Drugs, Pregnancy, And Lactation

The FDA Advisory on Paroxetine

Multiple studies over the past decade have been supportive of the reproductive safety of the selective serotonin reuptake inhibitors (SSRIs) when used during the first trimester; these studies include one recent metaanalysis and other extensive reviews. Particularly reassuring have been the prospective data on fluoxetine (Prozac) and citalopram (Celexa). As a result, clinicians have been relatively reassured about the absence of teratogenic risk associated with the SSRIs.

BY LEE COHEN, M.D.

New concerns were recently raised about the reproductive safety of paroxetine by a presentation at the Teratology Society annual meeting that reported an increased risk of omphalocele associated with first-trimester exposure. This report was based on preliminary, unpublished data from the National Birth Defects Center, which I reviewed in a recent column (Ob.Gyn. News, Oct. 15, 2005, p. 9). A weaker association was also found between omphalocele and other SSRIs.

A Food and Drug Administration public health advisory about paroxetine followed in December, describing preliminary results of two other unpublished studies indicating that paroxetine exposure in the first trimester may increase the risk of congenital malformations, particularly cardiac malformations. At the FDA's request, paroxetine manufacturer GlaxoSmithKline has changed the pregnancy category label for paroxetine from C to D.

It is surprising that the FDA's recommendation and advisory are based on preliminary analyses from several recent, unpublished, non–peer-reviewed epidemiologic studies, as these are data that should be considered, at least at this point, inconclusive.

Using data from the Swedish National Registry, one study found a 2% rate of cardiac defects among infants exposed during the first trimester to paroxetine vs. 1% among all registry infants. But a previous study using registry data that was based on a slightly smaller number of children exposed to paroxetine did not report this association (J. Clin. Psychopharmacol. 2005;25:59-73).

Another study, using data from a U.S. insurance claims database, found the rate of cardiovascular malformations was 1.5% among infants exposed to paroxetine during the first trimester vs. 1% among infants exposed to other antidepressants. The majority were atrial or ventricular septal defects, which are common congenital malformations.

The modest increases in relative risk of a common anomaly, when derived from a claims database with inherent methodologic limitations, make interpretation of these data problematic. Unfortunately, the language in the FDA advisory, suggesting that "the benefits of continuing paroxetine may outweigh the potential risk to the fetus," may get lost in the information patients receive.

Although there are not as many published studies on the teratogenic risk of paroxetine as for other SSRIs, it is noteworthy that prospective studies have not identified a higher rate of congenital or cardiac malformations associated with prenatal exposure to paroxetine.

How does the clinician then counsel women of reproductive age who suffer from major depression? And what is the best option for patients who are being treated with paroxetine who want to get pregnant or who have an unplanned pregnancy? Until the issue is clarified with more rigorously obtained and conclusive data, it is reasonable to avoid paroxetine in women who are actively trying to get pregnant or plan to in the future.

For those with major depression who are antidepressant-naive, it may be most prudent to prescribe an SSRI or an SNRI for which there are no unfavorable data to date, such as fluoxetine or citalopram/escitalopram, or an older tricyclic antidepressant such as nortriptyline.

What makes sense for those who have failed to respond to one of those medications previously, as in the all-too-common scenario of nonresponse to multiple SSRIs and response only to paroxetine? In this situation, the use of paroxetine in women who are planning to conceive or who are already pregnant should not be considered absolutely contraindicated.

If the medication is discontinued before or during pregnancy, it should be done gradually, as is consistent with standard clinical practice.

Until the data are peer-reviewed and published, decisions about use of this medicine in women who are planning a pregnancy or are pregnant will have to be made on a case-by-case basis. But we need to keep in mind that nothing is more critical than sustaining euthymia during pregnancy. Untreated depression in pregnancy is associated with compromised fetal well-being as well as increased risk for postpartum depression.

The FDA advisory is available online at www.fda.gov/cder/drug/advisory/paroxetine200512.htm.

Dr. Cohen *directs the Perinatal and Reproductive Psychiatry Program at Massachusetts General Hospital, Boston, which offers information about pregnancy and women's mental health at www.womensmentalhealth.org. He is a consultant to manufacturers of several antidepressant drugs, including paroxetine and other SSRIs.*

Hysteroscopy Can Shed Light on Miscarriages

BY PATRICE WENDLING
Chicago Bureau

Chicago — Preevacuation hysteroscopy is useful for identifying localized and systemic defects during morphogenesis in patients with unexplained recurring pregnancy loss, said Dr. Artin Ternamian.

"We're convinced that preevacuation hysteroscopy can help us understand and maybe explain a lot of the miscarriages that we take for granted," he said at the annual meeting of the AAGL (formerly the American Association of Gynecologic Laparoscopists).

Sonography, tissue analysis, and biochemical studies are generally used to evaluate recurrent pregnancy loss, which occurs in 1% of reproductive-age women. But once the evacuation or D&C has been performed, couple counseling becomes more difficult, if not impossible, and the willingness to investigate further wanes, he said.

