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Original contribution

The impact of depression and fluoxetine treatment on obstetrical outcome

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Summary

Introduction: This study prospectively followed women over the course of pregnancy to assess the impact of depression and/or antidepressant treatment on obstetrical outcome.

Method: Sixty-four outpatient women with an Axis I diagnosis of major depressive disorder or no psychiatric history were followed in each trimester of pregnancy with administration of the CES-D. A subset of the women with depression received treatment with fluoxetine during pregnancy. Subjects with a CES-D score greater than 16 at any time point were further assessed for the presence of an active major or minor depressive episode. Primary outcome variables included infant gestational age, birth weight, Apgar score, and admission to the neonatal intensive care unit.

Results: Analyzable data were available for 62 women. No significant differences were found in outcome variables between those women with exposure to medication and/or prenatal depressed mood and those women without a history of depression.

Conclusions: In contrast to other studies, our study did not demonstrate an adverse effect of fluoxetine exposure *per se* on obstetrical outcome. In addition, we did not find a significant impact of depression during pregnancy on obstetrical outcome.

Keywords: Pregnancy; depression; fluoxetine; obstetrical/neonatal outcome.

Introduction

Major depressive disorder is twice as common in women as men, with an age of onset that coincides with the childbearing years (Kessler et al., 1993). Psychiatrists commonly face the clinical dilemma of whether to prescribe antidepressant medications during pregnancy for women with active symptoms of depression or as prophylaxis for women with past histories of major depressive disorder. Due to a concern that antidepressants may harm the fetus, women frequently discontinue medications during pregnancy. However, for pregnant women with recurrent major depression who discontinue medication, the risk of relapse is high (Cohen et al., 1997; Einarson et al., 2001), and untreated maternal mental illness itself may compromise prenatal care (Cohen and Rosenbaum, 1998), obstetrical outcome (Istvan, 1986; Steer et al., 1992; Orr and Miller, 1995; Perkin et al., 1993; Cutrona, 1983; Sapolski and Meaney, 1986), and the postpartum course (O'Hara et al., 1991). Without further knowledge regarding the risks of untreated versus treated depression on the infant, clinicians and patients face the difficult task of making an informed decision about the management of psychiatric illness during pregnancy. This issue is of great importance for women who present with new onset illness during pregnancy, as well as for women with a past psychiatric history who are taking antidepressants but wish to discontinue them due to concerns about prenatal medication exposure.

Twelve studies have examined the impact of pharmacologic treatment of depression during pregnancy on the teratogenic risk to the fetus, focusing on the tricyclic antidepressants (Misri and Sivertz, 1991; Pastuszak, 1993; McElhatton et al., 1996; Nulman et al., 1997; Ericson et al., 1999; Simon et al., 2002), SSRI's (McElhatton et al., 1996; Chambers et al., 1996; Goldstein et al., 1997; Nulman et al., 1997; Kulin et al., 1998; Ericson et al., 1999; Simon et al., 2002; Hendrick et al., 2003; Einarson

et al., 2001), venlafaxine (Einarson et al., 2001), and nefazodone and trazodone (Einarson et al., 2003). An additional case series describes the use of mirtazapine in seven pregnant women (Saks, 2001). No association between the use of these antidepressants during pregnancy and an increased risk of major congenital malformations has been demonstrated.

Sixteen studies have examined the impact of antidepressant treatment on obstetrical outcome (Misri and Sivertz, 1991; Pastuszak, 1993; McElhatton et al., 1996; Chambers et al., 1996; Nulman et al., 1997; Kulin et al., 1998; Ericson et al., 1999; Simon et al., 2002; Hendrick et al., 2003; Einarson et al., 2001; Einarson et al., 2003; Goldstein, 1995; Cohen et al., 2000; Costei et al., 2002; Nulman et al., 2002; Zeskind and Stephens, 2004). Although five studies have reported some adverse outcome associated with SSRI exposure (Chambers et al., 1996; Cohen et al., 2000; Costei et al., 2002; Simon et al., 2002; Zeskind and Stephens, 2004), the nature of these adverse outcomes are inconsistently found across studies, and methodologic limitations exist.

