

ORIGINAL ARTICLE

Use of Oral Fluconazole during Pregnancy and the Risk of Birth Defects

Ditte Mølgaard-Nielsen, M.Sc., Björn Pasternak, M.D., Ph.D.,
and Anders Hviid, Dr.Med.Sci.

ABSTRACT

BACKGROUND

Case reports suggest that long-term, high-dose fluconazole treatment for severe fungal infections during pregnancy causes a pattern of birth defects. It is unclear whether commonly used lower doses increase the risk of specific birth defects.

METHODS

In a registry-based cohort of liveborn infants in Denmark, we evaluated first-trimester oral fluconazole exposure and the risk of birth defects overall and of birth defects previously linked to azole antifungal agents.

RESULTS

The majority of fluconazole-exposed pregnancies were in women who received common therapeutic doses of 150 mg (56% of pregnancies) or 300 mg (31%). Oral fluconazole exposure was not associated with an increased risk of birth defects overall (210 birth defects among 7352 fluconazole-exposed pregnancies [prevalence, 2.86%] and 25,159 birth defects among 968,236 unexposed pregnancies [prevalence, 2.60%]; adjusted prevalence odds ratio, 1.06; 95% confidence interval [CI], 0.92 to 1.21). In addition, oral fluconazole exposure was not associated with a significantly increased risk of 14 of 15 types of birth defects previously linked to azole antifungal agents: craniosynostosis, other craniofacial defects, middle-ear defects, cleft palate, cleft lip, limb defects, limb-reduction defects, polydactyly, syndactyly, diaphragmatic hernia, heart defects overall, pulmonary-artery hypoplasia, ventricular septal defects, and hypoplastic left heart. A significantly increased risk of tetralogy of Fallot was observed (7 cases in fluconazole-exposed pregnancies [prevalence, 0.10%] as compared with 287 cases in unexposed pregnancies [prevalence, 0.03%]; adjusted prevalence odds ratio, 3.16; 95% CI, 1.49 to 6.71).

CONCLUSIONS

Oral fluconazole was not associated with a significantly increased risk of birth defects overall or of 14 of the 15 specific birth defects of previous concern. Fluconazole exposure may confer an increased risk of tetralogy of Fallot. (Funded by the Danish Medical Research Council.)

From the Department of Epidemiology Research, Statens Serum Institut, Copenhagen. Address reprint requests to Ms. Mølgaard-Nielsen at Statens Serum Institut, Artillerivej 5, 2300 Copenhagen S, Denmark, or at dnl@ssi.dk.

N Engl J Med 2013;369:830-9.

DOI: 10.1056/NEJMoa1301066

Copyright © 2013 Massachusetts Medical Society

ORAL FLUCONAZOLE TREATMENT HAS been linked to a distinct pattern of birth defects in five infants of mothers who were treated for severe fungal infections with 400 to 800 mg daily during most or all of the first trimester of pregnancy.¹⁻⁴ Similar defects have been observed in animals exposed to systemic azole antifungal agents.⁵⁻⁷ In 2011, the U.S. Food and Drug Administration (FDA) issued a drug-safety announcement concerning the possible teratogenic risks conferred by long-term, high-dose fluconazole treatment. The FDA pregnancy category for fluconazole was consequently changed from C (adverse fetal effects in animals and no adequate human data) to D (evidence of human fetal risk, but benefits may warrant use), with the exception of the use of fluconazole, at a single dose of 150 mg, for the treatment of vaginal candidiasis.⁸ However, concern has been raised about whether common therapeutic doses of oral fluconazole used for frequent fungal infections of the skin or mucous membranes may similarly increase the risk of certain specific defects.⁹ The few epidemiologic studies of oral fluconazole (usually a single dose of 150 mg) suggest that it is not associated with an increased risk of birth defects overall¹⁰⁻¹⁴; however, with a sample of 1650 pregnancies exposed in the first trimester, these studies were not large enough to allow investigation of different doses or the risk of specific defects. In a study that examined the risk of craniofacial defects and heart defects among 1079 pregnancies exposed to fluconazole, no significantly increased risk was found.¹³ Another study, which assessed the association between selected birth defects and antifungal agents (mostly topical azoles or unspecified drugs), showed an elevated risk of hypoplastic left heart and diaphragmatic hernia.¹⁵

Assessment of any teratogenic potential of oral azole antifungal agents is important, because pregnant women are at increased risk for vaginal candidiasis,¹⁶ which is the most common clinical indication for these drugs. Although vaginal preparations of topical azole antifungal agents are first-line treatment for vaginal candidiasis during pregnancy,¹⁷ treatment with oral azole antifungal agents is used in cases of recurrence or when topical treatment has failed.

In a registry-based cohort study, we evaluated the association between first-trimester oral fluconazole exposure and the risk of major birth

defects, including analyses according to dose and analyses of defects previously linked to azole antifungal agents.