Preevacuation hysteroscopy allows physicians to examine the fetoplacental environment and provides excellent visualization of the surface anatomy before the tissue is eviscerated or contaminated, said Dr. Ternamian, director of gynecologic endoscopy, St. Joseph's Health Centre, University of Toronto.

In particular, one can examine the ventral bony clefts, which can be difficult to do with ultrasound and which reveals subtle skin surface changes, such as human papillomavirus skin lesions or raised corneal lesions that can be targeted for biopsy. The procedure can demonstrate most fetal extremity deformities and the exact topography of the limbs, identifying cystic hydromas and sacral coccygeal keratomas.

The accurate surface observation of hysteroscopy can identify congenital ear abnormalities such as clefts and congenital hairy nevi that are notoriously missed on ultrasound, he said. Preevacuation hysteroscopy can also confirm or rule out amniotic bands, Meckel-Gruber syndrome, Klippel-Trénaunay-Weber syndrome, and first-trimester varicella.

In a prospective, preliminary feasibility study, preevacuation hysteroscopy was performed using a continuous-flow resectoscope with a 12-degree lens in 12 consecutive patients with confirmed spontaneous pregnancy loss. Gestational ages ranged from 9 weeks to 19 weeks.

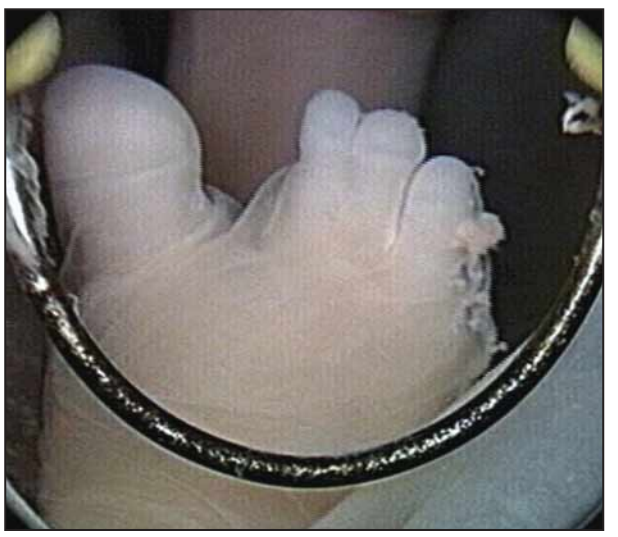
In this procedure, the cervix is dilated and a small amniotic membrane window created at a location away from the placenta and fetus, using a monopolar 5-by-8-mm cutting loop set at 100 W pure cut power. The often stained amniotic fluid is exchanged for 1.5% glycine while the hysteroscope is navigated through the amniotic window into the fetal compartment.

Abnormalities were detected in all but one patient. None of the abnormalities observed on hysteroscopy were identified on previous ultrasound scans or subsequent surgical pathology reports.

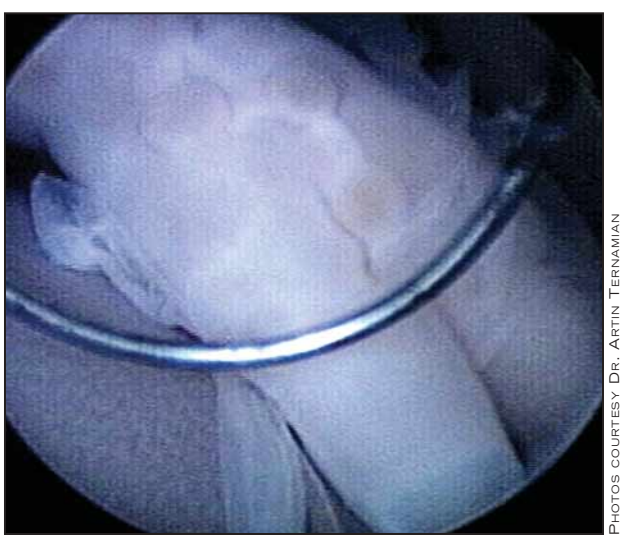
"The objective of a pathology report is to make sure that what you've retrieved is indeed fetal tissue and you've evacuated the uterus; [it] isn't intended to detect abnormalities," Dr. Ternamian said in an interview. "If, by chance, they see some gross histologic abnormalities that will be reported, but that's 1 in 10,000."

Hysteroscopy adds no more than 20 minutes to an evacuation or D&C, and the majority of patients offered the additional testing consent. Patients are advised not to decide at the first interview when the fetal death is discovered, and particular care is taken if the patient is pregnant for the first time.

"From the patient's point of view it's a horrendous area," he said. "To use hysteroscopy is the next logical step to help these patients, and, hopefully, we can take it to the next level, where, if you have a miscarriage, it becomes standard of care." ■



A preevacuation hysteroscopy revealed syndactyly and a missing second toe on this fetus's right foot.



Condylomatous coin lesions were identified on this fetus's left hand during a preevacuation hysteroscopy.

Photos courtesy Dr. Artin Ternamian