In the study by Chambers et al. (1996) infants exposed to fluoxetine during the third trimester ($N = 73$), compared with those exposed in only the first and second trimesters ($N = 101$), had significantly higher rates of premature deliveries (decreased gestational age), admission to special-care nurseries, poor neonatal adaptation, and lower birth weight. In contrast, Cohen et al. (2000) did not find differences in either gestational age or birth weight, nor Apgar scores or the timing of maternal-infant hospital discharge, among 64 infants with early ($N = 11$) versus late ($N = 53$) pregnancy fluoxetine exposure. While the frequency of special care nursery admissions and newborn complications were two to three fold higher in infants with late fluoxetine exposure compared with early exposure, the authors postulate that lack of statistical significance was most likely due to limited sample size.

Consistent with the findings for fluoxetine by Chambers et al. (1996), Costei et al. (2002) reported that 55 infants exposed to paroxetine in the third trimester of pregnancy had higher rates of neonatal complications, compared to a comparison group of 54 infants without third trimester exposure.

In the study by Simon et al. (2002), prenatal SSRI use was associated with higher rates of premature delivery (decreased gestational age) and consequent lower birth weight. In contrast to the findings of Cohen et al. (2000), third trimester SSRI use was associated with lower Apgar scores. A recent study by Zeskind and Stephens (2004) reported that 17 infants exposed to SSRI's in pregnancy had a shorter mean gestational age (38.66 ± 0.35) compared to 17 nonexposed infants (39.65 ± 0.02). In addition, SSRI exposed infants demonstrated greater motor activity and tremulousness, fewer rhythms in heart rate variability (HRV), fewer changes in behavioral state, and more rapid eye movement sleep with higher numbers of spontaneous startles. Effects on motor activity, startles, and HRV were not significant after gestational age was covaried. The studies above did not control for degree of prenatal depression (Chambers et al., 1996; Cohen et al., 2000; Costei et al., 2002; Simon et al., 2002; Zeskind and Stephens, 2004) (which may have been a reason for late pregnancy antidepressant exposure), and included women with tobacco and/or marijuana use (Chambers et al., 1996; Zeskind and Stephens, 2004) or the concomitant use of other psychotropic medications (Chambers et al., 1996; Cohen et al., 2000; Simon et al., 2002). Further, some of these studies did not have a normal comparison (control) group (Simon et al., 2002; Cohen et al., 2000), and thus, how either the early or late SSRI exposed groups would have compared to a normative group could not be assessed.

In order to better understand and weigh the potential adverse impact of active symptoms of depression versus the potential adverse impact of antidepressant medications on the developing fetus, further research on mood and pregnancy outcome is imperative. The goal of our study was to assess the impact of depression or antidepressant treatment on obstetrical outcome by following women prospectively over the course of pregnancy and compare these women to a group of subjects with neither (normal control sample).

Methods

This study was conducted at the University of California at Los Angeles Neuropsychiatric Institute and was reviewed and approved by the institutional review board (IRB). Written informed consent was obtained in a manner approved by the IRB for subjects who participated in the study. Sixty-four women were enrolled between 1997 and 2000 and followed naturalistically over the course of nine months of pregnancy. Subjects were recruited from outpatient obstetrician-gynecologist practices or from the UCLA outpatient Women's Life Center psychiatric clinic. Primary inclusion criteria consisted of outpatient women between the ages of 18 and 45 in the first trimester of pregnancy with either a history of major depressive disorder or no psychiatric history (for the control group). Exclusion criteria included the presence of psychotic symptoms, the use of medications that are known to adversely affect the fetus, the use of other psychotropic medications, the presence of suicidality, and the use of alcohol, cigarettes, or substances while

pregnant. All subjects underwent a Structured Clinical Interview for DSM-IV at study entry (Spitzer et al., 1995). Subjects were then followed once in each trimester with administration of the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1997). Subjects with a CES-D score greater than 16 at any measured time were considered to have symptoms of depression. The presence or absence of active major or minor depression was confirmed with the SCID-Mood Module and Research Diagnostic Criteria (RDC) (Spitzer et al., 1978), respectively. Primary outcome variables included infant gestational age, birth weight, Apgar score (at five minutes), and admission to the neonatal intensive care unit.

