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Risk of Preterm Delivery and Hypertensive Disorders of Pregnancy in Relation to Maternal Comorbid Mood and Migraine Disorders during Pregnancy

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Summary

We evaluated risks of preterm delivery and hypertensive disorders of pregnancy among pregnant women with mood and migraine disorders. We used data from a cohort study of 3,432 pregnant women. Maternal pre-gestational or early pregnancy (before 20 weeks gestational) mood disorder and pre-gestational migraine diagnoses were ascertained from in-person interview and medical record review. We fitted generalized linear models to derive risk ratios (RR) and 95% confidence intervals (CI) of preterm delivery and hypertensive disorders of pregnancy for women with isolated mood, isolated migraine, and comorbid mood-migraine disorders, respectively. Reported RRs were adjusted for maternal age, race/ethnicity, marital status, parity, smoking status, chronic hypertension or pre-existing diabetes mellitus, and pre-pregnancy body mass index. Women without mood or migraine disorders were defined as the reference group. The risks for preterm delivery and hypertensive disorders of pregnancy were more consistently elevated among women with comorbid mood-migraine disorders than among women with isolated mood or migraine disorder. Women with comorbid disorders were almost twice as likely to deliver preterm (adjusted RR=1.87, 95% CI 1.05–3.34) compared with the referent group. There was no clear evidence of increased risks of preterm delivery and its subtypes with isolated migraine disorder. Women with mood disorder had elevated risks of preeclampsia (adjusted RR=3.57, 95% CI 1.83–6.99). Our results suggest an association between isolated migraine disorder and pregnancy-induced hypertension (adjusted RR=1.42, 95% CI 1.00–2.01). This is the first study examining perinatal outcomes in women with comorbid mood-migraine disorders. Pregnant women with a history of migraine may benefit from depression screening during prenatal care, and vigilant monitoring, especially for women with comorbid mood-migraine disorders.

Keywords

Mood disorders; Migraine; Pregnant women; Preterm Delivery; Preeclampsia

INTRODUCTION

Depression, more prevalent among women than men, is particularly common among reproductive age women.^{1, 2} Perinatal depression encompasses major and minor mood episodes that occur either during pregnancy or within the first 12 months after delivery.³ Recent meta-analysis of perinatal depression in developed countries reported point

prevalence estimates between 6% and 13%.⁴ Depression around the time of pregnancy is of concern because it has been linked to negative health-related behaviors and outcomes, including poor nutrition, increased substance use, inadequate prenatal care, intra-uterine growth restriction, preeclampsia, and preterm delivery.^{5–8}

Migraine, a recurrent neurovascular headache disorder, is characterized by episodes of severe throbbing, pulsatile headache associated with nausea, vomiting, photophobia, phonophobia, and aversion to physical activity.⁹ Findings from the American Migraine Prevalence and Prevention study indicate that the prevalence of migraine rises from 4% before puberty to a peak of 25% in women during their childbearing years, with a decrease after menopause.¹⁰ Several studies in both clinic- and community-based populations have described associations between mood and migraine disorders.^{11, 12} Only one study has reported the association between these two disorders in pregnant women.¹³

Maternal depression during pregnancy and migraine have been found to be independent risk factors for preterm delivery and preeclampsia in some studies,^{14–16} but not all studies.^{17, 18} Chronic systemic inflammation and related endothelial dysfunction, observed in individuals with mood and migraine disorders,^{19, 20} have also been implicated in the pathogenesis of preterm delivery²⁰ and preeclampsia.²¹ Given the biological plausibility for associations of preterm delivery and preeclampsia with mood and/or migraine disorders, and the lack of published studies on the risks adverse perinatal outcomes among pregnant women with comorbid mood-migraine disorders, we conducted this study to examine preterm delivery and preeclampsia risks among women with comorbid mood-migraine disorders. We reasoned that evaluation of associations of comorbid mood-migraine disorders with preterm delivery and preeclampsia may add greater specificity to an existing literature focused on assessing risks of adverse perinatal risks among women with pre-gestational chronic disorders.

