregnancy; thus, underreporting of drug use may have contributed to the small number of exposed subjects in the study.

In addition, many antifungal medications for the treatment of vulvovaginal candidiasis are available as over-the-counter creams with a recommended duration of use of 1-7 days, and it is possible that case and control mothers tended to forget exposure to medications used for such a short period. The long time-to-interview period (up to 24 months) likely contributed to the failure of mothers to recall medication use, although this period was implemented to allow for attempts to contact mothers who were difficult to locate and to obtain sufficient medical data to confirm case diagnoses. Recall bias could have occurred if 1 study group underreported exposure, compared with another group, or if case mothers were more likely than control mothers to recall medication use to explain the occurrence of birth defects in their offspring. Therefore, recall bias cannot be ruled out as a possible explanation for the results.

Limitations in our exposure assessment also included the absence of information on dose and route of administration. For example, mothers exposed to ketoconazole reported the drug name as Nizoral, which is available for topical (McNeil Consumer, Fort Washington, PA) or oral (Janssen Pharmaceutica, Titusville, NJ) use, and the dose to which the mother (and fetus) is exposed is expected to vary, depending on the route of administration. Another limitation was that individual medications could not be identified when mothers reported use of unknown antifungal drugs or unknown vaginal creams; therefore, the number of women actually exposed to the individual antifungal drugs listed in Table 1 is likely to be higher than that presented. The unknown drugs reported may have also included antifungal medications other than those in Table 1.

In addition, it could not be clearly distinguished whether the observed increase in the risk of certain birth defects was due to the maternal infection or to the antifungal drugs used to treat the infection. Very few subjects reported having a fungal infection and being untreated; therefore, the risk of birth defects in infected but untreated subjects could not be obtained. Immunocompromised conditions can increase the probability of developing fungal infections[26]; however, separate analyses could not be performed for women having these conditions. A disadvantage of the study was that these women could not be reliably identified because no interview question asked specifically about such conditions. Finally, we considered participation bias as an alternative explanation for the results. Data were not available for nonparticipants (subjects who were eligible but did not perform an interview), and it is unknown whether the exposure-outcome association in this group differed from that of participants; however, it was unlikely that the participation of cases and controls was related to the use of antifungal drugs in pregnancy.

The results indicated that first-trimester use of antifungal drugs did not increase the risk for most of the birth defect groups studied. Antifungal drugs are often used by pregnant and nonpregnant women without known adverse consequences, and there is evidence of a reduced risk of preterm birth with gestational clotrimazole use[27]; therefore, there needs to be confirmation of a real association with birth defects before cautioning against use of these drugs in pregnancy. The increased risk of hypoplastic left heart syndrome associated with antifungals should be considered a preliminary result and causal inferences avoided, particularly because use among exposed cases was not confined to a single antifungal drug. Further studies should examine the risk of this specific defect in relation to antifungal drug exposure and should attempt to separate the effect of the medication from that of the infection. The observation that 2 of the 4 cases exposed to ketoconazole had isolated cardiovascular defects (right ventricular outflow tract obstructive defect–pulmonary valve stenosis and hypoplastic left heart syndrome) warrants that attention also be focused on this particular exposure. ■

ACKNOWLEDGMENTS

We thank Lenore Gensburg for her assistance with statistical analysis and providing comments on the manuscript. We appreciate the contributions made by the study centers that include the Arkansas Reproductive Health Monitoring System, the California Birth Defects Monitoring Program, the Metropolitan Atlanta Congenital Defects Program, the Iowa Birth Defects Registry, the Massachusetts Center for Birth Defects Research and Prevention Monitoring Program, the Birth Defects and Special Needs Registry of New Jersey, the New York State Congenital Malformations Registry, the Texas Birth Defects Monitoring Division, the North Carolina Birth Defects Monitoring Program, and the Utah Birth Defects Network.

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