DRUGS, PREGNANCY, AND LACTATION

Interrogating the Evidence: SSRIs and Autism

Every few months, it seems as if still another study appears in the literature linking fetal exposure to selective serotonin reuptake inhibitors (SSRIs) with an adverse outcome, such as increased risk for a particular congenital malformation or some other ill effect. Despite many studies that have examined a potential association between risk for malformations and prenatal SSRI exposure, a major indication that an agent is a teratogen is consistency of the finding *across studies,* which has not been the case with SSRIs.

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On the other hand, studies indicating that babies whose mothers use SSRIs during pregnancy might have symptoms of transient jitteriness for a period following birth (neonatal adaptation syndrome) have been more consistent – and this is generally accepted as a real risk following about 20%-25% of deliveries. Other major concerns raised about fetal exposure to SSRIs have not been supported by systematic scientific investigation.

Clinicians may then wonder why we are seeing an increasing number of reports of potential adverse outcomes associated with SSRI treatment during pregnancy. One reason is that technology has afforded us the ability to gather information from large administrative databases (such as Medicaid or large health maintenance organizations) about prescriptions written during pregnancy and a variety of obstetrical and neonatal outcomes data. Conclusions about a teratogenic outcome or adverse perinatal outcome are only as reliable as the quality of the data from which the conclusions are derived and, unfortunately, some of the data from these databases have been profoundly lacking.

In still another study using such data, published online in Archives of General Psychiatry in July, investigators from Kaiser Permanente Northern California reported an association between an increased risk for autism spectrum disorders (ASDs) in children and maternal SSRI use during pregnancy (doi:10.1001/archgenpsychiatry.2011.73).

The population-based case-control study used medical records of 298 children diagnosed with an ASD (autism, Asperger's syndrome, or pervasive developmental disorder not otherwise specified) and 1,507 children without an ASD diagnosis born within the Kaiser Permanente system in northern California between 1995 and 1999. The results suggested a greater risk of an ASD among children exposed to an SSRI in utero, compared with nonexposed children: The mothers of 6.7% of children with ASD (20 children) had been prescribed at least one antidepressant (mostly SSRIs) during the year before the child was born, compared with the mothers of 3.3 % of controls (50 children).

After a purported adjustment for maternal age and other possible confounding factors, maternal use of an SSRI during the year before delivery was associated with a twofold increased risk of an ASD; treatment during the first trimester was associated with almost a fourfold increased risk. Among the children whose mothers had a history of mental health treatment but did not take SSRIs, the risk of ASD was not increased.

This study has received considerable attention from the media and medical bloggers, and it has led to substantial concern among patients and clinicians struggling to understand the results. Most concerning about this type of report is the alarm that is frequently elicited when patients with an incomplete understanding of the relevant data available regarding a compound learn about a new finding that implies risk, even when such a finding derives from an analysis with great limitations.

As an example, after hearing about the study results, we were contacted by a patient treated with a moderate dose of an SSRI for a history of anxiety disorder, including during two pregnancies with healthy outcomes, with a question as to whether she should continue an IVF cycle. She asked whether she should complete the procedure because she was concerned about the study results. We referred her to some of the many articles and blogs that have attempted to qualify the findings, including our own hospital's blog at www.womensmentalhealth.org/posts/autism-spectrum-disorders-and-ssris.

We should keep in mind that this was a case-control study with a very small number of SSRI exposures in both the autism and control groups. So not only was the study limited by a small sample, but it also failed to adequately take into account exposure to illness during pregnancy as a variable. Another limitation was the failure to confirm actual ingestion of the drug by women who were prescribed an antidepressant.

While the investigators point out that an effort was made to adjust for the effects of underlying disease that led to treatment, it is hard to imagine how that was possible given the sparse data available to them. There was no measure of psychiatric disorder during pregnancy – or the severity of psychiatric disorder in the past – a critical issue because of the literature suggesting that exposure to stress and psychiatric disorder during pregnancy may drive adverse neonatal outcomes.