Statistical methods

Based on SCID diagnosis at study entry, mood symptoms during pregnancy, and antidepressant treatment during pregnancy, subjects were categorized as follows: 1) control group, 2) group with depression and no antidepressant treatment during pregnancy (unmedicated depressed group), 3) group with depression treated with fluoxetine at any time during pregnancy (medicated depressed group). The impact of prenatal medication and depression exposure was examined in analyses of variance comparing outcome variables in these three groups of subjects. These analyses were supplemented by separate analyses, defining groups on the basis of depression and antidepressant exposure in each trimester of pregnancy. Birth weight was adjusted for gestational age. In order to assess the impact of medication *per se*, simple t tests were done to compare outcomes for those infants who were exposed to fluoxetine versus those infants unexposed in each trimester. The effect of timing of medication exposure was assessed by comparing outcome variables for infants exposed to fluoxetine in at least the first trimester, versus those exposed in the second or third, but not the first trimester.

The impact of prenatal depression on outcome was examined by using a total depression score, calculated as the sum of CES-D scores during the three trimesters. The relationship between this total depression score, as well as depression scores in each trimester of pregnancy, and obstetrical outcome variables was analyzed using Pearson correlation coefficients.

In order to clarify interpretation of nonsignificant findings, standardized effect sizes and/or 95% confidence limits are presented for most results. The Breslow-Day Test for homogeneity, which examines differences in odds ratios between studies, was used to compare our findings to those of prior studies with a similar design and different results.

Results

Forty-six subjects met DSM-IV SCID criteria for a history of unipolar major depressive disorder at study entry.

Table 1. Sample demographics

	Group (Means, SD)				
	Controls (group 1) (N = 16)	Depressed no fluoxetine (group 2) (N = 18)	Depressed fluoxetine (group 3) (N = 28)	p-value	
Mean age (yrs)	34.4 ± 4.6	32.7 ± 4.2	35.0 ± 4.9	0.28	
Number of children	1.3 ± 1.2	1.6 ± 1.2	0.92 ± 1.1	0.21	
Mother's weight (lbs)	139.3 ± 26.4	136.9 ± 15.4	133.1 ± 18.6	0.63	
Ethnicity: white	11/15 (73.3%)	14/18 (77.8%)	26/27 (96.3%)	0.081	
Education: > college	13/16 (81.3%)	11/18 (61.1%)	23/28 (82.1%)	0.69	
Income: > $70,000	13/16 (81.3%)	12/16 (75.0%)	15/21 (71.4%)	0.91	
Prior miscarriages	6/16 (37.5%)	5/17 (29.4%)	8/27 (29.6%)	0.71	
Prior therapeutic abortions	5/16 (31.3%)	15/18 (83.3%)	21/28 (75.0%)	0.22	
History of major depressive disorder	0	16	28		
On antidepressant at study entry	0	0	14		
Euthymic at study entry	16	5	15		
Euthymic, on maintenance antidepressant at study entry	0	0	7		
Mean CES-D Score:					*Pairwise comparison*
Trimester 1	8.86 ± 6.43 (n = 14)	24.0 ± 11.23 (n = 15)	29 ± 15.3 (n = 22)	0.0001	Group 1 vs 2: p = .0021 Group 1 vs 3: p < .0001 Group 2 vs 3: p = .23
Trimester 2	6.29 ± 5.81 (n = 14)	21.79 ± 10.12 (n = 14)	19.65 ± 17.52 (n = 26)	0.0059	Group 1 vs 2: p = .0040 Group 1 vs 3: p = .0046 Group 2 vs 3: p = .64
Trimester 3	6.57 ± 4.91 (n = 14)	25.93 ± 10.78 (n = 15)	14.33 ± 12.02 (n = 27)	0.0001	Group 1 vs 2: p < .0001 Group 1 vs 3: p = .027 Group 2 vs 3: p = .0010

