

## BIRTH OUTCOMES IN PREGNANT WOMEN TAKING FLUOXETINE

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### ABSTRACT

**Background** Although fluoxetine is the most frequently prescribed antidepressant drug in the United States, its safety in pregnant women has not been established.

**Methods** From 1989 through 1995, we prospectively identified 228 pregnant women taking fluoxetine. We compared the outcomes of their pregnancies with those of 254 women identified in a similar manner who were not taking fluoxetine.

**Results** The rate of spontaneous pregnancy loss did not differ significantly between the women treated with fluoxetine and the control women (10.5 percent and 9.1 percent, respectively), nor was the rate of major structural anomalies significantly different (5.5 percent vs. 4.0 percent). Among the 97 infants exposed to fluoxetine who were evaluated for minor anomalies, the incidence of three or more minor anomalies was significantly higher than among 153 similarly examined control infants (15.5 percent vs. 6.5 percent,  $P=0.03$ ). As compared with the 101 infants exposed to fluoxetine only during the first and second trimesters, the 73 infants exposed during the third trimester had higher rates of premature delivery (relative risk, 4.8; 95 percent confidence interval, 1.1 to 20.8), admission to special-care nurseries (relative risk, 2.6; 95 percent confidence interval, 1.1 to 6.9), and poor neonatal adaptation, including respiratory difficulty, cyanosis on feeding, and jitteriness (relative risk, 8.7; 95 percent confidence interval, 2.9 to 26.6). Birth weight was also lower and birth length shorter in infants exposed to fluoxetine late in gestation.

**Conclusions** Women who take fluoxetine during pregnancy do not have an increased risk of spontaneous pregnancy loss or major fetal anomalies, but women who take fluoxetine in the third trimester are at increased risk for perinatal complications. (N Engl J Med 1996;335:1010-5.)

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**T**HE selective inhibitor of serotonin reuptake fluoxetine (Prozac) has become the most commonly used antidepressant drug in the United States. Despite its wide use in patients of both sexes and all ages, its safety in pregnant women has not been adequately evaluated.

According to outcome information on 783 pregnancies prospectively collected by the manufacturer of the drug through mid-1994, the rates of major anomalies (4.5 percent), spontaneous abortion or stillbirth (11.9 percent), and premature delivery (3.7 percent) associated with fluoxetine use did not exceed rates expected in the overall population. On

the basis of cases from the same data base, there was no increase in perinatal complications in 112 women who took fluoxetine during the third trimester.<sup>1</sup> However, these data are difficult to interpret in the absence of a comparison group and given the high proportion of pregnancies (379, or 32.6 percent of those prospectively ascertained) for which there was no information about outcome.

Between 1988 and 1992, the Michigan Medicaid surveillance program identified 109 infants whose mothers had received fluoxetine during pregnancy. The rate of major anomalies in the infants (1.8 percent) did not exceed the expected rate of 3 to 4 percent.<sup>2</sup> In another study of 128 women who received fluoxetine during the first trimester of pregnancy, there was no greater incidence of structural anomalies or perinatal complications than in pregnant women who received tricyclic antidepressant drugs.<sup>3</sup>

Our study was undertaken to determine the effects of treatment with fluoxetine during the first trimester of pregnancy on the frequency of major and minor structural anomalies in infants and the effects of treatment during the third trimester on birth size, gestational age, and neonatal adaptation.

### METHODS

From 1989 through 1995, the California Teratogen Information Service and Clinical Research Program received approximately 1500 calls requesting information on the potential teratogenic effects of fluoxetine. An estimated one third of these inquiries were made by pregnant women currently taking the drug. We selected 228 of these women for inclusion in the study on the basis of accessibility by telephone and willingness to participate. During this same period, pregnant women who called the program with questions about drugs and procedures not considered teratogenic — including acetaminophen use, dental radiography, and limited alcohol ingestion ( $\leq 1$  oz [30 ml] of 100 percent alcohol per week before pregnancy was recognized) — were asked to enroll in the study as a control group. From this group, 254 women were selected as controls because their inquiries were closest in time to those of the women taking fluoxetine. The majority of women in each group were enrolled in the study during the first trimester of their pregnancies (Table 1), and all were enrolled before any outcomes of the pregnancy were known, including knowledge of conditions that were diagnosed prenatally.

