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MATERNAL DEPRESSIVE SYMPTOMS, DEPRESSION AND PSYCHIATRIC MEDICATION USE IN RELATION TO RISK OF PRETERM DELIVERY

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Abstract

Purpose—This study examined associations among maternal depression, measured in several ways, psychiatric medication use in pregnancy, and preterm delivery (PTD).

Methods—Data were from 3,019 women enrolled in the Pregnancy Outcomes and Community Health Study (1998–2004), a prospective study of pregnant women in five Michigan communities. Information on depressive symptoms, history of depression and psychiatric medication use was ascertained through interviews at mid-pregnancy. These variables and other relevant covariates were incorporated into regression models with a binary outcome, i.e., term (≥ 37 weeks' gestation) as referent and PTD (< 37 weeks' gestation). A second set of models used a multi-category outcome, i.e., term as referent and PTD further subdivided by gestational weeks and clinical circumstances.

Main Findings—The odds of overall PTD was increased among women who used psychiatric medication during pregnancy and had either elevated levels of depressive symptoms at mid-pregnancy (adjusted odds ratio [AOR] = 2.0 [95% CI 1.1, 3.6]) or a history of depression prior to pregnancy (AOR= 1.6 [95% CI 1.1, 2.5]). The combination of psychiatric medication use in pregnancy and depression, prior to pregnancy or within pregnancy, was most strongly linked to a medically indicated delivery at < 35 weeks' gestation (AOR 2.9 and 3.6 respectively).

Conclusions—There are at least two plausible explanations for these findings. First, psychiatric medication use in pregnancy may pose an excess risk of PTD. Second, medication use may be an indicator of depressive symptom severity, which is a direct or indirect (i.e., alters behavior) contributing factor to PTD.

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Introduction and Background

Preterm delivery (PTD) is a persistent and poorly understood public health concern in the United States. Prematurity is a leading cause of infant morbidity and mortality, accounting for nearly one-half of all childhood neurodevelopmental disabilities and more than two-thirds of infant deaths (Callaghan, MacDorman, Rasmussen, Qin, & Lackritz, 2006). In addition to the human costs of PTD, the economic costs are profound. A recent analysis estimated that in 2005 the annual economic burden associated with PTD --including medical care through early childhood, maternal delivery services, early intervention and special education services, and lost household and labor market productivity--was at least $26 billion (Behrman & Butler, 2006).

Despite advances in obstetric care, the rate of PTD continues to increase. Pathways to PTD are not fully understood, and many cases have no known cause. These limitations in our knowledge have slowed progress toward the accurate prediction and effective prevention of PTD (Iams et al., 2001; Meis et al., 1998; Spong, 2002; Mercer et al., 1999).

Stress has been a frequently studied risk factor for PTD, because maternal psychological health has the potential to directly or indirectly affect the uteroplacental/fetal environment (Hoffman & Hatch, 1996; Austin & Leader, 2000; Cooper et al., 1996; Hedegaard, Henriksen, Secher, Hatch, & Sabroe, 1996; Wadhwa, Sandman, Porto, Dunkel-Schetter, & Garite, 1993). Despite the long tradition of research on the role of maternal stress and PTD, a related and potentially treatable condition--maternal depression--has only recently gained attention and its effects during pregnancy remain unclear (Hoffman & Hatch, 2000; Neggers, Goldenberg, Cliver, & Hauth, 2006; Adler, Fink, Bitzer, Hosli & Holzgreve, 2007). There is some evidence that antenatal depression may be positively associated with PTD (Li, Liu & Odouli, 2008; Dayan et al., 2006; Orr, James, & Blackmore-Prince, 2002; Steer, School, Hediger & Fischer, 1992). However, a large number of studies have reported no direct association (Orr, James, Blackmore-Prince, 2002; Berle et al., 2005; Andersson, Sundstrom-Poromaa, Wulff, Astrom, & Bixo, 2004; Mustillo et al., 2004; Larsson, Sydsjo, & Josefsson, 2004; Dole et al., 2004; Dole et al., 2003; Pekin, Bland, Peacock, & Anderson, 1993). Comparisons across studies have been problematic due to differences in study methodology and design, including use of various depression screening instruments, variable timing of depression screening in pregnancy, presence/absence of information on antidepressant use, and differences in composition of the sample and sample size. One potential reason for the contradictory results could be that antenatal depression, by itself, is not strongly associated with PTD overall. Depression may be a component of only certain pathways to PTD, and/or depression in combination with psychiatric medications may pose a greater risk for adverse birth outcomes. (Oberlander, Warburton, Misri, Aghajanian & Hertzman, 2006).

