# Urinary tract infections in pregnancy

Monica Lee RPh Pina Bozzo Adrienne Einarson RN Gideon Koren MD FRCPC

ABSTRACT

**QUESTION** My pregnant patients often present with urinary tract infections. Are the medications commonly used for the management of urinary tract infections safe to use during pregnancy?

**ANSWER** Existing data indicate that exposure to penicillins, cephalosporins, fluoroquinolones, nitrofurantoin, or phenazopyridine during pregnancy is not associated with increased risk of fetal malformations. Trimethoprim-sulfamethoxazole should be avoided, if possible, during the first trimester of pregnancy because of the antifolate effect associated with neural tube defects.

RÉSUMÉ

**QUESTION** Il arrive souvent que mes patientes enceintes présentent une infection des voies urinaires. Les médicaments utilisés couramment pour la prise en charge des infections des voies urinaires sont-ils sans risque durant la grossesse?

**RÉPONSE** Les données les plus récentes indiquent que l'exposition à la pénicilline, à la céphalosporine, au fluoroquinolone, à la nitrofurantoïne ou à la phénazopyridine durant la grossesse n'est pas associée à un risque accru de malformations fœtales. Il faudrait éviter dans la mesure du possible le triméthoprime-sulfaméthoxazole durant le premier trimestre en raison de son effet qui est de contrer l'acide folique, associé à des anomalies du tube neural.

Urinary tract infections (UTIs) are a common complication of pregnancy. Symptomatic UTI occurs in 1% to 2% of pregnancies, while asymptomatic bacteriuria has been reported in 2% to 13% of pregnant women.[1] Several anatomical and hormonal changes in pregnant women lead to ureteral dilatation and urinary stasis,[2] which contribute to the increased risk of developing UTIs. Untreated UTIs can lead to complications, such as pyelonephritis, low-birth-weight infants, premature delivery, and, occasionally, stillbirth[3]; therefore, prompt treatment of symptomatic UTIs and asymptomatic bacteriuria is warranted in pregnant women.

## Penicillins

Penicillins, such as amoxicillin, are commonly prescribed for the treatment of UTIs. The Collaborative Perinatal Project monitored 3546 mothers who were exposed to penicillin derivatives during their first trimesters, and 7171 mothers who were exposed at any time during their pregnancies. There was no increase noted in the rate of malformations.[4] The Michigan Medicaid surveillance study found that among 8538 newborns exposed to amoxicillin during the first trimester, a total of 317 (3.7%) major birth defects were observed, which is within the population risk.[5]

## Cephalosporins

Cephalosporins are alternative antibiotics for treating UTIs. Cephalexin is among the most commonly prescribed oral cephalosporin for this indication.[3] In the Michigan Medicaid surveillance study, a total of 176 (4.9%) major birth defects were observed (154 expected) among the 3613 newborns exposed to cephalexin during the first trimester.[5] The results of a Hungarian case-control study did not indicate human teratogenic potential for oral cephalexin.[6]

## Fluoroquinolones

Fluoroquinolones are also commonly prescribed for the treatment of UTIs, and include norfloxacin and ciprofloxacin. Concerns regarding the safety of this class of drugs originated from reports of arthropathy in animal studies[7]; such reports are rare in human cases.[8,9] Nevertheless, the safety of these drugs in pregnancy has been explored in a number of studies.[10-15] Based on existing data, fluoroquinolone exposure during human gestation is not associated with increased risk of major malformations, adverse effects in the fetal musculoskeletal system, spontaneous abortions, prematurity, intrauterine growth retardation, or postnatal disorders. However, because of the relatively higher cost of these agents and the concern about the emergence of antibiotic-resistant pathogens with frequent use, fluoroquinolones should not routinely be employed as first-line agents in uncomplicated UTIs.

