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The Safety of Fluoxetine During Pregnancy and Lactation

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Many women develop, or have a recurrence of, psychiatric illnesses during gestation. Recent studies show that up to 35% of women may be using psychoactive drugs during pregnancy (Goodman, '92). In addition, the postpartum period may be extremely vulnerable for the development of mood disorders while breastfeeding (Reich and Winokur, '70; Meleges, '68; Kendell et al., '87).

Depression is associated with significant morbidity and economic costs (Stoudemire et al., '86; Rice and Miller, '93; Rupp, '95). Left untreated, suicide may be as frequent as 15% (Georgatos, '85; Altshuler and Szyba, '94). The lifetime prevalence for major depression in women ranges from 9% to 26% (Goodman, '80; Boyd and Weissman, '81), and rates of current depression for mothers with children less than 5 years old in the United States range from 12% to 20% (Bromet et al., '86). The median age of onset is 25 years for unipolar and 18 years for bipolar depression (Christie et al., '88).

Although effective pharmacologic therapy has been available for more than 40 years, substantial degrees of adverse effects have led to inadequate dosing and premature discontinuation of therapy, often due to poor patient compliance.

Fluoxetine (Prozac®) was introduced to clinical use in 1988. This drug, the first selective serotinin reuptake inhibitor (SSRI), represents a major advance in the pharmacological management of depression. Although there is still debate whether fluoxetine is as effective as existing tricyclic antidepressants (TCAs) (Gram, '94), it lacks the dose-limiting adverse effects encountered by TCA. Because of its long elimination half-life, fluoxetine requires no titration and can be given once daily, which may lead to improved patients' compliance. The drug is also substantially safer in overdose (Gram, '94), an important characteristic, in view of the large number of suicide attempts among depressive patients (Goodwin, '90; Roose et al., '83).

Fluoxetine is currently the most widely prescribed antidepressant drug in the United States and Canada and is also widely used in other parts of the world. Its manufacturer has estimated the population of patients treated with fluoxetine in 1994 to be approximately 15 million worldwide.

Because more than one-half of the pregnancies in North America are unplanned (Sophocles and Manol Brozovich, '86), many unplanned fetal exposures occur. Indeed, similar to other Teratogen Information Services all over North America, the Motherisk program in Toronto has experienced a large number of inquiries regarding the safety of fluoxetine in pregnancy. As expected, physicians who consulted the manufacturer received the characteristic noncommitting statement. In its product monograph, the manufacturer (Eli Lilly, Canada, Inc., Ltd.) suggests that fluoxetine not be given to women of childbearing potential "unless, in the opinion of the treating physician, the expected benefits to the patient markedly overweigh the possible hazards to the child or fetus." Although such disclaimers represent an understandable medicolegal approach for drug manufacturers in a very litigious society, they leave physicians and patients confused. This approach is even more frustrating when the available body of knowledge is large, making the statement by the manufacturer that "safe use of fluoxetine during pregnancy and lactation has not been established" incorrect and even misleading. In our view, manufacturers should provide physicians with all available postmarketing data as part of their product monograph.

This article reviews available animal and human data on the reproductive safety of fluoxetine, we will consider this information in the context of the criteria used to identify human teratogens (Shepard, '86).

ANIMAL STUDIES

Pohland et al. ('89) used whole-body autoradiographic techniques to determine the placental transfer and fetal distribution of a single oral dose of 12.5 mg/kg of [^{14}C]-labeled fluoxetine in 12- and 18-day pregnant Wistar rats. Combined concentrations of fluoxetine and its metabolite norfluoxetine accounted for 63–80% of the fetal radiocarbon concentrations in embryonic/

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fetal tissue and radioactivity associated with [^{14}C]fluoxetine and/or its metabolites crossed the placenta and distributed throughout the 18-day fetus at 4 hr following drug administration. The highest fetal concentrations of radiocarbon were measured in the brain and thymus. This was the first direct evidence that fluoxetine and its main metabolite cross the placenta and distribute within the embryo or fetus.

Shuey et al. ('92) assessed craniofacial morphogenesis following exposure to mouse embryos in whole embryo culture to serotonin uptake inhibitors (sertraline, fluoxetine, and amitriptyline). Exposure to sertraline, fluoxetine, and amitryptiline at concentrations of 10 μmols/L, caused craniofacial malformations consistent with direct effect at 5-HT receptor sites. These concentrations are in order of magnitude higher than those achieved in patients receiving the drug. The craniofacial defects were associated with decreased proliferation and extensive cell death in mesenchymal tissue located 5–6 cell layers deep from the overlying epithelium, whereas the subepithelial mesenchymal layers showed normal or even elevated levels of proliferation. These observations suggest that inhibition of 5-Hydroxytzyptamine (5-HT) uptake into craniofacial epithelia may produce developmental defects by interference with serotonergic regulation of epithelial–mesenchymal interactions vital for normal craniofacial morphogenesis. Subsequent morphological studies performed in rats and rabbits receiving 9 and 11 times the maximum daily human dose per kg of body weight have failed to show evidence of teratogenicity of changes in reproductive parameters (Goldstein, '90). To date, no behavioral teratology study has been reported with fluoxetine in animals.