An increasing number of epidemiologic studies suggest that antenatal exposure to antidepressant medication is associated with increased risk of PTD (Oberlander, Warburton, Misri, Aghajanian & Hertzman, 2008; Davis et al., 2007; Wen et al., 2006; Simon, Cunningham, & Davis, 2002). A limitation of many of these studies is their reliance upon administrative health data with key covariates missing or unreliable. In addition, administrative health data provide information on medications prescribed and filled, but not on whether women are actually taking the medication. Finally all studies are challenged by the task of disentangling highly related factors, i.e., depression severity, medications used to treat depression, and the social and behavioral factors that may play mediating or confounding roles.

This analysis makes use of prospectively collected data from a multi-community study and assesses the associations among depressive symptoms/depression, antenatal psychiatric medication use, and PTD. The goals were: (1) to examine different modes of characterizing

depression in pregnant women, including a screen for depressive symptoms at mid-pregnancy, self-report history of depression, self-report depression during pregnancy, and a combination of depression measures and self-report of psychiatric medication use during pregnancy; and (2) to evaluate these different modes of capturing depression in relation to PTD and subtypes of PTD characterized by timing and clinical circumstances.

METHOD

Study sample

The Michigan-based Pregnancy Outcomes and Community Health (POUCH) study is a prospective cohort study of pregnant women living in five Michigan communities who received prenatal care at 1 of 52 participating clinics (Holzman et al., 2001). Women were enrolled at 15–27 weeks of pregnancy between September 1998 and June 2004. The cohort is a stratified random sample from the universe of women who were screened at 15–22 weeks' gestation for maternal serum alpha-fetoprotein (MSAFP), an early biomarker of interest in certain pathways leading to PTD. Sampling strata were based on race/ethnicity and MSAFP levels (normal, high). Eligibility criteria included maternal age ≥ 15 years, competency in English, singleton pregnancy with no known congenital or chromosomal abnormalities, and no history of diabetes prior to screening. The cohort was 65% non-Hispanic White, 25% Black, and 10% other ethnic groups. By design, women with unexplained high MSAFP levels (> 2 multiples of the median) were over-sampled and represented 7% of the cohort (typically 3–5% in the pregnant population). Of the 3,038 women enrolled, nineteen were lost to follow up resulting in the inclusion of 3,019 women in the overall study. The analyses reported here used self-identified race/ethnicity to separate participants into groups, either non-Hispanic White/others (n = 2276) or Black (n = 743). Women who selected multiple race/ethnic categories were asked to choose a single category. The number of women in the 'other' category was small, 160 Hispanic women and 98 women from other ethnic backgrounds.

Due to Health Insurance Portability and Accountability Act regulations it was not possible to determine an exact response rate or to compare characteristics of participants with those who declined enrollment in the POUCH study. However, comparisons were made between POUCH study data and data recorded on birth certificates of women who delivered in the five study communities in the year 2000. Ethnic-specific analyses (non-Hispanic White and Black), weighted by the proportion of women enrolled from each community, showed that the POUCH sample was very similar to community mothers on most factors measured, including age, parity, educational attainment, the proportion of women with Medicaid insurance, PTD, previous stillbirth, previous preterm infant, and previous low birthweight infant. The one exception was that the percentage of Black women over 30 years of age was lower in POUCH (14%) than in the community sample (21%).

Women who elected to have the MSAFP screening and received their prenatal care services at clinics participating in the study were asked to read an information sheet about the POUCH study and to sign if they were interested in receiving additional details about being a participant. From the pool of women who signed the POUCH approval sheet, laboratory results from the MSAFP screen were used to identify all women with unexplained high MSAFP levels and a sample of women with normal MSAFP. After screening, women were randomly sampled according to the sampling fractions described above. At 15–27 weeks' gestation, participants met with study interviewers at a clinic for approximately 2 hours to complete the interviewer-administered and self-administered questionnaires and for collection of biological samples. The study protocol was approved by human subjects review boards at participating institutions. Before enrollment, all participants provided written consent.

Measures

Depressive symptoms—Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression (CES-D) Scale, a 20-question instrument that measures depressive symptoms that occurred in the past week. This self-report screening instrument has well-established validity and reliability (Weissman et al., 1977). Missing responses were imputed for those records (< 1 %) having one to two missing responses (Raghunathan, Leplowski, Van Hoewyk, & Solenberger, 2001). The Cronbach's alpha for the current sample was 0.76. In this study, CES-D scores were dichotomized in two different ways to identify women with elevated scores. First, the customary cutoff score of 16 or higher was used (Radloff, 1977). Second, a cutoff of 24 or higher was selected (Radloff, 1986). Because symptoms of pregnancy may be indistinguishable from somatic manifestations of depression, and standard scores for pregnant women were unavailable, the second cutoff has been useful in improving the specificity of the CES-D in studies of pregnant women (Orr & Miller, 1995; Huffman, Lamour, Bryan, & Pederson, 1990). We found that the two different cutoffs produced almost identical results; therefore, we only presented results with the 24 or higher cutoff.

