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What is the Risk of Teratogenicity with the Use of Selective Serotonin Reuptake Inhibitors During Pregnancy?

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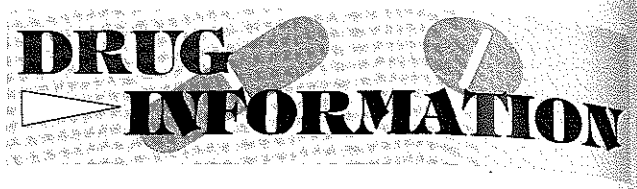
Question: What is the risk of teratogenicity with the use of selective serotonin reuptake inhibitors during pregnancy?



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Background

The lifetime prevalence of major depressive disorder in women is 10 to 25%, with an average age of onset in the mid-20s.[1] Over the nine years that the selective serotonin reuptake inhibitors (SSRIs) have been available, for many prescribers, they have become first-line agents in the treatment of depression. In addition, some of them are also being used in the treatment of obsessive-compulsive disorder and panic disorder. In light of these facts, it is not unlikely that women of childbearing age would be treated with one of the SSRIs.

In considering the risks of exposing a fetus to an SSRI, both structural malformation (i.e., teratogenesis) and long-term behavioral effects (i.e., behavioral teratogenesis) must be considered; in addition, possible side effects and withdrawal syndromes in the newborn must be assessed. It is impossible to be certain that any drug is absolutely safe for use in pregnancy; hence, only an estimate of relative risk can be attempted.

Findings

Most of the data available regarding the effects of SSRIs on the fetus involve the use of fluoxetine. In 1993, Pastuszak and coworkers reported on pregnancy outcome in 128 pregnant women exposed to fluoxetine in the first trimester as compared with two matched groups of women exposed during the first trimester to either tricyclic antidepressants or agents thought to be nonteratogens.[2] They concluded that use of fluoxetine during embryogenesis is not associated with an increased risk of major malformations. Women exposed to both fluoxetine and tricyclic antidepressants tended to report higher rates of miscarriage; however, the investigators could not separate the effects of the psychiatric condition from the associated drugs. Goldstein later reported for the manufacturer of fluoxetine, based on 112 prospectively identified fluoxetine-exposed pregnancies and a comparison with reported rates from the National Hospital Discharge Survey, that it is unlikely that maternal fluoxetine use during the third trimester results in significant postnatal complications.[3]

In 1996, Baum and Misri reviewed the literature on the effects of SSRIs during pregnancy and lactation.[4] They found an increased rate of miscarriage, a greater tendency for infants to be large for their gestational age, and one report of perinatal toxicity. In the same year, Nulman and Koren reported their preliminary findings regarding fluoxetine.[5] They evaluated the neurobehavioral development of 37 children exposed to fluoxetine during the first trimester and 18 infants who were exposed to the drug throughout pregnancy. They reported no significant difference in intelligence quotient (IQ) between fluoxetine-exposed children and controls and concluded that fluoxetine, in recommended doses, is not associated with an increased frequency of structural abnormalities or neurobehavioral impairment.

Chambers and coworkers prospectively studied 228 women taking fluoxetine who had called the California Teratogen Information Service and Clinical Research Program over a six year period and compared them with 254 pregnant women who had called the service with questions regarding drugs and procedures considered not to be teratogenic.[6] Approximately one third of the fluoxetine-treated group took other psychotropic agents, usually a benzodiazepine or other antidepressant. No significant differences were noted between groups with respect to spontaneous pregnancy loss or major structural abnormalities. However, the proportion of children with three or more minor anomalies (structural defects with no functional or cosmetic significance) was significantly higher in the fluoxetine group (15.5%) than in the control group (6.5%). Whether or not children born with three or more minor anomalies are more likely later to develop major structural anomalies is uncertain. The rate of premature deliveries was higher in the women who had taken fluoxetine later in pregnancy (14.3%) than in those exposed in the first and second trimesters (4.1%) or not at all (5.9%). Also, infants exposed to fluoxetine later in pregnancy had higher rates of admission to special-care nurseries (23%), poor neonatal adaptation (including respiratory difficulty, cyanosis on feeding, and jittering), and lower birth weight.

