Weight Gain in Infants Breastfed by Mothers Who Take Fluoxetine

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ABSTRACT. Objective. Despite the manufacturer's recommendation that fluoxetine not be used by women while breastfeeding, many women choose to do so. There is little information available in the literature to suggest that this practice is or is not safe. The purpose of this study was to examine weight gain in infants who are breastfed by mothers who take fluoxetine, compared with weight gain in infants who are breastfed by mothers who do not take any psychotherapeutic medication. A secondary goal was to assess the frequency of reported side effects in infants who are breastfed by mothers who take fluoxetine.

Methodology. A retrospective cohort study design was used. Subjects were identified from an ongoing pregnancy outcome study conducted through the California Teratogen Information Service and Clinical Research Program. A total of 64 women were interviewed who had taken fluoxetine during a pregnancy between the 1989 and 1997; 26 of these women breastfed their infants and continued to take the medication, and 38 breastfed their infants but did not take the medication. Postnatal weight gain was taken from pediatric records, and the frequency of side effects was measured by maternal response to the interview questionnaire.

Results. Using linear regression analysis, the infants who were breastfed by mothers taking fluoxetine demonstrated a growth curve significantly below that of infants who were breastfed by mothers who did not take the drug. The average deficit in measurements taken between 2 weeks and 6 months of age was 392 g (95% confidence interval: −5, −780). Using a repeated measures analysis of covariance for those infants with more than one postnatal weight measurement available, the difference between the two groups was similar, −1.2 standard deviations below the mean. In response to interview questions regarding side effects, no mother who breastfed her infant while taking fluoxetine reported any unusual symptoms that could be attributed to the medication.

Conclusions. These data do not suggest that women who breastfeed while taking fluoxetine are likely to note unusual behavior in their infants that they consider related to use of the medication. However, although there was no excess of infants in the fluoxetine group with postnatal weight measurements ≥2 standard deviations below the mean, these data indicate that breastfeeding while taking fluoxetine is associated with reduced growth that may be of clinical importance in situations in which infant weight gain is already of concern. Pediatrics 1999;104(5).
part of the pregnancy outcome study, information regarding the maternal socioeconomic status, health history, pregnancy exposures, and pregnancy complications was collected before the known pregnancy outcome. After the birth of each live born child, an extensive outcome questionnaire was administered and additional information was collected from hospital and pediatric records. Additional details of this study have been described elsewhere.‡

Between January 1989 and June 1997, all women who had enrolled in the CTIS project, who had taken fluoxetine sometime during pregnancy, and who had delivered live born, full term infants whom they breastfed were considered eligible for the study. After receiving human subject approval, women meeting these criteria were asked a standard set of questions on the telephone and/or mail. These questions pertained to the length of time they breastfed, use of any medications and/or tobacco during the period they breastfed, whether they supplemented with formula feedings, and whether they had noted any adverse effects in their infants while breastfeeding or after weaning. Women were retained as eligible subjects if they had breastfed their infants exclusively for ≥2 weeks postpartum. Pediatric records were reviewed to obtain postnatal weight measurements during the breastfeeding period up to and including 6 months of age.

From an initial pool of 202 women, 78 (39%) were ineligible attributable to formula feeding or discontinuation of breastfeeding within 2 weeks postpartum and 18 (9%) were unable to be located. The remaining 106 women (52%) had breastfed their infants exclusively for a minimum of 2 weeks postpartum. Of this group, 15 women (12%) were excluded attributable to prenatal exposure to agents potentially associated with postnatal growth retardation such as continued use of alcohol during pregnancy, and 3 (3%) were excluded for use of other psychotherapeutic medications while breastfeeding. Additionally, 3 (3%) were excluded because their infants had major malformations, and 3 (3%) were excluded because the mother already had been included in the study with a previous pregnancy. Of the remaining women, 20 (19%) were unable to provide pediatric records with a weight measurement within the breastfeeding period. A final sample consisting of 64 women (26 of whom had taken fluoxetine while breastfeeding and 38 of whom had used no psychotherapeutic medication during the breastfeeding period) was ascertained.

The maternal dose of fluoxetine while breastfeeding ranged from 20 mg to 40 mg per day. Although most women (21/26) took the lower dose, 1 mother in the group took 30 mg per day, 2 alternated between 20 and 40 mg per day, and 2 took 40 mg of fluoxetine every day while breastfeeding.