HUMAN STUDIES

A phenomenon related to the introduction of a new drug is that the manufacturer may be the first one contacted by physicians or pregnant women. This spontaneous reporting system, while having the immediacy of generating data quit soon after a new drug is released, suffers from serious methodological problems such as selection and reporting bias. For example, it has been shown with isotretinoin that prospectively collected cases had a malformation rate of 40%, whereas the company-notified cases had an 80% of major malformations, meaning that many unaffected cases exposed to the drug are unreported (Koren, '86).

Over the past few years, the manufacturer of fluoxetine has collected substantial teratological information in humans from clinical trials and from its postmarketing spontaneous reports. Clinical trials with fluoxetine included 75 pregnancy reports of first-trimester exposure and outcome information was available for 60. There were 23 normal live births, 25 therapeutic abortions with no abnormalities detected, 8 spontaneous abortions, and three twin pregnancies (Goldstein et al., '91). The extremely high rate of therapeutic abortions might have been the result of the nature, or lack, of information given to the women. Alternatively, it could be the result of the mental status of the patients.

In a postmarketing report that summarized the outcome of 1,446 spontaneous prospective reports of women exposed to fluoxetine during pregnancy, outcome data were available for 723 pregnancies. There were 476 normal live births, 20 premature births, and 105 therapeutic abortions, 81 spontaneous abortions, 14 twin pregnancies without malformations, three stillbirths, 14 perinatal major malformations, and 10 postperinatal malformations (e.g., pyloric stenosis). The above reports, while impressive in number, do not permit determination of a true incidence of any birth abnormality, because of major methodological problems, such as unknown original sources, absence of proper control groups, poor quality of the follow-up documentation, and reporting bias.

The California Teratogen Information Service has ascertained prospectively and followed 107 women treated with Prozac during pregnancy (Chambers et al., '93). Of the 107 completed cases there were 80 live births, 10 spontaneous abortions, 13 therapeutic abortions, and 3 cases lost to follow-up. There were six major malformations; however, two of them (an Ebstein's anomaly and the VATER Association) occurred in women whose exposure to fluoxetine began during the second trimester. Of the other four, one had Down's syndrome and one had a congenital hip dislocation. In terms of perinatal complications, 16 out of 80 neonates required admission to the neonatal intensive care unit, and 11 were born prematurely. The investigators noted that 39% of their infants were above the 90 percentile for birth weight. This suggestion, however, is difficult to confirm with the lack of an appropriate control group. Unfortunately, the brief nature of this report does not allow separation of data for first-trimester versus second-trimester exposure.

Pastuszak and colleagues ('93) reported the first prospective, controlled study of pregnancy outcome after fluoxetine exposure during the first trimester, with patients enrolled by four Teratogen Information Services in the United States and Canada. This collaborative study collected 128 women exposed to a daily mean of 25.8 ± 13 mg of Prozac during the first trimester and compared pregnancy outcome with matched groups of women exposed during the period of embryogenesis either to tricyclic antidepressants (TCA) or to nonteratogenic drugs (e.g., acetaminophen, penicillins, or dental x-rays). The rationale for a control group of depressed women treated with TCA was to account for any potential effects that depression may have, either directly or indirectly, on the fetus. There was no difference in the rates of major birth defects when the live births exposed to fluoxetine were compared with both control groups. (3.4% vs. 0 [TCA] vs. 3% nonteratogens). In an

analysis of the birth defects, no specific pattern of malformation was found. Women treated with both fluoxetine and TCAs had a tendency toward higher reported miscarriage rates than did the nonteratogen control group. The investigators speculated that this may represent either a true biological effect of the drug or of the psychiatric illness or a reporting bias, with "miscarriage" more socially acceptable than "elective abortion." In view of the high rates of elective abortions reported by the manufacturer (see above), this second option must be examined in future studies.

At that stage, it was concluded by the Motherisk Program and by other Teratogen Information Services that first trimester exposure to fluoxetine would not indicate a significant reproductive risk and should not be an indication for an elective termination of pregnancy. Yet unanswered questions remain to be addressed:

1. Does the drug affect adversely the development of the fetal central nervous system, causing anomalies (either anatomic or neurobehavioral) that may not be detected by routine follow-up, such as the evaluation conducted by Pastuszak et al. ('93)?
2. Can a women take fluoxetine to control depression throughout gestation?

