DRUGS, PREGNANCY, AND LACTATION

Reviewing the Safety of SSRIs

Over the past few years, several published studies have addressed the reproductive safety of the selective serotonin reuptake inhibitors. Recent studies have focused on the risk for neonatal discontinuation syndrome or symptoms of perinatal jitteriness associated with maternal use of SSRIs during the latter portions of pregnancy.

Estimates of risk of first-trimester exposure to SSRIs derive from data accumulated over the last 15 years, which support the absence of major congential malformations associated with first-trimester exposure.

BY LEE COHEN, M.D.

Data on the teratogenicity of SSRIs come from relatively small cohort studies and larger, international teratovigilance programs, and they have cumulatively supported the reproductive safety of fluoxetine (Prozac) and certain other SSRIs. These include a Scandinavian-based registry study of 375 women exposed to citalopram (Celexa) in the first trimester, which failed to indict SSRI as a teratogen.

A recent metaanalysis conducted by researchers at the Motherisk Program in Toronto supported the absence of teratogenicity associated with first-trimester exposure to a number of SSRIs.

Another recent report from the Swedish Medical Birth Registry failed to identify higher rates of congenital malformations associated with prenatal exposure to a number of SSRIs, including fluoxetine, citalopram, paroxetine (Paxil), and sertraline (Zoloft).

But at the Teratology Society's annual meeting in June, investigators from the University of British Columbia, Vancouver, reported an increased risk of omphalocele and craniosynostosis associated with first-trimester exposure to SSRIs. Using data from the National Birth Defects Prevention study, they compared data on 5,357 infants with selected major birth defects with 3,366 normal controls and interviewed mothers about exposures during pregnancy and other possible risk factors. Children with chromosomal anomalies or known syndromes were excluded.

They found an association between exposure to any SSRI during the first trimester and omphalocele (odds ratio of 3). Paroxetine accounted for 36% of all SSRI exposures and was associated with an odds ratio of 6.3 for omphalocele. Use of any SSRI during the first trimester was also associated with having an infant with craniosynostosis (odds ratio of 1.8). No association was noted between SSRI use and the other classes of major malformations studied.

This preliminary unpublished report is also described in a letter to physicians from GlaxoSmithKline, which markets paroxetine as Paxil. The letter also includes additional data from an uncontrolled study of SSRI use during pregnancy, which noted a twofold increased risk in overall congenital malformations and cardiovascular malformations (most were ventricular septal defects) in offspring exposed to paroxetine, compared with other SSRIs. These data were derived from an HMO claims database.

Many clinicians who prescribe SSRIs may be confused with the volley of new reports that suggest some potential teratogenic risk associated with this class of compounds. Indeed, previous reports fail to describe such an association. Many of the more recent findings derive from either retrospective data sets taken from HMO claims data or from case-control studies, which also have certain methodologic limitations, compared with prospective cohort studies.

These recent findings of increased risk with prenatal SSRI exposure are inconsistent with earlier published findings. Nevertheless, large case-control studies can uncover an association not previously identified because of the inadequate statistical power of previous cohort studies, which were not large enough to detect an infrequent anomaly.

Even if we assume the associations from the new case-control study are true and that they are indeed causal, an odds ratio of 6.4 is associated with an absolute risk for omphalocele of only 0.18%. Absolute risk is of far greater clinical value than relative risk and should be taken into account before patients are arbitrarily counseled to discontinue antidepressants during pregnancy.

The new findings are not necessarily a cause for alarm. Patients who are planning to conceive and are at significant risk for depressive relapse associated with antidepressant discontinuation may benefit from a switch to an antidepressant for which there are the greatest amount of data supporting reproductive safety. These antidepressants include the SSRIs fluoxetine, citalopram, escitalopram (Lexapro), as well as the older tricyclics.

However, for women who present when pregnant and still taking SSRIs, including paroxetine, discontinuation of the medication should not be arbitrarily pursued. Abrupt discontinuation of antidepressants can threaten maternal affective well-being. That is an unacceptable outcome, which can be stated absolutely.