METHODS

STUDY COHORT

We identified a nationwide cohort of all liveborn infants who were born in Denmark between January 1, 1996, and March 31, 2011, from the Medical Birth Registry.¹⁸ With the use of the unique personal identifiers used in all registries, individual-level data were obtained from the National Prescription Registry,¹⁹ the National Patient Register,²⁰ the Danish Civil Registration System,²¹ and Statistics Denmark and were linked to the cohort (the registries are described in the Supplementary Appendix, available with the full text of this article at NEJM.org). Records of gestational age in the Medical Birth Registry are primarily based on ultrasonography²²; infants with a missing or implausible gestational age at birth (<22 or >45 weeks) were excluded from the cohort. Pregnancy onset, defined as the first day of the last menstrual period, was estimated by subtraction of gestational age from the date of birth. The study was approved by the Danish Data Protection Agency. Informed consent is not required for registry-based research in Denmark.

ORAL AZOLE ANTIFUNGAL AGENTS

Information on prescriptions for oral fluconazole, itraconazole, and ketoconazole that were filled by the women in the cohort during pregnancy was obtained from the National Prescription Registry. The main exposure time window we examined was the first trimester of pregnancy, and the time of exposure was defined as the date on which the prescription was filled. In the analysis of different doses of fluconazole, we calculated the cumulative amount in milligrams of all prescribed drugs dispensed in the first trimester. Unexposed women were those who did not fill prescriptions for oral azole antifungal agents during the first trimester. Women who filled prescriptions for oral antifungal agents within 4 weeks before pregnancy onset were excluded from the study cohort to avoid potential misclassification of exposure status (i.e., classification of women who filled prescriptions shortly before pregnancy and used them during the first trimester as unexposed). Because we did not have data on anti-

fungal drug treatment of hospital inpatients, we excluded women with a fungal infection diagnosed during a hospital stay that occurred in the period from 4 weeks before pregnancy onset through the first trimester (see the Supplementary Appendix).

BIRTH DEFECTS

Cases of major birth defects were identified through the National Patient Register, which allowed for a 1-year follow-up of all infants. We investigated 15 specific birth defects previously associated with azole antifungal agents in case reports, reproductive animal models, or observational studies (4 defects previously associated with azole antifungal agents other than fluconazole were also included, because a teratogenic mechanism of these drugs could represent a class effect⁹): craniosynostosis,¹⁻⁴ cleft palate,^{2,5-7} cleft lip with or without cleft palate,^{6,7} other craniofacial defects,¹⁻⁴ middle-ear defects,⁷ limb defects,^{1,2,4,5,23} limb-reduction defects,^{6,7} polydactyly,²⁴ syndactyly,^{6,24} diaphragmatic hernia,¹⁵ heart defects,²⁵ tetralogy of Fallot,⁴ pulmonary-artery hypoplasia,⁴ ventricular septal defects,⁴ and hypoplastic left heart.¹⁵ We defined the category of birth defects overall according to the European Surveillance of Congenital Anomalies (EUROCAT) classification system.²⁶ We included all cases of major birth defects except for chromosomal aberrations, genetic syndromes, birth-defect syndromes with known causes, and congenital viral infections associated with malformation; we did not include minor defects (see the Supplementary Appendix).

STATISTICAL ANALYSIS

Prevalence odds ratios with 95% confidence intervals were estimated by logistic regression for each exposure category and each birth-defect outcome²⁷ with the use of SAS, version 9.1 (SAS Institute). The primary analyses included any exposure to fluconazole or exposure to different fluconazole doses and the outcome of either birth defects overall or birth defects previously linked with azole antifungal agents. No correction for multiple testing was applied. We used predefined categories of cumulative doses during the first trimester (150, 300, and 350 to 6000 mg); the categories were based on the standard treatment of vaginal candidiasis with one or two 150-mg doses of oral fluconazole,²⁸ with doses of at least 350 mg used for more complicated fungal infections, including recurrent vaginal candidiasis.

The secondary analyses included exposure to itraconazole and ketoconazole and assessed the outcome of birth defects overall.