METHODS

Study Design and Setting

We analyzed data from the Omega Study, a prospective cohort study designed to examine risk factors of adverse pregnancy outcomes including preeclampsia.²² Participants were recruited from women attending prenatal care clinics affiliated with Swedish Medical Center and Tacoma General Hospital in Seattle and Tacoma, Washington, USA. Recruitment began in December 1996. The study protocol was approved by the Institutional Review Boards of Swedish Medical Center and Tacoma General Hospital. All participants provided informed consent.

Eligible women were those who began prenatal care before 20 weeks gestation, spoke and read English, were 18 years of age, and planned to carry the pregnancy to term and deliver at either of the two hospitals. During early pregnancy, participants were asked to complete a structured interviewer administered questionnaire regarding socio-demographic characteristics, lifestyle habits, and medical and reproductive histories. Pregnancy outcome information was abstracted from hospital and clinic medical records.

Analytical Population

The analytical study population was derived from participants enrolled in the Omega Study between 1996 and 2008. During this period, 5,063 eligible women were approached and 4,000 (approximately 79%) agreed to participate. We excluded women with missing delivery information (n=169) or missing information on mood or migraine disorders diagnosis (n=217), and those whose pregnancy terminated before 20 weeks gestation (spontaneous abortion or voluntary termination of pregnancy) (n=65). We further excluded

117 women with multi-fetal pregnancies. A sample of 3,432 women remained for the present study. However, for some analyses (i.e., those analyses of risk of hypertensive disorders of pregnancy in relation to maternal mood-migraine disorders), we excluded 154 women with pre-gestational chronic hypertension, and 6 women with unknown pre-gestational hypertension status.

Data Collection

From structured questionnaire and medical records, we obtained information on covariates including maternal age, educational attainment, height, pre-pregnancy weight, reproductive and medical histories, and medical histories of first-degree family members. We also collected information on maternal smoking during pregnancy. Pre-pregnancy body mass index (BMI) was calculated as pre-pregnancy weight in kilograms divided by height in meters squared. Information about psychiatric diagnoses was derived from clinical records and participants' self-reported medical histories. Clinical records included information about specific type of psychiatric disorder (e.g., depression, bipolar disorder, or anxiety disorders) and the timing of diagnosis (e.g., pre-gestational or before 20 completed weeks gestation). Women were considered positive for mood or anxiety disorder if (1) they reported mood or anxiety disorder before the index pregnancy and had such diagnoses included in their antepartum or hospital medical records, or (2) received a new diagnosis of mood or anxiety disorder during the first 20 weeks of the index pregnancy, indicated in their antepartum clinic or hospital medical records. Maternal history of *migraine diagnosis* was determined by response to the questions "Has a doctor ever told you that you have migraine headache?"

The diagnosis of pregnancy-induced hypertension and preeclampsia were made using abstracted medical record data according to the American College of Obstetricians and Gynecologists (ACOG) guidelines.²³ These guidelines defined preeclampsia as sustained pregnancy-induced hypertension with proteinuria. Pregnancy-induced hypertension was defined as sustained blood pressure readings of 140/90 mmHg taken 6 hours apart on or after 20 weeks gestation. Proteinuria was defined as urine protein concentrations of 30 mg/dl on two or more random specimens collected at least 4 hours apart. We assessed risk of any hypertensive disorder (i.e., preeclampsia and pregnancy induced hypertension combined), and risk of each disorder separately.

Preterm delivery (PTD) was defined as a delivery that occurred at gestational age of more than 20 and before the completion of 37 weeks of gestation. Using the detailed information collected from medical records, we further categorized subtypes of preterm delivery cases according to spontaneity of preterm labor and delivery (i.e., spontaneous preterm labor or premature rupture of membrane-initiated preterm delivery, and medically indicated preterm delivery).

