Drugs, Pregnancy, And Lactation

Weighing New Evidence on SSRI Use

Until fairly recently, studies and reviews of global teratovigilance data have been relatively reassuring that SSRIs were particularly safe, especially with regard to their teratogenicity. In fact, there are more reproductive safety data available for SSRIs than for many medicines women take during pregnancy. However, new reports have raised concerns regarding the teratogenicity of paroxetine, which we have previously discussed (Ob.Gyn. News, Oct. 15, 2005, p. 9), as well as risk for putative neonatal distress syndromes and, most recently, possible increased rates of persistent pulmonary hypertension of the newborn (PPHN) following late-pregnancy exposure to SSRIs.

BY LEE S. COHEN, M.D.

What do the new reports describe and how do the findings inform clinical care? One study supports previous reports of a "neonatal abstinence syndrome" with characteristic symptoms of jitteriness, sleep disturbance, dysregulation, tachypnea, and myoclonus in infants whose mothers used antidepressants during pregnancy. In this prospective cohort study of 120 infants, examiners used a systematic scale to assess full-term SSRI-exposed newborns with respect to presence or absence of a wide range of previously reported symptoms.

Of the 60 infants exposed in utero to various SSRIs for a mean of 35.5 weeks, 8 had severe symptoms and 10 had mild symptoms, compared with none of the 60 infants who had not been exposed in utero to these drugs (Arch. Pediatr. Adolesc. Med. 2006;160:173-6). A particularly noteworthy finding is that no infant with symptoms required treatment intervention; symptoms were transient and of little if any clinical significance.

In the second study, investigators using a case-control design described an elevated risk for PPHN, a far more serious syndrome associated with severe respiratory failure, in newborns with in utero exposure to SSRIs late in pregnancy. In this study, which enrolled almost 400 women whose infants had PPHN, matching them to more than 800 control mothers and infants, the use of SSRIs at any point during pregnancy was not associated with PPHN, but there was a significant association between PPHN and in utero exposure to an SSRI after 20 weeks' gestation (N. Engl. J. Med. 2006;354:579-87).

The study describes a very disturbing and striking finding. But an accompanying editorial points out that the number of cases reported is small (N. Engl. J. Med. 2006;354:636-8). And though not mentioned in the editorial, the vulnerability to reporting bias in such a study is great. One wonders whether women without an adverse outcome may be reluctant to disclose use of an antidepressant during pregnancy, compared with those with an adverse outcome as serious as PPHN. Because the conclusions are based on a small number of PPHN cases, a difference of a small number of cases in either direction can strengthen or attenuate a positive finding.

The authors of the second study suggest that the incidence of PPHN associated with SSRI exposure in late pregnancy approaches 1%. However, given the hundreds of women who have used SSRIs during late pregnancy, it is unlikely that such a dramatic clinical finding would not have been reported, even anecdotally, prior to this particular study—the first of such reports.

These studies, which have had considerable media attention, have understandably alarmed women who are taking antidepressants. In fact, they were published just weeks after we reported the results of a prospective study of 201 women with a history of major depression who were prospectively followed during pregnancy. Women who discontinued their antidepressant medication proximate to conception were at a fivefold greater risk for depressive relapse during pregnancy, compared with those who continued with an antidepressant (JAMA 2006;295:499-507).

These data certainly suggest that pregnancy is not protective with respect to depression and that many women who stop antidepressants will relapse during pregnancy.

While some women will still stop antidepressant therapy during pregnancy, patients should be informed that depression during pregnancy can increase the risk for other neonatal complications and can substantially increase their risk for postpartum depression. Other women will choose to continue antidepressant use during pregnancy, regardless of the findings of some of these more recent studies, given what for some patients will be viewed as a modest risk for the neonatal outcomes described. Regardless of individual choices, which will be extremely variable, it is crucial to present all available information to reproductive-age women on antidepressants who plan to conceive or who are pregnant, so that collaborative decisions can be made based on these data and personal wishes.

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Study Undercuts Antioxidants

Vitamins C, E *from page 1*

of investigators that suggested a protective effect of supplementation (Lancet 1999; 354:810-6).

"It's quite possible that our previous findings were an error as a result of our small numbers," Dr. Poston said, explaining that the previous study included only 160 women, with an 8% rate of preeclampsia.