## Nitrofurantoin

Numerous studies have demonstrated the safety of nitrofurantoin in pregnancy. Case-control studies and case

← FOR PRESCRIBING INFORMATION SEE PAGE 914

series involving thousands of women who received nitrofurantoin in pregnancy reported no increase in major malformations among the newborns.[5,16,17] In addition, a meta-analysis conducted by Motherisk failed to show teratogenic risk with first-trimester use of nitrofurantoin.[18] The drug can theoretically induce hemolytic anemia in the fetus or newborn, particularly in those with glucose-6-phosphate dehydrogenase deficiency; however, cases of this toxicity are rare.[19,20]

## Phenazopyridine

Phenazopyridine is used to relieve UTI symptoms, such as burning, pain, urgency, and frequency, associated with irritation of the lower urinary tract caused by infection. The Collaborative Perinatal Project monitored 219 women with first-trimester exposure and 1109 women with exposure at any time during pregnancy. There was no increase in the rates of major malformations or any other adverse effects.[4]

## Trimethoprim–sulfamethoxazole

Trimethoprim-sulfamethoxazole (TMP-SMX) combination is widely used to treat UTIs. Sulfonamides as a group do not appear to pose a serious teratogenic risk[21]; however, trimethoprim is a folic acid antagonist and its use during the first trimester has been associated with structural defects, such as neural tube and cardiovascular defects. A detailed review of this drug was published in a previous Motherisk Update.[22] Whenever clinically feasible, trimethoprim alone or TMP-SMX combinations should be avoided during the first trimester of pregnancy. Also, sulfamethoxazole can persist in neonatal circulation for several days after delivery if taken near term. There is a theoretical risk of sulfonamides increasing unbound bilirubin owing to competitive protein binding[21]; however, there have been no reports in the literature of this actually occurring. As other drugs are available and there is potential toxicity to the newborn, TMP-SMX should be avoided after 32 weeks of gestation.[22]

## Conclusion

Urinary tract infections during pregnancy can lead to serious consequences if left untreated. Antibiotics commonly used for this condition have not been found to be associated with an increased risk of birth defects when used during pregnancy. Using products containing trimethoprim is discouraged during the first trimester, and sulfonamides should be avoided in late pregnancy.

