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Treating UTIs in reproductive-age women—Proceed with caution

A new study suggesting that nitrofurantoin and sulfonamides are teratogenic highlights the need for a risk-benefit analysis when your patient is a woman of reproductive age.

PRACTICE CHANGER

Nitrofurantoin and sulfonamides may cause major birth defects and should be used with caution—if at all—in women of reproductive age.¹

STRENGTH OF RECOMMENDATION

B: Population-based case-control study

Crider KS, Cleves MA, Reefhuis J, et al. Antibacterial medication use during pregnancy and risk of birth defects: National Birth Defects Prevention Study. *Arch Pediatr Adolesc Med.* 2009;163:978-985.

ILLUSTRATIVE CASE

A 24-year-old woman comes to your clinic because of frequent urination for the past 2 to 3 days. She is not taking any medication, but does take a daily prenatal vitamin because she and her husband are trying to conceive. After your examination, you order a urinalysis and perform a urine pregnancy test. The urinalysis shows bacteriuria $\geq 100,000$ cfu/mL, and the pregnancy test is positive.

What will you prescribe to treat her urinary tract infection?

Antibacterial agents are among the most commonly used medications during pregnancy because treatment of infections is critical to both maternal and fetal well-being.¹ Urinary tract infections (UTIs) are the most common medical complication during pregnancy, with *Esch-*

erichia coli contributing to roughly 90% of the infections.² Screening for and treating asymptomatic bacteriuria is also recommended during pregnancy to prevent pyelonephritis and increased maternal and fetal morbidity.³ In addition, UTIs are common in reproductive-age women who may not know they are pregnant or who become pregnant during treatment with antibiotics. And nitrofurantoin and sulfonamides are commonly prescribed antibiotics for the treatment of UTIs, both in pregnant women and women of reproductive age.

Prior warnings only address near-term pregnancy

Prior to the study detailed in this PURL, no clinical trials had reported a teratogenic risk associated with either nitrofurantoin (current pregnancy category B) or sulfonamide (current pregnancy category C).⁴ It is recommended, however, that both of these antibacterials be avoided in pregnant women who are near term because of the risk of hemolytic disease in patients with glucose-6-phosphate dehydrogenase deficiency associated with nitrofurantoin and the risk of kernicterus in neonates exposed to sulfamethoxazole.⁵

But a rise in *E coli* resistance to penicillins (resistance to amoxicillin, for example, can be as high as 30-40%⁶) has led to greater use of nitrofurantoin. The drug has been viewed as a safe and effective alternative treatment for UTIs

associated with *E coli*.⁷ Indeed, nitrofurantoin has been considered to be the preferred antibiotic for bacteriuria suppression, as both ampicillin and cephalosporins can interfere with the normal gastrointestinal flora. Thus, nitrofurantoin is used extensively in pregnant women. Sulfonamides are also prescribed for pregnant women, although not as frequently.^{7,8}

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and periconceptional smoking and/or alcohol use.

Nitrofurantoin was associated with anophthalmia or microphthalmos (adjusted odds ratio [AOR]= 3.7; 95% confidence

interval [CI], 1.1-12.2), hypoplastic left heart syndrome (AOR=4.2; 95% CI, 1.9-9.1), atrial septal defects (AOR=1.9; 95% CI, 1.1-3.4), and cleft lip with cleft palate (AOR=2.1; 95% CI, 1.2-3.9).

Sulfonamides were associated with anencephaly (AOR=3.4; 95% CI, 1.3-8.8), hypoplastic left heart syndrome (AOR=3.2; 95% CI, 1.3-7.6), coarctation of the aorta (AOR=2.7; 95% CI, 1.3-5.6), choanal atresia (AOR=8.0; 95% CI, 2.7-23.5), transverse limb deficiency (AOR=2.5; 95% CI, 1.0-5.9), and diaphragmatic hernia (AOR=2.4; 95% CI, 1.1-5.4).

Some links between other antibiotics and birth defects were also found. For example, erythromycins were associated with anencephaly and transverse limb deficiency, penicillins with intercalary limb deficiency, and cephalosporins with atrial septal defects. The authors noted, however, that these agents, which are commonly prescribed for pregnant women, were not associated with many birth defects—and that because of limited sample sizes for these drug classes, the associations may be spurious.