Prior history of depression and antenatal depression—At enrollment, self-reported maternal history of depression was ascertained by asking women the following two questions: (1) if they had been diagnosed with depression that required medication during a period when they were not pregnant; or (2) visited a health care provider for depression/anxiety the year prior to pregnancy. Previous studies have shown the validity of two-question screening instruments in accurately detecting depression in primary care settings (Mitchell & Coyne, 2007; Whooley, Avins, Miranda, & Browner, 1997). Self-reported depression during pregnancy was ascertained by first asking women if they had emotional and/or mental health problems during pregnancy. Those who confirmed they had depression during this period of time were considered positive for antenatal depression. Depression prior to the pregnancy and depression in pregnancy were modeled as dichotomous variables.

Psychotropic medication—Information on psychotropic medications used during pregnancy was obtained through self-report and covered the interval from the last menstrual period up through the day of study enrollment. Study interviewers asked women if they had used any psychotropic medications defined by the following three broad categories: (1) psychiatric medications; (2) tranquilizers/sedatives; or (3) sleeping pills. For each of these categories, use of psychotropic medication was determined by women responding yes or no.

Sociodemographic, behavioral, and clinical characteristics—Potential confounding factors and known mediators for PTD were defined from findings of previous studies. Self-reported data on potential confounders included maternal age (modeled as a dichotomous variable), race (Black, non-Hispanic White/others), parity (no previous live births, one or more births), and Medicaid use (yes, no). Potential mediators (smoking, prepregnancy body mass index, alcohol use, caffeine use, and illicit drug/substance use) were also assessed in the analysis. Smoking was included as a four-level variable (smoked but quit before enrollment, smoking less than half a pack of cigarettes at enrollment, smoking half a pack or more at enrollment, and no smoking in pregnancy). Prepregnancy body mass index (BMI) was also a four-level variable using CDC cutpoints: underweight (BMI < 18.5), normal weight (BMI 18.5 – 24.9), overweight (BMI 25.0 – 29.9), and obese (BMI ≥ 30). Caffeinated drinks were modeled as a continuous variable, while alcohol and illicit drug/substance use were modeled as dichotomous variables.

Preterm delivery—Gestational age (GA) at delivery was determined by the GA estimated from the date of the first day of the last menstrual period (LMP). However, if GA derived from

early ultrasound differed from the LMP estimated GA by 2 or more weeks, the ultrasound age was given preference. In the present study, PTD was defined as delivery at < 37 completed weeks of gestation. In addition, preterm deliveries were categorized into four groups based on clinical presentations and timing: (1) medically indicated at < 35 weeks; (2) medically indicated at 35–36 weeks; (3) spontaneous at < 35 weeks; and (4) spontaneous at 35–36 weeks (Moutquin, 2003). This was done because these subgroups may differ in their primary causes. Medically indicated PTD was defined as a delivery at < 37 weeks that begins by induction or C-section and not by spontaneous labor (cervix dilated ≥ 2cm and regular contractions) or rupture of the membranes as an initiating event. All other cases of PTD were considered spontaneous.

Analytic strategy

Unadjusted odds ratios and 95% confidence intervals were generated for individual associations between each of the depression variables and the overall risk of PTD (SAS version 9.1, SAS Institute Inc, Cary, NC). This approach was repeated using polytomous logistic regression with a five-level outcome variable: term (reference), medically indicated PTD at < 35 weeks, medically indicated PTD at 35–36 weeks, spontaneous PTD at < 35 weeks, and spontaneous PTD at 35–36 weeks.

In the next set of analyses, four-level exposure variables were created by combining measures of depression with psychiatric medication use. These variables were designed to: 1) capture the influence of psychiatric medications used most often among women with depression; 2) separately consider depression severe enough to warrant medication in pregnancy; and 3) examine whether depression without psychiatric medication use had any relation to PTD. The first combined exposure variable included: low CES-D score (< 24) and no medication (reference), low CES-D score (< 24) and medication use, high CES-D (≥ 24) score and no medication, and high CES-D score (≥ 24) and medication use. The other exposure variables were modeled in a similar manner, except CES-D score was replaced with prepregnancy history of depression and depression during pregnancy.