Each woman who enrolled in the study completed a questionnaire that included her history of previous pregnancies and family medical history, socioeconomic and demographic information for each woman and her partner, and exposures during the current pregnancy. The exposure history included dosages, dates, and indi-

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**TABLE 1.** CHARACTERISTICS OF WOMEN TAKING FLUOXETINE AND CONTROL WOMEN AND OUTCOMES OF PREGNANCY.

VARIABLE	FLUOXETINE GROUPS		CONTROL GROUP	P VALUE
	EXPOSED EARLY	EXPOSED LATE		
<b>Maternal characteristics*</b>				
Age — yr	32±5	32±6	30±5	<0.001
Gravidity — no.	3.0±1.8	3.3±1.9	2.4±1.4	<0.001
Parity — no.	0.9±1.1	1.0±1.2	0.8±1.0	0.35
No. of previous spontaneous abortions	0.4±0.9	0.4±0.7	0.3±0.7	0.43
No. of previous therapeutic abortions	0.7±1.0	1.0±1.4	0.4±0.7	<0.001
Weight gain — kg†	17±7	14±7	—	0.01
Average dose of fluoxetine — mg	28±15	25±10	—	0.15
Trimester of entry into the study — no. of women (%)				0.001
First	82 (82.0)	45 (61.6)	137 (61.4)	
Second	16 (16.0)	16 (21.9)	57 (25.6)	
Third	2 (2.0)	12 (16.4)	29 (13.0)	
Trimester of fluoxetine therapy — no. of women (%)				
First only	93 (93.0)			
First and second	7 (7.0)			
First, second, and third		60 (82.2)		
Second and third		7 (9.6)		
Third only		4 (5.5)		
First and third		2 (2.7)		
Cesarean section	35 (35.0)	29 (39.7)	45 (20.2)	<0.001
First cesarean section	22 (22.0)	20 (27.4)	33 (14.8)	0.04
<b>Birth outcome and examination‡</b>				
Live-born infant — no. (%)	101 (65.2)§	73 (98.6)	226 (87.6)§	<0.001
Mode of infant examination — no. (%)				0.07
By investigator	60 (59.4)	44 (60.2)	153 (67.7)§	
By own physician	33 (32.7)§	21 (28.8)	43 (19.0)§	
By maternal report	8 (7.9)	8 (11.0)	30 (13.3)§	
Spontaneous abortion — no. (%)	23 (10.0)¶		22 (8.5)	0.59
Stillbirth — no. (%)	0	1 (0.4)	2 (0.8)§	1.00
Ectopic pregnancy — no. (%)	1 (0.4)		0	0.47
Therapeutic abortion — no. (%)	22 (9.6)		7 (2.7)	0.002
Loss to follow-up — no. (%)	8 (3.5)		1 (0.4)	0.02

\*Data on maternal characteristics were available for 100 mothers of live-born infants in the exposed-early group, 73 in the exposed-late group, and 223 in the control group. Plus-minus values are means ±SD.

†Values include women with full-term pregnancies only; there were insufficient data on the control group.

‡Data on birth outcomes were available for all 154 women in the exposed-early group, all 74 women in the exposed-late group, and all 254 women in the control group.

§Values include twins.

¶Values were calculated with a denominator of 228 women treated with fluoxetine; among fluoxetine-treated women who enrolled in the study during the first trimester and who had first-trimester exposure, the rate of spontaneous abortion was 23 of 169 (13.6 percent).

cations for all medications; use of caffeine; use of supplemental vitamins; occupational exposures; infectious or chronic disease; prenatal testing or other medical procedures; and use of recreational drugs, tobacco, and alcohol. Each woman was provided with a diary in which she was asked to keep a record of any additional exposures that might occur before delivery. We supplemented this record by calling the women throughout their pregnancies.