Data on additional risk factors or possible confounders, such as maternal age, parity, gestational age, ethnicity, and socioeconomic status, were collected from records accumulated during the pregnancy outcome study. In addition, a standard depression scale questionnaire, the Center for Epidemiologic Studies Depression (CES-D) scale, reflecting the self-reported frequency of depressive symptoms during the middle of the index pregnancy was completed by some women. The scores from these questionnaires were used as a measure of the severity of the mother’s underlying condition.

Statistical analysis was performed using two methods. First, a linear regression model was constructed using the latest postnatal weight measurement in grams as the dependent variable and using the breastfeeding medication group (fluoxetine: yes/no) as the independent variable of interest. By necessity, the model was adjusted for birth weight (grams), gender, and infant age (weeks) at the time of the postnatal measurement. The second approach was a Repeated Measures Analysis of Covariance that permitted use of more than one postnatal weight measurement per subject. To accomplish this, the dependent variable was transformed to z scores using gender- and age-specific curves generated from a pooled dataset of breastfed infant weight compiled by the WHO Working Group on Infant Growth.§ Birth weight was included as a covariate, and the grouping variable was the breastfeeding medication group.

All analyses were performed using SPSS 1995 Version 6.1 for the Macintosh (SPSS Inc, Chicago, IL). All statistical tests were two-sided and conducted using an α level of 0.05 to judge significance.

RESULTS

Characteristics of the mothers and infants were similar between the two breastfeeding groups with the exceptions of the proportion of women who used fluoxetine during the third trimester of pregnancy and of the mean infant birth weight (Table 1). This was expected based on the results of the pregnancy outcome study from which these women were selected, ie, women with exposure to fluoxetine late in pregnancy were more likely to have lower birth weight infants and were also more likely to breastfeed while continuing to use the medication. In addition, more infants in the fluoxetine group had been admitted to a special care nursery at the time of delivery. However, the hospital stay for each of these infants ranged from 1 to 4 days and did not preclude breastfeeding.

With respect to postnatal weight gain, the mean infant age at the weight measurement used in the

<table>
<thead>
<tr>
<th>Maternal characteristics*</th>
<th>Fluoxetine n = 26</th>
<th>No Medication n = 38</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>31.8 ± 5.5</td>
<td>34.1 ± 4.8</td>
<td>.07</td>
</tr>
<tr>
<td>Ethnic group white (%)</td>
<td>95.8</td>
<td>85.3</td>
<td>.38</td>
</tr>
<tr>
<td>Socioeconomic status &gt;midpoint (%)‡</td>
<td>69.6</td>
<td>73.0</td>
<td>.87</td>
</tr>
<tr>
<td>Parity &gt;1 (%)</td>
<td>52.2</td>
<td>60.6</td>
<td>.72</td>
</tr>
<tr>
<td>Prepregnancy weight (kg)</td>
<td>69.0 ± 16.6</td>
<td>69.6 ± 16.8</td>
<td>.89</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>167.3 ± 6.3</td>
<td>165.7 ± 6.6</td>
<td>.70</td>
</tr>
<tr>
<td>Diagnosis depression (%)</td>
<td>85.2</td>
<td>84.6</td>
<td>1.00</td>
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<tr>
<td>CES-D score§</td>
<td>15.6 ± 15.4</td>
<td>17.0 ± 13.3</td>
<td>.75</td>
</tr>
<tr>
<td>Smoked cigarettes while breastfeeding (%)</td>
<td>7.7</td>
<td>2.6</td>
<td>.56</td>
</tr>
<tr>
<td>Average daily dose fluoxetine while breastfeeding (mg)</td>
<td>22.7 ± 6.0</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine used in 3rd trimester of pregnancy (%)</td>
<td>100.0</td>
<td>10.5</td>
<td>&lt;.01</td>
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<tr>
<td>Infant characteristics*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td>39.4 ± 1.2</td>
<td>38.8 ± 1.8</td>
<td>.41</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3479.5 ± 417.5</td>
<td>3711.7 ± 459.4</td>
<td>.04</td>
</tr>
<tr>
<td>Male infant (%)</td>
<td>46.2</td>
<td>34.2</td>
<td>.48</td>
</tr>
<tr>
<td>Admitted to special care nursery at birth (%)</td>
<td>19.2</td>
<td>2.6</td>
<td>.04</td>
</tr>
</tbody>
</table>