Statistical Analyses

We compared the frequency distribution of maternal sociodemographic, lifestyle, behavioral and medical history characteristics according to the following four study groups: (1) no mood-migraine disorders (reference); (2) mood disorders only; (3) migraine disorder only; and (4) comorbid mood-migraine disorders. We fitted generalized linear models to derive risk ratios (RR) and 95% confidence intervals (CI) of preterm delivery or hypertensive disorders of pregnancy. We assessed confounding by entering covariates into the regression model one at a time, and adjusted RRs were compared to unadjusted RRs. We evaluated the following characteristics, reported in interviews, as potential confounders: maternal age, race/ethnicity, marital status, parity, smoking status, chronic hypertension or preexisting diabetes mellitus, family history of chronic hypertension and pre-pregnancy body mass index. Final regression models included covariates that altered unadjusted RRs by 10%.²⁴

We present continuous variables as mean with standard deviation (SD). All reported p-values are 2-tailed with statistical significance set at 0.05

RESULTS

Selected maternal sociodemographic, lifestyle and medical characteristics, and perinatal outcomes of the study cohort are summarized in Table 1. In this sample of women, 4.4% had isolated mood disorder, 16.0% had isolated migraine disorder and 2.1% had comorbid mood-migraine disorders. Compared with other women in this sample, women with comorbid mood-migraine disorders tended to be under 30 years old or over 40 years old, unmarried, multiparous and smoked during pregnancy. These women also tended to have chronic hypertension, pre-gestational diabetes and family histories of hypertension and diabetes. Women with isolated mood disorder were more likely than other women in this sample to have fewer years of education. Women with isolated mood disorder (36.4%) or comorbid mood-migraine disorders (35.6% each) were more likely to deliver by cesarean section compared with women without either disorder (28.1%) or isolated migraine disorder (30.2%). The occurrence of preterm births was highest among women with comorbid disorders (17.8%) followed by women with isolated mood disorder (13.3%) versus 8.0% without either disorder (Table 1).

Estimated associations between preterm delivery and its subtypes with maternal mood and migraine disorders are shown in Table 2. There were 202 spontaneous and 83 medically-indicated preterm deliveries. Preterm delivery was elevated among women with comorbid mood-migraine disorders (RR=1.87, 95% CI 1.05–3.34) when compared with women without either disorder after adjusting for maternal age, race/ethnicity, marital status, parity, smoking status, chronic hypertension or preexisting diabetes mellitus, and pre-pregnancy body mass index. There was no clear evidence of increased risk of preterm delivery with isolated migraine disorder. Similar pattern of associations were observed when we examined the relationship between subtypes of preterm delivery (spontaneous and medically-indicated) and maternal mood and migraine disorders. Women with comorbid mood-migraine disorders had an almost 2-fold (adjusted RR=1.94, 95% CI 0.94–3.98) increased risk of spontaneous preterm delivery and a 2-fold increased risk (adjusted RR=2.02, 95% CI 0.78–5.22) of medically-indicated preterm delivery when compared with women without either disorder (Table 2). However, these estimates are imprecise due to small sample sizes.

Women with isolated mood (adjusted RR=1.49, 95% CI 0.92–2.40), isolated migraine (adjusted RR=1.32, 95% CI 0.97–1.80) and comorbid mood-migraine (adjusted RR=2.05, 95% CI 1.05–4.02) disorders had increased risks of hypertensive disorders during pregnancy compared with women without either disorder (Table 3). However, only the association between comorbid mood-migraine disorders and hypertensive disorders of pregnancy was statistically significant. Women with isolated migraine disorder, compared with those in the reference group, had a 1.42-fold increased risk (95% CI 1.00–2.01) of pregnancy-induced hypertension. Women with isolated mood disorder had an elevated risk of preeclampsia (adjusted RR=3.57, 95% CI 1.83–6.99). Even though there was an elevated risk for preeclampsia among women with comorbid mood-migraine disorders (RR=3.49, 95% CI 1.07–11.36), this estimate is imprecise due to small sample size.