Birth outcome was recorded on a standard form completed by telephone interview with each mother shortly after delivery, and medical records were examined after their release. In addition, the infant's physician was asked to return a form reporting the presence or absence of any major anomaly, defined as a structural defect occurring in less than 4 percent of the general population that has cosmetic or functional importance. When possible, infants were examined by one of us (K.L.J.) for both major and minor anomalies, the latter defined as structural defects that have no cosmetic or functional importance and that are known to occur

in less than 4 percent of the general population.<sup>4</sup> Infants with minor anomalies were evaluated with the use of a standard checklist itemizing 132 such anomalies; the examiner was not aware of the mothers' study groups. A small proportion of birth outcomes (11.5 percent) were reported only by the mother. In all cases, physical examinations were performed and medical records were released only after informed consent was given by the mothers.

We evaluated socioeconomic status using data collected during the initial survey to calculate the Hollingshead four-factor index (Hollingshead AB: unpublished working paper, 1975), which is a modernized version of a previously published and well-validated index.<sup>5</sup>

**Evaluation of Outcomes**

With respect to major structural anomalies, all infants exposed to fluoxetine during the first trimester were included in the anal-

**TABLE 2.** MAJOR AND MINOR STRUCTURAL ANOMALIES IN INFANTS OF FLUOXETINE-TREATED WOMEN AND CONTROL WOMEN.

VARIABLE	INFANTS EXPOSED TO FLUOXETINE IN THE FIRST TRIMESTER		CONTROL INFANTS	P VALUE
	number (percent)			
Major structural anomalies*				
Multiple malformation syndromes			1	
VATER association†				
Total	0		1 (0.4)	
Major malformations				
Ventricular septal defect	1		1	
Ventricular septal defect, with bilateral cryptorchidism	1			
Atrial septal defect	1			
Nasal dermoid sinus	1			
Coccygeal dermal sinus	1			
Hypospadias	1		2	
Bilateral inguinal hernia			2	
Cleft palate			1	
Total	6 (3.7)		6 (2.7)	0.57
Deformations				
Sagittal synostosis	1			
Bilateral hip dysplasia	2			
Unilateral hip dysplasia			2	
Total	3 (1.8)		2 (0.9)	0.65
All major structural anomalies	9 (5.5)		9 (4.0)	0.63
Minor structural anomalies‡				
0-1	56 (57.7)	119 (77.8)		0.002
2	26 (26.8)	24 (15.7)		0.04
≥3	15 (15.5)	10 (6.5)		0.03

\*Data on major structural anomalies were available for 164 live-born infants exposed to fluoxetine during the first trimester and 226 live-born infants in the control group.

†VATER is a nonrandom association of vertebral defects, imperforate anus, and esophageal atresia with tracheoesophageal fistula and renal dysplasia.

‡Data on minor structural anomalies were available for 97 live-born infants exposed to fluoxetine during the first trimester and 153 live-born infants in the control group.

ysis. The assessment of minor anomalies was restricted to the infants exposed during the first trimester who were examined by one of us (K.L.J.).

Because we hypothesized that birth size, gestational age, and neonatal adaptation were influenced by exposure to fluoxetine late in gestation, the women treated with fluoxetine were then divided into two groups on the basis of trimester of exposure. The first group of women, subsequently referred to as the exposed-early group, discontinued the drug in the first or second trimester (before 25 weeks of gestation) and never resumed taking it. The second group, subsequently referred to as the exposed-late group, continued to take the drug into the third trimester (after 24 weeks of gestation).

Prematurity was defined as spontaneous delivery at less than 37 weeks' gestation. Admission to a special-care nursery was defined as admission to a level 2 or 3 nursery for any length of time. Poor neonatal adaptation was defined as reported jitteriness, tachypnea, hypoglycemia, hypothermia, poor tone, respiratory distress, weak or absent cry, or desaturation on feeding. These items were extracted from newborn nursery records for 85 percent of exposed infants. Infants were classified according to neonatal-adaptation status by one of the investigators and then by a second observer, who was unaware of the infants' exposure status (kappa statistic, 0.93).

### Statistical Analysis

We conducted univariate categorical analyses using the chi-square test or Fisher's exact test. Two-sample t-tests were used for two-group comparisons and analysis of variance for three-group comparisons of normally distributed continuous variables. Kruskal-Wallis analysis of variance was used to compare three groups when the data were nonparametric.