All analyses were repeated after substituting any psychotropic medication used in pregnancy in place of psychiatric medication. This was done because women may have misclassified medication type or may have been self-medicating with other forms of psychotropic medication. Subsequent polytomous logistic regression models tested the effects of adding socio-demographic variables, prepregnancy BMI, and health behaviors during pregnancy as potential confounders/mediators. Because women with high MSAFP levels were over-sampled into the cohort (3–5% in the population but 7% in the cohort), analyses were repeated after removing these women to test for any bias.

Results

Table 1 presents a summary of sociodemographic, behavioral, and clinical characteristics of the sample. Overall, 335 (11%) women delivered preterm; 228 (8%) preterm deliveries were spontaneous and 107 (3%) were medically indicated. In this sample, 17% of women had CES-D scores of ≥ 24 at mid-pregnancy, 21% reported depression prior to the pregnancy, 4% experienced depression during the first half of pregnancy, and 10% used a psychotropic medication during the first half of pregnancy.

Among women reporting depression in pregnancy, 75% had a history of depression (data not shown) and 62% used psychiatric medications in the first half of pregnancy (Table 2). An elevated CES-D cutoff score was not particularly discriminating for psychotropic medication use in pregnancy. Twenty percent of those with elevated depressive symptoms (score ≥ 24) reported psychotropic medication use in pregnancy

In logistic regression models, depressive symptoms, depression, and use of psychiatric medication in pregnancy were not significantly related to PTD overall (Table 3). In polytomous logistic regression models that considered PTD divided by clinical circumstances and gestational weeks, depression during pregnancy was significantly associated with medically indicated PTD at < 35 weeks (unadjusted odds ratio [OR] = 3.3; 95% confidence interval [CI]: 1.3, 8.6). Use of psychiatric medications also increased maternal odds for medically indicated PTD at < 35 weeks (unadjusted OR=2.5) but the lower bound of the confidence interval was 1.

A second set of models used variables that combined psychiatric medication use in pregnancy with depressive symptoms or reported depression (Table 4). The odds of overall PTD was elevated among women with CES-D scores of ≥ 24 who also reported use of psychiatric medication compared to those with low CES-D scores and no medication use (unadjusted OR = 2.2; 95% CI: 1.2, 3.9). In these models, elevated CES-D scores without psychiatric medication use showed little association with PTD.

The combinations of psychiatric medication use in pregnancy and depression prior to or in pregnancy were not significantly related to overall PTD (Table 4). However, these combinations were strongly associated with medically indicated PTD at < 35 weeks among women with depression prior to pregnancy and psychiatric medication use in pregnancy (unadjusted OR = 2.9; 95% CI: 1.2, 7.1), and among women with depression during pregnancy and psychiatric medication use in pregnancy (unadjusted OR = 3.5; 95% CI: 1.1, 12). There was also some evidence that women who reported depression during pregnancy but did not use psychiatric medication in the first half of pregnancy might be at increased risk of medically indicated PTD at < 35 weeks, but the confidence interval for the OR included 1.

A series of polytomous logistic regression models were constructed by using the combined variables of psychiatric medication use and depressive symptoms or depression and other covariates. The addition of race did not alter effects observed in the unadjusted models. Similarly, little change was noted after including prepregnancy BMI, alcohol use, marijuana, caffeine, and other illicit substance/drug use (data not shown). In the final models, key risk factors for PTD were retained (race, maternal age, parity, Medicaid status, smoking status, and prepregnancy BMI) (Table 4). Results from these models were similar to those in unadjusted models, with the exception that the combination of depression prior to pregnancy and psychiatric medication use in pregnancy was now significantly related to overall PTD (adjusted OR = 1.6; 95% CI: 1.1, 2.5). Analyses were repeated after substituting any psychotropic medication in place of psychiatric medication and after removing women with high MSAFP and results remained comparable (data not shown).

Conclusions and Discussion

In this prospective cohort study of pregnant women living in five Michigan communities we found that the relation between depression and PTD was influenced by how depression was assessed, the inclusion of information on psychiatric medication, and the approach used to model PTD (early versus late, spontaneous versus medically indicated). A positive screen for depressive symptoms was associated with PTD only among women who also reported using psychiatric medication in pregnancy. The approximate two-fold increase in odds was related to overall risk of PTD. For women who reported a history of depression or depression during pregnancy and who were taking psychiatric medications in pregnancy, their elevated risk was primarily for medically indicated PTD at < 35 weeks, with a three to three and half fold increase in odds.