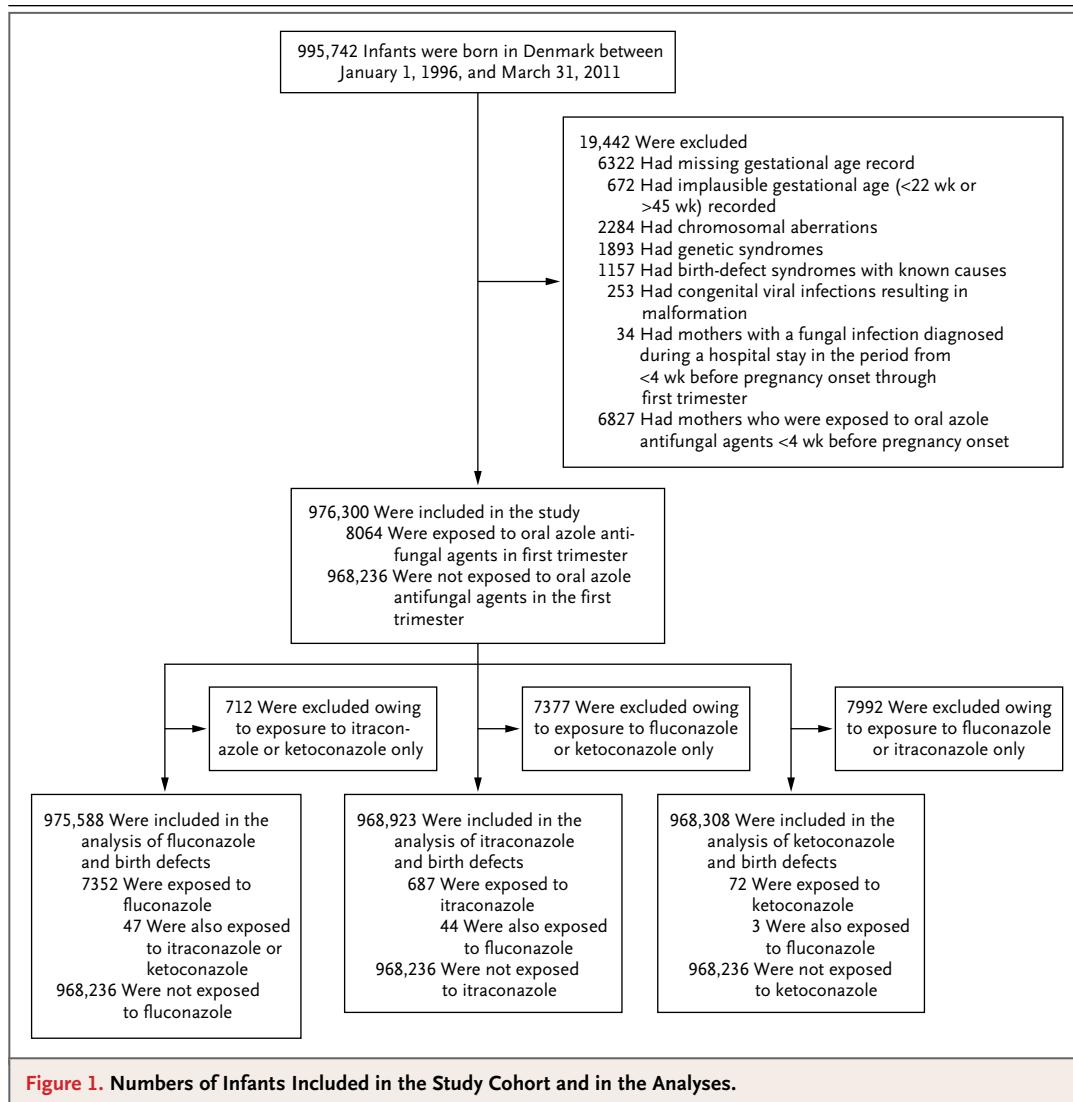
The covariates in our adjusted regression models were based on information available in registries and on the potential for association with both exposure to antifungal agents and birth defects. The covariates included calendar year; demographic characteristics; socioeconomic variables; and status with respect to smoking, previous births with malformation, selected coexisting conditions, and treatment with oral antibiotic agents, immunosuppressive agents, oral corticosteroids, antiepileptic agents, oral contraceptives, or drugs for in vitro fertilization (Table S2 in the Supplementary Appendix).

In preplanned sensitivity analyses of any fluconazole exposure and birth defects overall, we examined whether results changed when we used different exposure time windows and exclusion criteria. Our analyses were based only on live births, which could introduce a bias toward the null hypothesis as a result of excluding pregnancies that were terminated because of fetal malformation; therefore, we conducted analyses modeling the effect of including terminated pregnancies, with the use of data from a subcohort in Denmark (see the Supplementary Appendix). Sensitivity analyses examining different exposure time windows and exclusion criteria were also conducted for individual defects if the adjusted prevalence odds ratio was significantly increased. Furthermore, post hoc analyses were performed to determine whether additional adjustment for exposure to drugs in FDA pregnancy categories D and X (evidence of human fetal risk; should not be used in pregnancy) or for prepregnancy body-mass index (in a subcohort for the period from 2004 through March 2011) could explain the positive associations. For positive associations, the adjusted number of excess cases due to fluconazole exposure was calculated.

RESULTS

STUDY COHORT

A total of 976,300 liveborn infants were included in the study (Fig. 1). The characteristics of mothers exposed to oral azole antifungal agents and unexposed mothers in the study cohort are presented in Table 1 and in Table S2 in the Supplementary Appendix.



ORAL FLUCONAZOLE

Figure 2 shows the prevalence odds ratios for associations of first-trimester fluconazole exposure with birth defects overall and with 15 specific birth defects. No significantly increased risk of birth defects overall was observed among 7352 pregnancies exposed to any fluconazole, as compared with 968,236 unexposed pregnancies (adjusted prevalence odds ratio, 1.06; 95% confidence interval [CI], 0.92 to 1.21); evaluating exposure according to cumulative doses of 150, 300, and 350 to 6000 mg did not change this result.