DISCUSSION

To the best of our knowledge, there has been no published report on perinatal risks of comorbid mood-migraine disorders. Our results suggesting increased risk for preterm delivery and hypertensive disorders of pregnancy among pregnant women with comorbid

mood-migraine disorders are novel findings. The estimates were robust to adjustment for confounding factors.

Several potential limitations should be considered when interpreting these results. First, the prevalence of mood disorder of 4.4% in this sample is well below the national prevalence estimate reported by other investigators.²⁵ As a result, it is likely that a considerable number of women with psychiatric illnesses were misclassified as not having mood or anxiety disorder in our cohort. This under-ascertainment of psychiatric illnesses would generally serve to underestimate the true magnitude of associations detected in our study. In addition we did not have information on clinical diagnoses of specific mood and migraine disorders, and medications used during pregnancy. We were not able to confirm the self-reported diagnoses nor were we able to evaluate the influence of medications used to treat mood and migraine disorders on the perinatal outcomes of interest. Second, inferences from some of our analyses were hindered by our relatively small sample size and the imprecision of some estimated measures of associations. For example, there were only five women with comorbid mood-migraine disorders who had medically-indicated preterm deliveries in this cohort, and three women with comorbid mood-migraine disorders who had preeclampsia. Much larger prospective studies are needed to confirm the associations between mood and migraine disorders on preterm delivery and preeclampsia risks. Third, we did not assess the effect of treatment for mood or migraine disorders on preterm delivery and hypertensive disorders of pregnancy. Fourth, findings from this hospital-based study that included mostly white, highly educated, and normal weight women may not be generalizable to other pregnant women. Finally, although we adjusted for multiple confounding factors, as with all observational studies, we cannot exclude the possibility of some residual confounding from unmeasured factors.

Women with comorbid mood-migraine disorders were almost twice as likely to deliver preterm as compared to women without mood and migraine disorders. Other investigators¹⁴ have reported positive associations between maternal mood disorders and preterm delivery risks, though none have evaluated preterm delivery risk in relation to comorbid mood-migraine disorders.

Kurki et al.²⁶ observed that depression was associated with a 2.5-fold increased risk of preeclampsia (95% CI 1.2–5.3) in 623 pregnant Finnish women, and this observation was confirmed by Qiu et al.⁵ in their study of 676 Peruvian women. The authors⁵ reported a 2.3-fold increased risk for preeclampsia (95% CI 1.2–4.4) in women with moderate mood symptoms. Our results suggest that women with isolated mood disorder (adjusted RR=3.57, 95% CI 1.83–6.99) have increased preeclampsia risks compared with their unaffected counterparts. In addition, our results suggest that isolated migraine disorder increased pregnancy-induced hypertension. Some investigators have reported that migraine does not appear to negatively impact pregnancy outcomes,⁹ but others have reported associations between migraine and an increased risk for preeclampsia¹⁶ and stroke during pregnancy.²⁷ Investigators of a prospective cohort study²⁸ examined the risk of hypertensive disorders in pregnancy among Italian women and found that migraineurs had a higher risk of developing either gestational hypertension or preeclampsia compared with non-migraineurs (AOR=2.85; 95% CI 1.40–5.81).

Several biological mechanisms may plausibly account for the observed positive associations of maternal comorbid mood-migraine disorders with risks for preterm delivery and hypertensive disorders of pregnancy. Increases in hypothalamic-pituitary-adrenal (HPA) activity, one of the most robust pathophysiological findings associated with mood disorders,²⁹ is regarded as one important mechanism for observed associations between maternal psychiatric illness and adverse pregnancy outcomes, including preterm delivery³⁰

and preeclampsia.¹⁵ Chronic systemic inflammation and related endothelial dysfunction (reflected by elevated plasma C-reactive protein, platelet hyperactivity, and other pro-inflammatory markers) have been observed among individuals with mood disorders³¹ and migraine,¹⁹ and are also implicated in the pathogenesis of preterm delivery and preeclampsia.^{20, 22} In addition, depression during pregnancy may cause altered excretion of vasoactive hormones or other neurotransmitters,³² which may increase the risk of hypertension and preeclampsia. Additional information from clinical studies designed to assess neuroendocrine, hemodynamic and vascular effects of maternal psychiatric and migraine disorders (and treatment of these disorders) in pregnant women are needed before any firm conclusions can be drawn about these mechanistic hypotheses.