The literature on depression and PTD has been inconsistent with some, but not all, studies suggesting a positive association (Hoffman & Hatch, 2000; Dayan et al., 2006; Orr, James, & Blackmore-Prince, 2002; Steer, Scholl, Hediger & Fischer, 1992; Berle et al., 2005; Andersson, Sundstrom-Poromaa, Wulff, Astrom, & Bixo, 2004; Mustillo et al., 2004; Larsson, Sydsjo, & Josefsson, 2004; Dole, et al., 2004; Dole et al., 2003; Pekin, Bland, Peacock, & Anderson, 1993). Previous studies have primarily screened women for depressive symptoms and modeled results by using a single cut-point or a continuous variable (Hoffman & Hatch, 2000; Dayan et al., 2006; Orr, James, & Blackmore-Prince, 2002; Steer, Scholl, Hediger & Fischer, 1992; Mustillo et al., 2004; Larsson, Sydsjo, & Josefsson, 2004; Dole et al., 2004; Dole et al., 2003; Pekin, Bland, Peacock, & Anderson, 1993). On occasion, studies measured depression using DSM-IV diagnostic criteria (Andersson, Sundstrom-Poromaa, Wulff, Astrom, & Bixo, 2004). Some previous studies have subdivided PTD according to its clinical circumstances (Dayan et al., 2006; Orr, James, & Blackmore-Prince, 2002; Andersson, Sundstrom-Poromaa, Wulff, Astrom, & Bixo, 2004; Dole et al., 2004; Dole et al., 2003). One earlier study tested whether the presence of psychotropic medications in pregnancy modified the relation between depression and spontaneous PTD (Dayan et al., 2006). This study showed there was an association between antenatal depressive symptoms and spontaneous PTD (adjusted OR = 3.3, 95% CI: 1.2, 9.2). However, the odds increased when psychotropic users were excluded from the analysis (adjusted OR = 4.9, 95% CI: 1.6, 14.9), suggesting that the association between depression and PTD is weaker among women who used psychotropic medication. This finding is contrary to the results in the present study, as well as a growing number of studies that have found an increased risk of PTD among women who used psychiatric medications in pregnancy (Oberlander, Warburton, Misri, Aghajanian & Hertzman, 2008; Davis et al., 2007; Wen et al., 2006; Simon, Cunningham, & Davis, 2002).

Our decision to model depression using multiple modes, i.e. symptoms, history of depression, and depression during pregnancy, is warranted for several reasons. Depression can be a chronic disease with remission, relapse and reoccurrence (Lin et al., 1998; Nierenberg, Petersen, & Alpert, 2003). The biologic mechanisms and/or behaviors that might mediate an association between depression and PTD are speculative and the relevant time windows are also uncertain. Depressive symptoms and self-report of depression may capture overlapping and distinct features which are relevant to pregnancy outcome. As an example, we observed that elevated levels of depressive symptoms combined with psychiatric medication use were associated with overall PTD, while maternal reports of depression and psychiatric medication use were primarily associated with medically indicated PTD. This contrast raises questions about potential mediating mechanisms through different behaviors, different medications, or different hormonal influences that characterize women grouped by various measures of depressive symptoms/depression.

Teasing apart effects of depressive symptoms/depression from effects of psychotropic medication during pregnancy is not easy, particularly because use of antidepressants and other medications might be inextricably tied to severity of depression and other unmeasured confounders. We did find that in the absence of psychiatric medication use, elevated levels of depressive symptoms at mid-pregnancy and history of depression did not pose an increased risk for PTD. The one exception was the small group of women (N = 47) who reported depression during pregnancy but did not report psychiatric medication use and still had elevated risks for medically indicated PTD at < 35 weeks. One possibility is that these women used psychiatric medications in pregnancy, but only after the enrollment interview. To test this explanation we checked medication information from prenatal and labor and delivery records that were abstracted in a subcohort of study women. Among the 47 women, 26 were in the subcohort. Four (15%) of the 26 women had evidence of psychiatric medication use at some time in pregnancy. Therefore we can not assume that the group of 47 women never used psychiatric medication throughout the entire pregnancy.

Recent studies have reported links between prenatal exposure to antidepressants, specifically tricyclic and selective serotonin reuptake inhibitors (SSRI) and increased risk of adverse pregnancy outcomes (Oberlander, Warburton, Misri, Aghajanian & Hertzman, 2008; Davis et al., 2007; Suri et al., 2007; Wen et al., 2006; Simon, Cunningham, & Davis, 2002; Oberlander, Warburton, Misri, Aghajanian & Hertzman, 2006). One study showed that infants born to mothers with depression who were treated with antidepressants had significantly lower gestational ages than that of infants born to mothers with depression who were not treated with antidepressants (Wen et al., 2006). Oberlander and colleagues (2008) reported that length rather than timing of antenatal exposure to SSRI use was associated with reduced gestational age after accounting for maternal mental illness and medication dosage.