Multiple studies published over the past decade indicate that ASD is a highly heritable illness. Genetic factors clearly play an important role, and family history of psychiatric disorder is a major risk factor for ASD. Other studies have suggested a multifactorial model that includes environmental and genetic factors as possible causative factors.

Therefore, while the authors suggest that SSRI exposure may contribute to risk for ASD, they have failed to adequately or accurately quantify one of the strongest, most well-established risk factors for ASD, namely family or personal history of psychiatric disorder. One can hypothesize that women with a more severe underlying psychiatric disorder would be using antidepressants during pregnancy, given the high threshold for using these medicines or any other medicines during pregnancy.

Opportunities to refine our understanding of clinical questions with major public health implications are always welcome. But one does have to wonder about the value of these analyses, when the quality of data in the studies is of questionable reliability.

Clearly, decisions regarding use of any medication, including psychotropics, have to be made on a case-by-case basis. But at least some of these new findings tend to complicate, if not obscure, the most thoughtful clinical path as patients struggle to understand frequently conflicting data in the literature about SSRIs, which are frequently prescribed during pregnancy. Perhaps clinicians then should consider this latest study as a very preliminary report with findings that are far from definitive until we have better prospectively ascertained data regarding the longer-term behavioral sequelae of fetal exposure to SSRIs. ■

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Rise in Postpartum Strokes Linked to Heart Disease, HT

BY HEIDI SPLETE

FROM STROKE

The rate of any type of pregnancy-related hospitalization for stroke in the United States increased from approximately 4,000 in 1994-1995 to about 6,000 in 2006-2007, based on data from a nationwide sample of more than 64 million pregnant women.

This 54% increase can be explained largely by postpartum hospitalizations in women with heart disease or hypertensive disorders, said Dr. Elena V. Kuklina and her associates at the Centers for Disease Control and Prevention in Atlanta.

The researchers compared ICD-9 code data from 1994 to 1995 with data from 2006 to 2007. Types of stroke included cerebral venous thrombosis, hemorrhagic, ischemic, subarachnoid, transient ischemic attack, and unspecified (Stroke 2011 J [doi:10.1161/strokeaha.110.610592]). Overall, hypertensive disorders were present in 11%, 23%, and 28% of prenatal, delivery, and postpartum hospitalizations, respectively, in 1994-1995, and these numbers increased to 17%, 29%, and 41% in 2006-2007. Only the increase in postpartum hospitalizations for stroke was statistically significant.

Heart disease was a complication in pregnancy-related hospitalizations for stroke in 16% of prenatal hospitalizations, 8% of delivery hospitalizations, and 9% of postpartum hospitalizations in 1994-1995, whereas that was the case in 16%, 8%, and 12% of the hospitalizations, respectively, in 2006-2007.

VITALS

Major Finding: Pregnancy-related hospitalizations for stroke in the United States increased by 54% from 1994-1995 to 2006-2007.

Data Source: A review of ICD-9 code data from 64,023,525 women nationwide.

Disclosures: Dr. Kuklina and her associates said they had no relevant financial disclosures.

The rate of any stroke per 1,000 deliveries increased significantly for prenatal hospitalizations and postpartum hospitalizations between the two time periods (from 0.15 to 0.22 and from 0.12 to 0.22, respectively). However, the rate of any stroke during delivery hospitalizations remained unchanged at 0.27.

After adjustiment for confounding variables, patients who were hospitalized with hypertensive disorders during pregnancy, during delivery, and post partum were 1.8, 5.6, and 3.5 times more likely, respectively, to have indications of stroke, compared with patients without hypertensive disorders, the researchers noted.

In addition, patients who were hospitalized with heart disease during the prenatal period and the delivery period were, respectively, 9.4 times as likely and 5.4 times as likely to have indications of stroke.

The current recommendations from the American Heart Association and the American Stroke Association for managing pregnant women with a history of noncardioembolic stroke or at risk of cardioembolic stroke include treatment with anticoagulant therapy in the form of unfractionated heparin or low-molecular-weight heparin until week 13, followed by low dose aspirin for the rest of the pregnancy (Stroke 2011;42:227-76). ■