



Disclaimer: This newsletter, provided by ITIS, is funded by a grant from the Illinois Department of Public Health and supported by Northwestern Memorial Hospital and Northwestern University Medical School. It is for educational purposes only and is meant to summarize the information available at the time of its creation. It should be construed neither as medical advice nor opinion on any specific clinical situation. For more information on a specific clinical situation, or updated information, please consult your health care provider.

Fluoxetine and Pregnancy

Vol 4#3, December 1995

Eugene Pergament, MD, Ph.D.; Amy Schechtman, MS, CGC; Stacy Owen, BA

Fluoxetine (Prozac) is a medication used in North America by millions of patients with major depression (Pastuszak et al., 1993). It is probably the most commonly prescribed anti-depressant. This medication is an oral anti-depressant which selectively inhibits serotonin reuptake by neurons, thus prolonging the action of this neurotransmitter. Not chemically related to the more traditional tricyclic anti-depressants, fluoxetine has enhanced specificity and potency. These properties are due to its specific effects on serotonin uptake and the long elimination half-life in vivo of fluoxetine (2-3 days) and its active metabolite, norfluoxetine (7-9 days) (Pohland et al., 1989). Moreover, one of the medical benefits of prescribing this medication rather than a tricyclic anti-depressant is that fluoxetine use results in fewer and milder dose-related side effects (Edwards et al., 1994).

A significant number of women of reproductive age suffer from depression, necessitating long-term therapy with psychotropic drugs. It is important therefore to consider the potential reproductive effects of fluoxetine. It is estimated that as many as 10% of pregnant women meet the criteria for major and minor depression and that even larger numbers are affected during the post-partum period (O'Hara et al., 1994). Manufacturers and health providers often suggest that women not be treated with psychotropic medications during gestation. This generalized recommendation fails to acknowledge the role that a psychotropic medication, such as fluoxetine, may play in maintaining the health and well-being of some affected women. It is important to consider that the discontinuation of therapy may endanger the health of women and the safety of their pregnancies.

Thus, the potential benefits of therapy to a woman must be considered in relation to any potential reproductive risks associated with the medication. This issue of RISK||NEWSLETTER will review the potential reproductive risks of fluoxetine use in pregnant women.

RISK FOR CONGENITAL MALFORMATIONS

Human studies and case reports provide no evidence to suggest that fluoxetine is teratogenic. A cohort study performed at four teratogen information services found that the incidence of congenital anomalies was not increased among infants born to 128 women who took fluoxetine during the first trimester of pregnancy (Pastuszak et al., 1993). The rate of major malformations in the infants exposed to fluoxetine during the first trimester was not statistically different from the rate reported in the unexposed control group (2% vs. 1.8%; $p=.38$) (Pastuszak et al., 1993). Similar findings have been reported in an abstract by Schick-Boschetto and Zuber (1992).

A separate abstract from the California Teratogen Information Service reported the pregnancy outcome

of 107 women who had been exposed to fluoxetine during their pregnancies. Although a control group was not included in this study, there was no evidence of an increased incidence of birth defects among the infants born to the women in this cohort (Chambers et al., 1992).

The frequency of congenital anomalies did not appear to be increased among the infants of 485 women voluntarily reporting to the manufacturer during pregnancies in which fluoxetine was prescribed. In this population, 13 malformations were reported, with an incidence of 3.4%. Among 28 infants with major congenital anomalies which were retrospectively reported to the manufacturer, no recurrent pattern of malformations were apparent (Goldstein and Marvel, 1993). The inconsistent pattern of anomalies does not suggest a causative relationship between fluoxetine and congenital malformations.

Data from animal studies also suggest that fluoxetine is unlikely to pose a substantial teratogenic risk. According to the manufacturer (Eli Lilly), the frequency of malformations was not increased among the offspring of rats administered 9-11 times the maximum dose of this medication generally prescribed for humans (Byrd et al., 1989).

A second animal study found an increased incidence of skin hematomas in the offspring of rats that were administered fluoxetine on a mg/kg basis in doses which were 17 times higher than those generally prescribed for humans (Stanford and Patton, 1993). This study suggests that exposure to fluoxetine in utero may affect the serotonergic aspects of vascular activity and cause exposed offspring to be highly susceptible to bruising and hematomas during the birth process. However, this study did not suggest that long term susceptibility to bleeding and bruising results from in utero exposure (Stanford and Patton, 1993). No reports of hematomas have been made in the offspring of women exposed to fluoxetine during pregnancy.