Multiple linear regression analysis was used to assess the relation between exposure and birth weight in full-term infants. Unconditional logistic-regression analysis was used to evaluate prematurity, admission to special-care nurseries, and neonatal adaptation. In the regression models, a confounding factor was included if it changed the estimate of the effect of exposure by more than 10 percent. Additional risk factors such as maternal age and average dose of fluoxetine were also included, whether or not they were confounders. All variables were entered simultaneously. Data analyses were conducted with the use of the SPSS statistical-software package, version 6.1. All statistical tests were two-tailed.

### RESULTS

The characteristics of the women in the three study groups who had live-born infants are shown in Table 1. The women in all groups were predominantly white, and most received early prenatal care. Less than 1 percent of the women had a previous child with a birth defect. Of the 100 women in the exposed-early group, 93 (93.0 percent) discontinued fluoxetine in the first trimester and did not resume taking it. Of the 73 women in the exposed-late group, 60 (82.2 percent) took fluoxetine throughout their pregnancies. With respect to the presumed presence of the drug in the infants at birth, 66 (90.4 percent) of the exposed-late group took the drug within two days of delivery.

The primary indication for treatment with fluoxetine was depression (133 women [76.9 percent]); other conditions included anxiety (14 women [8.1 percent]), panic disorder (11 women [6.4 percent]), bipolar disorder (10 women [5.8 percent]), and obsessive-compulsive disorder (7 women [4.0 percent]).

Approximately 30 percent of the women in the fluoxetine groups were taking other psychotherapeutic medications, most commonly a benzodiazepine (clonazepam or alprazolam [17.5 percent]), trazodone (5.2 percent), or a tricyclic antidepressant drug (5.2 percent). Substantial alcohol use (>1 oz of 100 percent alcohol per week) was reported infrequently (exposed-early group, 5.0 percent; exposed-late group, 1.5 percent; control group, 0 percent). Less than 1 percent of all the women reported the use of recreational drugs. The proportion of women who continued to smoke after they knew they were pregnant was higher in both fluoxetine groups (exposed-early group, 10.0 percent; exposed-late group, 17.8 percent) than in the control group (3.8 percent).

Nine of the 163 women who took fluoxetine in the first trimester of their pregnancies delivered live-born infants with major structural anomalies (Table 2). In addition, one fetus was prenatally found to have trisomy 21 and was electively aborted. A second spontaneously aborted fetus was found to have

femoral hypoplasia–unusual facies syndrome, a condition associated with maternal diabetes. The rate of major structural anomalies in the offspring of women in the two fluoxetine groups (5.5 percent) was not significantly higher than in the offspring of women in the control group (4.0 percent), nor was any pattern evident. Similarly, in the 97 infants examined for minor anomalies in the fluoxetine groups, no pattern was recognized, although the proportion of these infants with three or more minor anomalies was significantly higher than that of the 153 infants in the control group who underwent the same examination (15.5 percent vs. 6.5 percent,  $P=0.03$ ).

Several birth outcomes were significantly more common in the exposed-late group (Table 3). With the exclusion of twin gestations and second pregnancies in women who had participated in the study during previous pregnancies, the rate of prematurity was significantly higher in the exposed-late group (14.3 percent) than in the exposed-early group (4.1 percent) or the control group (5.9 percent) ( $P=0.03$ ).

With the exclusion of preterm infants, the rate of admission to special-care nurseries among infants of mothers in the exposed-late group was 23.0 percent, significantly higher than among infants of mothers in the exposed-early group (9.5 percent) or the control group (6.3 percent) ( $P<0.001$ ). Poor neonatal adaptation was described in 31.5 percent of the exposed-late group, as compared with 8.9 percent of the exposed-early group.