Our results suggest that preterm delivery and preeclampsia may be more strongly related to isolated mood disorder and comorbid mood-migraine disorders than isolated migraine disorder. The comorbidity of mood and migraine disorders supports the need for integration of both mental and physical disorders in clinical evaluation and treatment of patients with depression and/or headaches.³³ If confirmed in other cohorts, these results may be instrumental in motivating increased vigilance in screening and monitoring pregnant women, particularly those with comorbid disorders. Suitable alterations in therapeutic approaches in this particularly high risk population of pregnant women may serve to control symptoms, and potentially reduce the occurrence of adverse perinatal outcomes. Future longitudinal studies with prospective clinical assessments of symptoms and management of maternal mood and migraine disorders are needed to confirm and extend the findings from this study.

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Characteristics of subjects of the Omega study population according to maternal mood and migraine disorder status, Seattle and Tacoma, Washington, 1996–2008

Table 1

Characteristic	No mood or migraine disorder (N = 2,658)	Mood disorder only (N = 151)	Migraine only (N = 550)	Mood and migraine disorders (N = 73)
Maternal age (years)	32.6 ± 4.4	33.7 ± 4.7	32.4 ± 4.4	32.4 ± 5.5
<30	22.0	19.2	25.8	32.9
30–34	53.5	43.0	50.6	38.3
35–39	21.0	31.5	20.9	23.3
40	3.5	5.3	2.7	5.5
Nulliparous	63.6	61.6	60.0	50.7
Non-Hispanic white	85.3	94.7	87.5	95.9
High school or less	3.5	6.6	4.6	4.1
Unmarried	8.4	9.3	10.6	13.7
Prenatal vitamin intake	97.4	96.7	97.3	97.3
Smoked in pregnancy	5.5	11.9	5.6	12.3
Inactive in pregnancy	12.9	11.9	12.6	13.7
Chronic hypertension	3.8	4.6	6.2	17.8
Pre-gestational diabetes	1.2	0.7	0.7	4.1
Family history diabetes	14.3	13.9	15.8	20.6
Family history hypertension	49.4	49.7	52.4	58.9
Pre-pregnancy BMI (kg/m ²)	23.4 ± 4.5	24.6 ± 5.9	24.3 ± 5.8	25.6 ± 8.3
< 18.5	4.3	4.6	3.5	6.8
18.5 – 24.9	72.1	56.3	67.8	64.4
25 – 29.9	15.8	27.2	17.3	5.5
30	7.8	11.9	11.4	23.3
C-section delivery	28.1	36.4	30.2	35.6
Gestational age at delivery (weeks)	38.9 ± 1.9	38.4 ± 1.9	38.7 ± 2.1	38.4 ± 1.7
Preterm delivery	8.0	13.3	7.1	17.8
Infant birthweight (grams)	3,460 ± 556	3,351 ± 528	3,454 ± 555	3,314 ± 581

* Data are means ± standard deviation (SD) or percent.

Table 2

The estimated risk ratios (RR) and 95% confidence intervals (CI) of preterm delivery (PTD) and subtypes according to maternal mood and migraine disorders, Seattle and Tacoma, Washington, 1996–2008.

