DRUGS, PREGNANCY, AND LACTATION

Drugs Approved in 2010

In 2010, the Food and Drug Administration approved 21 new chemical entities, 3 of which have human pregnancy data: polidocanol (Asclera; pregnancy risk category C), tocilizumab (Actemra; C), and velaglucerase alfa (VPRIV; B).

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Included in the classifications are three products that will not be discussed: estradiol valerate/dienogest (Natazia; X), a combination oral contraceptive; alglucosidase alfa (Lumizyme; B), a metabolic agent for Pompe disease that is nearly identical to Myozyme (same generic name); and a formulation of botulinum toxin type A (Xeomin; C). The latter two products are reviewed in the 9th edition (2011) of "Drugs in Pregnancy and Lactation" under alglucosidase alfa and botulinum toxin type A.

It is best to avoid prescribing new drugs for women of childbearing potential or during pregnancy, and to use older agents with human pregnancy experience. But what if the new drug is a major breakthrough or is the only or most efficacious drug to treat your patient's condition? How do you counsel the patient about a drug's risk to her embryo or fetus when there is little or no human pregnancy data? Fortunately, the package insert provides data for three of the four factors that can be used to give some estimate of risk: drug class, potential to cross the placenta, and animal data. Then, when your patient asks "What are the risks?" you don't have to say "We just don't know."

The new IV cephalosporin antibiotic, ceftaroline (Teflaro; B) is indicated for acterial skin infections and community-acquired bacterial pneumonia. It shares the benefits and risks of other cephalosporins and is compatible with pregnancy.

Dabigatran etexilate (Pradaxa; C) is a direct thrombin inhibitor used to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. The animal data suggest moderate risk. The drug probably crosses the human placenta, and uterine bleeding is a potential complication.

The antigout agent pegloticase (Krystexxa; C), a pegylated uric acid–specific enzyme, is given as an intravenous infusion every 2 weeks. The high molecular weight should prevent the enzyme from crossing the placenta.

An ophthalmic formulation, alcaftadine (Lastacaft; B) is used for itching associated with allergic conjunctivitis. It produces very low systemic levels and, as for all antihistamines, should be safe to use in a pregnant woman.

The antineoplastic agents are cabazitaxel (Jevtana; D) for prostate cancer and eribulin (Halaven; D) for metastatic breast cancer. Exposure to cabazitaxel is highly unlikely. Eribulin is given on days 1 and 8 of 21-day cycles; it is best avoided in pregnancy. The animal data suggest risk, and the properties of the drugs suggest that they will cross the placenta.

The antipsychotic, lurasidone (Latuda; B) is indicated for schizophrenia. The animal data suggest low risk, but the properties suggest that the drug will cross the placenta. As with similar agents, extrapyramidal symptoms and/or withdrawal are potential complications in newborns exposed during the third trimester. The benefits of maternal therapy with lurasidone might outweigh the risks but must be judged on a case-by-case basis.

There are no human pregnancy data on the two new agents for the treatment of multiple sclerosis, dalfampridine (Ampyra; C) and fingolimod (Gilenya; C). Dalfampridine is a potassium channel blocker indicated to improve walking, whereas the immunologic agent, fingolimod, is indicated to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability. Although the animal data for both agents suggest moderate risk, the maternal benefit will probably outweigh the unknown embryo-fetal risk. However, the mother should be informed of the lack of data.

The other two immunologic agents, both monoclonal antibodies, are denosumab (Prolia; C), indicated for postmenopausal women with osteoporosis, and tocilizumab (Actemra; C), indicated for rheumatoid arthritis. Denosumab will probably cross the placenta in the third trimester and should not be used in pregnancy. Tocilizumab caused abortion and embryo death in monkeys. The known pregnancy outcomes in 31 patients exposed to the drug were 7 spontaneous abortions, 13 elective abortions, 10 healthy term newborns, and 1 neonatal death of a term infant at 3 days of age. One reference recommends stopping tocilizumab 3 months before conception (Curr. Opin. Rheumatol. 2011;23:293-8).

Ulipristal (ella; X) is a new emergency contraceptive that can be taken up to 120 hours after unprotected intercourse. It acts by inhibiting or delaying ovulation, but also may alter the endometrium to prevent implantation.

Collagenase clostridium histolyticum (Xiaflex; B) is given intramuscularly for the treatment of Dupuytren's contracture with a palpable cord. Because it has not been detected in the systemic circulation, it poses no direct risk to a pregnancy. However, all patients develop antibodies against the drug and the effect of the antibodies on the embryo-fetus is unknown.