For full-term infants, mean birth weight was significantly lower and birth length significantly shorter in the exposed-late group than in either the exposed-early or the control group. Similarly, the proportion of full-term infants at or below the 10th percentile for birth weight according to the growth curves of the National Center for Health Statistics was higher in the exposed-late group.<sup>6</sup> Persistent pulmonary hypertension developed in two full-term infants (2.7 percent) in the exposed-late group (the rate of this complication in the general population has been estimated at 0.07 percent to 0.1 percent).<sup>7</sup> By logistic-regression analysis, the adjusted relative risks were 4.8 for prematurity, 2.6 for admission to special-care nurseries, and 8.7 for poor neonatal adaptation in the exposed-late group, as compared with the exposed-early group (Table 4).

By multiple linear regression analysis, the only variables significantly related to the birth weight of full-term infants in the model that contained maternal age, dose of fluoxetine, smoking status, level of alcohol use, socioeconomic status, race, sex of the infant, gestational age, time of exposure, whether the mother had gestational diabetes mellitus, whether the mother used other psychotherapeutic medications, and whether the mother had hypertension were level of alcohol use, gestational age, and time of exposure (there was a reduction of 188 g in the birth weights of infants who were exposed late as compared with infants who were exposed early [95 percent confi-

**TABLE 3.** GESTATIONAL AGE, NEWBORN COMPLICATIONS, AND BIRTH SIZE IN INFANTS OF WOMEN TREATED WITH FLUOXETINE AND CONTROL WOMEN.

	FLUOXETINE GROUPS		CONTROL GROUP	P VALUE
	EXPOSED EARLY	EXPOSED LATE		
Live-born infants — no. (%)				
<37 weeks' gestation*	4 (4.1)	10 (14.3)	13 (5.9)	0.03
37–42 weeks' gestation*	91 (92.8)	59 (84.3)	203 (92.3)	
>42 weeks' gestation*	3 (3.1)	1 (1.4)	4 (1.8)	
Admission to a special-care nursery†	12 (11.9)	23 (31.5)	20 (8.8)	<0.001
Poor neonatal adaptation‡	9 (8.9)	23 (31.5)	—	<0.001
Full-term infants‡				
Birth size				
Weight — g	3589±500	3392±485	3556±50	0.04
Length — cm	51.5±2.5	50.4±2.7	51.5±2.5	0.01
Head circumference — cm	34.8±1.5	34.3±1.6	34.5±1.5	0.19
Birth weight ≤10th percentile — no. (%)	3 (3.2)	7 (11.5)	7 (3.3)	0.02
Microcephalic (<3rd percentile) — no. (%)	2 (2.2)	2 (3.3)	2 (1.0)	0.41

\*Values exclude twins and second pregnancies of mothers with previous live-born infants in the study. Data were available for 98 infants in the exposed-early group, 70 infants in the exposed-late group, and 220 infants in the control group.

†Data were available for 101 infants in the exposed-early group, 73 infants in the exposed-late group, and 226 infants in the control group.

‡Data on full-term infants were available for 95 infants in the exposed-early group, 61 infants in the exposed-late group, and 209 infants in the control group. Plus-minus values are means ±SD.

**TABLE 4. RELATIVE RISKS OF SELECTED OUTCOMES IN INFANTS OF WOMEN WITH LATE EXPOSURE TO FLUOXETINE AS COMPARED WITH INFANTS OF WOMEN WITH EARLY EXPOSURE.**

OUTCOME	CRUDE RELATIVE RISK (95% CI)*	ADJUSTED RELATIVE RISK (95% CI)†‡
Prematurity (<37 wk of gestation)‡	3.5 (1.1–10.7)	4.8 (1.1–20.8)§
Admission to special-care nursery	2.7 (1.4–5.0)	2.6 (1.1–6.9)¶
Poor neonatal adaptation	5.7 (2.5–13.1)	8.7 (2.9–26.6)**

\*CI denotes confidence interval.

†Adjusted relative risks and confidence intervals were approximated from the adjusted odds ratios obtained by logistic-regression analysis.

‡Values exclude twins and second pregnancies of mothers with previous live-born infants in the study.

§Values were adjusted for multiparity; previous spontaneous abortion; preeclampsia, eclampsia, and hypertension; smoking status; maternal age; socioeconomic status; race; average dose of fluoxetine; gestational diabetes; use of other psychotherapeutic drugs; alcohol use; and evidence of maternal or neonatal infection near delivery.

