Maternal use of fluconazole and risk of congenital malformations: a Danish population-based cohort study

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Objectives: Fluconazole is widely used for the treatment of candidiasis. Although the drug is also prescribed to pregnant women, data on the safety of use of fluconazole during pregnancy are limited. We examined the association between the maternal use of fluconazole during pregnancy and the risk of congenital malformations.

Patients and methods: In this population-based cohort study in Northern Denmark, we included 1079 women who had a live birth or a stillbirth after the 20th week of gestation and who redeemed at least one prescription for fluconazole during the first trimester. The reference cohort comprised 170 453 pregnant women who redeemed no fluconazole prescription during pregnancy. The women were identified through the Danish Medical Birth Registry. Data on drug use, birth outcome and covariates were extracted from population-based healthcare databases. We used logistic regression to estimate the prevalence odds ratio (POR) for congenital malformations after fluconazole exposure, while adjusting for maternal smoking, parity, maternal age and concurrent prescriptions for antiepileptics or antidiabetics.

Results: Among 1079 women who filled a fluconazole prescription during the first trimester, 797 (74%) received a total of 150 mg of fluconazole, 235 (22%) received 300 mg of fluconazole, 24 (2%) received 350 mg of fluconazole and 23 (2%) received 600 mg of fluconazole. These women gave birth to 44 (4.1%) children with congenital malformations. The 170 453 women without fluconazole prescriptions gave birth to 6152 (3.6%) children with congenital malformations. For congenital malformations overall, the adjusted POR associated with the first-trimester fluconazole use was 1.0 (95% confidence interval: 0.8–1.4).

Conclusions: We found no overall increased risk of congenital malformations after exposure to short-course treatment with fluconazole in early pregnancy.

Keywords: drug safety, pregnancy, antifungals, epidemiology

Introduction

Fluconazole, a triazole antifungal, is widely used in the treatment of vaginal, oropharyngeal and cutaneous candidiasis.1 The prevalence of vaginal candidiasis is increased among pregnant women,2 probably due to depression of the T cell-mediated immune response and high oestrogen levels. Although topical antifungals are recommended as first choice among pregnant women, oral fluconazole is used for prophylaxis and for the treatment of mycotic infections among pregnant women also.3 Human data on its safety during pregnancy are, however, limited. Case reports have suggested a link between the maternal use of fluconazole and craniofacial abnormalities in the newborn.4–8 In contrast, one case series of 60 women who took fluconazole at some time after their last menstrual period,9 another case series of 16 pregnant women exposed during the first trimester10 and three formal epidemiological studies including a total of 581 fluconazole-exposed pregnant women11–13 failed to show an increase in the overall risk of birth defects among fluconazole users, compared with non-users. However,
the low prevalence of specific birth defects has a major impact on sample size requirements for providing the definitive assurances of the safety of fluconazole during pregnancy.\textsuperscript{14} Thus, more data are required to determine whether and to what extent fluconazole is associated with an increased risk of birth defects.

We extended an earlier Danish study\textsuperscript{12} to examine the association between the maternal use of fluconazole during pregnancy and the risk of congenital malformations.

\section*{Methods}

\subsection*{Study population and design}

We conducted a cohort study in four Danish counties, which, with their 1.6 million inhabitants, account for 31\% of the Danish population. We used data from the counties’ computerized prescription databases collected during three time periods corresponding to the time of data availability: 1991–2005 (North Jutland County), 1996–2005 (Aarhus County) and 1998–2005 (Ringkøbing and Viborg Counties). We included all female residents of the counties, who during the periods covered by the prescription registries gave a live birth or a stillbirth after the 20th week of gestation. The women were identified through the Danish Medical Birth Registry,\textsuperscript{15} which contains computerized records of all births in Denmark since 1 January 1973. Data are recorded by midwives or physicians responsible for deliveries. The main variables in the registry include maternal age, parity, birth weight, gestational age, self-reported maternal smoking status and data about delivery. Records in the birth registry and in prescription databases were linked via a 10-digit civil registration number, which is a unique identifier assigned, since 1968, to all Danish residents by the Central Office of Civil Registration and used in all Danish healthcare registries.

The Danish Data Protection Agency had approved the study; record no. 2003-41-3103.

\subsection*{Data on fluconazole and other drugs}

The Danish National Health Service partially reimburses patients’ expenditures on many prescribed medicines including fluconazole. The four counties are served by pharmacies equipped with an electronic accounting system that registers the civil registration number, information on the prescribed drug coded according to The Anatomical Therapeutic Chemical Classification System (ATC), the amount prescribed and the date of drug dispensing. All data are transferred to the prescription database at Aarhus University. We obtained data on all the women’s prescriptions for fluconazole dispensed from the beginning of first trimester until the end of each pregnancy. The ATC code for fluconazole was J02A C01. We also retrieved data on prescriptions for antiepileptics and antidiabetics during the first trimester or 30 days before conception, because the use of antiepileptics and diabetes has been associated with an increased risk of congenital malformations.\textsuperscript{16–18} The ACT code for antiepileptics was N03A and for antidiabetics A10.

