DRUGS, PREGNANCY, AND LACTATION

Do NSAIDs Cause Birth Defects?

BY GERALD G. BRIGGS, B.PHARM.

Both prescription and over-the-counter nonsteroidal anti-inflammatory drugs are frequently used in pregnancy, including during the first trimester. When used around the time of conception, there is evidence that NSAIDs impair fertility by interfering with blastocyst implantation, resulting in spontaneous abortions.

Exposure to these agents in the latter part of the second trimester and throughout the third is known to cause functional toxicity in the fetus and newborn consisting of renal impairment, oligohydramnios, premature closure of the ductus arteriosus, and primary pulmonary hypertension of the newborn. Increased risks for other toxicities—such as intraventricular hemorrhage, necrotizing enterocolitis, patent ductus arteriosus requiring ligation, platelet dysfunction, and gastrointestinal bleeding—have been reported in association with prenatal exposure to NSAIDs, but a causative role has not yet been proved.

When used in the first 3 months of gestation, there have been conflicting reports associating the use of NSAIDs with structural anomalies. However, a Canadian study published in September has strengthened the argument that NSAIDs can cause birth defects, particularly cardiac septal defects. In the following discussion, the evidence for and against this association is examined:

► A large observational cohort study conducted in Denmark compared the outcomes of 1,106 pregnancies exposed to NSAIDs in the first trimester with 17,529 controls and found no significant association between NSAID use during pregnancy and congenital defects (BMJ 2001;322:266-70). A weakness of this study was that it included only women who had received an NSAID prescribed at doses equivalent to 400 mg or 600 mg of ibuprofen. The study did not identify women who might have taken NSAIDs that were available as OTC products at doses equivalent to 200 mg of ibuprofen.

► A Food and Drug Administration analysis of Michigan Medicaid data on a large number of women exposed in the first trimester to three NSAIDs between 1985 and 1992 found no evidence of an increased risk of cardiac or orofacial defects for any of the drugs. There were 19 birth defects among the 258 women (7.4%) exposed to diflunisal, 143 birth defects among the 3,178 women (4.5%) exposed to ibuprofen, and 70 birth defects among the 1,448 women (4.8%) exposed to naproxen. These rates were higher than the expected number of birth defects (10, 129, and 62, respectively), but these types of studies only raise hypotheses and cannot show causation (Briggs GG, Freeman RK, Yaffe SJ. Drugs in Pregnancy and Lactation. 5th ed. Baltimore: Williams & Wilkins, 1998: ix).

► A 2001 prospective observational cohort study that examined the relationship between first-trimester exposure to NSAIDs in 2,557 women and congenital defects found no association with birth defects in general. However, significant associations with cardiac defects and orofacial clefts were noted: There were 36 cardiac defects, representing an odds ratio of 1.86, and 8 orofacial defects, an odds ratio of 2.81. Both were statistically significant increases over the expected rates (Reprod. Toxicol. 2001;15:371-5).

► A 2003 study using data from Swedish health registers of 1,142 infants with orofacial clefts (isolated or nonisolated) found a greater risk associated with naproxen exposure. Compared to the expected number (2.9), 8 of the infants had been exposed to naproxen, a relative risk of 2.72 (Cleft Palate Craniofac. J. 2003;40:624-8).

Another study identified 5,015 infants in the same registry with cardiovascular defects, and compared them with 577,730 controls, finding no significant association when all NSAIDs were grouped together or with individual agents, with the exception of naproxen. Among babies born to 1,679 naproxen-exposed women, 24 had cardiovascular defects, a statistically significant odds ratio of 1.7 (Reprod. Toxicol. 2003;17:255-61).

► A case-control study conducted in Quebec found a significant association between congenital anomalies, specifically cardiac septal defects, and the use of NSAIDs in the first trimester. Case infants were those with any congenital anomaly diagnosed in the first year of life, who were matched with up to 10 controls (infants without a congenital anomaly) for maternal age, urban or rural residence, gestational age, and diabetes status.