* Mean ± standard deviation or proportion (%) of subjects with characteristic.
† Two-tailed values for Fisher’s exact test or Pearson χ² for categorical variables and the Student’s t test for continuous variables.
‡ Socioeconomic status as measured by Hollingshead categories based on the occupation and education of the breastfeeding mother and her partner. Values above the midpoint refer to the highest two of five categories.
§ Scores available for 77% of fluoxetine group and 58% of no medication group.
linear regression analysis did not differ significantly between the breastfeeding medication groups (12.2 ± 7.9 weeks and 11.7 ± 6.5 weeks in the medication and no medication groups, respectively; \(P = .81\)). The best model fit was achieved by eliminating from the analysis 6 infants who were either small or large for gestational age at birth (<2500 g or >4000 g). The final model accounted for 72% of the variance in the latest postnatal weight measurement. The estimate for the effect of fluoxetine was an average deficit of 392 g (95% confidence interval: -5 to 780 g) in postnatal weight in a model containing the breastfeeding medication group, gender, birth weight, and age of the infant at the time of measurement (Table 2). Other maternal variables tested in the model included maternal age, ethnic group, socio-economic status, parity, prepregnancy weight and height, CES-D score, and use of tobacco. Infant variables tested in the model included gestational age and admission to a special care nursery. In the final model, no variable was retained as an independently significant risk factor, and no variable modified the estimate of the effect of the medication group in a material way (\(P = .10\)).

The repeated measures analysis of covariance required two postnatal growth measurements within the breastfeeding period, and therefore, the sample size was reduced to 19 in the fluoxetine group and to 11 in the no medication group. The mean age of infants at both the first and second postnatal weight measurements did not differ significantly between the groups (6.2 ± 4.7 weeks in the fluoxetine group and 6.1 ± 2.4 weeks in the no medication group at the first measurement; \(P = 1.0\); 15.0 ± 8.0 weeks in the fluoxetine group and 13.9 ± 5.9 weeks in the no medication group at the second measurement; \(P = .69\)). The mean length of time between the first and second measurements was 8.8 ± 7.1 weeks in the fluoxetine group and 7.7 ± 4.8 weeks in the no medication group and was not significantly different (\(P = .65\)).

Using age- and gender-specific \(z\) scores for the repeated measures outcome variable and birth weight as the covariate, the between-group variable (breastfeeding medication group) was significant (\(P = .005\)). The difference between the fluoxetine group and the no medication group was ~1.2 standard deviations. The difference in mean adjusted \(z\) scores by medication group from the repeated measures analysis is shown in Fig 3.

With respect to the adequacy of weight gain in these infants, using \(>2\) \(z\) score units (standard deviations) below a mean of 0 to define inadequate weight gain, 8% and 6% of infants in the fluoxetine and the no medication groups, respectively, fell into this classification at the time of the first postnatal measurement. At the time of the second postnatal measurement, no infants measured \(>2\) \(z\) score units below a mean of 0.

Regarding the secondary purpose of this study, no mothers in the fluoxetine group, in response to the standard interview question about adverse effects, reported any unusual behavior in their infants that they attributed to the medication.

**TABLE 2. Linear Regression Estimates**

<table>
<thead>
<tr>
<th>Variable</th>
<th>(\beta)</th>
<th>Standard Error (\beta)</th>
<th>95% CI Lower Bound</th>
<th>95% CI Upper Bound</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeding group*</td>
<td>-392.46</td>
<td>193.06</td>
<td>-779.70</td>
<td>-5.22</td>
<td>.05</td>
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<tr>
<td>Age (wk)</td>
<td>154.98</td>
<td>13.34</td>
<td>128.23</td>
<td>181.73</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gender†</td>
<td>466.58</td>
<td>198.71</td>
<td>68.01</td>
<td>865.14</td>
<td>.02</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>0.81</td>
<td>0.26</td>
<td>0.28</td>
<td>1.34</td>
<td>.004</td>
</tr>
</tbody>
</table>

\(\beta\) indicates confidence interval.
* Fluoxetine breastfed group relative to no medication group.
† Males relative to females.

Figure 1: Infant weight by breastfeeding group.