DR. COHEN *directs the perinatal 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 SSRIs.*

Prenatal Alcohol Exposure May Stunt Child's Growth

BY BETSY BATES
Los Angeles Bureau

SANTA BARBARA, CALIF. — Children of older mothers who drank during pregnancy were shorter and had smaller head circumferences at ages 7 and 14 years than other children at those ages, it was reported at the annual meeting of the Research Society on Alcoholism.

Children of mothers who were 30 or older at delivery were affected above a threshold of moderate alcohol consumption, defined as about one alcoholic drink a day at the time of conception.

Many women reduced their drinking during pregnancy, but the heaviest drinkers reduced their drinking less.

"Even if women reduce their drinking during pregnancy, their early drinking before they realize they are pregnant may have an impact on the infant," said Sandra W. Jacobson, Ph.D., professor of psychiatry and behavioral neurosciences at Wayne State University in Detroit, a senior author on the study. "We see effects in infants whose mothers drink as little as one drink/day, on average."

Although the study suggests children of mothers age 30 and older are most vulnerable to prenatal alcohol exposure, all women should be urged to stop drinking.

Dr. Jacobson stressed that "average" drinks per day did not reflect actual drinking patterns among women in the study. Just 1 woman of 480 in the Detroit Longitudinal Prenatal Alcohol Exposure study drank daily.

Many of the others concentrated their drinking on 1-2 days a week, in some cases drinking three to four drinks at each session, she explained following the meeting.

Mean alcohol intake at conception was about two drinks/day in the study of economically disadvantaged African American women and their children.

Mean alcohol consumption dropped during pregnancy to a little more than two drinks per week.

Prenatal alcohol exposure was associated with lower birthweight and length in the entire sample of women, even after researchers controlled for smoking and other possible confounders.

For mothers over 30 at conception, the repercussions were long lasting.

With a cutoff point of 0.5 ounces of alcohol per day at conception, older mothers' children were 1.2 cm, 3.1 cm, and 3.7 cm shorter at birth, 7.5 years, and 14 years, respectively, than children of mothers with minimal alcohol exposure.

Their mean head circumference was smaller by 4.6 mm, 7.3 mm, and 14.5 mm at birth, 7.5 years, and 14 years.

"Prenatal alcohol exposure was not related to weight or body mass index at 7.5 or 14 years, suggesting that the effects on height and head circumference were not attributable to poor maternal nutrition," the researchers reported in their poster presentation.

Smoking during pregnancy resulted in lower birthweight and reduced length and head circumference at birth, but had no discernible impact on children's growth over time.

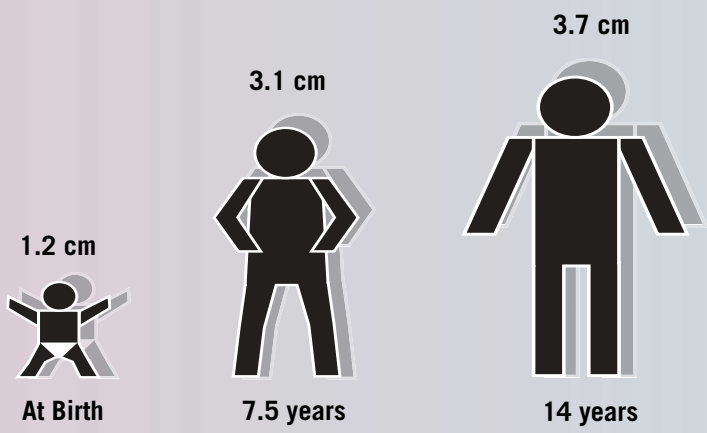
In contrast, prenatal alcohol exposure's impact on size was evident at birth and became magnified over time.

Although the study suggests that children of older mothers are most vulnerable to prenatal alcohol exposure, all women considering pregnancy should be urged to stop drinking or to cut down as much as possible. "At this time, no drinking is considered safe," said Dr. Jacobson.

The study was supported by grants from the National Institute on Alcohol Abuse and Alcoholism and the Joseph Young, Sr., Fund of Michigan.

Douglas Fuller, a research assistant in the Wayne State University department of psychiatry and behavioral neurosciences, contributed to the study. ■

Prenatal Alcohol Exposure Linked to Height Deficit



Note: Children of older women with moderate alcohol consumption at conception were shorter than children of older women with minimal alcohol use.
Source: Dr. Jacobson