STUDY SUMMARY

First trimester use linked to many defects

The study by Crider et al¹ was based on the National Birth Defects Prevention Study, an ongoing, population-based case control study of an estimated annual birth population of roughly 482,000, including cases identified by birth defects surveillance registries in 10 states.⁹ The researchers identified pregnancies affected by any of 30 types of birth defects from 1997 to 2003 (n=13,155). The controls (n=4941) were randomly selected from similar geographic locations, and matched for race/ethnicity, age, and prepregnancy body mass index. Exposure to antibacterials from 1 month prepregnancy through the end of the first trimester was recorded.

Crider et al interviewed all the participants up to 24 months after delivery to obtain their exposure history to penicillins, erythromycins, nitrofurantoin, sulfonamides, cephalosporins, quinolones, tetracyclines, other miscellaneous beta-lactams, aminoglycosides, antimycobacterial agents, and other antibiotics. (Exposure to antivirals, antifungals, and antiparasitic agents was not addressed.) Women who didn't know whether they had been exposed to these agents or could not remember the timing of exposure were excluded.

Overall, antibacterial use ranged from 2% to 5.8%, and peaked in the third month of pregnancy. Penicillins were the most commonly used antibiotics. Odds ratios obtained for birth defects were adjusted for confounders such as maternal age, race, education level, prepregnancy body mass index, time from estimated date of delivery to the interview, use of folic acid or multivitamins from 1 month prior to pregnancy through the first month,

WHAT'S NEW

A large-scale study provides evidence of risk

Previous case studies and meta-analysis have shown no link between the use of nitrofurantoin and congenital abnormalities.⁸ Similarly, sulfonamides have not appeared to pose significant teratogenic risk. This is the first large-scale study evaluating the risk of birth defects associated with antibiotic use during pregnancy, and therefore provides evidence of risk not previously available.

CAVEATS

Study design raises questions of recall bias

The retrospective case-control methodology used in this study leaves open the possibility of recall bias, misclassification bias, and

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QUESTION

Do you prescribe nitrofurantoin for UTIs in women of reproductive age?

- Frequently; it is safe and effective for infections associated with *E coli*
- Only after ruling out pregnancy
- For most women, except those who are pregnant and near term
- Infrequently; I usually choose a cephalosporin instead
- Other _____

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confounding bias. The length of time from actual exposure to data collection could affect the accuracy of participants' memories. The data gathered were not cross-verified against medical records, and other issues, such as the possible effect of medications for other infections (eg, antivirals and antifungals), could not be measured. However, women who did not know or were unsure of their medication exposure history were excluded from the analysis, which should reduce the risk of this potential bias.

The investigators also controlled for several important sources of potential confounding bias, and the reporting rates were similar among participants in both the case and control groups. These measures provide some assurance that the outcomes are valid.

It would be unethical (and extraordinarily expensive) to conduct a prospective randomized controlled trial to confirm these findings. Case-control methodology is the most practical way to assess for the risk of birth defects, and our literature review suggests that this is the most rigorous study to date. In our view, the potential harm from continuing to use these antibiotics for pregnant women and women who may become pregnant far outweighs the risk that these findings may be erroneous.

That said, a final caveat is the fact that even a several-fold increase in the risk of a rare major

birth defect such as those reported in this study is still a rare risk. There may be clinical situations in which the benefits of using nitrofurantoin or sulfonamides in women who are or may become pregnant outweigh the potential risks.

CHALLENGES TO IMPLEMENTATION

Finding an alternative treatment

The main challenge to implementing this new recommendation lies in choosing alternative antibiotics with which to treat UTIs in reproductive-age women and bacteriuria in pregnancy. Obtaining a pregnancy test in sexually active patients of reproductive age who are not using a reliable form of contraception seems like a prudent first step.

If the pregnancy test is positive, cephalexin should be a good initial choice until the results of culture and sensitivities are available. In the event of *Enterococcus* infection (for which cephalosporins are not active) or other organisms resistant to cephalosporins, the sensitivity results should provide guidance.³ **JFP**

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ERRATUM

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