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Perinatal Outcomes of Pregnancies Complicated by Maternal Depression with or without SSRI Therapy

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INTRODUCTION

Depression is common during pregnancy, with an estimated prevalence of 7 to 13% [1–3]. Approximately 7% of pregnant women receive an antidepressant, most frequently selective serotonin reuptake inhibitors (SSRIs) [3,4]. The management of maternal depression during pregnancy is accompanied by difficult decisions regarding the risks and benefits of medication therapy for both mother and baby.

Untreated depression during pregnancy has been associated with increased risks of alcohol and tobacco use, miscarriage, preterm birth, low birth weight, and impaired fetal and postnatal development [1,5–7]. While there are clear risks associated with untreated depression, there have been mixed results from studies looking at the effect of SSRIs on fetal outcomes. Some studies report increased risk of cardiovascular malformations [8–12], craniosynostosis [13], and omphalocele [10,13] upon exposure to any SSRI in early pregnancy. Other studies show increased risk of preterm delivery [2,14–16], low birth weight and small for gestational age (SGA) infants [2,16], neonatal abstinence syndrome [2,17–20], and persistent pulmonary hypertension of the newborn [21]. Conversely, some studies have failed to replicate these findings [22,23].

Given the prevalence of depression and SSRI utilization in pregnancy, it is important to improve our current knowledge regarding the risks of depression and its treatment on maternal and fetal outcomes. Thus, we sought to compare the perinatal outcomes of women carrying a diagnosis of depression during pregnancy that either received an SSRI or did not.

MATERIALS AND METHODS

Study Population

This study was approved by the University of Iowa Institutional Review Board and informed consent was waived. Linked maternal-neonatal records of women who delivered at the University of Iowa Hospitals and Clinics (UIHC) from 4/1/2009–3/2/2011 were obtained. The records were screened for the diagnosis of depression by separating them based on the presence or absence of the following ICD-9 codes: 311 (depressive disorder, not elsewhere classified), 296.2 (major depressive disorder, single episode), 296.3 (major depressive disorder, recurrent episode), 300.4 (anxious depression) and 309.0 (adjustment disorder with depression). An equal number of women ($n = 238$) who gave birth during the same time period who did not have any of these ICD-9 codes for depression were randomly selected by hospital record number as potential controls.

Maternal Medical Record Review

Prenatal clinic notes, psychiatry clinic notes, and hospital admission notes were reviewed for the duration of pregnancy. The use of antidepressants during pregnancy was identified based on medication record and medical chart review. The maternal medical records were reviewed for the diagnosis of depression and completion of the Patient Health Questionnaire (PHQ-9), a nine-item questionnaire widely-used to screen for depression [24]. The PHQ-9 is used in the Obstetrical clinic at UIHC to screen pregnant women at the initial clinic visit. Each item on the PHQ-9 is rated on a four-point Likert scale with a score of 5–10 suggesting mild depression, 11–16 suggesting moderate depression, and > 16 suggesting severe depression. If multiple PHQ-9 forms were completed by a pregnant woman, the initial score was recorded. Maternal age at delivery, BMI at onset of pregnancy, and weight gain during pregnancy were recorded. Alcohol and tobacco use were defined as consumption between the time of conception and delivery as noted in the patient's medical chart. No information was collected on non-pharmacologic therapies to treat depression.

Neonatal Medical Record Evaluation

The admission notes, progress notes, and discharge notes of infants born to selected mothers were reviewed during the delivery encounter. Gestational age and birth weight were recorded. Repeated measurements of heart rate, blood pressure, and respiratory rate during the initial 24 hours after birth were recorded. Birth weight percentiles were calculated based on data from 6,690,717 births in the 1999–2000 US Natality Datasets [5]. Admission to the neonatal intensive care unit (NICU) and admission diagnosis were obtained when applicable.

Statistical Analysis

Data are presented as mean $\pm$ SEM. Statistical comparisons were made with Students two-tailed t-test or Chi-squared analysis, as appropriate. Chi squared tests and bivariate logistic regression were used to determine factors associated with NICU admission. A binary logistic regression model was created to assess the effect of depression and SSRI use on NICU admission, adjusting for significant covariates within the entire study population. All

variables included in the final models were chosen based on previously known associations for modifying or confounding maternal depression outcomes, and/or a bivariate association with the outcome variable with a P value <0.2. Statistical analysis was done using SAS (SAS Institute Inc., Cary, NC) and SPSS (SPSS, Chicago, IL). A two-sided 0.05 level test was considered significant.

