

Yeast Infection in Pregnancy? Think Twice About Fluconazole

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

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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.¹

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 the latter are recommended as firstline therapy, the ease of oral therapy makes it an attractive option.^{3,4}

However, the safety of oral flu-

conazole during pregnancy has recently come under scrutiny. Case reports have linked high-dose use with congenital malformation.^{5,6} These case reports led to epidemiologic studies in which no such association was found.^{7,8}

A large cohort study involving 1,079 fluconazole-exposed pregnancies and 170,453 unexposed pregnancies found no increased risk for congenital malformation 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 miscarriage.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 in early pregnancy is associated with increased rates of spontaneous abortion and stillbirth, compared to topical azoles.

STUDY SUMMARY

Increased risk for 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 four 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 by 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. Of the total cohort, 3,315 pregnancies were exposed to oral fluconazole between 7 and 22 weeks' gestation. Spontaneous abortion occurred in 147 of these pregnancies and in 563 of 13,246 unexposed, matched pregnancies (hazard ratio [HR], 1.48).

Rates of stillbirth. Of 5,382 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). In a sensitivity analysis, however, higher doses of fluconazole (350 mg) were four times more likely than lower doses (150 mg) to be associated with stillbirth (HRs, 4.10 and 0.99, respectively).

Oral fluconazole vs topical azole. Use of oral fluconazole in pregnancy was associated with an increased risk for spontaneous abortion, compared to topical

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azole use (130 of 2,823 pregnancies vs 118 of 2,823 pregnancies; HR, 1.62)—but not an increased risk for stillbirth (20 of 4,301 pregnancies vs 22 of 4,301 pregnancies; HR, 1.18).

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 for spontaneous abortion. By comparing treatments in a sensitivity analysis, the researchers were able to eliminate *Candida* infections causing spontaneous abortion as a confounding factor. In addition, this study challenges the balance between ease of use and safety.

CAVEATS

A skewed population?

This cohort study using a Danish hospital registry may not be generalizable to a larger, non-Scandinavian population. Those not seeking care through a hospital were likely missed; if those seeking care through the hospital had a higher risk for abortion, the results could be biased. However, this would not have affected the results of the comparison between the two 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 four unexposed pregnancies, these limitations likely had little influence on the overall findings.

CHALLENGES TO IMPLEMENTATION

Balancing ease of use with safety

Given the ease of using oral fluconazole, compared with daily topical azole therapy, many clinicians and patients may still opt for oral treatment.

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