The three endocrine products are carglumic acid (Carbaglu; C) for treatment of hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS); tesamorelin (Egrifta; X) a growth hormone–releasing factor analog for reduction of excess abdominal fat in HIV-infected patients; and velaglucerase alfa (VPRIV; B) given for long-term enzyme replacement in patients with Gaucher disease. Daily doses of carglumic acid will be required if a woman is deficient in NAGS. The effect on the embryo-fetus is unknown, but the animal data suggest moderate risk. Tesamorelin is contraindicated in pregnancy because an increase in visceral adipose tissue is a normal metabolic and hormonal change. The animal data suggest moderate risk. There are human data for VPRIV, a drug given as an IV infusion every other week. Because it has the same amino acid sequence as the endogenous enzyme, it appears to be compatible with pregnancy.

The second metabolic agent is liraglutide (Victoza; C), given as daily subcutaneous injections to enhance insulin secretion in type 2 diabetics. Animal data suggest risk, but there are no human data. Nevertheless, insulin remains the standard for glucose control in pregnancy, and liraglutide is best avoided.

Polidocanol (Asclera; C), a sclerosing agent used to treat varicose veins in the lower extremity, has also been used during pregnancy for esophageal varices and for upper gastrointestinal bleeding due to Mallory-Weiss syndrome. In the fetus, polidocanol has been used for fetal intralobar bronchopulmonary sequestration and for congenital cystic adenomatoid malformation of the lung. In all of these cases, normal term outcomes were observed without apparent fetal harm. The drug has also has been used to treat varicoceles in infertile men and has enabled some of these men to father children.

The agents that should not be used during breastfeeding are the antineoplastics cabazitaxel and eribulin, carbaglu (which causes toxicity in nursing animals), and tesamorelin (which is used in HIV-infected patients). The other drugs appear to be compatible with breastfeeding, but infants should be closely monitored for signs and symptoms of toxicities commonly seen in adults. ■

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Epilepsy Drugs Seen Linked to Host of Pregnancy Risks

BY JENNIE SMITH

FROM BJOG: AN INTERNATIONAL JOURNAL OF OBSTETRICS AND GYNAECOLOGY

Pregnant women taking antiepileptic drugs have higher odds for preeclampsia, bleeding, labor induction, caesarean section, and major malformations of the newborn, Norwegian researchers have learned.

The findings add to mounting evidence that pregnancy risks for epileptic women may be linked to antiepileptic drugs (AEDs) rather than epilepsy itself.

Dr. Ingrid Borthen of Haukeland University Hospital, in Bergen, Norway, and her associates retrospectively compared obstetric outcomes for 205 deliveries by 170 women with a past or present history of epilepsy (57% of whom were taking AEDs) and 205 matched, nonepileptic control patients.

The women in both groups had a mean age of 28 years.

Epileptic women taking AEDs had higher odds of severe preeclampsia (odds ratio, 5.0; 95% confidence interval, 1.3-19.9), bleeding in early pregnancy (OR, 6.4; 95% CI, 2.7-15.2), labor induction (OR, 2.3; 95% CI, 1.2-4.3), c-section (OR, 2.5; 95% CI, 1.4-4.7), and malformations in the offspring (OR, 7.1; 95% CI, 1.4-36.6).

The comparisons of outcomes between the two groups were controlled for confounding factors, including smoking during pregnancy, mother's age, highest maternal education, parity, body mass index of 30 kg/m^2 or greater, diabetes and medical conditions, and previous caesarean section, bleeding, and preeclampsia on comparisons of birth outcomes, Dr. Borthen and her associates said.

Women with active epilepsy (defined as seizures within 5 years of conception) not using the drugs did not have increased odds for any of these outcomes; however, they did have higher odds for vaginal forceps delivery and preterm birth.

Which specific drugs may be implicated is still difficult to say, said Dr. Borthen, but the study showed that lamotrigine is associated with a higher risk (BJOG 2011 [doi: 10.1111/j.1471-0528.2011.03004.x]).

Dr. Borthen and her colleagues noted that the proportion of women using AEDs during pregnancy may represent a larger group than epileptic women, as there is "growing use of AEDs for pain and psychiatric conditions."

One limitation of the study, Dr. Borthen and her colleagues wrote in their analysis, was a lack of data on seizure type and severity.

The study was funded by the Norwegian Research Council. Dr. Borthen and her colleagues declared that they had no conflicts of interest. ■