She said although it has long been accepted that preeclampsia is associated with oxidative stress, her results suggest that rather than being the cause, oxidative stress may simply be a consequence of the condition. "I'm afraid to say that oxidative stress is probably an innocent bystander in preeclampsia as a result of the disease process," she noted.

This concept is consistent with mainstream cardiology research, she said. "There is overwhelming evidence that atherosclerosis and other cardiovascular complications are associated with oxidative stress, but when people have been supplemented with antioxidants there has been no effect on mortality or morbidity."

The study analyzed 2,395 pregnant women who were at risk for preeclampsia and randomized them at 14-22 weeks' gestation to either high-dose antioxidant therapy or placebo. Subjects who were already taking prenatal vitamins at randomization were allowed to continue taking them.

High-dose antioxidant therapy failed to protect against preeclampsia, which occurred in 15% of the high-dose antioxidant group and 16% of the placebo group.

Additionally, there was an association between high-dose antioxidant therapy and low birth weight, defined as less than 2.5 kg. Low-birth-weight babies comprised 28% of the babies in the high-dose antioxidant group, compared with 24% of the placebo group (risk ratio 1.15).

Regarding secondary outcomes, high-dose antioxidant therapy again compared unfavorably with placebo, resulting in higher risks of arterial cord pH less than 7 (RR 2.2), intravenous antihypertensive therapy (RR 1.9), magnesium sulfate therapy for preeclampsia (RR 1.8), gestational hypertension (RR 1.5), and antenatal steroid use (RR 1.4). An additional exploratory analysis of the data revealed that high-dose antioxidants were associated with a greater risk of stillbirth (RR 2.7), but a lower risk of death due to immaturity (RR 0.2), although these results could be due to chance, since they were generated from a post hoc analysis, she said.

The harmful potential of large doses of antioxidants is particularly troubling, but consistent with some controversial evidence that high-dose vitamin E has an adverse effect on mortality and morbidity in people with cardiovascular disease, Dr. Poston noted. "It could be that a little bit of oxidative stress is actually a good thing," she suggested. "Oxidative stress is involved in a lot of biological processes and it could be there is some fundamental biological process that depends on a little bit of oxidative stress."

The study raises ethical concerns about ongoing antioxidant research in populations that are at risk for preeclampsia, said Dr. Poston. However, she said she has contacted investigators on similar U.S. (National Institutes of Health) and Canadian (Medical Research Council) studies who have decided, after performing interim analyses, to continue their studies despite her findings.

Another smaller study presented in a poster at the meeting also found no protective effect of high-dose antioxidant therapy against preeclampsia. However, the study was done in a normal, nulliparous population, rather than a high-risk group. In fact, there was a trend toward higher preeclampsia rates among women taking high doses of antioxidants (16.7%) compared with those taking placebo (9.7%), said Dr. Heather Mertz, an ob.gyn. at Wake Forest University, Winston-Salem, N.C.

The study of 177 women did show a significant benefit of high-dose antioxidant therapy on neonatal outcome, Dr. Mertz said, but overall, her study did not provide enough evidence to counsel patients either for or against high-dose antioxidant therapy during pregnancy. ■

For Late-Pregnancy Choking, Use Heimlich Maneuver on the Floor

Pasadena, Calif. — The Heimlich maneuver becomes unwieldy during the late stages of pregnancy, requiring adaptations, Dr. J. Gerald Quirk said at the annual meeting of the Obstetrical and Gynecological Assembly of Southern California.

Breast enlargement, diaphragm displacement, and the size and weight of a pregnant woman all contribute to difficulty in performing the traditional emergency maneuver to prevent choking during late pregnancy.

First described in 1974 by Dr. Henry Heimlich, a thoracic surgeon, the Heimlich maneuver involves standing behind a choking victim and placing a fist, thumb side in, underneath the diaphragm.

Using the other hand to push against the fist, a series of abrupt upward thrusts can usually dislodge a piece of food from the airway.

Not only is it difficult to hold a woman in this position during late pregnancy, it is also hard to exert the force necessary to perform the maneuver correctly, said Dr. Quirk, professor and chair of obstetrics, gynecology, and reproductive medicine at Stony Brook (N.Y.) University.

"The best thing to do is lay her on the floor and press down on the lower part of the sternum," he said.

The woman should be tilted slightly to one side to prevent aortocaval compression.

Dr. Quirk said several case reports suggest that this adaptation is effective in late pregnancy.

—Betsy Bates