\subsection*{Outcome data}

Data on congenital malformations were retrieved from the Danish National Registry of Patients. This registry was established in 1977 and includes dates of admission and discharge, surgical procedures and up to 20 discharge diagnoses coded by medical doctors at discharge according to the International Classification of Diseases, 8th revision (ICD-8) until the end of 1993 and 10th revision (ICD-10) thereafter. The codes for malformations were 740–759 in ICD-8 and Q00–Q99 in ICD-10. We only included malformations registered during the first year of life. We excluded diagnoses of congenital dislocation of the hip and undescended testes due to their poor validity.\textsuperscript{19} Further, we excluded children with known chromosomal aberration such as Down’s syndrome.\textsuperscript{20}

Through the Danish National Registry of Patients, we also retrieved information on maternal diagnoses of diabetes (ICD-8 code: 249, 250 and ICD-10 code: E10, E11) registered before the date of conception.

Through the Danish Medical Birth Registry, we retrieved information on birth weight, gestational age and stillbirth.

\subsection*{Statistical analysis}

\subsection*{Descriptive data}

Among 171 532 women who had a live birth or stillbirth during the study period, a total of 1079 (0.6\%) women redeemed a prescription on fluconazole during the first trimester. Among these 1079 women, 797 (74\%) received 0.75 DDDs corresponding to 150 mg of fluconazole, 235 (22\%) received 1.5 DDDs (300 mg of fluconazole), 24 (2\%) received 1.75 DDDs (350 mg of fluconazole) and only 23 (2\%) received 3 DDDs (600 mg of fluconazole). Moreover, 1286 women had redeemed a prescription anytime during pregnancy. Compared with women who did not have fluconazole prescriptions, those with a fluconazole prescription tended to be younger and were more likely to have prescriptions for antiepileptics and antidiabetics (Table 1). We excluded 260 births in which the children had known chromosomal defects. None of these had been exposed to fluconazole.
Among the 1079 women with a fluconazole prescription during the first trimester, there were 44 births with congenital malformations (4.1%), compared with a prevalence of 3.6% among the unexposed. The crude POR for any malformation after fluconazole exposure was 1.1 (95% CI: 0.8–1.5), and the adjusted POR was 1.0 (95% CI: 0.8–1.4).

Table 2 shows the distribution of specific types of malformations among the 44 fluconazole-exposed children. Ten of them had craniofacial malformations, corresponding to a prevalence of 0.9%, compared with a prevalence of 0.6% among the unexposed. The crude POR was 1.6 (95% CI: 0.9–3.1), and the adjusted POR was 1.3 (95% CI: 0.6–2.6). Congenital heart malformations were registered in 15 children (1.4%) (one of these children had multiple malformations), compared with 1686 (1.0%) congenital heart malformations among the 170 453 fluconazole-unexposed children, yielding a crude POR of 1.4 (95% CI: 0.8–2.4) and an adjusted POR of 1.3 (95% CI: 0.7–2.1).

We found no increased risk of low birth weight [adjusted POR 1.1 (95% CI: 0.7–1.6)], pre-term birth [adjusted POR 1.0 (95% CI: 0.8–1.3)] or stillbirth [adjusted POR 1.1 (95% CI: 0.4–3.5)].

### Pooled analysis

We pooled the odds ratios from the three existing cohort studies and arrived at a pooled OR of 0.9 (95% CI: 0.5–1.6). When we replaced the previous Danish study with the odds ratio from our present study, the pooled estimate changed to 1.0 (95% CI: 0.7–1.3).

### Discussion

This study, based on over 1000 exposed pregnancies, 121 of which had been included in an earlier analysis, provided no evidence for an overall association between short-course maternal use of fluconazole during the first trimester of pregnancy and the increased risk of congenital malformations in the
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offspring. Neither did we find an association between exposure to fluconazole anytime during pregnancy and pre-term birth, low birth weight, or still birth. Although larger than that of the previous studies, our sample size remained insufficient for examining the risks of specific birth defects. We did not find trends in the distribution of birth defects, which would suggest a causal association. We found a nearly null effect for craniofacial or cardiac malformations, but the size of our cohort enables one to rule out a 2.6- to 3.1-fold increased risk for those malformations. Studies in rodents have shown a dose-dependent teratogenic effect of fluconazole, manifested as branchial arch malformations. If fluconazole exposure in humans were similarly associated with branchial arch malformations, we would expect to observe a higher risk for craniofacial malformations than we actually did. However, it is uncertain whether all craniofacial malformations have the same aetiology.

