SSRIs Tied to Neonatal Withdrawal Symptoms

BY ELIZABETH MECHCATIE
Senior Writer

International reports of withdrawal symptoms in 93 newborns whose mothers had taken selective serotonin reuptake inhibitors during pregnancy raise concerns about a possible causal relationship between such symptoms and drugs in this class, particularly paroxetine, according to authors of a study that identified these cases.

Nearly two-thirds (64) of these cases were seen in babies whose mothers had taken paroxetine (Paxil), which the authors concluded should not be used in pregnancy, "or, if used, should be given at the lowest effective dose."

The use of other SSRIs "should be carefully monitored and new cases promptly communicated to the pharmacovigilance systems," wrote Emilio Sanz, M.D., professor of clinical pharmacology at the University of La Laguna (Spain), and associates (Lancet 2005;365:482-7).

When asked to comment on the study, two experts on drug therapy during pregnancy disagreed with the authors' conclusions, which they said fail to balance the risks and benefits of these drugs in pregnant women with depression.

Gideon Koren, M.D., director of the Motherisk Program, a teratogen information service at the Hospital for Sick Children, Toronto, said that while the identification of these cases in an international database was commendable, he took issue with the conclusion that paroxetine should not be used in pregnancy. This recommendation is not based on an appropriate risk-benefit analysis, he said, and it does not take into account the increased risk of maternal morbidity associated with untreated maternal depression—the strongest predictor of postpartum depression.

Moreover, the authors fail to take into account a study published last year, which found that in a large Swedish database, the association between paroxetine and these symptoms was no greater than with other SSRIs, added Dr. Koren, who said he has no financial ties to manufacturers of antidepressants.

He noted that neonatal withdrawal symptoms are self-limited and that the syndrome has "a very benign course," which also was not discussed by the authors. He and his associates at Motherisk have conducted many prospective case-control studies on the effects of different drugs in pregnancy. One of the studies, published in 2002, found a significantly higher rate of neonatal withdrawal symptoms in newborns exposed to paroxetine in the third trimester, compared with unexposed controls.

Lee Cohen, M.D., director of the perinatal psychiatry program at Massachusetts General Hospital, Boston, emphasized that while an appropriate level of vigilance is warranted in neonates who have been exposed to SSRIs in the third trimester, the cases in the study represent spontaneous reports, not controlled data. They are "not a clap of thunder" but represent another data set that is starting to suggest that there is some association between SSRI exposure and risk for perinatal syndrome, Dr. Cohen said in an interview.

What complicates the situation is that use of these drugs in the general population and in pregnant women is significant, but the incidence of these symptoms is probably extremely small. There are no controlled data available that can be used to reliably estimate the prevalence of these symptoms in pregnant women on antidepressants, added Dr. Cohen, who is a consultant to manufacturers of several antidepressants.

What concerns him most, Dr. Cohen said, is that the study could not only lead to a reduction in antidepressant use during the peripartum period, but could affect a woman's willingness to take medication she may need at other points during pregnancy. The study also could affect the clinicians' willingness to prescribe therapy when needed during pregnancy.

The study, published last month, involved a search for reports of cases in the WHO adverse drug reaction database, where spontaneous reports of suspected adverse drug reactions are sent from centers in 81 countries. The first case, which was associated with fluoxetine, was reported in 1995. As of November 2003, 93 suspected cases of SSRI-associated neonatal withdrawal syndrome had been reported. In 73 of those cases, no concomitant medications were reported or the concomitant medications were thought to be unrelated to the symptoms.

For 10 of the remaining 20 cases, an association with the SSRIs was considered "doubtful," because of the concomitant use of medications that included antipsychotics or other drugs for which an association with neonatal withdrawal symptoms have not been clearly established. Another 10 were considered as "probably not" associated with SSRIs, because concomitant medications included drugs like opioids or tricyclics, according to the authors.

The most common neurological symptoms reported were nervousness, abnormal crying, tremors, and hypertonia. Other symptoms included digestive symptoms (vomiting, feeding disorders, or diarrhea), and respiratory symptoms (including two cases of respiratory depression). There were 13 cases of neonatal convulsions—11 listed as neonatal convulsions and 2 as grand mal convulsions.