RISK FOR MISCARRIAGE

The rate of miscarriage was evaluated in the prospective study of 128 women treated with therapeutic doses of fluoxetine during the first trimester of pregnancy (Pastuszak et al., 1993). Two matched control groups were selected for this study: one with exposure to non-teratogens and one with exposure to tricyclic anti-depressants. There was a tendency for a higher percentage of miscarriages in the 128 fluoxetine patients in comparison to the non-exposed group, but it did not reach statistical significance (14.8% vs. 7.8%; RR 1.9%; 95% CI, 0.92-3.92). However, the sample size of this cohort had limited power to show statistical significance. In addition, women exposed to tricyclic anti-depressants tended to report higher rates of miscarriage when compared to the control group (13.5% fluoxetine group; 12.2% tricyclic antidepressant group; 6.8% control group). The authors suggest that additional studies are necessary to document this finding and to determine whether the reported tendency towards higher rates of miscarriage results from the psychotropic medications or the effects of a psychiatric condition (Pastuszak et al., 1993).

Data from the prospective study of Chambers et al., (1993) did not suggest an increased risk for miscarriage among women exposed to fluoxetine. However, the data suggested an association between maternal exposure to fluoxetine and large-for-gestational age infants. In this study, 39% of the infants born to women who had taken fluoxetine during pregnancy were above the 90th percentile in weight. No other studies have reported a similar association between maternal use of fluoxetine during pregnancy and infants who are born large-for-gestational age.

RISK FOR NEUROBEHAVIORAL EFFECTS

Fluoxetine alters neurotransmitters in the brain of a person who is exposed to this medication.

Therefore, there is a theoretical risk that this medication could potentially affect brain development in an exposed fetus.

Most of the information that is available concerning this issue has come from animal studies. One study evaluated the behavioral effects of fluoxetine on the offspring of rats treated with doses as high as 12 mg/kg/day. At no dose was there evidence in the offspring of behavioral abnormalities attributed to the maternal fluoxetine treatment (Vorheers et al., 1994).

In contrast, at least one published study reported a short-term effect on the neurobehavior of rats exposed prenatally to fluoxetine (Montero, 1990). However, it has not been determined whether these findings in an animal model have relevance to human pregnancy.

There has been one case report of a neonate with transient central nervous system toxicity with measurable cord blood levels of fluoxetine and its metabolite norfluoxetine (Spencer, 1993). In this case the symptoms reportedly resolved four days after birth. In the future, long term studies will be required to rule out potential neurodevelopmental teratology of fluoxetine (Pastuszak et al., 1993).

RISK FROM BREASTFEEDING

It is known that fluoxetine is excreted into human breast milk. An estimate of total fluoxetine intake by a suckling infant is 15-20 ug/kg/day, which contributes a very low level of exposure (Birchland and Wells, 1992). Although the level of exposure in breast feeding infants is seemingly low, the concern about possible effects on neonates exposed to fluoxetine has been raised in case reports. One group reported a possible association between exposure to fluoxetine and colic in one infant (Lester et al., 1993). A second report of increased irritability in a suckling infant during the first two weeks of therapy has also been made (Isenberg, 1990). However, it is important to note that there were differences among those who observed these infants in regard to the infants' symptoms and their association with fluoxetine exposure.

Serotonin is an inhibitor of suckling-induced oxytocin release. This effect has been intensified by exposure to fluoxetine in anesthetized rats (Moos, 1983). This finding raises the possibility that fluoxetine may hinder the nursing process. However, inhibition of oxytocin release was not consistent throughout the study by Moos (1993). Serotonin inhibition of oxytocin release was not observed among rats given fluoxetine but not anesthetized (Spencer, 1993).

Based on limited data, the American Academy of Pediatrics considers the effects of fluoxetine on a nursing infant to be undetermined. Concern about possible effects of this medication on exposed neonates has led the manufacturer to revise its label for fluoxetine and to recommend that it not be used by nursing mothers (Nightengale, 1994). Those women who use fluoxetine during lactation should be advised to be aware of any changes in their infants behavior (e.g., agitation, irritability, drowsiness, ect.), which may be associated with neonatal fluoxetine exposure.

SUMMARY

Based on human and animal studies, there is no evidence to suggest that the use of fluoxetine during pregnancy is associated with an increased risk for major congenital malformations. Concern regarding a relationship between an increased risk for miscarriage among women who have used fluoxetine or tricyclic anti-depressant has been raised. However, the results were not found to be statistically significant. Additional studies will be necessary to document this finding and to determine whether the reported tendency towards higher rates of miscarriage results from the psychotropic medications or the effects of a psychiatric conditions. No information is available concerning what effect, if any, fetal or

neonatal exposure may have on neurobehavioral development.

Based on the available data, it can be concluded that there are potential benefits and risks to using fluoxetine during pregnancy and lactation. Thus, the use of fluoxetine should only be recommended if the benefit of anti-depressant therapy to the woman outweighs any potential reproductive risks.

For more on the web: [about Prozac](#)