It is important to acknowledge strengths and weaknesses of our study when interpreting its results. We used population-based data on malformations recorded during the first year of life, but we did not consider malformations leading to a miscarriage or to an elective abortion after pre-natal diagnosis. If use of fluconazole is related to an increased risk of malformation-related miscarriage and/or elective abortion, the risk and the risk ratio for malformations among the fluconazole-exposed women would be underestimated.

Data on malformations were obtained from a discharge registry, with data entered by trained medical staff. Validation studies have shown high quality of these diagnoses, with misclassification rates of 11.8% for congenital malformations overall and 12.0% for congenital cardiac malformations. Any misclassification of the malformation diagnoses is unlikely to be related to fluconazole exposure and would, therefore, lead us to underestimate any association.

Because we measured the exposure to fluconazole by redeemed prescriptions, we do not know whether the patients actually took the drug. However, as the patients were required to pay part of the costs, we assume high compliance. One major limitation of the exposure data is that the prescription databases only record the overall amount of prescribed drugs, but not the daily dosage. Based on recommendations used in Denmark, we can assume the treatment of vaginal candidiasis to be a single dose of 150 mg of fluconazole. None of the pregnant women received more than 600 mg of fluconazole corresponding to a 4 day regimen. We were, however, unable to examine the potential effects of multiple weekly doses of fluconazole on the risk of malformations.

We had data on potential confounding factors: use of antidiabetics or antiepileptics and self-reported smoking status. Including these variables in the analysis resulted in only a modest change in the overall estimate of effect. It is unlikely that unknown or unmeasured confounding could be substantial, as no association between fluconazole and congenital malformations was detected in the crude analysis, thus implying that any effect of a possible unmeasured confounder would have to be protective.

Our study corroborates the findings from the three earlier cohort studies (Table 3). Based on the same source of data as in this study, Sørensen et al. have previously reported no increased risk of congenital malformations among offspring of 121 pregnant women who resided in one of the counties included here and were exposed to fluconazole in the first trimester. Mastroiacovo et al. compared pregnancy outcomes among 226 women who contacted three teratology information service centres in Italy because of exposure to fluconazole with outcomes among 452 women who contacted the same teratology service centres because of exposure to non-teratogenic drugs and found no difference in the prevalence of malformations. It has, however, been suggested that self-selecting women who contact teratology services may represent a group of women with a relatively low prevalence of malformations in general. On the basis of the General Practitioners Research Database, Jick identified 234 women exposed to fluconazole and 429 women exposed to topically administered azole preparations and compared the pregnancy outcome in these two groups with those among 1629 women unexposed to any azole preparation. The relative risk of having a child with congenital malformations for women exposed to fluconazole was 1.1 (95% CI: 0.4–3.3). In a prescription-event monitoring study, Inman et al. identified 289 women who were prescribed fluconazole at some time during the months before or during pregnancy. However, only 60 of these women were prescribed fluconazole after the last menstrual period preceding pregnancy. Five of the 289 women gave birth

<table>
<thead>
<tr>
<th>Type of study</th>
<th>No. of pregnancies exposed in the first trimester</th>
<th>No. of unexposed</th>
<th>Prevalence of malformations among exposed %</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inman et al.</td>
<td>case series</td>
<td>60</td>
<td>—</td>
<td>0</td>
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<tr>
<td>Mastroiacovo et al.</td>
<td>cohort</td>
<td>226</td>
<td>452</td>
<td>3.1</td>
</tr>
<tr>
<td>Sørensen et al.</td>
<td>cohort</td>
<td>121</td>
<td>13 327</td>
<td>3.3</td>
</tr>
<tr>
<td>Jick</td>
<td>cohort</td>
<td>234</td>
<td>1629</td>
<td>1.7</td>
</tr>
<tr>
<td>Pooled estimate of the above-mentioned studies</td>
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<td></td>
<td></td>
<td>0.9</td>
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<tr>
<td>Pooled estimate including the present study</td>
<td></td>
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<td>1.0</td>
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A pooled estimate is given for the existing literature with and without inclusion of the present study.

*Only specified that the women were exposed to fluconazole after the last menstrual period before pregnancy.

The study by Sørensen et al. was replaced by the present study.
to a child with congenital malformations, and these five women were all exposed to fluconazole before the last pre-pregnancy menstrual period. Overall, as shown by our pooled analysis, the above-mentioned studies suggested no increased risk of congenital malformations associated with pre-natal exposure to fluconazole. Adding our study to the pooled analysis confirmed the absence of an association, while improving the precision of the pooled estimate.

In conclusion, our data and the pooled analysis indicated no overall increased risk of congenital malformations associated with pre-natal exposure to fluconazole. However, we need larger cohorts of fluconazole-exposed pregnant women to rule out increased risks for specific malformations.

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Transparency declarations
None to declare.

References