RESULTS

Maternal Characteristics

Of the 3695 women who delivered during the study period, 238 (6.4%) had an ICD-9 code for depression with the majority (94%) carrying the ICD-9 code 311 for depressive disorder, not elsewhere classified. Of the 3457 women who did not have an ICD-9 code for depression, 238 randomly-selected charts were reviewed. 16 women (6.7%) had depression listed in their medical records but did not have an ICD-9 code for depression. Their data were removed from the non-depressed group and combined with those of the 238 women carrying an ICD-9 code for depression for subsequent analysis.

Table 1 compares the demographic characteristics of women with and without a diagnosis of depression. The PHQ-9 was completed by 65% of women in the sample, with women with depression rating significantly higher, albeit in the mild range. Depression was strongly associated with the use of alcohol and tobacco during pregnancy as well as obesity at conception.

Of the 254 women with depression, 126 (50%) were prescribed an SSRI and 23 (9%) were prescribed an antidepressant other than SSRIs. In addition, two women received an SSRI plus bupropion, and one woman received sertraline plus bupropion and nortriptyline (Table 2). SSRI therapy was not associated with PHQ-9 scores (Table 3). Likewise, the 105 depressed women that received no pharmacotherapy for depression did not significantly differ in PHQ-9 scores from those who received any antidepressant (no-treatment 7.24 ± 0.5 , pharmacotherapy 7.06 ± 0.5 , $p=0.83$). Compared to women with depression that did not receive an SSRI, those that did receive an SSRI did not differ in the frequency of alcohol and tobacco use or obesity (Table 3).

Neonatal Characteristics

The mean duration of gestation was more than one week shorter and the rate of prematurity was higher in infants born to mothers with depression compared to mothers without (Table 1). When corrected for gestational age at delivery, birth weight was not significantly altered by maternal depression. The frequency of NICU admission nearly doubled for infants born to mothers with depression, and this was driven by an increase in admission for respiratory distress (Table 1). Looking specifically at pregnancies in mothers with depression, SSRI use did not significantly alter the timing of delivery, birth weight, or the rate of NICU admission (Table 3). Using logistic regression to analyze univariate predictors of NICU admission, maternal depression, maternal SSRI use, obesity, and tobacco use were all associated with NICU admission ($P < 0.05$) (Table 4). With the multivariate model, tobacco use, obesity, and

diagnosis of depression, but not SSRI use, were independently associated with NICU admission (Table 5).

DISCUSSION

Due to the high prevalence of antenatal depression and common use of SSRIs to treat depression, it is important to understand their effects on perinatal outcomes. Using linked maternal-fetal records for births at the UIHC over an approximate two-year time period, we were able to compare outcomes between SSRI-treated depression, depression without SSRI therapy, and a control population without depression. Women with depression had higher rates of substance use, preterm delivery, and subsequent neonatal intensive care admission and these deleterious outcomes did not appear to be affected by the prescription of SSRI treatment. A strength of this case-control study is that we accounted for several confounding variables which can affect both depression as well as neonatal outcomes. Between these two groups, maternal depression was associated with alcohol use, tobacco use, and obesity. Another strength of our study was that women with depression had similar disease severity on SSRI therapy and not on SSRI therapy, potentially limiting bias when measuring neonatal outcomes. Mean PHQ-9 scores for depressed women all indicated mild severity of disease, regardless of treatment with an SSRI (7.4), alternative antidepressants (5.0), or no antidepressants (7.2). This, however, could reflect a medication-induced improvement in symptoms among those receiving pharmacotherapy.

In our study, neonates born to depressed mothers had increased risk of NICU admission and this was unaffected by the presence of maternal SSRI prescription. To help control for confounding variables, logistic regression was used to assess the effect of depression and SSRI use on NICU admission. When a multivariate model was used, tobacco use, obesity, and depression were associated with NICU admissions. SSRI use, when adjusted for other variables, was not associated with an increase or decrease in NICU admissions. In our study, a significant percentage of infants were admitted to the NICU, even in the control group (23%). UIHC is a tertiary care center and is the primary referral center in the state of Iowa which may contribute to the high number of NICU admissions. In addition, there are no continuous monitoring capabilities in our newborn nursery necessitating NICU admission for infants with mild distress. The majority of admissions were for respiratory distress. Overall, 13.1% of our population had either an ICD-9 diagnosis of depression or self-reported depression, consistent with national prevalence rates of maternal depression [1–3].