An editorial, by Elizabeth Robert, accompanying the Chambers report, however, identifies several flaws in study design.[7] The study was not randomized; the contribution of maternal depressive illness to birth outcomes was not excluded; the fluoxetine-treated group may not have been adequately matched with the control group (i.e., maternal age was higher in the women taking fluoxetine than in the controls and maternal

weight gain differed between women who had taken fluoxetine early in pregnancy and those who had taken it later which could have accounted for much of the difference in infant birth weights). Robert, therefore, argues that this study provides insufficient evidence to withhold fluoxetine from women who require it during pregnancy.

Most recently, Nulman and coworkers reported their updated findings in the children of 80 mothers who had received a tricyclic antidepressant drug during pregnancy, 55 children whose mothers had received fluoxetine during pregnancy, and 84 children whose mothers had not been exposed during pregnancy to any agent known to affect the fetus adversely.[8] The children's global IQ and language development were assessed between 16 and 86 months of postnatal age. The mean IQ scores were 118 in the children of tricyclic-treated mothers, 117 in those of fluoxetine-treated mothers, and 115 in those in the control group; in addition, the language skills were similar in all three groups. The results were similar in children exposed to a tricyclic antidepressant or fluoxetine during the first trimester and those exposed throughout pregnancy. No significant differences in temperament, mood, arousability, activity level, distractibility, or behavior problems in the three groups of children were noted. The authors concluded that in utero exposure to either tricyclic antidepressants or fluoxetine does not affect global IQ, language development, or behavioral development in preschool children.

Conclusion

There may be some risk of adverse effects on the newborn associated with the use of fluoxetine during pregnancy, especially when taken late in pregnancy. However, the currently available literature leaves the issue incompletely answered. In addition, there is no information on possible teratogenic effects that may become apparent in adolescence or adulthood. To complicate the matter further, the teratogenic potential of untreated major depression in the pregnant woman is unknown. It is clear, however, that there is considerable morbidity and mortality associated with depressive illness. Hence, if SSRI treatment is being considered in a woman of childbearing age, an agent with a relatively short half-life (e.g., sertraline or paroxetine) could be considered rather than fluoxetine; if pregnancy occurred, the drug could be discontinued, and it would clear out of the body more quickly than fluoxetine and its metabolite, norfluoxetine. Unfortunately, though, little is published about the teratogenic effects of the SSRIs other than fluoxetine.

As a general rule, if a woman is being treated prior to becoming pregnant or needs to begin treatment during pregnancy, the lowest effective dose should be used for the shortest possible period of time. Both parents must be informed of the potential risks — both known and unknown — of drug treatment, as well as lack of treatment, and a decision needs to be made in collaboration with the prescriber. That such an informed, collaborative decision has been made should be clearly documented in the patient's medical record.

About the Authors

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References

1. Weissman MM, Bland RC, Canino FJ, Faravelli C, et al. Cross-national epidemiology of major depression and bipolar disorder. *JAMA*. 1996;276:293-9.

2. Pastuszak A, Schick-Boschetto B, Zuber C, Feldkamp M, et al. Pregnancy outcome following first-trimester exposure to fluoxetine (Prozac). *JAMA*. 1993;269:2246-8.

3. Goldstein DJ. Effects of third trimester fluoxetine exposure on the newborn. *J Clin Psychopharmacol*. 1995;15:417-20.

4. Baum AL, Misri S. Selective serotonin-reuptake inhibitors in pregnancy and lactation. *Harvard Rev Psychiatry*. 1996;4:117-25.

5. Nulman I, Koren G. The safety of fluoxetine during pregnancy and lactation. *Teratology*. 1996;53:304-8.

6. Chambers CD, Johnson KA, Dick LM, Felix RJ, et al. Birth outcomes in pregnant women taking fluoxetine. *N Engl J Med*. 1996;335:1010-15.

7. Robert E. Treating depression in pregnancy (editorial). *N Engl J Med*. 1996;335:1056-58.

8. Nulman I, Rovet J, Stewart DE, Wolpin J, et al. Neurodevelopment of children exposed in utero to antidepressant drugs. *N Engl J Med*. 1997;336:258-62.