Little is known about mechanisms that might mediate any direct causal link between prenatal exposure to psychotropic medication and PTD (Oberlander, Warburton, Misri, Aghajanian & Hertzman, 2006; Wen et al., 2006). Studies have shown that SSRIs readily cross the placenta (Hendrick et al., 2003), are present in amniotic fluid (Loughhead et al., 2006) and newborns may experience withdrawal like symptoms after birth (Moses-Kolko et al., 2005). Suri and colleagues (2008) noted higher estriol levels in the latter part of pregnancy among women using anti-depressants, and this may indicate increased/accelerated fetal production of estriol precursors. SSRIs can also lower serotonin levels in platelets which, in some studies have shown clinical evidence of compromised coagulation and predisposition to hemorrhage (Looper, 2007).

Our strongest finding was between the combination of depression and psychiatric medication use and medically indicated PTD at < 35 weeks' gestation. In the POUCH study, detailed abstraction of medical records showed that most physician initiated preterm deliveries were due to maternal complications such as pre-eclampsia and gestational hypertension, poor fetal growth, or acute hemorrhage associated with placental abruption. This is in agreement with other studies on circumstances surrounding medically indicated preterm deliveries (Ananth & Vintzileos, 2008). These conditions can originate from abnormal placentation, maternal endothelial dysfunction, and problems with homeostasis, and perhaps these processes are exaggerated in women with depression and psychiatric medication use. The slightly weaker associations we observed with overall PTD do not contradict these explanations, as we and others have shown that the same vascular conditions that motivate medically indicated PTD are also linked to spontaneous PTD (Kelly R, Holzman C, Senagore P, Wang J, Tian Y, Rahbar MH, & Chung H, *In press*)

A number of limitations should be considered when interpreting the findings of our study. We did not use diagnostic tools to ascertain depression prior to or during pregnancy, rather we relied on self- reports of diagnoses of prepregnancy depression and antenatal depression. We did not collect information on depression or psychiatric medication use later in the pregnancy, after enrollment. Within our observational study, we could not rule out the possibility that psychiatric medication use was a proxy for depression severity. Lastly we did not have data on individual psychiatric medications in the whole cohort, and therefore we could not evaluate the specific link between SSRIs and PTD risk.

Despite these limitations, our study had several advantages. Women were sampled from 52 clinics in five Michigan communities thereby enhancing the generalizability of the results. The prevalence of history of depression (21%) and any psychotropic medication use (10%) closely matched those reported in national surveys of similar age women (Hasin, Goodwin, Stinson, & Grant, 2005; Paulouse-Ram, Safran, Jonas, Gu, & Orwig, 2007). Depressive symptoms and reports of depression were assessed prior to delivery, thus eliminating problems of recall bias. We considered all PTD and PTD categorized by weeks of gestation and clinical circumstances, thereby exploring specificity for certain underlying pathways. We also had information on

many potential confounding and mediating factors and we were able to show that effects of depression and psychiatric medications were not explained by prepregnancy BMI, smoking or other illicit substance use. We might also infer that our results were probably not confounded by factors related to genital tract infections because infection is typically associated with spontaneous PTD at < 35 weeks, a PTD subtype that was not related to depression or psychotropic medication in our data.

Our findings highlight the need for carefully planned studies that can clarify associations between depression, psychiatric medications, and PTD. Ideally, these studies would prospectively gather data during the prepregnancy, pregnancy, and postpartum periods, include detailed assessments of all psychotropic medications, and measure depressive symptoms and clinical depression. In addition, studies should consider different methods for categorizing PTD to better elucidate underlying processes linked to depression or medication use. Women with depression face difficult decisions regarding the benefits and risks of using psychotropic medications in pregnancy. Therefore, a focus on disentangling medication effects and depression effects on mother and offspring health should be a major priority.

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TABLE 1

Maternal characteristics of the POUCH study women (N=3019)*

Maternal Characteristics	No.	%
Age (years)		
<20	460	15
20–29	1711	57
≥30	848	28
Race/Ethnicity		
White / Others	2276	75
Black	743	25
Maternal Education		
<12 yrs (age<20)	292	10
<12 yrs (age ≥20)	265	9
12 yrs	885	29
>12 yrs	1577	52
Medicaid Insured		
No	1562	52
Yes	1454	48
Parity		
0 live birth	1293	43
≥ 1 live birth	1725	57
Week of Pregnancy At Enrollment		
<20 wks	445	15
20–24 wks	2162	71
25–27 wks	412	14
Smoking		
No smoking during pregnancy	2157	72
Stopped before enrollment	303	10
Smoked < 1/2 pack/day at enrollment	368	12
Smoked ≥ 1/2 pack/day at enrollment	185	6
Body Mass Index		
Underweight (BMI < 18.5)	140	5
Normal (BMI: 18.5 – 24.9)	1383	46
Overweight (BMI: 25.0 – 29.9)	705	23
Obese (BMI ≥ 30)	788	26
Use of alcohol during pregnancy		
No	2457	82
Yes	547	18
Use of illicit drugs during pregnancy		
No	2496	83
Yes	512	17
Pregnancy Outcome		
Term	2684	89