Few studies have been completed comparing neonatal outcomes of unmedicated and medicated depressed mothers. A recent review summarizes these studies [6]. Suri found no significant differences in birth weight, gestational age, or intensive care admissions for depressed mothers treated prenatally with fluoxetine compared to unmedicated depressed mothers and non-depressed mothers [6,7], but only included 62 women. The exclusion criteria included presence of psychotic symptoms, use of other psychotropic medications, and use of alcohol, cigarettes, or illicit substances while pregnant [7], suggesting that women with mild to moderate depression were included. Although our study also included mildly depressed women at the time of information intake, alcohol use, tobacco use, and obesity were assessed and were significantly higher in the depressed population. Oberlander

et al. found in a large population-based linked health data study that neonates exposed to depression had shorter gestations, lower birth weights, and longer hospital stays than control neonates [2,6]. When comparing the depressed groups, they found neonates of the medicated depressed mothers had shorter gestation period and longer hospital stays compared to unmedicated depressed mothers [2,6]. Marroun et. al also found increased incidence of alcohol and tobacco use in depressed mothers, but they found the SSRI-treated group twice as likely to have preterm births [25].

Beyond the implications of depression on the mother and child, the high prevalence of maternal obesity in our population-based cohort warrants mention. Studies have increasingly shown maternal BMI correlates with birth weight and the subsequent risk of metabolic syndrome in the offspring [26]. Perhaps this underlies the trend towards increased birth weight percentile seen in our depressed population, despite the presence of risk factors for decreased birth weight, including alcohol and tobacco use during pregnancy. This co-morbid maternal obesity may have contributed to the adverse pregnancy outcomes experienced by those with depression, including the higher incidence of NICU admission.

Several limitations do exist in this study. First, we do not know if women on SSRI therapy were compliant. No drug levels were measured and we did not assess prescription filling information. In addition, it was not possible to determine whether the ICD-9 codes for depression were entered by psychiatrists, psychologists, or other health care professionals. We do not know severity of depression in patients on medical therapy prior to initiation of treatment or when treatment was initiated in relation to time of conception. In our depressed group, approximately 10% of women were not on an SSRI, but were on another type of antidepressant which may have influenced outcomes. To exclude potential bias, a sensitivity analysis was performed comparing pharmacologically treated depressed women versus non-treated depressed women which did not significantly change our findings. We did not assess the use of any non-psychopharmacologic treatments. All of these factors could have influenced maternal and fetal outcomes. In addition, our sample size was limited, but the effect size we found in our study does not suggest a larger study would likely identify a clinically relevant independent effect of maternal SSRI therapy on NICU admission rates.

Among women with depression, the use of an SSRI was not associated with significant differences in any of the measured maternal or neonatal parameters. Evaluating neonatal outcomes in the context of maternal depression continues to be challenging. Multiple variables likely contribute to the puzzle including maternal health, adverse effects of depression, potential adverse effects from pharmacotherapy, and environmental factors including social support, financial resources, and substance use. The literature continues to be sparse when evaluating psychotropic effects on neonates. Clearly, prenatal interventions are needed to lessen the impact of illicit substance use, obesity, and psychiatric illness.

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Table 1

Demographic variables for women delivering from 4/1/09 – 3/2/11 with or without depression and their infants.