**Competing interests**

*None declared*

**References**

1. Dwyer PL, O'Reilly M. Recurrent urinary tract infection in the female. *Curr Opin Obstet Gynecol* 2002;14(5):537-43.
2. Le J, Briggs GG, McKeown A, Bustillo G. Urinary tract infections during pregnancy. *Ann Pharmacother* 2004;38(10):1692-701. Epub 2004 Aug 31.
3. Christensen B. Which antibiotics are appropriate for treating bacteriuria in pregnancy? *J Antimicrob Chemother* 2000;46(Suppl 1):29-34.
4. Heinonen OP, Slone D, Shapiro S. *Birth defects and drugs in pregnancy.* Littleton, MA: Publishing Sciences Group; 1977. p. 297-313, 435.
5. Briggs GG, Freeman RK, Yaffe SJ. *Drugs in pregnancy and lactation*. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005. p. 74, 268, 1153.
6. Czeizel AE, Rockenbauer M, Sørensen HT, Olsen J. Use of cephalosporins during pregnancy and in the presence of congenital abnormalities: a population-based, case-control study. *Am J Obstet Gynecol* 2001;184(6):1289-96.
7. Ingham B, Brentnall DW, Dale EA, McFadzean JA. Arthropathy induced by antibacterial fused *N*-alkyl-4-pyridone-3-carboxylic acids. *Toxicol Lett* 1977;1:21–6.
8. Chevais MP, Reinert P, Rondeau MC, Tobelem R, Albengres E, Riant P, et al. Critical risk/benefit analysis of pefloxacine use in children under 15 years—the problem of arthralgias. *Int J Clin Pharmacol Ther Toxicol* 1987;25(6):306–9.
9. Chysky V, Kapila K, Hullmann R, Arcieri G, Schacht P, Echlos R. Safety of ciprofloxacin in children: worldwide clinical experience based on compassionate use. Emphasis on joint evaluation. *Infection* 1991;19(4):289–96.
10. Berkovitch M, Pastuszak A, Gazarian M, Lewis M, Koren G. Safety of the new quinolones in pregnancy. *Obstet Gynecol* 1994;84(4):535-8.
11. Pastuszak A, Andreou R, Schick B, Sage S, Cook L, Donnenfeld A, et al. New postmarketing surveillance data supports a lack of association between quinolone use in pregnancy and fetal and neonatal complications. *Reprod Toxicol* 1995;9:584.
12. Schaefer C, Amoura-Elefant E, Vial T, Ornoy A, Garbis H, Robert E, et al. Pregnancy outcome after prenatal quinolone exposure. Evaluation of a case registry of the European Network of Teratology Information Services (ENTIS). *Eur J Obstet Gynecol Reprod Bio* 1996;69(2):83-9.
13. Loebstein R, Addis A, Ho E, Andreou R, Sage S, Donnenfeld AE, et al. Pregnancy outcome following gestational exposure to fluoroquinolones: a multicenter prospective controlled study. *Antimicrob Agents Chemother* 1998;42(6):1336-9.
14. Wilton LV, Pearce GL, Mann RD. A comparison of ciprofloxacin, norfloxacin, ofloxacin, azithromycin and cefixime examined by observational cohort studies. *Br J Clin Pharmacol* 1996;41(4):277-84.
15. Larsen H, Nielsen GL, Schønheyder HC, Olesen C, Sørensen HT. Birth outcome following maternal use of fluoroquinolones. *Int J Antimicrob Agents* 2001;18(3):259-62.
16. Hailey FJ, Fort H, Williams JC, Hammers B. Foetal safety of nitrofurantoin macrocrystals therapy during pregnancy: a retrospective analysis. *J Int Med Res* 1983;11(6):364-9.
17. Czeizel AE, Rockenbauer M, Sørensen HT, Olsen J. Nitrofurantoin and congenital abnormalities. *Eur J Obstet Gynecol Reprod Biol* 2001;95(1):119-26.
18. Ben David S, Einarson T, Ben David Y, Nulman I, Pastuszak A, Koren G. The safety of nitrofurantoin during the first trimester of pregnancy: meta-analysis. *Fundam Clin Pharmacol* 1995;9(5):503-7.
19. Gait JE. Hemolytic reactions to nitrofurantoin in patients with glucose-6-phasephate dehydrogenase deficiency: theory and practice. *DICP* 1990;24(12):1210-3.
20. Bruel H, Guillemant V, Saladin-Thiron C, Chabrolle JP, Lahary A, Poinsot J. [Hemolytic anemia in a newborn after maternal treatment with nitrofurantoin at the end of pregnancy.] *Arch Pediatr* 2000;7(7):745-7. French.
21. Sulfamethoxazole/trimethoprim [Product Monograph]. In: Repchinsky C, Editor-in-Chief. *Compendium of pharmaceuticals and specialties. The Canadian drug reference for health professionals.* Ottawa, ON: Canadian Pharmacists Association; 2007. p. 2254-8.
22. Sivojelezova A, Einarson A, Shuhaiber S, Koren G. Trimethoprim-sulfonamide combination therapy in early pregnancy. *Can Fam Physician* 2003;49:1085-6.

MOTHERISK

Motherisk questions are prepared by the Motherisk Team at the Hospital for Sick Children in Toronto, Ont. **Ms Lee** is a doctoral candidate in the Faculty of Pharmacy at the University of Toronto. **Ms Bozzo** is a member of the Motherisk Program. **Ms Einarson** is Assistant Director and **Dr Koren** is Director of the Motherisk Program. **Dr Koren** is supported by the Research Leadership for Better Pharmacotherapy during Pregnancy and Lactation. He holds the Ivey Chair in Molecular Toxicology at the University of Western Ontario in London.

Do you have questions about the effects 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**) and also on the Motherisk website (**www.motherisk.org**).