There were 93 infants (8.8%) with congenital anomalies born to 1,056 mothers who had filled prescriptions for NSAIDs in the first trimester. Among controls, there were 2,478 infants (7%) with anomalies born to 35,331 mothers. Among women who had filled a prescription for an NSAID during the first trimester, the adjusted odds ratio for any congenital anomaly was 2.21, and the adjusted odds ratio for cardiac septal closure was 3.34. Both odds ratios were statistically significant. There were no significant associations for oral clefts or defects involving other major organ systems.

The five NSAIDs most commonly used by these women were naproxen (35%), ibuprofen (26%), rofecoxib (15%), diclofenac (9%), and celecoxib (9%). The only statistically significant association was between ibuprofen prescriptions in the first trimester and congenital defects (Birth Defects Res. B. Dev. Reprod. Toxicol. 2006;77:268-79).

Taken in sum, the data from these studies provide increasingly convincing evidence that NSAIDs are human teratogens, especially for cardiac septal defects and, possibly, for orofacial clefts. Additional research is needed, but women who may become pregnant or are pregnant should be counseled regarding this possible risk. Importantly, they should be made aware that NSAIDs are available without a prescription and that although the OTC strength is lower than the strength of the prescription product, a safe dose has not been determined.

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Adalimumab Found to Be Safe in Pregnancy

BY MITCHEL L. ZOLER
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BERLIN — Treatment of pregnant women with the biologic immunomodulator adalimumab did not appear to adversely affect fetuses or pregnancies in preliminary data from a prospective study that currently includes 23 exposed pregnancies.

Limited data suggest that the use of these drugs during pregnancy does not lead to malformations, spontaneous abortions, or prematurity.

"The findings do not suggest an increased risk for adverse pregnancy outcomes with exposure to adalimumab early in pregnancy," Diana L. Johnson said at the 14th United European Gastroenterology Week.

Adalimumab (Humira) is a fully human antibody to tumor necrosis factor (TNF)–α, which gives it a mechanism of action like that of other biologic TNF-α inhibitors including etanercept (Enbrel), infliximab (Remicade), and certolizumab (Cimzia). To date, limited data suggest that the use of these drugs during pregnancy does not lead to malformations, spontaneous abortions, or prematurity, said Ms. Johnson, a toxicologist and study manager at the University of California, San Diego.

The data—from a larger study of autoimmune diseases in pregnancy that has been developed by the Organization of Teratology Information Specialists—so far include birth outcomes of 23 women who were treated with adalimumab early in pregnancy.

These women have had a total of 21 live births and two spontaneous abortions, Ms. Johnson reported at the meeting, sponsored by the United European Gastroenterology Federation. Of the 21 deliveries, 20 were term; the single premature birth involved an infant with congenital hip dysplasia.

Women with severe Crohn's disease who are on a successful anti-TNF regimen are usually advised to continue their medication if they become pregnant, although the pros and cons of ongoing treatment are discussed with them, commented Dr. Pia Munkholm, a gastroenterologist at Herlev Hospital in Copenhagen. "There is an incentive to keep these patients in remission," she said. ■

Few Women on Leflunomide Advised to Avoid Pregnancy

TUCSON, ARIZ. — Only 35% of women taking the category X medication leflunomide recall their rheumatologist advising them to avoid pregnancy at the time of refilling their prescription, results from a small survey indicate.

'Pregnancy prevention may require repeated reminders at prescription refill' from pharmacists and physicians.

MS. JOHNSON

"Pregnancy prevention may require repeated reminders at prescription refill, both from the pharmacists as well as from the prescribing physician," Diana Johnson said at the annual meeting of the Teratology Society.

She and her fellow associates conducted a phone survey of 20 women with rheumatoid arthritis who became pregnant while taking leflunomide, which is contraindicated in pregnancy.

Most of the women (75%) had been pregnant before, and 65% had at least one child prior to leflunomide exposure, said Ms. Johnson, of the department of pediatrics at the University of California, San Diego.

All women reported that they were advised to avoid pregnancy at the time they first received a prescription for leflunomide. But only 60% were using some form of birth control when they received the prescription, and only 35% recalled their rheumatologist's having advised them to avoid pregnancy at the time of refilling their prescription.

"At the time of conception, only 15% of survey respondents were using the most reliable form of birth control, and 65% were not using any form of birth control," Ms. Johnson said.

—Doug Brunk