Of the 93 cases, 64 were associated with exposure to paroxetine, followed by 14 associated with fluoxetine (Prozac), 9 with sertraline (Zoloft), and 7 with citalopram (Celexa). Information on doses and duration of treatment during pregnancy were reported in a minority of cases.

A spokesperson for Paxil manufacturer GlaxoSmithKline said the company had no statement on the Lancet report but pointed out that the FDA required this label change for all SSRIs and selective norepinephrine reuptake inhibitors (SNRIs). ■

Drugs, Pregnancy, And Lactation

SSRIs and Neonatal Withdrawal

BY LEE COHEN, M.D.

Multiple articles over the past several years have cited perinatal symptoms in newborns whose mothers were taking an antidepressant late in pregnancy, including transient restlessness, jitteriness, tremulousness, and difficulty feeding.

There have now been enough reports to suggest that certain vulnerable children or subgroups of newborns who were exposed in utero may be at a slightly increased risk for this syndrome. Indeed, last year the Food and Drug Administration required the addition of related information to the labels of SSRIs and SNRIs.

The results of a recent study of 93 cases worldwide (including 64 associated with paroxetine) from a World Health Organization adverse event reporting database do not represent new findings. The reports include descriptions of nervousness, agitation, abnormal crying, and tremors, which the authors consider a "signal" for perinatal or neonatal toxicity. The study also refers to 11 reports of neonatal convulsions and 2 reports of grand mal seizures, with no further description of the cases (Lancet 2005;365:482-7).

Although the report of neonatal convulsions is relatively new, the study itself has several notable limitations. It is difficult to interpret these results because they are from a spontaneous adverse event reporting system, where typically adverse outcomes are overreported and do not provide adequate information on when the drug was used, the duration of illness, or whether the woman was depressed during pregnancy. And the absence of a controlled sample makes it difficult to estimate the incidence of this type of problem, which likely is very low, considering the wide use of these medications among reproductive age women. Moreover, depression in the mother has been associated with many of the newborn symptoms reported.

The use of the term "withdrawal" syndrome is a dicey clinical call at best. Based on what we know about the kinetics and placental passage of these medications, certainly what we're seeing is not acute withdrawal, like we see with heroin or methadone use during pregnancy. The main metabolites of the drugs remain in the baby's circulation for at least days to weeks, so to see something so early and so transient, even for paroxetine (which has a shorter half-life than the other SSRIs), is not consistent with the pharmacokinetics of the compounds being described.

I don't disagree with these findings. Acknowledging the probable biases involved with collecting and reporting these cases, the report provides another data set that calls attention to the possibility of some type of perinatal syndrome associated with SSRI exposure later in pregnancy, which may not necessarily be a causal relationship. The authors suggest their findings are more of a "signal" that a problem may exist, rather than a definitive causal link.

When considered with other case series in the literature, this study may indicate the potential risk for some type of perinatal syndrome associated with the use of these medications, particularly around the acute peripartum period.

What is of concern, however, is the impact this report may have on appropriate prescribing of these drugs to pregnant women, and that patients, as well as physicians, will uniformly and arbitrarily avoid these drugs during pregnancy.

The article falls profoundly short in terms of helping the clinician. While the results indicate that more vigilance is necessary during the peripartum period in cases of SSRI use, the data do not imply that any particular SSRI should be avoided in women of reproductive age. The authors conclude that the signal is stronger for paroxetine, which they say should either not be used during pregnancy or used at the lowest effective dose. I certainly would not rule out using paroxetine in women of reproductive age on the basis of this report, with the possible exception of a woman with immediate plans to become pregnant or a woman with recurrent disease.

A reduction in the appropriate use of these drugs in depressed pregnant women would be a serious problem because relapse of recurrent depression during pregnancy is exceedingly common, and depression during pregnancy is the strongest predictor of risk for postpartum depression. Reducing the dose or discontinuing the antidepressant around the time of labor and delivery increases the risk of relapse, although some women may tolerate this approach, particularly if the drug is reinstituted immediately post partum.

Physicians should remain vigilant and carefully plan their treatment approach. The data in this study may, in fact, be a signal that a problem exists. But a signal should be some kind of beacon that guides the clinician. In this particular case, we have more fog obscuring any type of guidance for the clinician than we have clarification of an already complicated situation.

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