To address the first question, we began a prospective study in 1993, in which the neurobehavioral development of children exposed in utero to fluoxetine was assessed. This was part of a larger prospective study of women exposed to monotherapy with several different antidepressants (Nulman et al., '96). The control group for this study consisted of children exposed in utero to nonteratogens whose mothers had been counseled prospectively by the Motherisk Program in a similar manner. We have enrolled and evaluated of 37 children exposed to fluoxetine during the first trimester and an additional 18 children who had been exposed to the drug throughout pregnancy.

Children aged 18–30 months were tested by means of the Bayley scales of infant development (Bayley, '69) and beyond that age with the McCarthy test (McCarthy, 1972). The global IQ scores for children (n = 40) of the younger group ranged from 84 to 150, with a very favorable mean of 117 ± 17. In the older children measured with the McCarthy tests (n = 14) the lowest IQ score was 85 and the highest 145, with a favorable mean of 114 ± 16 (Table 1). We found a significant correlation between maternal and child's IQ. While full evaluation of other neurobehavioral tests will be completed in the near future, these data are reassuring. Similar results were obtained for the relatively small group of 18 offspring exposed to fluoxetine during the whole pregnancy.

A summary of the information available on the fetal effects of fluoxetine is presented in Table 2, along with the characteristics of a human teratogen (Shepard, '86). Although some long-term neurobehavioral studies after whole gestation exposure are unavailable, data are encouraging.

TABLE 1. IQ in children exposed in utero to fluoxetine monotherapy

	Fluoxetine	NTC	*P*
Bayley MDI	117 ± 17	115 ± 14	NS
McCarthy GCI	114 ± 16	114 ± 13	NS

NTC, nonteratogenic controls; NS, nonsignificant.
MDI-Mental Development Index
GCI-General Cognitive Index

It appears that, when used clinically in recommended doses, in humans, fluoxetine has not been shown to produce an increase in the frequency of morphological abnormalities or effects on neurobehavior.

PERINATAL EFFECTS

A case of possible toxicity in a neonate exposed to 20 mg/day fluoxetine throughout gestation was reported by (Spenser, '93). Starting at 4 hr of age the baby exhibited marked acrocyanosis, tachypnea, jitteriness, temperature instability, opistotonic head position, eye rolling, and seizures. At 96 hr of age all symptoms disappeared. The cord blood level of fluoxetine was 26 ng/ml and of norfluoxetine, an active metabolite of fluoxetine, was 54 ng/ml.

SAFETY OF FLUOXETINE DURING BREASTFEEDING

The advantages of breastfeeding are well known. This makes it mandatory for a physician caring for the mother and her infant to be very careful before recommending that it be discontinued. Similarly, stopping antidepressant therapy abruptly may lead to serious consequences to maternal well-being. Until recently two negative (Burch and Wells, '92; Isenberg, '90) and one positive case reports (Lester et al., '93) were the only data to assist physicians in this difficult situation. In the positive case, an infant was colicky while being breastfed by a mother who received 20 mg of fluoxetine daily. Four days after switching to a formula, the symptoms subsided. However, the symptoms recurred 3 weeks later while still on formula feeding, suggesting that fluoxetine might not have been the cause for the colics.

We recently completed the first study to measure the amounts of fluoxetine and its active metabolite, norfluoxetine, in breast milk, and evaluated short-term adverse effects in nursing infants during maternal therapy (Taddio et al., '94). Ten women nursing 11 infants collected milk samples while using a mean daily dose of 0.39 mg/kg of fluoxetine. Fluoxetine and norfluoxetine milk concentrations were measured by gas–

TABLE 2. Evaluation of the teratogenic potential of fluoxetine by adapted criteria

Criterion	Evidence or potential	Conclusion
Exposure during critical times of development	Yes	Yes
Biological plausibility	Potential interference with developing neurotransmitters	Yes
Animal dysmorphology	Negative studies with doses up to 10-fold higher than human per kg body weight	No
Clustering of case reports	No	No
Homogeneity in case reports	No	No
Controlled human studies	Negative results	No
Animal behavioral teratology	Unavailable	Unavailable
Human behavioral teratology	First-trimester exposure—normal IQ whole pregnancy exposure—normal IQ No other neurodevelopmental data yet available	"Partial" No

From Shepard ('86).

liquid chromatography. Mothers reported any clinical events they observed in the infant.

The average infant dose of total fluoxetine (fluoxetine and the metabolite norfluoxetine) estimated for an exclusively breast-fed infant was 6.7% ± 1.4% of the corresponding maternal dose on a milligram-per kilogram basis (mean ± SD; range, 4.8–9.2%). The infant dose correlated highly with the maternal dose ($r^2 = 0.86$). In the 11 infants studied, no short-term adverse events were reported by the mothers. From these observations, we concluded that less than 10% of the adult therapeutic dose of fluoxetine (per kilogram body weight) is delivered to the nursing infant during chronic maternal therapy. While future studies which assess the potential long-term effects are warranted, we presently encourage women to continue breastfeeding while using fluoxetine (Taddio et al., '94).

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