In the analysis of 15 birth defects previously linked to azole antifungal agents, we found no significantly increased risk of craniosynostosis, cleft palate, cleft lip with or without cleft palate, limb defects, limb-reduction defects, polydactyly,

syndactyly, diaphragmatic hernia, heart defects overall, or ventricular septal defects associated with any dose of fluconazole. There were no cases of other craniofacial defects, middle-ear defects, or pulmonary-artery hypoplasia among fluconazole-exposed pregnancies, which is consistent with an absence of significantly increased risk, but we were not able to estimate prevalence odds ratios. The adjusted prevalence odds ratio for hypoplastic left heart was 2.03, but it was based on three exposed cases and was nonsignificant. The risk of tetralogy of Fallot among fluconazole-exposed pregnancies was three times as high as that among unexposed pregnancies, a significant increase, and was based on seven exposed cases. We observed similar results when the 15 birth defects were evalu-

Table 1. Characteristics of the 975,588 Women in the Study Cohort According to Whether They Were Exposed to Oral Fluconazole in the First Trimester of Pregnancy.*

Characteristic	Exposed (N = 7352)	Unexposed (N = 968,236)†
Cumulative dose of fluconazole — no. (%)		
150 mg	4082 (56)	—
300 mg	2252 (31)	—
350–6000 mg‡	1018 (14)	—
Previous births — no. (%)		
0	3465 (47)	438,327 (45)
≥1	3887 (53)	529,909 (55)
Age at pregnancy onset — yr	29±4.9	30±4.8
Married or living with a partner — no. (%)	5966 (81)	839,194 (87)
Bachelor's degree or higher educational level — no. (%)	2044 (28)	312,089 (32)
Household income in third quintile for overall study cohort — no. (%)	1417 (19)	193,764 (20)
Smoking during pregnancy — no. (%)	1481 (20)	177,619 (18)
One or more previous births with congenital malformations — no. (%)	395 (5)	49,072 (5)
Coexisting conditions and other medications taken — no. (%)		
Infectious disease in first trimester	128 (2)	8,811 (1)
Immunodeficiency at any time before pregnancy through first trimester	7 (0.1)	445 (0.05)
Diabetes mellitus at any time before pregnancy through first trimester	156 (2)	13,893 (1)
Oral antibiotics in first trimester	1937 (26)	118,331 (12)
Immunosuppressive agent during period from 3 months before pregnancy through first trimester	49 (0.7)	13,031 (1)
Oral contraceptives or drugs for in vitro fertilization in first trimester	455 (6)	62,260 (6)

* Plus-minus values are means ±SD. Percentages may not sum to 100 because of rounding. For additional characteristics, see Table S2 in the Supplementary Appendix.

† Women who did not fill any prescriptions for oral azole antifungal drugs in the first trimester of pregnancy were classified as unexposed.

‡ The mean dose in this group was 722±689 mg.

ated according to cumulative fluconazole dose, although the numbers in each exposure category were small (Fig. S1 in the Supplementary Appendix).

ORAL ITRACONAZOLE AND KETOCONAZOLE

No significantly increased risk of birth defects overall was observed among the 687 and 72 pregnancies exposed to itraconazole and ketoconazole, respectively, and no apparent clustering of malformations was observed (Tables S3 and S4 in the Supplementary Appendix).

ADDITIONAL ANALYSES

In preplanned sensitivity analyses in which we explored the effects of different exposure windows and exclusion criteria, the adjusted prev-

alence odds ratios for birth defects overall associated with any fluconazole exposure were similar to those in the primary analyses (Table 2). When the effect of including pregnancies that were terminated because of a fetal anomaly was modeled, the risk estimates for all but 1 of the 15 specific birth defects were found to be similar to those in the primary analyses (Table S5 in the Supplementary Appendix). The exception was hypoplastic left heart, for which the prevalence odds ratio, which was 2.03 in the primary analysis, rose to 2.82 (95% CI, 1.23 to 6.45) when the proportion of terminated pregnancies was assumed to be doubled among the exposed pregnancies.

The robustness of the observed increased risk of tetralogy of Fallot was evaluated in a number