Table 2. Obstetrical outcomes for controls, unmedicated depressed, and medicated depressed women treated with fluoxetine (means, SD) and statistical results

Outcome	Group (Means, SD)			Statistical results			95% Confidence Interval		
	Controls (N = 15–16)	Depressed no fluoxetine (N = 17–18)	Depressed fluoxetine[1] (N = 27–28)	Test statistic	p-value	Effect size[2]	Controls vs depressed no fluoxetine	Depressed no fluoxetine vs depressed fluoxetine	Controls vs depressed fluoxetine
Gestational age (weeks)	38.8 ± 1.8	39.6 ± 1.7	39.0 ± 1.2	F = 1.51 (df = 2.59)	0.23	f = 0.23	[−2.02–0.42]	[−0.33–1.53]	[−1.22–0.82]
Birth weight (kg)[3]	3.3 ± 0.6	3.7 ± 0.43	3.3 ± 0.5	F = 2.96 (df = 2.57)	0.06	f = 0.32	[−0.76–−0.04]	[0.13–0.67]	[−0.36–0.36]
Apgar (5 minute)	9.0 ± 0.4	8.8 ± 0.6	8.7 ± 0.5	F = 1.48 (df = 2.56)	0.24	f = 0.23	[−0.15–0.55]	[−0.24–0.44]	[0.02–0.58]
NICU admissions	3 (19%)	2 (11%)	3 (11%)	$\chi^2 = 0.66$ (df = 2)	0.73	w = 0.01	[0%–32%]	[0%–21.3%]	[0%–32.2%]

[1] 14 women were on fluoxetine in all three trimesters.
[2] Effect sizes for ANOVAs are Cohen's f, the standardized variance of means; for NICU admissions the effect size is Cohen's w, a function of the contingency coefficient; by convention, f = 0.10 is ''small'', f = 0.25 is ''medium'', f = 0.50 is ''large'', and w = 0.10 is ''small''.
[3] Analysis convariance of birth weight controlled for gestational age.

Table 3. Comparison of outcome variables between infants exposed and unexposed to fluoxetine in each trimester of pregnancy

Variable	First trimester			Second trimester			Third trimester		
	fluoxetine (N = 18–19)	no fluoxetine (N = 40–43)	Cohen's d[1]	fluoxetine (N = 25–26)	no fluoxetine (N = 34–36)	Cohen's d	fluoxetine (N = 28–33)	no fluoxetine (N = 29–33)	Cohen's d
Gestational age (wks)	39.2 ± 1.2	39.1 ± 1.7	0.04	39.1 ± 1.2	39.2 ± 1.7	0.08	39.0 ± 1.2	39.2 ± 1.8	0.12
Birth weight (kg)[2]	3.3 ± 0.4	3.5 ± 0.6	0.4	3.3 ± 0.5	3.5 ± 0.6	0.41	3.3 ± 0.1	3.5 ± 0.1	0.34
Apgar-5 minutes	8.6 ± 0.6	8.9 ± 0.5	0.51	8.7 ± 0.5	8.9 ± 0.5	0.3	8.7 ± 0.5	8.9 ± 0.5	0.35
NICU admissions	0.1 ± 0.3	0.1 ± 0.4	0.1	0.1 ± 0.3	0.1 ± 0.4	0.07	0.10 ± 0.3	0.2 ± 0.4	0.14

14 women were on fluoxetine in all 3 trimesters.
[1] Cohen's d reflects standardized effect sizes, which are the differences between covariance-adjusted means (controlling for gestational age) divided by the root mean square error from the analysis of covariance; by convention, d = 0.2 is ''small'', d = 0.5 is ''medium'', d = 0.8 is ''large'' (Cohen, 1998).
[2] Adjusted for gestational age.