¶Values were adjusted for prematurity; preeclampsia, eclampsia, and hypertension; smoking status; maternal age; socioeconomic status; race; average dose of fluoxetine; gestational diabetes; mode of delivery; alcohol use; evidence of maternal or neonatal infection near delivery; and therapy with other psychotherapeutic drugs near delivery.

||This analysis was restricted to cases for which medical records were available.

\*\*Values were adjusted for prematurity; use of preterm-labor medications; preeclampsia, eclampsia, and hypertension; smoking status; maternal age; socioeconomic status; race; average dose of fluoxetine; gestational diabetes; alcohol use; evidence of maternal or neonatal infection near delivery; and therapy with other psychotherapeutic drugs near delivery.

dence interval, 32 to 344;  $P=0.02$ ]). Maternal weight gain, an important predictor of birth weight, was significantly correlated with the timing of exposure.<sup>8</sup> When the variable of maternal weight gain was added to the model, the timing of exposure was no longer significant ( $P=0.10$ ).

## DISCUSSION

Although we cannot rule out weak associations in a study of this size, finding no significant increase in major anomalies in the infants of women taking fluoxetine in the first trimester is reassuring. However, the increased incidence of three or more minor anomalies in the infants of fluoxetine-treated mothers arouses some concern. The combination of any three minor anomalies in a single child is an unusual finding. In two previous studies of a total of 8717 newborn infants, three or more minor anomalies were found in 0.5 percent and 3.7 percent, of whom 90 percent and 20 percent, respectively, had major structural anomalies.<sup>4,9</sup> Therefore, infants with three or more minor anomalies are at increased risk of having an associated major anomaly. Some of the major anomalies are occult, such as defects in brain development, and are therefore not recognizable at birth.

The 15.5 percent incidence of more than three minor anomalies in infants of women in the exposed groups indicates that fluoxetine therapy during the first trimester of pregnancy has an effect on embryonic development. This finding raises the possibility of an associated defect in the development of the central nervous system that may become evident when the infant is older.

The 30 percent rate of therapy with other psychotherapeutic drugs in the fluoxetine-treated women raises questions about the effect of other medications, some of which may be associated with neonatal complications. These drugs were treated as confounders and were controlled for in the regression models. Minor anomalies were evaluated by univariate methods only; however, the incidence of three or more minor anomalies remained high (15.0 percent) after infants exposed to benzodiazepines were eliminated from the analysis ( $P=0.06$ ).

With respect to prematurity, some studies have suggested that maternal stress may increase the risk of preterm delivery.<sup>10</sup> The women who took fluoxetine during the third trimester, in whom the rate of preterm delivery was increased, may have had more severe depression or anxiety and therefore been at higher risk for preterm delivery. However, those who continued to take fluoxetine may have been less symptomatic than those who discontinued it.

With respect to neonatal adaptation, hospital workers may have been aware of the mothers' medications, which could have biased the contents of the chart notes used to evaluate adaptation. However, the consistency in terms used and the similarity the observed behavior bears to common side effects of fluoxetine therapy in adults, such as nervousness and tremor, lend credibility to the validity of this finding.<sup>11</sup> Similarly, the rate of admission to a special-care nursery could be biased by physicians' prior knowledge of maternal fluoxetine therapy or by variations in individual hospital practice. However, the infants were delivered in 109 different hospitals, and deliveries at any one facility did not contribute disproportionately to any adverse outcome measured.

The finding of decreased birth weight and its relation to maternal weight gain is consistent with the results of a recent study in which pregnant rats treated with fluoxetine had poorer weight gain and delivered smaller pups.<sup>12</sup> It seems plausible that weight loss, one of the well-known side effects of fluoxetine therapy in nonpregnant women and in men, could be related to lowered maternal weight gain, which in turn could limit fetal growth.

On the basis of the results of this study, the primary concern about fluoxetine therapy during pregnancy relates to babies whose mothers take fluoxetine late in pregnancy. The extent to which these findings may be due to the underlying maternal condition is unknown. Nevertheless, these data suggest

that if pregnant women are unable to discontinue fluoxetine therapy before the third trimester, the risk of perinatal complications is increased.

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