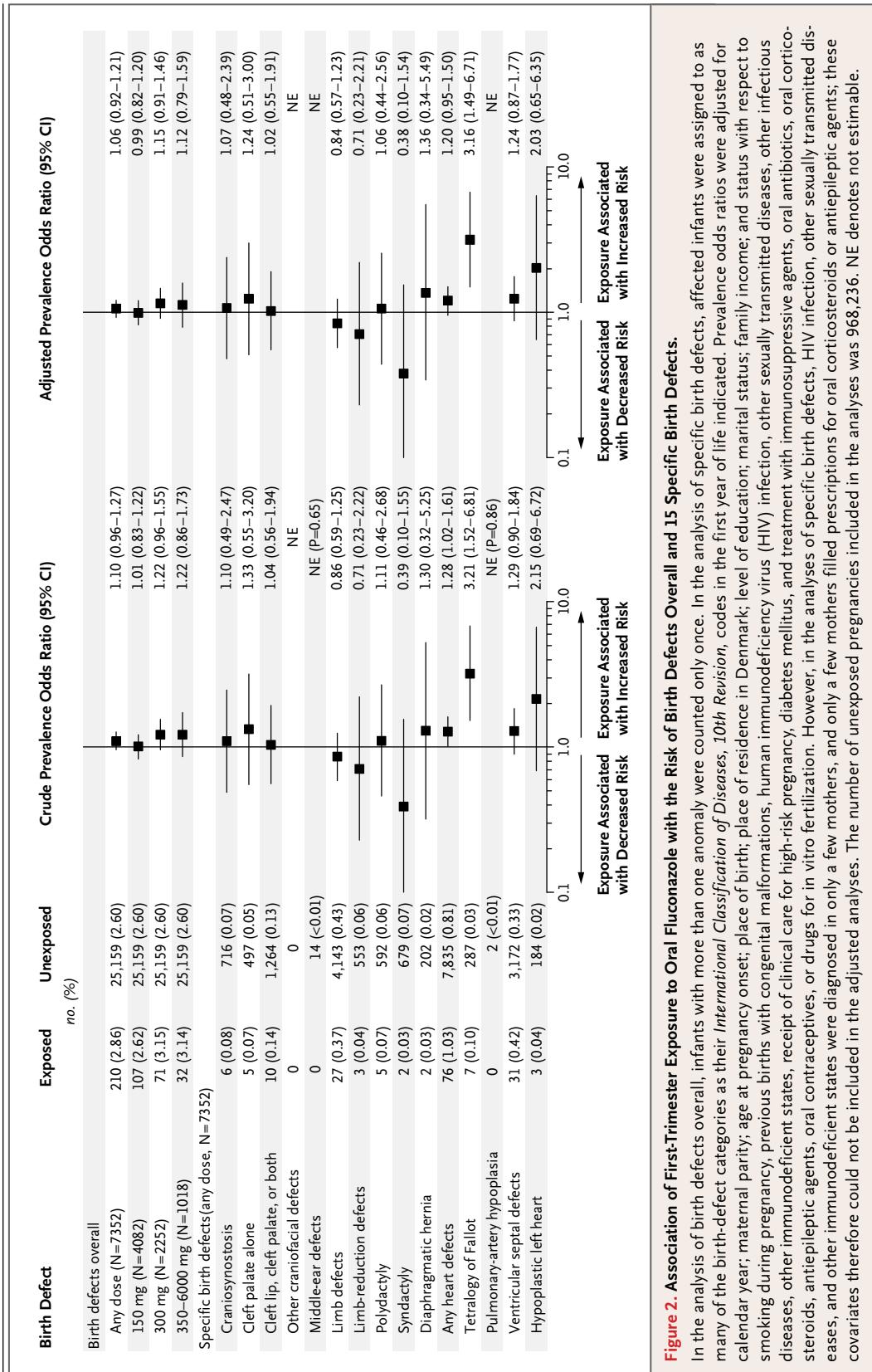


Figure 2. Association of First-Trimester Exposure to Oral Fluconazole with the Risk of Birth Defects Overall and 15 Specific Birth Defects.

In the analysis of birth defects overall, infants with more than one anomaly were counted only once. In the analysis of specific birth defects, affected infants were assigned to as many of the birth-defect categories as their *International Classification of Diseases, 10th Revision*, codes in the first year of life indicated. Prevalence odds ratios were adjusted for calendar year; maternal parity; age at pregnancy onset; place of birth; place of residence in Denmark; level of education; marital status; family income; and status with respect to smoking during pregnancy, previous births with congenital malformations, human immunodeficiency virus (HIV) infection, other sexually transmitted diseases, other infectious diseases, other immunodeficient states, receipt of clinical care for high-risk pregnancy, diabetes mellitus, and treatment with immunosuppressive agents, oral antibiotics, oral corticosteroids, antiepileptic agents, oral contraceptives, or drugs for in vitro fertilization. However, in the analyses of specific birth defects, HIV infection, other sexually transmitted diseases, and other immunodeficient states were diagnosed in only a few mothers, and only a few mothers filled prescriptions for oral corticosteroids or antiepileptic agents; these covariates therefore could not be included in the adjusted analyses. The number of unexposed pregnancies included in the analyses was 968,236. NE denotes not estimable.

Table 2. Sensitivity Analyses of the Association between Oral Fluconazole Exposure (Any Dose) and Birth Defects Overall.

Analysis	Birth Defects Overall*	Adjusted Prevalence Odds Ratio (95% CI)†
	no./total no. (%)	
Exposure in 5th to 10th wk of gestation	45/1716 (2.62)	0.95 (0.71–1.28)
Exposure only in second or third trimester	75/2477 (3.03)	1.11 (0.88–1.40)
Exclusion of multiple births	198/7139 (2.77)	1.06 (0.92–1.22)
Exclusion of women with missing data	192/6946 (2.76)	1.03 (0.90–1.19)

* Data are the number of cases of birth defects overall, shown as a percentage of the total number of pregnancies with fluconazole exposure.

† The prevalence odds ratio was adjusted for calendar year; maternal parity; age at pregnancy onset; place of birth; place of residence in Denmark; level of education; marital status; family income; and status with regard to smoking during pregnancy, previous births with congenital malformations, human immunodeficiency virus infection, other sexually transmitted diseases, other infectious diseases, other immunodeficient states, receipt of clinical care for high-risk pregnancy, diabetes mellitus, and treatment with oral antibiotics, immunosuppressive agents, oral corticosteroids, antiepileptic agents, oral contraceptives, or drugs for in vitro fertilization.

of additional analyses (Table 3). An adjusted prevalence odds ratio indicating an increased risk of tetralogy of Fallot persisted when the exposure time window was restricted to the period during which the fetus is most sensitive to teratogenic insults, when the association was examined according to cumulative fluconazole dose, when multiple births and persons with missing data were excluded, when adjustment was made for treatment with pregnancy category D and X drugs, and when adjustment was made for body-mass index. There was no increased risk associated with fluconazole exposure in the second or third trimester. In absolute terms, we estimated that fluconazole use would give rise to 6.5 (95% CI, 1.5 to 17) excess cases of tetralogy of Fallot per 10,000 infants exposed in the first trimester (Table S6 in the Supplementary Appendix). In a post hoc exploratory analysis, fluconazole was not associated with a significantly increased risk of conotruncal heart defects (a subgroup that includes tetralogy of Fallot), although the adjusted prevalence odds ratio was 1.65 (Table S7 in the Supplementary Appendix). Table S8 in the Supplementary Appendix shows a review of registry records of the 7 cases of tetralogy of Fallot associated with fluconazole exposure.

