Fetal Alcohol Linked To Childhood AML

BY ELIZABETH MECHCATIE

FROM CANCER, EPIDEMIOLOGY, BIOMARKERS & PREVENTION

Alcohol intake during pregnancy was associated with a significant increase in the risk of acute myeloid leukemia in children who were exposed during pregnancy, but not with an increased risk of acute lymphoblastic leukemia, in a review and meta-analysis of case-control studies from numerous countries.

VITALS

Major Finding: A significant positive association was identified between maternal consumption of alcohol during pregnancy and childhood AML, but not with childhood ALL, when compared with nonexposed controls.

Data Source: 21 case-control studies.

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The results "indicate that the risk of childhood AML increases with maternal alcohol consumption during pregnancy," reported Dr. Paule Latino-Martel of the University of Paris XIII and associates (Cancer Epidemiol. Biomarkers Prev. 2010;19:OF1-23).

This was the first meta-analysis the authors were aware of that investigated the role of in utero exposure to alcohol in relation to childhood leukemia. The studies had limitations, they said, and more studies with detailed information on alcohol exposure are needed.

The 21 studies included in the review comprised 20 different study populations, for a total of 8,128 cases and 10,207 controls. Because data collection varied among the studies, only relevant studies were included in categorical and dose-response meta-analyses.

A meta-analysis of nine studies found the significant positive association between maternal alcohol consumption during pregnancy and the risk of childhood acute myeloid leukemia (AML), with an odds ratio of 1.56. Maternal consumption of alcohol during pregnancy was not significantly associated with an increased risk of acute lymphoblastic leukemia (ALL), compared with no exposure.

A few studies included data that made it possible to do a dose-response analysis, which was "consistent with a stronger association with AML compared with ALL." An increase of one drink per week was associated with odds ratios of 1.04 for ALL and 1.24 for AML, but the authors said that the results were heterogenous, and no conclusions could be made about the amount of alcohol intake that was associated with an increased risk. More studies with more details on alcohol exposure are needed, they added.

Examining the data on childhood age, the authors found no association between maternal alcohol intake during pregnancy and ALL that was diagnosed at age 0-4 years. But the association between in utero exposure to alcohol and AML that was diagnosed in children aged 0-4 years was significant in five studies (OR, 2.68), which the authors said was "consistent with the potential role of prenatal exposure to alcohol in the etiology of AML."

"The biological plausibility of this association is supported by the fact that alcoholic beverages are recognized as carcinogenic for humans and are involved in several fetal alcohol-related diseases," they said. But the reason why in utero exposure to alcohol "may specifically modify the risk of AML in young children is unknown," the authors said. They pointed out that the peak of AML cases in children is earlier than that of ALL, which suggests "a stronger association or shorter latency of AML with prenatal exposures."

With little information in the studies on alcohol type, the authors were not able to determine whether maternal consumption of one type of alcohol over another (beer vs. wine vs. spirits) was associated with a greater risk of leukemia.

Based on a meta-analysis of studies that provided information on alcohol intake by trimester, the authors found no association between childhood ALL and alcohol consumption in any trimester. Data were limited for AML, but in the two studies that included this information, the odds ratio "tended to be slightly higher when alcohol was consumed in the second and third trimesters compared with the first trimester," they said. ■

DRUGS, PREGNANCY, AND LACTATION

Drugs Approved in 2009

BY GERALD G. BRIGGS, B.PHARM.

In 2009, the Food and Drug Administration approved 19 new chemical entities, and, except for 1, human pregnancy experience is lacking. The exception is vigabatrin, an antiepileptic drug (AED) that has been available for nearly 2 decades outside the United States.

As with any new drug, it is best to avoid prescribing these 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 the drug's risk to her embryo or fetus?

Fortunately, the package insert provides data for three of the four factors that can be used to estimate risk: drug class, potential to cross the placenta, and animal data.

The immunomodulators are canakinumab (Ilaris; pregnancy class C), indicated for cryopyrin-associated periodic syndrome, and golimumab (Simponi; B), indicated (with or without methotrexate) for ankylosing spondylitis, active psoriatic arthritis, or rheumatoid arthritis. The animal data for both agents suggest low risk. These two agents have long half-lives, 26 and 14 days, so fetal exposure is a potential complication.

