DRUGS, PREGNANCY, AND LACTATION

Treatment of Lower Urinary Tract Disorders

Lower urinary tract disorders are common in women and, among other risk factors, increase with age and a history of previous pregnancies. These disorders include incontinence, painful bladder syndrome, urinary frequency (overactive bladder), painful bladder syndrome, and bacterial cystitis.

BY GERALD G. BRIGGS, B.PHARM., FCCP

Although most of these disorders occur in later years and do not involve a pregnant patient, women are at risk for these complications throughout their reproductive years.

Exposure of the embryo or fetus can occur if a woman becomes pregnant during treatment or if she is treated in a known or unknown pregnancy. Moreover, drug treatment can occur during lactation and expose a nursing infant to the therapy. The probability of pregnancy and lactation exposure has increased as more women have delayed starting a family until later years. Thus, the treatment of lower urinary tract disorders must take into account the possible presence of an embryo, a fetus, or a nursing infant.

Several drugs are available to treat urinary tract disorders; however, few have been studied in pregnancy or during breastfeeding. Nevertheless, these agents do not appear to pose a significant risk to the embryo, fetus, or nursing infant. The agents most commonly used can be categorized into five primary pharmacologic subclasses: anti-infectives for acute bladder infections, urinary germicides, analgesics, anticholinergics (antispasmodics), and cholinergics. The Food and Drug Administration risk categories for the drugs are shown in brackets below (no category designation is provided if the drug has not been rated).

Nearly all anti-infectives used to treat bacterial cystitis are compatible in pregnancy and lactation. These include the penicillins [all B], cephalosporins [all B], aminoglycosides [C or D], sulfonamides [C], and fosfomycin (Monurol) [B]. Tetracyclines [D] should be avoided in pregnancy, but they are compatible with nursing, and sulfonamides should be avoided near term because of the theoretical risk of kernicterus. If sulfonamides are combined with trimethoprim (such as in Bactrim and Septra) [C], concurrent folic acid (such as in most prenatal vitamins) must be taken because trimethoprim is a folate antagonist. Its first-trimester use without the vitamin has been associated with cardiovascular defects, neural tube defects, and possibly oral clefts.

Urinary germicides include cinoxacin (Cinobac) [C], methenamine [C], nalidixic acid (NegGram) [C], and nitrofurantoin (Macrodantin) [B]. These agents are used for prophylaxis or suppression/elimination of recurring urinary tract infections when long-term therapy is required. All are compatible with breastfeeding. Cinoxacin and nalidixic acid are quinolones that have little or no data regarding use in pregnancy. Either agent is probably low risk for use in gestation, but one study did find an association between third-trimester nalidixic acid exposure and pyloric stenosis (Int. J. Gynecol. Obstet. 2001;73:221-8), but confirming studies have not appeared.

Methenamine, either as the mandelate or hippurate salt, is an old drug that is now rarely used in pregnancy. One surveillance study, but not another, found an association with congenital anomalies. Reports confirming the association have not been located. Methenamine is broken down in the urine (not in serum) to ammonia and the active agent formaldehyde.

Among the germicides, nitrofurantoin has the most human pregnancy data. No apparent embryo or fetal risk has been found when used throughout gestation except near term. Use near term has been associated with rare cases of hemolytic anemia in newborns with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Newborns without G6PD deficiency also are at risk because of immature erythrocyte enzyme systems (glutathione instability). Although the manufacturer states that the drug is contraindicated at term (38-42 weeks), many physicians will stop the drug at 36 weeks.

Urinary analgesics are used for symptomatic relief of pain in the lower urinary tract mucosa (phenazopyridine [Pyridium]) [B] and interstitial cystitis (pentosan [Elmiron]) [B]. The human data for phenazopyridine are limited, but there is no evidence that this drug produces toxicity in the embryo or fetus. Although there is no information about its excretion into breast milk, its properties suggest that at least some will be excreted. Phenazopyridine is a dye and will impart an orange-red tinge to urine and, probably, milk.