DISCUSSION

In this nationwide cohort, exposure to any oral fluconazole or to a cumulative dose of 150, 300, or 350 to 6000 mg during the first trimester of pregnancy was not associated with a significantly increased risk of birth defects overall, and neither was exposure to oral itraconazole or ketoconazole. For this study, we identified 15 birth defects that had been linked to azole antifungal agents and found no evidence of an association between fluconazole exposure and 14 of these defects. The findings from this study are therefore largely reassuring. However, the risk of tetralogy of Fallot was three times as high after fluconazole exposure, and this increased risk was found in all analyses.

Case reports have described a pattern of specific malformations, including tetralogy of Fallot (in one case), in infants exposed to 400 to 800 mg of fluconazole daily during the first trimester of pregnancy.⁴ In our study, the fluconazole-exposed infants with tetralogy of Fallot had no noncardiac defects, in contrast to the malformation pattern described in the earlier case reports. Furthermore, no mothers and only one sibling of affected infants had heart defects, which suggests that the affected infants did not have a genetic predisposition (although paternal information and data from before 1978 were not available). In our exploratory analyses of conotruncal defects, tetralogy of Fallot represented 70% of the conotruncal defects in fluconazole-exposed infants and 36% of those in unexposed infants; the nonsignificant increased risk of conotruncal defects was therefore driven by tetralogy of Fallot. This indicates that if fluconazole causes tetralogy of Fallot, the mechanism is probably not related to other malformations of the cardiac outflow tract that are otherwise etiologically similar. Antibiotics were dispensed to all except one of the mothers of exposed infants with tetralogy of Fallot. Maternal febrile illness and some penicillins have been associated with heart defects (although not tetralogy of Fallot specifically²⁹), but adjustment for antibiotic use did not affect the observed estimate.

Previous observational studies of fluconazole use in pregnancy have focused on the outcome of birth defects overall; most of the women included in these studies were exposed to a single

Table 3. Sensitivity Analyses of the Association between Oral Fluconazole Exposure and Tetralogy of Fallot.*

Analysis	Tetralogy of Fallot†	Adjusted Prevalence Odds Ratio (95% CI)‡
	no./total no. (%)	
Exposure in 5th to 10th week of gestation	3/1716 (0.17)	5.86 (1.87–18.35)
Exposure only in second or third trimester	1/2477 (0.04)	1.39 (0.20–9.93)
Cumulative fluconazole dose in first trimester		
150 mg	4/4082 (0.10)	3.18 (1.18–8.55)
300 mg	2/2252 (0.09)	3.03 (0.75–12.21)
350–6000 mg	1/1018 (0.10)	3.37 (0.47–24.06)
Exclusion of multiple births	7/7139 (0.10)	3.42 (1.61–7.26)
Exclusion of women with missing data	7/6946 (0.10)	3.48 (1.64–7.39)
Additional adjustment for drugs in FDA pregnancy categories D and X	7/7352 (0.10)	3.14 (1.48–6.68)
Additional adjustment for prepregnancy BMI in a subcohort from 2004 through March 2011	5/3855 (0.13)	4.55 (1.85–11.19)

* BMI denotes body-mass index, and FDA Food and Drug Administration.

† Data are the number of cases of tetralogy of Fallot, shown as a percentage of the total number of pregnancies with fluconazole exposure.

‡ The prevalence odds ratio was adjusted for calendar year; maternal parity; age at pregnancy onset; place of birth; place of residence in Denmark; level of education; marital status; family income; and status with regard to smoking during pregnancy, previous births with congenital malformations, infectious diseases other than human immunodeficiency virus (HIV) infection and other sexually transmitted diseases, receipt of clinical care for high-risk pregnancy, diabetes mellitus, and treatment with immunosuppressive agents, oral antibiotics, oral contraceptives, or drugs for in vitro fertilization. HIV infection, other sexually transmitted diseases, and other immunodeficient states were diagnosed in only a few mothers, and only a few mothers filled prescriptions for oral corticosteroids or antiepileptic agents; therefore, these covariates could not be included in the adjusted analyses.

150-mg dose of fluconazole, and the total number of pregnancies with exposure in the first trimester was 1650, as compared with 7352 in our study.¹⁰⁻¹⁴ Our finding that a 150-mg dose of fluconazole was not associated with an increased risk of birth defects overall confirms the results of previous studies; our study also adds to these safety data by reporting risk estimates for doses higher than 150 mg.