Table 4. Correlation of depression scores and obstetrical outcome variables in all subjects (with 95% confidence limits)

Outcome variable	Entire pregnancy	1st trimester	2nd trimester	3rd trimester
Gestational age (wks)	0.02 (−0.25–0.29)	0.05 (−0.22–0.31)	−0.03 (−0.30–0.24)	0.03 (−0.23–0.29)
Birth weight (kg)[1]	0.16 (−0.12–0.41)	0.14 (−0.13–0.39)	0.07 (−0.20–0.33)	0.16 (−0.11–0.41)
Apgar, (5 min)	−0.16 (−0.44–0.12)	−0.18 (−0.45–0.10)	−0.02 (−0.30–0.26)	−0.15 (−0.43–0.12)
NICU admission	0.13 (−0.14–0.41)	0.02 (−0.25–0.29)	0.12 (−0.16–0.39)	0.18 (−0.08–0.45)

Pearson correlation used; CES-D scores were used as the measure of depression.
[1] Birth weight is partial correlation controlling for gestational age; N's include women on and off antidepressants and range from 52–56; p-values range from 0.15–0.89 (median $p = 0.37$); By convention, $r = 0.10$ is "small", $r = 0.30$ is "medium", $r = 0.50$ is "large" (Cohen, 1988).
Reference: Cohen, J. Statistical power for the behavioral sciences, 2nd Edition. Lawrence Erlbaum, Hillsdale, NJ, 1988.

Two of these women gave birth to twins, and their obstetrical data were not included in the analysis because their pregnancy outcomes (e.g. size) are not comparable to singleton pregnancies. Eighteen women had no history of an Axis I disorder at study entry. Thus, analyzable data were available for 62 women.

Of the eighteen women without any history of an Axis I disorder at study entry, sixteen remained euthymic throughout pregnancy and comprised the control group. Eighteen women experienced depression during some portion of pregnancy and were not treated with antidepressants (unmedicated depressed group). Twenty-eight women were treated with fluoxetine for at least some portion of pregnancy (medicated depressed group). Twenty-four of these women had symptoms of depression at some point during pregnancy, while only four of these women remained euthymic throughout their pregnancy. The mean dose of fluoxetine was 30.98 ± 15.67 mg and the mean duration of fluoxetine exposure was 29.82 ± 10.14 weeks. Table 1 presents the demographic variables for the control, the unmedicated depressed, and the medicated depressed groups. Demographic variables did not differ significantly between the three groups.

In comparing all three groups of subjects, gestational age, adjusted birth weight, Apgar scores, and admissions to the NICU were not significantly different (Table 2). A similar analysis was performed for medication and depression exposure by each trimester of pregnancy. Obstetrical outcome variables, including gestational age and adjusted birth weight, did not differ significantly in a one-way analysis of the three groups for each trimester.

In the analysis of the impact of medication on pregnancy outcome, no significant differences were found in outcome variables between the group of infants whose mothers took fluoxetine during each trimester of pregnancy and those infants whose mothers were not treated with fluoxetine (Table 3). Furthermore, gestational age ($p = 0.4$) and birth weight ($p = 0.5$) were not significantly different between the group of infants exposed to fluoxetine in at least the first trimester, versus those exposed in the second or third, but not the first, trimester. Differences in the other outcome variables were also nonsignificant ($p = 0.2$ for Apgar score, $p = 0.9$ for NICU admissions). The group with late medication exposure, compared with early exposure, had significantly higher CES-D scores in the second (30.2 vs 13.7, $p = 0.01$) and third (22.7 vs 10.9, $p = 0.01$) trimesters.

In the analysis of the impact of depression on pregnancy outcome, total depression score was not significantly correlated with any of the outcome variables (Table 4). The impact of depression scores in each trimester on obstetrical outcome was also examined (Table 4). Gestational age, birth weight, Apgar scores, and admissions to the NICU were not significantly correlated with CES-D scores in each trimester.

In an attempt to understand our results in relation to those of two earlier studies with antidepressant exposed and unexposed populations (Chambers et al., 1996; Simon et al., 2002), we compared our results for premature birth (gestational age <37 weeks) and low birth weight (<2500 gms) using the Breslow-Day Test for homogeneity. The stratified chi-square analysis (SAS Freq) demonstrated that our results for premature birth were significantly different from those of Simon et al. (2002) (Beslow-Day Statistic = 4.49, df = 1, $p = 0.03$) and Chambers et al. (1996) (Breslow-Day Statistic = 4.53, df = 1, $p = 0.03$).