Pentosan is a low-molecular-weight heparinoid compound that has anticoagulant and fibrinolytic effects. The only reported human pregnancy experience involved eight women given an intravenous dose in the second trimester immediately before undergoing elective abortion. Anticoagulant effects were noted in the mothers but not in the cord blood of the fetuses before abortion. The data suggest that fetal exposure is nil, but the effects in the mothers have little relevance because the drug is available only as an oral capsule and absorption is very low (about 3%). Breastfeeding probably is compatible because of the low systemic concentrations.

There are seven anticholinergics that are used as antispasmodics for the treatment of overactive bladder: darifenacin (Enablex) [C], fesoterodine (Toviaz) [C], flavoxate (Urispas) [B], oxybutynin (Ditropan) [B], solifenacin (Vesicare) [C], tolterodine (Detrol) [C], and trospium (Sanctura) [C]. There are either limited or no human pregnancy data for these agents. However, except for solifenacin, the animal data suggest low risk. Moreover, an association with structural anomalies and other aspects of developmental toxicity has not been found with any anticholinergic agent. Although there are also no human data regarding the excretion of these drugs into breast milk, the American Academy of Pediatrics classifies the prototype anticholinergic atropine as compatible with breastfeeding. There is no reason to believe that the seven agents would be classified differently. The only potential exception is tolterodine because it has an equipotent active metabolite.

The cholinergics oral bethanechol (such as Urecholine) [C] and injectable neostigmine (Prostigmin) [C] are used for urinary retention, and bethanechol is used for postpartum nonobstructive urinary retention. Bethanechol also is used off label for the treatment of reflux esophagitis. The reported human pregnancy experience with bethanechol is very limited, and the drug has not undergone reproductive testing in animals. Use of the drug in pregnancy is probably low risk, but the absence of human data prevents a better risk assessment. Short-term use during breastfeeding probably is compatible.

Although intramuscular or subcutaneous injections of neostigmine are used for urinary retention and off label to stimulate the bowel, nearly all of the pregnancy data come from its use for symptomatic control of myasthenia gravis. It also has no relevant animal reproductive data but is considered low risk in pregnancy. It has not been studied during human lactation but probably is compatible with breastfeeding.

Taken in sum, the agents used for lower urinary tract disorders exhibit little potential risk for the embryo, fetus, or nursing infant. Nevertheless, their use should be confined to short intervals because, with few exceptions, most have little or no reported human pregnancy or breastfeeding experience. ■

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Maternal Obesity Linked to Fetal Structural Anomalies

BY MARY ANN MOON

Maternal obesity is associated with a significantly increased risk of fetal structural anomalies, including neural tube defects and cardiac malformations, according to a meta-analysis.

The risk for some of these anomalies also was elevated among women who were overweight but not obese. Future studies should investigate whether there is a dose-response relationship between maternal weight and risk of structural abnormalities, said Katherine J. Stothard, Ph.D., and her associates at Newcastle University, Newcastle upon Tyne, England (JAMA 2009;301:636-50).

The researchers reviewed 39 relevant articles in the English literature and performed a meta-analysis of 18 of those that were the most scientifically sound, excluding studies with fewer than 150 cases of a particular congenital anomaly and studies of abnormalities that were chromosomal or syndromic in origin.

The investigators included cases in which pregnancies were terminated when congenital anomalies were discovered.

Compared with mothers at recommended body weights, obese mothers were nearly twice as likely to have a pregnancy affected by neural tube defects, including spina bifida and anencephaly. Their risk ranged from 1.2 to 1.7 times to have a fetus with a cardiovascular anomaly such as a septal defect, a facial malformation such as cleft palate or cleft lip, or other anomalies including anorectal atresia, hydrocephaly, and limb reduction.

Some types of anomalies could not be examined in this meta-analysis because the studies of those defects were not sufficiently powered to detect significant effects.

However, the literature review showed that the association with maternal obesity approached significance for omphalocele, craniosynostosis, and simultaneous multiple anomalies.

Both neural tube defects and cardiac anomalies also were more likely to occur in mothers who were overweight but not frankly obese. Future studies should assess structural congenital anomalies across "the complete range of [body mass index]," Dr. Stothard and her associates said.

"It is notable that many of the congenital anomalies implicated in this review have similar developmental timing and responsiveness to folic acid, suggesting a common underlying etiology," they added.

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