There have been few studies of specific defects. A cohort study of 1079 fluconazole-exposed women showed no significant increased risk of craniofacial defects or heart defects.¹³ In a case-control study of selected defects, the risk of hypoplastic left heart was twice as high in association with the use of antifungal agents, and there was a nonsignificant elevated risk of diaphragmatic hernia, but the specific types of drugs were mostly topical azoles or unknown.¹⁵ In another case-control study, first-trimester ketoconazole use was associated with a risk of heart defects that was three times as high as that in the control group; however, the result

was not significant and was based on only two exposed cases.²⁵

With respect to other oral azole antifungal agents, our findings suggest that itraconazole is unlikely to be associated with more than a moderate excess risk of birth defects overall and that ketoconazole is not a major human teratogen. These findings are in accordance with the results of three previous studies investigating the relationship between exposure to these agents and birth defects.^{11,25,30}

Our study has strengths and limitations. The registry-based design allowed us to assemble a nationwide cohort with independent ascertainment of exposure and outcome and complete 1-year follow-up of all infants. Validation studies of the National Patient Register have shown that registrations are correct for 88% of birth defects overall and for 89 to 90% of cardiac malformations, including tetralogy of Fallot.^{31,32} The use of filled prescriptions as a measure of exposure eliminates recall bias and increases the accuracy of information on

specific types of drugs, as compared with self-reported use. However, noncompliance would bias results toward no effect. Although information on topical azole antifungal agents (including vaginal preparations) was not included in the study, since most are purchased over the counter, their teratogenic potential is small because of their minimal systemic absorption.^{33,34} We took into account many possible confounding factors, but ascertainment of maternal illnesses may be incomplete because the National Patient Register does not include diagnostic information from primary care. Unmeasured confounding factors are always a possibility in observational studies, but the absence of an association between fluconazole exposure in the second or third trimester and birth defects indicates a modest effect of unmeasured confounding factors (assuming that these women have characteristics similar to those exposed in the first trimester). Because we studied only live-born infants, our estimates would be biased toward the null hypothesis if fluconazole use were associated with malformation-related miscarriage or elective termination. To address this issue, we conducted analyses modeling the effect of including pregnancies terminated after prenatal diagnosis. The findings were almost identical to those of the primary analyses, indicating that any bias toward the null hypothesis as a result of excluding pregnancy terminations was minimal. However, this was not the case for hypoplastic left heart, for which there was a relatively high prevalence of terminations (45.5%).

Chance could explain the significantly in-

creased risk of tetralogy of Fallot, considering that 15 specific birth defects were analyzed. However, our selection of defects was based on previous associations, and we therefore place greater reliance on our findings than we would if this were the first report of such associations. The nonsignificant adjusted prevalence odds ratio for hypoplastic left heart may be a false negative finding, given that the upper limit of the confidence interval exceeds 6; this warrants further investigation. In the analyses according to fluconazole dose, the highest dose category is heterogeneous, with a mean dose of 722 mg, and the results should be interpreted accordingly. Furthermore, in the analyses of the 15 specific birth defects according to fluconazole dose, the number of exposed pregnancies was small, especially for cumulative doses of 350 to 6000 mg.

In conclusion, this large cohort study provides comprehensive safety information for oral fluconazole use during pregnancy and adds knowledge regarding itraconazole and ketoconazole. Our analyses showed that first-trimester fluconazole exposure was not associated with an excess risk of birth defects overall, including analyses according to fluconazole dose and most of the analyses of specific birth defects of previous concern. Although fluconazole may confer an increased risk of tetralogy of Fallot, the absolute risk was small and the association needs to be confirmed.

Supported by the Danish Medical Research Council.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

- Aleck KA, Bartley DL. Multiple malformation syndrome following fluconazole use in pregnancy: report of an additional patient. *Am J Med Genet* 1997; 72:253-6.
- Lee BE, Feinberg M, Abraham JJ, Murthy AR. Congenital malformations in an infant born to a woman treated with fluconazole. *Pediatr Infect Dis J* 1992;11: 1062-4.
- Lopez-Rangel E, Van Allen MI. Prenatal exposure to fluconazole: an identifiable dysmorphic phenotype. *Birth Defects Res A Clin Mol Teratol* 2005;73:19-23.
- Pursley TJ, Blomquist IK, Abraham J, Andersen HF, Bartley JA. Fluconazole-induced congenital anomalies in three infants. *Clin Infect Dis* 1996;22:336-40.
- Tiboni GM, Marotta F, Del Corso A, Giampietro F. Defining critical periods for itraconazole-induced cleft palate, limb defects and axial skeletal malformations in the mouse. *Toxicol Lett* 2006;167:8-18.
- Mineshima H, Fukuta T, Kato E, et al. Malformation spectrum induced by ketoconazole after single administration to pregnant rats during the critical period — comparison with vitamin A-induced malformation spectrum. *J Appl Toxicol* 2012;32:98-107.
- Tiboni GM, Giampietro F. Murine teratology of fluconazole: evaluation of developmental phase specificity and dose dependence. *Pediatr Res* 2005;58:94-9.
- Food and Drug Administration. Use of long-term, high-dose Diflucan (fluconazole) during pregnancy may be associated with birth defects in infants. 2011 (<http://www.fda.gov/Drugs/DrugSafety/ucm266030.htm>).
- Marotta F, Tiboni GM. Molecular aspects of azoles-induced teratogenesis. *Expert Opin Drug Metab Toxicol* 2010;6: 461-82.
- Inman W, Pearce G, Wilton L. Safety of fluconazole in the treatment of vaginal candidiasis: a prescription-event monitoring study, with special reference to the outcome of pregnancy. *Eur J Clin Pharmacol* 1994;46:115-8.
- Jick SS. Pregnancy outcomes after maternal exposure to fluconazole. *Pharmacotherapy* 1999;19:221-2.
- Mastroiacovo P, Mazzone T, Botto LD, et al. Prospective assessment of pregnancy outcomes after first-trimester exposure to fluconazole. *Am J Obstet Gynecol* 1996;175:1645-50.
- Nørgaard M, Pedersen L, Gislum M, et al. Maternal use of fluconazole and risk

