DRUGS, PREGNANCY, AND LACTATION

Antibacterial Use in Pregnancy

Antibacterial medications are among the most commonly used in pregnancy. Despite decades of use in obstetric practice for some of these medications, large-scale studies of human teratogenicity have been lacking. In recent years, some of the gaps in knowledge about specific medications and risks for specific birth defects have been addressed by ongoing work being conducted through the National Birth Defects Prevention Study, a multisite U.S. population-based case control study with sufficient sample size and power to explore associations between medication exposure in the first trimester and approximately 30 selected major birth defects.

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However, as data emerge from this study, interpretation can present dilemmas in obstetric practice when commonly used treatments are called into question regarding safety. One such analysis published in 2009 explored the relationship between selected major congenital anomalies and 11 categories of antibacterial medications taken for any number of days in the month before pregnancy through the first trimester. A total of 13,155 mothers of infants with birth defects were interviewed and the prevalence of maternally reported exposure to antibacterial medications in the periconceptional period was compared to that reported by 4,941 mothers of nonmalformed control infants (Arch. Pediatr. Adolesc. Med. 2009;163:978-85).

This study confirmed the high prevalence of exposure in pregnancy to at least one of these agents – about 30% of women in both groups recalled taking an antibacterial medication sometime in pregnancy, although over 30% of those could not recall the specific type. The study findings were reassuring regarding most categories of treatments studied, including penicillins and erythromycins. However, of concern, two categories of medications used to treat urinary tract infections, nitrofurantoins and sulfonamides, were found to be significantly associated with four and six types of congenital anomalies, respectively.

The authors acknowledged the limitation that documentation of exposure to antibacterials was based on maternal recall up to 2 years post partum, and that the underlying disease being treated could have been contributory. In addition, more than 300 comparisons were made in this study, and it was impossible to pinpoint specific gestational days of exposure to the medications that might have plausibly been related to the wide variety of embryologic timing for each of the specific defects. Furthermore, a previously published Hungarian case-control study of nitrofurantoin use in pregnancy found no evidence of an increased risk with first trimester exposure to this drug. The authors of the U.S. study appropriately concluded that their findings called for additional scrutiny.

However, taken in context, further research takes time, and clinical treatment decisions must be made now. As a result, in June of 2011 the American College of Obstetricians and Gynecologists issued a Committee Opinion (#494) on this topic. Based on the limitations of the study, lack of corroborating evidence, and the necessity of treatment, the committee concluded that the two antibiotics in question could be used by pregnant women in the first trimester if there was no appropriate alternative.

This is one example of many similar situations that are likely to occur in the future as findings from large case-control studies like the National Birth Defects Prevention Study are published. More good quality research on the risks or lack of risks of medications in pregnancy is a huge positive step forward for public health, and is long overdue. However, at the same time, a systematic and swift means for evaluating how these often hypothesis-generating findings should impact clinical practice (e.g., the ACOG Committee Opinion) is needed, as well as a systematic and relatively quick means for testing the hypothesis in one or more other data sets – whether it's a large claims database or one of the many other rich data resources that are being developed to explore the risks and benefits of drugs in pregnancy. ■

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Prenatal Exposure to SSRIs May 'Modestly' Raise Autism Risk

BY MARY ANN MOON

FROM ARCHIVES OF GENERAL PSYCHIATRY

Prenatal exposure to selective serotonin reuptake inhibitors, particularly during the first trimester, may "modestly" raise the risk of autism spectrum disorders, a preliminary study has shown.

"The fraction of cases of [autism spectrum disorders] that may be attributed to use of antidepressants by the mother during pregnancy is less than 3% in our population, and it is reasonable to conclude that prenatal SSRI exposure is very unlikely to be a major risk factor for ASD," said Lisa A. Croen, Ph.D., of Kaiser Permanente Northern California, Oakland, and her associates.

"Although these findings indicate that maternal treatment with SSRIs during pregnancy may confer some risk to the fetus with regard to neurodevelopment, this potential risk must be balanced with the risk to the mother or the fetus of untreated mental health disorders," they noted.

"We recommend that our findings be considered as preliminary and treated with caution, pending results from further studies designed to address the very complex question of whether prenatal exposure to SSRIs may be etiologically linked to later diagnoses of ASD in offspring," the investigators added.

The study was a population-based case-control assessment of mothers' antidepressant use during pregnancy and the later diagnosis of ASD in their children. The sample was drawn from the Childhood Autism Perinatal Study, and it included 298 children with ASD and 1,507 unaffected controls matched for age, sex, and area of residence within Northern California.

VITALS

Major Finding: Maternal use of SSRIs during pregnancy was associated with a twofold risk of autism in the exposed offspring, and SSRI use during the first trimester was associated with a threefold risk.

Data Source: A population-based case-control study examining the prenatal exposures to antidepressants of 298 children with ASD and 1,507 unaffected children.

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Twenty case mothers (6.7%) and 50 control mothers (3.3%) had at least one prescription for an antidepressant during the year before the birth of the child. Most of these prescriptions – for 5% of the case mothers and 2.3% of the control mothers – were for SSRIs.

After the data were adjusted to account for maternal age, race/ethnicity, and education level and for the child's birth weight and sex, "we found an approximately twofold increased risk of ASD associated with treatment with SSRIs ... and an approximately threefold increased risk associated with treatment during the first trimester," Dr. Croen and her colleagues said (Arch. Gen. Psychiatry 2011 [doi:10.1001/archgenpsychiatry 2011.73]).

Mothers of children later diagnosed as having ASD were twice as likely as other mothers to have had at least one antidepressant prescription during the year preceding the birth. In addition, mothers with a prescription for an antidepressant were more than twice as likely as other mothers to have a child who was later diagnosed as having ASD. No such associations were seen among women prescribed any non-SSRI antidepressants, but the number of women in that group was quite small.

The link between SSRIs and ASD risk remained robust in several further statistical analyses. It remained strong when the analysis was restricted to only term births, as well as when it was restricted to only cases in which only one child in the family was affected with ASD ("simplex" cases).

The correlation also remained strong regardless of the indication for which the mother took the drugs. Moreover, ASD risk did not correlate with a history of mental health disorders. These two findings indicate that the SSRIs themselves, not the underlying indications for taking the medications, were the relevant contributing factor, Dr. Croen and her associates said.

However, they cautioned that "despite the significant association, the number of women in this [study] population exposed to SSRIs was modest, and the proportion of children with ASD in this population that can be statistically attributed to SSRI exposure is quite low: 2.1% for exposure during the year before delivery, and 2.3% for exposure during the first trimester."

There are several biologically plausible explanations for this link between SSRI exposure and ASD. Many studies have implicated serotonin abnormalities and anomalies in serotoninergic pathways in autism.

And several animal studies "suggest the possibility that prenatal exposure to SSRIs may operate directly on the developing brain, perhaps selectively in fetuses with abnormalities in serotonin-related genes," they said.

"To our knowledge, our study is the first to directly examine antidepressant use during pregnancy as a potential risk factor for childhood ASD. A substantial strength of our study is our reliance on data documented in medical records and thus recorded at the time of diagnosis or treatment, avoiding potential biases associated with the mothers' recall after diagnosis of ASD in the children," the investigators wrote. ■