Maternal Characteristics	No.	%
Preterm Medically Indicated	107	3
Preterm Spontaneous PTL / PPROM	228	8
CES-D Score[†]		
< 24	2503	83
≥ 24	507	17
Prepregnancy history of depression[§]		
No	2392	79
Yes	624	21
Depression during pregnancy		
No	2901	96
Yes	117	4
Use of psychotropic medicines during pregnancy[§]		
No	2710	90
Yes	306	10

[*] For each maternal characteristic data may be missing for 1 (parity) to 15 (use of alcohol) women.

[†] Data missing for 9 women.

[§] Data missing on 3 women.

Table 2

Measures of maternal depressive symptoms, depression, and psychotropic medication use during pregnancy ascertained at enrollment (15–27 weeks gestation)

	Psychotropic medication use during pregnancy*							
	No medication N (%)		Psychiatric only N (%)		Psychiatric, tranquilizers, sedative, and sleeping pills N (%)		Tranquilizers, sedative, and sleeping pills only N (%)	
CES-D score†								
CES-D < 24	2297	(92)	106	(4)	13	(1)	86	(3)
CES-D ≥ 24	406	(80)	64	(13)	10	(2)	26	(5)
Prepregnancy history of depression (self-report)								
No	2296	(96)	19	(1)	1	(0.04)	75	(3)
Yes	414	(66)	152	(24)	22	(4)	35	(6)
Depression during pregnancy (self-report)								
No	2665	(92)	111	(4)	13	(0.45)	110	(4)
Yes	45	(38)	60	(51)	10	(9)	2	(2)

†Center for Epidemiologic Studies Depression Scale

*As reported by women at enrollment; therefore captures exposure approximately the first half of pregnancy.

Table 3

Measures of maternal depressive symptoms, depression, and psychiatric medication use during pregnancy in relation to risk of preterm delivery subtypes in the POUCH study (1998–2004).

		Preterm	Preterm Subtype			
	N	Unadjusted OR (95% CI)*	Medically Indicated 35–36 wks: Unadjusted OR (95% CI)*	Medically Indicated < 35 wks: Unadjusted OR (95% CI)*	Spontaneous 35–36 wks: Unadjusted OR (95% CI)*	Spontaneous <35 wks: Unadjusted OR (95% CI)*
CES-D† score						
CES-D < 24	2503	1.0	1.0	1.0	1.0	1.0
CES-D ≥ 24	507	1.0 (0.7, 1.3)	1.0 (0.5, 2.0)	0.8 (0.3, 2.0)	1.1 (0.7, 1.6)	0.7 (0.4, 1.4)
Prepregnancy history of depression (self-report)						
No	2392	1.0	1.0	1.0	1.0	1.0
Yes	624	1.2 (0.9, 1.6)	1.2 (0.7, 2.2)	1.7 (0.9, 3.3)	1.2 (0.7, 2.2)	0.9 (0.4, 2.3)
Depression during pregnancy (self-report)						
No	2901	1.0	1.0	1.0	1.0	1.0
Yes	117	1.1 (0.6, 1.9)	0.8 (0.2, 3.4)	3.3 (1.3, 8.6)	0.9 (0.2, 3.6)	0 (0)
Use of medications‡ during pregnancy						
No	2822	1.0	1.0	1.0	1.0	1.0
Yes	194	1.4 (0.9, 2.1)	1.3 (0.5, 3.2)	2.5 (1.0, 5.9)	1.6 (0.9, 2.8)	0.4 (0.1, 1.8)

† Center for Epidemiologic Studies Depression Scale

‡ Include psychiatric medication with or without tranquilizers, sedative, and sleeping pills.

* Term delivery is reference group.

Table 4

Unadjusted and adjusted odds ratios for combined measures of maternal depressive symptoms, depression, and psychiatric medication use during pregnancy in relation to risk of preterm delivery subtypes in the POUCH study (1998–2004).

