

## MOTHERISK UPDATE

Anna Sivojelezova    Adrienne Einarson, RN    Samar Shuhaiber, MSC    Gideon Koren, MD, FRCPC

## Trimethoprim-sulfonamide combination therapy in early pregnancy

### ABSTRACT

**QUESTION** One of my patients presented with bacteriuria early in her pregnancy. Urine culture was positive for *Escherichia coli*. I would like to prescribe a trimethoprim-sulfamethoxazole combination because it worked well for her in the past. What is known about the safety of this medication during early pregnancy?

**ANSWER** Evidence-based studies report an association between trimethoprim-sulfonamide combinations in early pregnancy and several major malformations, such as neural tube defects and cardiovascular defects. If clinically possible, physicians are advised to use alternative antimicrobial medications for treatment of urinary tract infections during early pregnancy.

### RÉSUMÉ

**QUESTION** L'une de mes patientes présente une bactériurie en début de grossesse. La culture d'urine démontre la présence d'*Escherichia coli*, j'aimerais lui prescrire une association triméthoprim-sulfaméthoxazole parce que cette thérapie s'est révélée fructueuse pour elle antérieurement. Que connaît-on de l'innocuité de ce médicament durant les premiers mois de grossesse?

**RÉPONSE** Des études fondées sur des données scientifiques signalent un lien entre l'association triméthoprim-sulfaméthoxazole au début de la grossesse et plusieurs malformations majeures comme des défauts du tube neural et cardiovasculaires. S'il est cliniquement possible, on conseille aux médecins d'utiliser d'autres médicaments antimicrobiens pour le traitement des infections aux voies urinaires au début de la grossesse.

Urinary tract infections (UTIs) are common among pregnant women. Untreated UTIs can progress to acute pyelonephritis and other ascending infections. There is a link between untreated genitourinary infections in pregnancy and premature labour that could be explained by the cytokines and prostaglandins released by microorganisms.<sup>1</sup> In the United States, 40% of preterm deliveries are thought to be the result of infections.<sup>1</sup> The goal of treating genitourinary

infections during pregnancy is to administer appropriate antimicrobial medications to eradicate susceptible infection and to protect the developing fetus.

Trimethoprim-sulfonamide (TMP-SMX) combinations are used to treat a variety of infections caused by Gram-positive and Gram-negative bacteria. Trimethoprim-sulfonamide combinations have been widely indicated for acute and uncomplicated UTIs in women. Several European and American surveys on antibiotic use indicate that trimethoprim alone or TMP-SMX combinations are among the first-line treatments for UTIs.<sup>2,3</sup> Both trimethoprim and sulfonamide antibiotics inhibit

Do you have questions about the safety of drugs, chemicals, radiation, or infections in women who are pregnant or breastfeeding? We invite you to submit them to the Motherisk Program by fax at (416) 813-7562; they will be addressed in future Motherisk Updates. Published Motherisk Updates are available on the College of Family Physicians of Canada website ([www.cfpc.ca](http://www.cfpc.ca)). Some articles are published in *The Motherisk Newsletter* and on the Motherisk website ([www.motherisk.org](http://www.motherisk.org)) also.

Motherisk questions are prepared by the Motherisk Team at the Hospital for Sick Children in Toronto, Ont.

Ms Sivojelezova, Ms Einarson, and Ms Shuhaiber are members and Dr Koren is Director of the Motherisk Program.

Dr Koren, a Senior Scientist at the Canadian Institutes for Health Research, is supported by the Research Leadership for Better Pharmacotherapy during Pregnancy and Lactation and, in part, by a grant from the Canadian Institutes for Health Research.

nucleic acid synthesis by interfering with bacterial production of folic acid. Although trimethoprim and sulfonamide are highly specific to bacteria, several recent studies have suggested that folic acid antagonists taken during pregnancy are associated with increased risk of neural tube defects (NTDs) and other congenital defects.

