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Yeast infection in pregnancy? Think twice about fluconazole

This study's findings regarding the risk of miscarriage may mean it's time to forego fluconazole in favor of topical azoles as first-line treatment.

PRACTICE CHANGER

Avoid prescribing oral fluconazole in early pregnancy because it is associated with a higher rate of spontaneous abortion than is topical azole therapy.¹

STRENGTH OF RECOMMENDATION

B: Based on a large cohort study performed in Denmark.

Molgaard-Nielsen D, Svanström H, Melbye M, et al. Association between use of oral fluconazole during pregnancy and risk of spontaneous abortion and stillbirth. *JAMA*. 2016;315:58-67.

ILLUSTRATIVE CASE

A 25-year-old woman who is 16 weeks pregnant with her first child is experiencing increased vaginal discharge associated with vaginal itching. A microscopic examination of the discharge confirms your suspicions of vaginal candidiasis. Is oral fluconazole or a topical azole your treatment of choice?

Because of the increased production of sex hormones, vaginal candidiasis is common during pregnancy, affecting up to 10% of pregnant women in the United States.^{1,2} Treatment options include oral fluconazole and a variety of topical azoles. Although topical azoles are recommended as first-line therapy,³ the ease of oral therapy makes it an attractive treatment option.⁴ The safety of oral fluconazole during pregnancy, however, has recently come under scrutiny.

Case reports have linked high-dose fluconazole use during pregnancy with con-

genital malformations.^{5,6} These case reports led to epidemiological studies evaluating fluconazole's safety, but, in these studies, no association with congenital malformations was found.^{7,8}

A large cohort study involving 1079 fluconazole-exposed pregnancies and 170,453 unexposed pregnancies found no increased risk of congenital malformations or stillbirth; rates of spontaneous abortion and miscarriage were not evaluated.⁹ A prospective cohort study of 226 pregnant women found no association between fluconazole use during the first trimester and miscarriages.¹⁰ However, the validity of both studies' findings was limited by small numbers of participants. The current study is the largest to date to evaluate whether use of fluconazole compared to that of topical azoles in early pregnancy is associated with increased rates of spontaneous abortion and stillbirth.

STUDY SUMMARY

Fluconazole significantly increases risk of miscarriage, but not stillbirth

This nationwide cohort study, conducted using the Medical Birth Register in Denmark, evaluated more than 1.4 million pregnancies occurring from 1997 to 2013 for exposure to oral fluconazole between 7 and 22 weeks' gestation. Each oral fluconazole-exposed pregnancy was matched with up to 4 unexposed pregnancies (based on propensity score, maternal age, calendar year, and gestational age)

and to pregnancies exposed to intravaginal formulations of topical azoles. Exposure to fluconazole was documented based on filled prescriptions from the National Prescription Register. Primary outcomes were rates of spontaneous abortion (loss before 22 weeks) and stillbirth (loss after 23 weeks).

■ **Rates of spontaneous abortion.**

From the total cohort of more than 1.4 million pregnancies, 3315 were exposed to oral fluconazole between 7 and 22 weeks' gestation. Spontaneous abortions occurred in 147 of the 3315 fluconazole-exposed pregnancies and in 563 of 13,246 unexposed, matched pregnancies (hazard ratio [HR]=1.48; 95% confidence interval [CI], 1.23-1.77).

■ **Rates of stillbirth.** Of 5382 pregnancies exposed to fluconazole from week 7 to birth, 21 resulted in stillbirth; 77 stillbirths occurred in the 21,506 unexposed matched pregnancies (HR=1.32; 95% CI, 0.82-2.14). In a sensitivity analysis, however, higher doses of fluconazole (350 mg) were 4 times more likely to be associated with stillbirth (HR=4.10; 95% CI, 1.89-8.90) than lower doses (150 mg) (HR= 0.99; 95% CI, 0.56-1.74).

■ **Oral fluconazole vs topical azole.**

Use of oral fluconazole in pregnancy was associated with an increased risk of spontaneous abortion when compared to topical azole use: 130 of 2823 pregnancies vs 118 of 2823 pregnancies, respectively (HR=1.62; 95% CI, 1.26-2.07), but not an increased risk of stillbirths: 20 of 4301 pregnancies vs 22 of 4301 pregnancies, respectively (HR=1.18; 95% CI, 0.64-2.16).

WHAT'S NEW

A sizeable study with a treatment comparison

The authors found that exposure in early pregnancy to oral fluconazole, as compared to topical azoles, increases the risk of spontaneous abortion. By comparing treatments in a sensitivity analysis, the confounder of *Candida* infections causing spontaneous abortion was removed. In addition, when considering the ease of dosing of fluconazole as compared with topical imidazoles, this study challenges the balance of ease of use with safety.

CAVEATS

A skewed population and limited generalizability?

This large cohort study using the National Patient Register in Denmark may not be generalizable to a larger, non-Scandinavian population. Since a hospital registry was used, those not seeking care through the hospital were likely missed. If patients seeking care through the hospital had a higher risk of abortion, this may have biased the results. However, this would not have affected the results for the comparison between the 2 active treatments.

In addition, the study focused on women exposed from 7 to 22 weeks' gestation; the findings may not be generalizable to fluconazole exposure prior to 7 weeks. Likewise, the registry is unlikely to capture very early spontaneous abortions that are not recognized clinically. In all, given the large sample size and the care taken to match each exposed pregnancy with up to 4 unexposed pregnancies, these limitations are likely to have had little influence on the overall findings of the study.

CHALLENGES TO IMPLEMENTATION

Balancing ease of use with safety

Given the ease of using oral fluconazole vs daily topical azole therapy, many physicians and patients may still opt for oral treatment. **JFP**

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➤ Given the ease of using oral fluconazole vs daily topical azole therapy, many physicians and patients may still opt for oral treatment.

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