Discussion

This study prospectively followed women over the course of pregnancy to assess the impact of depression or antidepressant treatment on obstetrical outcome. Our study was limited by its overall small sample size, as

well as a small group of fluoxetine treated women who remained euthymic during pregnancy. However, unlike the majority of earlier studies of obstetrical outcome, our study included a normal comparison sample as well as a depressed untreated sample. Many of the women in our study who were ''fluoxetine-exposed'' were started on medication because of depression during pregnancy. Thus, we were not able to accomplish one of our original goals of assessing the impact of medication exposure (in the absence of depression) versus depression exposure on infant outcome. Nonetheless, we found no significant differences in outcome variables between the group with depression and medication exposure, the untreated depressed group, and the control group, suggesting that, in this small sample of women not using alcohol, cigarettes or other recreational substances of abuse and not taking other psychotropic medications, neither depressive symptoms nor exposure to medication substantially impacted obstetrical outcome. Early (first trimester) versus only late (second and/or third trimester) fluoxetine exposure did not affect outcome in our sample.

This study differs in its results from four earlier studies examining the impact of prenatal antidepressant use on obstetrical outcome. While Chambers et al. (1996) and Cohen et al. (2000) found high rates of special care nursery admissions with late pregnancy fluoxetine use (most likely nonsignificant in the study by Cohen et al., 2000 due to small sample size) a substantial proportion of the fluoxetine-treated women received other psychotropic medications, including benzodiazepines which can adversely impact neonatal outcome (Aarskog, 1975; Saxen and Saxen, 1975; St Clair and Schirmer, 1992; Fisher et al., 1985; Gillberg, 1997; Mazzi, 1977; Rementeria and Bhatt, 1977; Rowlatt, 1978; Speight, 1977; Whitelaw et al., 1981; Ohmi et al., 2002). The studies by Chambers et al. (1996) and Costei et al. (2002) included pregnant women who used cigarettes during pregnancy, a factor which increases the risk of preterm birth (Ohmi et al., 2002). Zeskind and Stephens (2004) included SSRI-exposed women who used marijuana during pregnancy, a variable that can influence birth weight (Visscher et al., 2003). Thus, the exclusion criteria of our study may have further reduced the risk factors associated with depression, such as cigarette and/or substance use, that mediate poor obstetrical outcome (Zuckerman et al., 1989).

Costei et al. (2002) speculate that their report of neonatal complications in infants exposed to paroxetine in the third trimester may be consistent with a discontinuation/withdrawal syndrome, and the differences in findings between their study and ours may also be related to the differences in half-life between paroxetine and fluoxetine. Finally, the lack of a control group in the study by Simon et al. (2002) makes it difficult to interpret their findings relative to a nonpsychiatric population. Though a one-way analysis of the three groups in our study did not find significant differences in infant birth weight, if we had only examined the medicated depressed and unmedicated depressed groups, without the control population, women with medication exposure would also have appeared to have babies who were significantly lower in adjusted birth weight than women without medication exposure ($p = 0.025$), as others have found. The inclusion of a normal control comparison group, however, allowed us to see that outcomes for the treated group looked more similar to the normal control group and that the unusual sample was actually the untreated depressed group.

Earlier studies may have also been limited by a lack of consideration for the possible effects of depression on neonatal outcome. While information about the impact of untreated maternal prenatal depression on birth outcome is limited, a study of 389 pregnant adult women showed an increased risk of delivery of a low birth weight, pre-term, or small-for-gestational-age infant in women with a maternal Beck Depression Score greater than 21 at 28 weeks gestation (Steer et al., 1992). A second study of 1433 low-income urban African American women reported a significant association between a high prenatal CES-D score and premature birth (Orr and Miller, 1995). We were surprised that our depressed population did not have higher rates of premature birth or low birth weight, in contrast to these two prior reports (Steer et al., 1992; Orr and Miller, 1995). Our study included a majority of Caucasian, well-educated subjects of high socioeconomic status who may have differed from subjects in the other two studies in variables such as level of prenatal care.