		Preterm		Preterm Subtype							
				Medically Indicated 35–36 weeks		Medically Indicated < 35 week		Spontaneous 35–36 weeks		Spontaneous <35 weeks	
	N	Unadjusted OR (95% CI)*	Adjusted§ OR (95% CI)*	Unadjusted OR (95% CI)*	Adjusted§ OR (95% CI)*	Unadjusted OR (95% CI)*	Adjusted§ OR (95% CI)*	Unadjusted OR (95% CI)*	Adjusted§ OR (95% CI)*	Unadjusted OR (95% CI)*	Adjusted§ OR (95% CI)*
CES-D† score and use of medications‡ during pregnancy											
CES-D < 24, Meds No (reference)	2383	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
CES-D < 24, Meds Yes	119	0.9 (0.5, 1.6)	0.9 (0.5, 1.7)	0.4 (0.1, 2.8)	0.4 (0.1, 2.8)	2.5 (0.9, 7.1)	2.5 (0.9, 7.4)	1.1 (0.5, 2.5)	1.1 (0.5, 2.5)	0 (0)	0 (0)
CES-D ≥ 24, Meds, No	432	0.8 (0.5, 1.1)	0.6 (0.4, 0.9)	0.7 (0.3, 1.6)	0.6 (0.3, 1.4)	0.7 (0.2, 1.9)	0.7 (0.2, 1.9)	0.9 (0.5, 1.4)	0.8 (0.5, 1.3)	0.6 (0.3, 1.3)	0.5 (0.2, 1.0)
CES-D ≥ 24 Meds, Yes	74	2.2 (1.2, 3.9)	2.0 (1.1, 3.6)	2.8 (1.0, 8.0)	2.5 (0.9, 7.3)	2.3 (0.5, 9.7)	2.3 (0.5, 9.8)	2.4 (1.1, 5.2)	2.2 (1.0, 4.8)	1.2 (0.3, 4.9)	1.1 (0.3, 4.8)
Prepregnancy history of depression (self-report) and use of medications‡ during pregnancy											
No, Meds No (reference)	2371	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
No, Meds Yes	20	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Yes, Meds No	449	1.1 (0.8, 1.5)	1.1 (0.8, 1.5)	1.1 (0.5, 2.2)	1.1 (0.6, 2.3)	1.2 (0.5, 2.9)	1.3 (0.5, 2.9)	0.9 (0.6, 1.5)	0.9 (0.5, 1.4)	1.4 (0.7, 2.5)	1.7 (0.9, 3.1)
Yes, Meds Yes	174	1.6 (1.0, 2.4)	1.6 (1.1, 2.5)	1.5 (0.6, 3.8)	1.5 (0.6, 3.8)	2.9 (1.2, 7.1)	2.9 (1.2, 7.2)	1.8 (1.0, 3.2)	1.8 (1.0, 3.1)	0.5 (0.1, 2.2)	0.6 (0.1, 2.6)
Depression during pregnancy(self-report) and use of medications‡ during pregnancy											
No, Meds No (reference)	2775	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
No, Meds Yes	124	1.4 (0.8, 2.3)	1.4 (0.8, 2.4)	1.2 (0.4, 3.8)	1.1 (0.3, 3.7)	2.0 (0.6, 6.6)	2.0 (0.6, 6.7)	1.8 (1.0, 3.5)	1.8 (0.9, 3.5)	0.3 (0.0, 2.5)	0.4 (0.1, 2.9)
Yes, Meds No	47	0.8 (0.3, 2.1)	0.7 (0.2, 2.0)	0 (0)	0 (0)	3.3 (0.8, 14)	3.2 (0.7, 14)	0.8 (0.2, 3.5)	0.8 (0.2, 3.2)	0 (0)	0 (0)

		Preterm		Preterm Subtype							
				Medically Indicated 35–36 weeks		Medically Indicated < 35 week		Spontaneous 35–36 weeks		Spontaneous <35 weeks	
	N	Unadjusted OR (95% CI)*	Adjusted§ OR (95% CI)*	Unadjusted OR (95% CI)*	Adjusted§ OR (95% CI)*	Unadjusted OR (95% CI)*	Adjusted§ OR (95% CI)*	Unadjusted OR (95% CI)*	Adjusted§ OR (95% CI)*	Unadjusted OR (95% CI)*	Adjusted§ OR (95% CI)*
Yes, Meds Yes	70	1.4 (0.7, 2.7)	1.4 (0.7, 2.7)	1.4 (0.3, 5.9)	1.4 (0.3, 6.0)	3.5 (1.1, 12)	3.6 (1.1, 12)	1.2 (0.4, 3.3)	1.2 (0.4, 3.2)	0.6 (0.1, 4.4)	0.7 (0.1, 4.8)

† Center for Epidemiologic Studies Depression Scale

‡ Include psychiatric medication with or without tranquilizers, sedative, and sleeping pills.

* Term delivery is referent group.

§ Adjusted for maternal race, age, parity, Medicaid status, smoking status, and BMI.