Maternal Mood and Migraine Disorders	Preterm Delivery (n, % from cohort)	Unadjusted RR (95%CI)	Adjusted RR (95%CI)
No mood or migraine disorder (N=2658)	213 (8.0)	1.00 (Reference)	1.00 (Reference)
Mood disorder only (N=151)	20 (13.3)	1.65 (1.05–2.61)	1.56 (0.98–2.47)
Migraine only (N=550)	39 (7.1)	0.88 (0.63–1.24)	0.86 (0.61–1.21)
Mood and migraine disorders (N=73)	13 (17.8)	2.22 (1.27–3.89)	1.87 (1.05–3.34)
<i>p-value for interaction term</i>		0.29	0.40
<i>Subtypes of Preterm Delivery</i>			
<i>Spontaneous PTD* (n, % from cohort)</i>			
No mood or migraine disorder	155 (5.8)	1.00 (Reference)	1.00 (Reference)
Mood disorder only	14 (9.3)	1.62 (0.93–2.80)	1.58 (0.91–2.74)
Migraine only	25 (4.6)	0.78 (0.51–1.19)	0.79 (0.51–1.20)
Mood and migraine disorders	8 (11.0)	1.97 (0.97–4.02)	1.94 (0.94–3.98)
<i>p-value for interaction term</i>		0.37	0.37
<i>Medically-indicated PTD (n, % from cohort)</i>			
No mood or migraine disorder	58 (2.2)	1.00 (Reference)	1.00 (Reference)
Mood disorder only	6 (4.0)	1.89 (0.82–4.38)	1.67 (0.71–3.93)
Migraine only	14 (2.6)	1.15 (0.64–2.06)	1.03 (0.57–1.85)
Mood and migraine disorders	5 (6.9)	3.32 (1.33–8.28)	2.02 (0.78–5.22)
<i>p-value for interaction term</i>		0.53	0.81

* Spontaneous preterm delivery including spontaneous preterm labor or premature rupture of membrane initiated preterm delivery.

[†] Adjusted for maternal age, race/ethnicity, marital status, parity, smoking status, chronic hypertension or pre-existing diabetes mellitus, and pre-pregnancy body mass index

Table 3

The estimated risk ratios (RR) and 95% confidence intervals (CI) of hypertensive disorders of pregnancy (pregnancy-induced hypertension (PIH) and preeclampsia) according to maternal mood and migraine disorders, Seattle and Tacoma, Washington, 1996–2008

Maternal Mood and Migraine Disorders	Hypertensive Disorders of Pregnancy (n, % from cohort)	Unadjusted RR (95%CI)	Adjusted RR (95%CI)
No mood or migraine disorder (N=2553)	180 (7.1)	1.00 (Reference)	1.00 (Reference)
Mood disorder only (N=143)	19 (13.3)	1.88 (1.17–3.02)	1.49 (0.92–2.40)
Migraine only (N=516)	52 (10.1)	1.43 (1.05–1.95)	1.32 (0.97–1.80)
Mood and migraine disorders (N=60)	9 (15.0)	2.13 (1.09–4.16)	2.05 (1.05–4.02)
<i>p-value for interaction term</i>		0.59	0.92
Subtypes of Hypertensive Disorder of Pregnancy			
	PIH (n, % from cohort)		
No mood or migraine disorder	135 (5.3)	1.00 (Reference)	1.00 (Reference)
Mood disorder only	8 (5.6)	1.13 (0.55–2.30)	0.91 (0.44–1.86)
Migraine only	42 (8.1)	1.54 (1.09–2.18)	1.42 (1.00–2.01)
Mood and migraine disorders	6 (10.0)	1.96 (0.86–4.43)	1.86 (0.82–4.24)
<i>p-value for interaction term</i>		0.83	0.51
	Preeclampsia (n, % from cohort)		
No mood or migraine disorder	45 (1.8)	1.00 (Reference)	1.00 (Reference)
Mood disorder only	11 (7.7)	4.38 (2.26–8.46)	3.57 (1.83–6.99)
Migraine only	10 (1.9)	1.13 (0.57–2.25)	1.08 (0.55–2.15)
Mood and migraine disorders	3 (5.0)	2.99 (0.93–9.61)	3.49 (1.07–11.36)
<i>p-value for interaction term</i>		0.49	0.89

* N=154 women with pre-gestational chronic hypertension and 6 women with unknown pre-gestational hypertension status were excluded, leaving 3,272 women in this specific analysis.

[†] Adjusted for maternal age, race/ethnicity, marital status, parity, smoking status, family history of chronic hypertension and pre-pregnancy body mass index