It is also possible that our untreated depressed women were less depressed than those of the earlier studies (mean CES-D scores ranged from 21.79 to 25.93 in each trimester). The study by Orr and Miller (1995) used the CES-D scale, similar to ours, but categorized subjects into the upper 10% and lower 90% of CES-D scores. As it did not report actual CES-D scores, it is difficult to compare the results of their study to our results. We did find that women who took antidepressants in the latter part of pregnancy were more depressed than those who received treatment with antidepressants earlier in pregnancy. Thus, it is possible that earlier studies of

late-pregnancy antidepressant use and adverse obstetrical outcome (Chambers et al., 1996; Simon et al., 2002; Cohen et al., 2000; Costei et al., 2002) included women with more severe depression in the latter part of pregnancy than our population or women who, because of their depression, also had other factors (smoking, use of other psychotropic medications) that could impact obstetrical outcome. Our study also did not standardize the week in which women were evaluated, and assessments occurred at only one time point per trimester, so it is possible that depressions between study visits were not captured.

Finally, our study did not include measurements of prenatal stress and anxiety, symptoms which often accompany depression and have also been associated with lower birth weight and decreased gestational age (Wadhwa et al., 1993).

Both Simon et al. (2002) and Chambers et al. (1996) found higher rates of premature delivery in SSRI exposed infants compared to unexposed infants. While the reasons for differences in our results compared to those of these earlier two studies are not clear, we speculate that differences in the populations of subjects *per se* may have played an important role. Calculations of the Breslow-Day Test for homogeneity suggest that our negative findings are significantly different from both reported positive findings in the two prior studies (Chambers et al., 1996; Simon et al., 2002), one involving a comparison between treated women and non-depressed controls (Chambers et al., 1996) and the other between treated and untreated depressed women (Simon et al., 2002). Thus, it is unlikely that differences in our findings from these earlier reports are due to chance but rather that there is something substantially different about the populations of women in these studies. Some possibilities (other medications, cigarette use, for example) have been discussed above.

While the literature on antidepressants and pregnancy is increasing, our study is unique in its prospective design, the lack of confound with other psychotropic medications or substances of abuse/dependence, documentation of mood over the course of pregnancy, and the inclusion of a control group. The results of this study suggest that maternal fluoxetine exposure *per se* does not appear to adversely impact obstetrical outcome. The impact of at least mild depressive symptoms, in the absence of alcohol, cigarette, and substance use, also does not appear *per se* to adversely affect pregnancy outcome. Our results are encouraging, but given the small sample size of our study, a false negative finding (Type II error) cannot be ruled out. Interpretation of negative findings, particularly in relatively small samples, must be done with caution. To guide readers, we have included 95% confidence limits for most of the results of our study. In many cases, even medium effects fall either at the ends or outside these limits, suggesting that true effects are probably small, at best, for many of the variables studied and probably are not clinically significant. The presence of a control group in our study has helped in some instances to see that it is difficult to interpret differences between treated and untreated women without some clear normative frame of reference.

Our study only followed women until birth, and thus the enduring impact of in utero exposure to medication or depression on neonatal/infant development cannot be assessed by our results. In the study by Simon et al. (2002) antidepressant exposure was not associated with increased rates of developmental delay or neurologic disorders in infants up to two years of age, consistent with the findings of Nulman et al. (1997; 2002) who followed children up to the age of seven. However, duration of maternal depression and number of episodes of postnatal depression have been shown to correlate negatively with children's cognitive and language development, respectively, while treatment for maternal depression has been shown to be a positive predictor for language development (Nulman et al., 2002).

In conclusion, in utero exposure to fluoxetine or to depressive symptoms in combination with fluoxetine did not appear, in our sample, to be associated with adverse obstetrical outcome. Clearly, more studies are needed to help guide clinicians in providing appropriate clinical care to this special population.

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