- of congenital malformations: a Danish population-based cohort study. *J Antimicrob Chemother* 2008;62:172-6.
14. Wilton LV, Pearce GL, Martin RM, Mackay FJ, Mann RD. The outcomes of pregnancy in women exposed to newly marketed drugs in general practice in England. *Br J Obstet Gynaecol* 1998;105:882-9.
15. Carter TC, Druschel CM, Romitti PA, Bell EM, Werler MM, Mitchell AA. Antifungal drugs and the risk of selected birth defects. *Am J Obstet Gynecol* 2008;198(2):191.e1-191.e7.
16. Sobel JD. Vulvovaginal candidosis. *Lancet* 2007;369:1961-71.
17. Eckert LO. Acute vulvovaginitis. *N Engl J Med* 2006;355:1244-52. [Erratum, *N Engl J Med* 2006;355:2797.]
18. Knudsen LB, Olsen J. The Danish Medical Birth Registry. *Dan Med Bull* 1998;45:320-3.
19. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health* 2011;39: Suppl: 38-41.
20. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011;39:Suppl:30-3.
21. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011;39:Suppl:22-5.
22. Jørgensen FS. Ultrasonography of pregnant women in Denmark 1999-2000: description of the development since 1980-1990. *Ugeskr Laeger* 2003;165:4409-15. (In Danish.)
23. Briggs GG, Freeman RK, Yaffe SJ. Itraconazole. In: Shaw R, ed. *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk*. 8th ed. Philadelphia: Lippincott Williams & Wilkins, 2008:994-6.
24. Kazy Z, Puhó E, Czeizel AE. The possible association between the combination of vaginal metronidazole and miconazole treatment and poly-syndactyly: population-based case-control teratologic study. *Reprod Toxicol* 2005;20:89-94.
25. *Idem*. Population-based case-control study of oral ketoconazole treatment for birth outcomes. *Congenit Anom (Kyoto)* 2005;45:5-8.
26. Coding and classification. In: *EUROCAT guide 1.3 and reference documents: instructions for the registration and surveillance of congenital anomalies*. Ulster, United Kingdom: EUROCAT, 2012.
27. Clayton D, Hills M. Poisson and logistic regression. In: Clayton D, Hills M, eds. *Statistical models in epidemiology*. Oxford, England: Oxford University Press, 2001:227-36.
28. Nilas L, Hansen BL. Candidat vaginit, 2012 (<https://www.sundhed.dk/sundhedsfaglig/laegehaandbogen/gynaekologi/tilstande-og-sygdomme/infektioner/candida-vaginit/>).
29. Jenkins KJ, Correa A, Feinstein JA, et al. Noninherited risk factors and congenital cardiovascular defects: current knowledge: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young: endorsed by the American Academy of Pediatrics. *Circulation* 2007;115:2995-3014.
30. Bar-Oz B, Moretti ME, Bishai R, et al. Pregnancy outcome after in utero exposure to itraconazole: a prospective cohort study. *Am J Obstet Gynecol* 2000;183:617-20.
31. Agergaard P, Hebert A, Bjerre J, Sørensen KM, Olesen C, Ostergaard JR. Children diagnosed with congenital cardiac malformations at the national university departments of pediatric cardiology: positive predictive values of data in the Danish National Patient Registry. *Clin Epidemiol* 2011;3:61-6. [Erratum, *Clin Epidemiol* 2011;3:131.]
32. Larsen H, Nielsen GL, Bendtsen J, Flint C, Olsen J, Sørensen HT. Predictive value and completeness of the registration of congenital abnormalities in three Danish population-based registries. *Scand J Public Health* 2003;31:12-6.
33. Daneshmend TK. Systemic absorption of miconazole from the vagina. *J Antimicrob Chemother* 1986;18:507-11.
34. Ritter W, Patzschke K, Krause U, Stettendorf S. Pharmacokinetic fundamentals of vaginal treatment with clotrimazole. *Chemotherapy* 1982;28:Suppl 1:37-42.

Copyright © 2013 Massachusetts Medical Society.

JOURNAL ARCHIVE AT NEJM.ORG

Every article published by the *Journal* is now available at NEJM.org, beginning with the first article published in January 1812. The entire archive is fully searchable, and browsing of titles and tables of contents is easy and available to all. Individual subscribers are entitled to free 24-hour access to 50 archive articles per year. Access to content in the archive is available on a per-article basis and is also being provided through many institutional subscriptions.