Which antibiotics should be used with caution in pregnant women with UTI?

Nitrofurantoin and trimethoprim-sulfamethoxazole have study data indicating their teratogenicity, and ACOG has recommended against use of these 2 agents in the first trimester of pregnancy unless other antibiotics are unlikely to be effective. Despite this recommendation, a recent large commercial database study indicated that 43% of women were prescribed nitrofurantoin or trimethoprim-sulfamethoxazole in their first trimester. These agents should be used with caution during the early part of pregnancy.

FAST TRACK

One goal of treating bacteriuria and cystitis is to prevent ascending infection (pyelonephritis); another is to use an antibiotic that eradicates the uropathogen without causing harm to the mother or fetus

Ailes EC, Summers AD, Tran EL, et al. Antibiotics dispensed to privately insured pregnant women with urinary tract infections—United States, 2014. MMWR Morb Mortal Wkly Rep. 2018;67(1):18–22.

EXPERT COMMENTARY

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Lower urinary tract infection (UTI) is one of the most common medical complications of pregnancy. Approximately 5% to 10% of all pregnant women have asymptomatic bacteriuria, which usually antedates the pregnancy and is detected at the time of the first prenatal appointment. Another 2% to 3% develop acute cystitis during pregnancy. The dominant organisms that cause lower UTIs in pregnant women are *Escherichia coli, Klebsiella pneumoniae, Proteus* species, group B streptococci, enterococci, and *Staphylococcus saprophyticus*.

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One goal of treating asymptomatic bacteriuria and acute cystitis is to prevent ascending infection (pyelonephritis), which can be associated with preterm delivery, sepsis, and adult respiratory distress syndrome. Another key goal is to use an antibiotic that eradicates the uropathogen without causing harm to either the mother or fetus.

In 2009, Crider and colleagues reported that 2 of the most commonly used antibiotics for UTIs, sulfonamides and nitrofurantoin, were associated with a disturbing spectrum of birth defects.[1] Following that report, in 2011 the American College of Obstetricians and Gynecologists (ACOG) published a committee opinion that recommended against the use of these 2 agents in the first trimester of pregnancy unless other antibiotics were unlikely to be effective.[2]

Details of the study

Centers for Disease Control and Prevention investigators recently conducted a study to assess the effect of these ACOG recommendations on clinical practice. Ailes and coworkers used the Truven Health MarketScan

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Commercial Database to examine antibiotic prescriptions filled by pregnant women with UTIs.

The database included 482,917 pregnancies in 2014 eligible for analysis. A total of 7.2% (n = 34,864) of pregnant women were treated as outpatients for a UTI within the 90-day interval before the last menstrual period or during the pregnancy. Among these women, the most commonly prescribed antibiotics during the first trimester were nitrofurantoin (34.7%), ciprofloxacin (10.5%), cephalexin (10.3%), and trimethoprim-sulfamethoxazole (7.6%).

The authors concluded that 43% of women used an antibiotic (nitrofurantoin or trimethoprim-sulfamethoxazole) in the first trimester that had potential teratogenicity, despite the precautionary statement articulated in the ACOG committee opinion.[2]

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Pending the publication of additional investigations, I believe that the guidance outlined below is prudent.

Trimethoprim-sulfamethoxazole should not be used for treating UTIs in the first trimester of pregnancy unless no other antibiotic is likely to be effective. This drug also should be avoided just prior to expected delivery because it can displace bilirubin from protein-binding sites in the newborn and increase the risk of neonatal jaundice.

There may be instances in which trimethoprim-sulfamethoxazole should be used even early in pregnancy, such as to provide prophylaxis against *Pneumocystis jiroveci* infection in women with human immunodeficiency virus.

To exercise an abundance of caution, I recommend that nitrofurantoin not be used in the first trimester of pregnancy unless no other antibiotic is likely to be effective.

Alternative antibiotics that might be used in the first trimester for treatment of UTIs include ampicillin, amoxicillin, cephalexin, and amoxicillin-clavulanic acid. Substantial evidence supports the safety of these antibiotics in early pregnancy. Unless no other drug is likely to be effective, I would not recommend use of a quinolone antibiotic, such as ciprofloxacin, because of concern about the possible injurious effect of these agents on cartilaginous tissue in the developing fetus.

Neither trimethoprim-sulfamethoxazole nor nitrofurantoin should be used at any time in pregnancy in a patient who has glucose-6-phosphate dehydrogenase deficiency or who may be at increased risk for this disorder.[2]

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Antibiotic-associated effects

Of all the antibiotics that could be used to treat a lower UTI in pregnancy, nitrofurantoin probably has the greatest appeal. The drug is highly concentrated in the urine and is very active against all the common uropathogens except *Proteus* species. It is not absorbed significantly outside the lower urinary tract, and thus it does not alter the natural flora of the bowel or vagina (such alteration would predispose the patient to antibiotic-associated diarrhea or vulvovaginal candidiasis). Nitrofurantoin is inexpensive and usually is very well tolerated.

In the National Birth Defects Prevention Study by Crider and colleagues, 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).[1] Other investigations, including one published as recently as 2013, have not documented these same associations.[3]

Similarly, the combination of trimethoprim-sulfamethoxazole also has considerable appeal for treating lower UTIs in pregnancy because it is highly active against most uropathogens, is inexpensive, and usually is very well tolerated. The report by Crider and colleagues, however, was even more worrisome with respect to the possible teratogenicity of this antibiotic.[1] The authors found that use of this antibiotic in the first trimester was associated with anencephaly (AOR, 3.4; 95% CI, 1.3–8.8), coarctation of the aorta (AOR, 2.7; 95% CI, 1.3–5.6), hypoplastic left heart (AOR, 3.2; 95% CI, 1.3–7.6), 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). Again, other authors, using different epidemiologic methods, have not found the same associations.[3]

Study strengths and weaknesses

The National Birth Defects Prevention Study by Crider and colleagues was a large,

well-funded, and well-designed epidemiologic study. It included more than 13,000 patients from 10 different states.

Nevertheless, the study had certain limitations.[4] The findings are subject to recall bias because the investigators questioned patients about antibiotic use *after*, rather than *during,* pregnancy. Understandably, the investigators were not able to verify the prescriptions for antibiotics by reviewing each individual medical record. In fact, one-third of study participants were unable to recall the exact name of the antibiotic they received. The authors did not precisely distinguish between single-agent sulfonamides and the combination drug, trimethoprim-sulfamethoxazole, although it seems reasonable to assume that the majority of the prescriptions were for the latter. Finally, given the observational nature of the study, the authors could not be certain that the observed associations were due to the antibiotic, the infection for which the drug was prescribed, or another confounding factor.

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