	Control	Depression	P value
N	222	254	
PHQ9 Score	3.2 ± 0.2	7.1 ± 0.3	<0.001
Maternal Age, years	29.0 ± 0.3	28.3 ± 0.4	0.22
Alcohol Use	2 (0.9%)	17 (6.7%)	<0.01
Tobacco Use	20 (9%)	89 (35%)	<0.001
Baseline Maternal BMI	26.4 ± 0.5	30.4 ± 0.6	<0.001
BMI > 30	39 (18%)	105 (41%)	<0.001
Maternal Weight Gain, kg	13.5 ± 0.4	13 ± 0.5	0.43
Gestation at Delivery, wk	38.2 ± 0.2	36.9 ± 0.3	<0.001
Gestational Age < 37 weeks	36 (16%)	74 (29%)	<0.01
Birth Weight, g	3194 ± 46	3091 ± 54	0.15
Birth Weight Percentile	46 ± 2	49 ± 2	0.17
Birth Weight < 10 th Percentile	28 (13%)	30 (12%)	0.90
NICU Admission	50 (23%)	106 (42%)	<0.001
Respiratory Distress	24 (11%)	62 (24%)	<0.001
Preterm	14 (6%)	38 (15%)	<0.01
Term	10 (5%)	24 (9%)	<0.05
Prematurity Alone	7 (3%)	11 (4%)	0.63
Congenital Anomalies	9 (4%)	13 (5%)	0.66
Presumed Sepsis	5 (2%)	8 (3%)	0.59
Hypoglycemia	4 (2%)	7 (3%)	0.55
Narcotic Withdrawal	0	3 (1%)	0.25
Hyperbilirubinemia	1 (<1%)	2 (1%)	1.00

* PHQ-9 scores were available for 133 patients without depression and 174 patients with depression.

Table 2

Antidepressant use among 254 pregnant women with depression. Some women received more than one medication.

Any SSRI	126 (50%)
Sertraline	75 (30%)
Citalopram	21 (8%)
Escitalopram	16 (6%)
Fluoxetine	13 (5%)
Paroxetine	1 (<1%)
No SSRI	128 (50%)
No antidepressant	105 (41%)
Bupropion	14 (6%)
Venlafaxine	8 (3%)
Buspirone	2 (1%)
Nortriptyline	2 (1%)
Amitriptyline	1 (<1%)

Table 3

Demographic variables for women with depression delivering from 4/1/09 – 3/2/11 with or without SSRI therapy and their infants.

	Any SSRI	No SSRI	P Value
N	126	128	
PHQ9 Score	7.4 ± 0.5	6.8 ± 0.4	0.44
Maternal Age, years	28.5 ± 0.6	28.2 ± 0.5	0.75
Alcohol Use	9 (7.1%)	8 (6.3%)	0.97
Tobacco Use	42 (33%)	47 (37%)	0.66
Baseline Maternal BMI	30.7 ± 0.8	30.2 ± 0.8	0.68
BMI > 30	55 (44%)	50 (39%)	0.54
Maternal Weight Gain, kg	13.2 ± 0.6	12.8 ± 0.7	0.65
Gestation at Delivery, wk	37.1 ± 0.3	36.7 ± 0.5	0.48
Gestational Age < 37 weeks	39 (31%)	35 (27%)	0.62
Birth Weight, g	3094 ± 76	3088 ± 71	0.95
Birth Weight Percentile	50 ± 3	49 ± 3	0.80
Birth Weight < 10 th Percentile	13 (10%)	17 (13%)	0.59
NICU Admission	55 (44%)	51 (40%)	0.63
Respiratory Distress	33 (26%)	29 (23%)	0.56
Preterm	19 (15%)	19 (15%)	1.00
Term	14 (11%)	10 (8%)	0.40
Prematurity Alone	7 (6%)	4 (3%)	0.37
Congenital Anomalies	4 (3%)	9 (7%)	0.25
Presumed Sepsis	3 (2%)	5 (4%)	0.72
Hypoglycemia	5 (4%)	2 (2%)	0.28
Narcotic Withdrawal	2 (2%)	1 (1%)	0.62
Hyperbilirubinemia	1 (1%)	1 (1%)	1.00

* PHQ-9 scores were available for 89 patients with SSRI therapy and 85 patients without SSRI therapy.

Table 4

Univariate predictors of NICU admission.

	NICU Admission	No NICU Admission	P Value
N	156	320	
Depression	106 (68%)	148 (46%)	<0.0001
SSRI Use	55 (35%)	74 (23%)	0.005
Obesity	64 (41%)	80 (25%)	0.001
Tobacco Use	54 (35%)	55 (17%)	<0.0001
Alcohol Use	7 (4.5%)	12 (3.8%)	0.70

Table 5

Multivariate predictors of NICU admission.

	OR	95% CI	P Value
Depression	1.671	1.008, 2.771	0.047
SSRI Use	1.145	0.688, 1.906	0.60
Obesity	1.689	1.096, 2.605	0.018
Tobacco Use	2.148	1.331, 3.465	0.002
Alcohol Use	0.679	0.249, 1.854	0.45