Dronedarone (Multaq, X) is an antiarrhythmic agent that is indicated for patients with atrial fibrillation or atrial flutter. Major birth defects in rats and rabbits and embryo and fetal death in one species were observed at doses comparable to those used in humans. The effects of exposure after the first trimester are unknown.

Bepotastine (Bepreve; C), an antihistamine, and besifloxacin (Besivance; C), a quinolone antibiotic, are new ophthalmic products. Both have very low systemic bioavailability and low risk in animals, so they can be classified as low risk in pregnancy.

Telavancin (Vibativ; C), a synthetic derivative of vancomycin given intravenously, is indicated for complicated skin and skin structure infections resulting from gram-positive bacteria. The manufacturer states that pregnancy must be excluded because of limb shortening and polydactyly in three animal species. This drug does not appear to offer for the indication a clear advantage over other available antibiotics with pregnancy experience.

The animal data for vigabatrin (Sabril; C), an equal mixture of active and inactive enantiomers, suggest risk, as do the human data. However, in all of the reports, the agent was combined with first-generation antiepileptic drugs known to cause human birth defects. The contribution of vigabatrin to the toxicity cannot be determined until more data are available. For now, a more pressing concern is the vision loss, sometimes permanent, that occurs in a high percentage of those treated.

Milnacipran (Savella; C), a selective serotonin-norepinephrine reuptake inhibitor (SNRI), is the fourth antidepressant in this class, but is indicated for fibromyalgia. The fetal risks from SNRIs are primarily in the second half of pregnancy and include low birth weight, prematurity, and neonatal serotonin or behavioral syndromes. Using the lowest possible dose may reduce these toxicities.

The antigout agent, febuxostat (Uloric; C), caused no developmental toxicity at exposures equal to or less than 10 times the human exposure, so it can be listed as low risk.

Pitavastatin (Livalo, X) is another statin and, as with the other six agents in this class, is contraindicated in pregnancy.

The four antineoplastics are everolimus (Afinitor; D), a protein-tyrosine kinase inhibitor for advanced renal cell carcinoma; ofatumumab (Arzerra; C), a monoclonal antibody for chronic lymphocytic leukemia; pazopanib (Votrient; D), a tyrosine kinase inhibitor for advanced renal cell carcinoma; and romidepsin (Istodax; D), a histone deacetylase inhibitor for cutaneous T-cell lymphoma. Although there is a potential risk to the fetus with any antineoplastic agent, the maternal benefits from the first three drugs appear to outweigh the risks. However, romidepsin competes with estradiol for estrogen receptors and should be avoided in pregnancy.

Asenapine (Saphris, C) and iloperidone (Fanapt, C) are atypical antipsychotics (i.e., they have a reduced ability or an inability to cause extrapyramidal syndrome). Both drugs will probably cross the placenta, but there is no evidence that other atypicals cause embryo or fetal harm. Although the American College of Obstetricians and Gynecologists does not recommend routine use of atypicals, a risk-benefit assessment may indicate that such use is appropriate (Obstet. Gynecol. 2008;111:1001-19).

The hematologic agents are ecallantide (Kalbitor, C) for acute attacks of hereditary angioedema, a rare genetic disorder, and prasugrel (Effient, B) to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome who are to be managed with percutaneous coronary intervention. Ecallantide's properties suggest that exposure of the fetus will be low. A major concern, though, is the nearly 4% risk of anaphylaxis in patients. The prodrug prasugrel is not detected in plasma, but the active and inactive metabolites are and may cross the placenta. Nevertheless, the maternal benefit appears to outweigh any embryo or fetal risks.

Tolvaptan (Samsca, C) is a selective vasopressin receptor antagonist that is used to treat nonurgent, resistant symptomatic hyponatremia. Tolvaptan probably crosses the placenta, but the animal data suggest low risk.

Bepotastine, besifloxacin, ecallantide, golimumab, ofatumumab, prasugrel, telavancin, and vigabatrin appear to be compatible with breastfeeding, but there are human data only for vigabatrin. Everolimus, golimumab combined with methotrexate, pazopanib, and pitavastatin, should be classified as contraindicated. There is potential toxicity for a nursing infant from the other agents, but human data are needed to quantify the risks.

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