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DISCUSSION

The data set forth in this study indicate that infants who are breastfed by mothers who take fluoxetine track a growth curve significantly below that of infants breastfed without the medication. The following are possible explanations for this finding.

Because weight loss is a commonly noted side effect of fluoxetine use in adults, it is possible that the drug acts directly to limit weight gain in infants who receive it through breast milk. Data set forth by Taddio et al, estimating that approximately 10% of the maternal dose of fluoxetine is transferred to the nursing infant on a weight-adjusted basis, argue against that explanation. In fact, however, 2 infants, reported to have side effects possibly caused by fluoxetine in breast milk, had serum levels slightly below and somewhat above typical maternal serum levels. Thus, it is possible that there is individual and age-related variability in an infant’s ability to metabolize fluoxetine and that some infants are more susceptible than others but that the overall effect on a group basis is relatively small.

Women with an underlying condition requiring a psychotherapeutic medication may breastfeed less often or engage in other behaviors that influence postnatal weight gain in their infants. Zuckerman et al have suggested that maternal depressive symptoms, measured by the CES-D score during pregnancy, are associated with newborn irritability. Although only 70% of the women in our study completed a CES-D questionnaire, the fact that the scores were similar for the two groups suggests that maternal condition is not a major contributor to reduced infant weight gain. However, it is possible that maternal depressive symptoms, reported mid-pregnancy, did not reflect accurately the maternal state in the postpartum period and that mothers who breastfed while taking fluoxetine were more severely depressed.

Most infants who were breastfed by mothers who took fluoxetine also had the longest prenatal exposure period. Thus, although adjustment was made for the effect of birth weight, the effect on postnatal growth could be of prenatal onset. The sample size is insufficient to address this question adequately. Among the 3 infants whose mothers used the drug late in pregnancy but discontinued the medication during breastfeeding, the adjusted mean z scores were still higher by 0.86 units, compared with the adjusted mean scores of infants with postnatal exposure whose mothers also had used the drug late in pregnancy. Furthermore, among infants whose mothers breastfed without using fluoxetine, postnatal weight gain was similar in those whose mothers had used the drug late in pregnancy, compared with those whose mothers had discontinued use of fluoxetine before the third trimester (adjusted mean z scores: 0.68 and 0.72, respectively). This suggests that postnatal growth deficits are not entirely attributable to prenatal exposure to the medication.

A significantly greater proportion of infants in the fluoxetine group, compared with the no medication...
group, had been admitted to a special care nursery, raising the possibility that, despite the relatively short length of stay, establishment of the breast milk supply could have been impacted negatively. However, excluding these 6 infants and then reconstructing the regression model resulted in essentially the same point estimate of the effect of medication group on postnatal weight gain.

Finally, it is possible that the effect of fluoxetine is indirect in that it could influence milk production or composition which, in turn, might influence infant weight gain. Oxytocin is the hormone associated with letdown and milk ejection. In animal models, long-term fluoxetine administration blocks the oxytocin release induced by serotonergic drugs. However, fluoxetine also has been reported to cause galactorrhea in nonpuerperal humans. The most likely explanation is that serotonin inhibits dopamine centrally, thereby increasing prolactin secretion. It is unclear how these two somewhat opposing effects might influence milk production or composition.

With respect to potential sources of bias in the study sample, the initial cohort through which these women were identified is a self-selected population and may not be representative of all women who use fluoxetine during pregnancy. It is also possible that women who were able to be located for participation in the breastfeeding study somehow differ from those women who could not be located. However, the small proportion of potentially eligible subjects who could not be found (18 or 9%) is unlikely to have impacted the study results strongly.

Despite the fact that infants breastfed by mothers who took fluoxetine demonstrated less robust weight gain than the comparison group, it is reassuring that there was no significant excess of infants with weight measurements >2 standard deviations below the mean. Furthermore, there is no evidence from these data to indicate that mothers who breastfeed their infants while taking fluoxetine should be concerned about side effects attributable to the medication. With respect to later development of these children, a neuropsychologic follow-up component of the original birth outcome study is currently underway.

However, in the short term, for infants whose weight gain is less than adequate, being breastfed by a mother who takes fluoxetine should be considered as one potentially contributing factor.

ACKNOWLEDGMENTS
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REFERENCES
1. Nightingale SL. Fluoxetine labeling revised to identify phentoin interaction and to recommend against use in nursing mothers. JAMA. 1994;271:1067