A recent case-control study of birth defects in the United States and Canada reported that women giving birth to children with NTDs had an odds ratio (OR) of 2.8 (95% confidence interval [CI] 1.7-4.6) of having been exposed to TMP-SMX during early pregnancy compared with women giving birth to healthy children.<sup>4</sup>

Another case-control study of birth defects in Hungary examined the safety of TMP-SMX combinations during pregnancy.<sup>5</sup> A higher rate of trimethoprim-sulfamethazine and TMP-SMX use was reported among mothers of children with cardiovascular and multiple birth defects (OR 6.4, 95% CI 2.0-20.3 and OR 2.1, 95% CI 1.4-3.3, respectively). Treatment with TMP-SMX during the first month of pregnancy was associated with a significant increase in NTDs (OR 4.3, 95% CI 2.1-8.6). The study also reported that, when women receiving therapy with TMP-SMX were taking additional folic acid

supplementation of 6 mg/d, fewer of them had babies with birth defects (OR 1.87, 95% CI 1.25-2.77).

The Michigan Medicaid surveillance study found that, among 2296 children exposed to TMP-SMX combinations in utero, 37 (1.6%) babies developed cardiovascular defects (only 23 cardiac defects were expected).<sup>6</sup> Overall, there were 126 (5.5%) birth defects observed in this study (only 98 were expected). Other confounding factors, such as maternal age, disease, and other drug use, were not evaluated. Another large retrospective study, the Collaborative Perinatal Project, monitored 1455 mother-child pairs exposed to sulfonamides during the first trimester and found no association with any particular group of birth defects.<sup>7</sup>

In theory, sulfonamides should also be avoided after 32 weeks' gestation because of their associated toxicity in newborns. Sulfonamides could displace bilirubin from albumin-binding sites and could cause severe jaundice leading to kernicterus.<sup>8</sup> Practical evidence of this risk, however, is sparse. Acute hemolytic anemia is another complication that could occur in newborns with glucose-6-phosphate dehydrogenase deficiency.<sup>9</sup>

In summary, trimethoprim alone or TMP-SMX combinations should

be avoided if possible during the first trimester of pregnancy. Whenever clinically feasible, alternative antibiotics should be considered for treatment of UTIs. Other classes of antibiotics, such as penicillins, cephalosporins, nitrofurantoin, and macrolides, are relatively safe choices for treating bacterial infections during pregnancy.<sup>10</sup> If TMP-SMX is clinically required during the first month of pregnancy, a higher dose of folic acid (4 mg/d) should be given to prevent NTDs. ❖

#### References

1. Cram L, Zapata MI, Toy E, Baker B III. Genitourinary infections and their association with preterm labour. *Am Fam Physician* 2002;65(2):241-8.
2. Naber KG. Survey on antibiotic usage in the treatment of urinary tract infections. *J Antimicrob Chemother* 2000;46(Suppl 1):49-52.
3. Huang E, Stafford RS. National patterns in the treatment of urinary tract infections in women by ambulatory care physicians. *Arch Intern Med* 2002;162(1):41-7.
4. Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. Neural tube defects in relation to use of folic acid antagonists during pregnancy. *Am J Epidemiol* 2001;153(10):961-8.
5. Czeisel A, Rockenbaer M, et al. The teratogenic risk of trimethoprim-sulfonamides: a population based case-control study. *Reprod Toxicol* 2001;15:637-46.
6. Michigan Medicaid surveillance study.
7. Heinonen OP, Slone D, Shapiro S. *Birth defects and drugs in pregnancy*. Littleton, Md: Publishing Sciences Group; 1977.
8. Dunn PM. The possible relationship between the maternal administration of sulphamethoxypyridazine and hyperbilirubinaemia in the newborn. *J Obstet Gynaecol Br Commonw* 1964;71:128-31.
9. Perkins RP. Hydrops fetalis and stillbirth in a male glucose-6-phosphate dehydrogenase-deficient fetus possibly due to maternal ingestion of sulfisoxazole. *Am J Obstet Gynecol* 1971;111:379-81.
10. Einarson A, Shuhaiber S, Koren G. effects of antibacterials on the unborn child. *Paediatr drugs* 2001;3(11): 803-16.