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Research Article

Maternal Depressive Disorder and Neonatal Birth Outcomes

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Abstract

Objective: To examine the risk of preterm birth and small for gestational age (SGA) outcomes in relation to maternal depressive disorders.

Methods: This study utilized the discharge records of 2,680,437 women who had given birth during the years of 2009, 2010, and 2011 in the U.S. Maternal depressive disorders, preterm birth, and SGA were identified using ICD9 codes. Logistic regression models were used to examine the association of maternal depressive disorders diagnosed prior to or during pregnancy with preterm birth or SGA in the offspring while controlling for several demographic, clinical and perinatal factors.

Results: Compared to women with no depressive disorders, the adjusted odds ratios (aOR) for mothers with depressive disorders to have preterm birth or SGA babies were 1.18 (CI:1.14-1.22, $p < 0.001$) and 1.19 (CI:1.13-1.26, $p < 0.001$), respectively while controlling for confounding variables. Examining the association of depressive disorders with preterm birth or SGA in different racial/ethnic groups revealed similar associations.

Conclusions: Preterm birth and SGA outcomes are increased in pregnant women with depressive disorders. Future research should focus on prompt screening of pregnant women for maternal depressive disorders and provide proper care that may modify risks of theses adverse outcomes.

Keywords: Preterm Birth; Small for Gestational Age; Adverse Birth Outcomes; Mental Illness During Pregnancy; Maternal Depressive Disorders; Maternal Depression

Background

Women of childbearing age are at high risk for major depression [1,2]. Ten percent of pregnant women experience a mental health disorder worldwide [1]. In developing countries this is even higher, (i.e. 15.6% during pregnancy) [1]. Depression during pregnancy may result in poor prenatal care which may lead to preterm birth, low birth weight, and possibly other neonatal morbidities [3-10]. Perinatal depression often goes unrecognized because many of the discomforts of pregnancy and the postpartum period are similar to symptoms of depression [11-13]. Prenatal depressive disorders encompass preexisting depression or pregnancy associated depression and may present as major or minor episodes that start during pregnancy and may last up to 12 months after birth [7,8]. Women who experience prenatal depression may have increased vulnerability to hormonal changes, which in turn, trigger symptoms of depression [7,8]. Moreover, genetics, psychosocial factors and life stressors all may play a role in triggering a prenatal depressive episode. As pregnancy involves fluctuating hormone levels, distinguishing between symptoms of depression and responses to the experiences of pregnancy may be challenging [9]. Since screening for depression is not a standard of practice for pregnant women, symptoms of maternal depression may be missed [6-10]. It is not clear, whether negative outcomes in the developing fetus are attributable to the mental illness of the mother or its treatment.

Approximately 4 million pregnancies occur each year in the United States [1]. More than a half million babies in the United States are born premature each year; and more than 100,000 infants may have birth defects [2]. The mothers' age, genetics, medical health, socioeconomic status, behaviors, access to health care, and environmental exposures all affect their ability to conceive, carry, and deliver a healthy full-term baby [2,11-15]. Prematurity is the leading cause of infant mortality and disability among children in U.S [2-5]. Preterm birth is defined as giving birth prior to completing 37 weeks gestation [2]. Low birth weight (LBW) is defined as an infant weighing less than 2500 grams at birth regardless of being full term or preterm [2]. Although advances in perinatal care have improved outcomes for infants born early and at those who are LBW, these conditions still pose a major challenge to healthcare providers and families as well [3-5]. The majority of LBW infants are also premature but other in utero factors can result in term infants who weigh <2500g [2]. In addition to threatening healthy overall growth and maturation, premature infants and LBW term infants may experience a disruption of important processes involved in early brain development [3-5]. As a result, preterm and LBW infants are at increased risk for adverse developmental outcomes, psychological adjustment, and intellectual functioning, delayed motor and social development or learning disabilities [3-8].

Prenatal depression affects fetal growth. A cross-sectional study conducted on a sample of 98 pregnant women assessed the effects of prenatal depression on estimated fetal weight. The study showed that prenatal depression was negatively related to fetal head circumference and estimated fetal weight, while controlling for gestational age. These findings are consistent with research relating LBW to maternal depression where a significant number of mothers with high cortisol values had fetuses with below average estimated fetal weight [16,17].

Similarly, there is accumulated evidence that suggests a potential pathway to explain the role of depression in the occurrence of preterm birth. In particular, cortisol and stress hormones whose production increase with depression have been shown to increase placental corticotrophins-releasing hormone (CRH) levels, which plays a role in the initiation of childbirth [13,14]. The intrauterine exposure to excess cortisol levels may lead to dysregulation of the fetal autonomic nervous system activity or increased uterine artery vasoconstriction and therefore impair fetal growth and development on one end, and precipitate for early delivery on the other end [7]. Another potential pathway is the activation of the inflammatory response which is associated with increased pro-inflammatory cytokines, prostaglandin E2, and negative immune-regulatory cytokines. The increased cortisol and cytokines lead to increased prostaglandin E2 which stimulate uterine contractions. In addition, increased levels of inflammatory cytokine response have been associated with premature rupture of fetal membranes [8-10].

Depression is relatively common during pregnancy and the postpartum period [6-10]. Women with current depression or a history of depression warrant close monitoring and evaluation. Addressing maternal mental health needs will benefit the mothers and potentially safeguard newborns from negative birth outcomes. In this study we assessed the association of maternal depressive disorders with preterm birth and infants born small for gestational age from a large national data set. The specific aims were: 1) to determine if depression had a direct negative association with preterm birth or SGA birth outcome, 2) to determine the extent to which demographic, clinical and perinatal variables are related to these outcomes.

Methods

Data sources and management

In this study, the de-identified datasets produced by the Healthcare Cost and Utilization Project (HCUP) from the federal Agency for Healthcare Research and Quality (AHRQ) were used [17]. HCUP datasets, the largest health care database in the U.S., are reproduced from an all-payer national database collected annually from millions of inpatient hospitalization records across. These datasets represent more than 1000 hospitals with various care levels (primary - tertiary), types of insurance (public, private), and academic settings (university - general). Data on hospitalization records were coded by medical records hospital staff using International Classification of Disease 9 (ICD 9) for clinical variables and Current Procedural Terminology (CPT) for surgical and non-surgical procedures done for the patient during the hospitalization. HCUP datasets include more than 100 data elements for each hospital stay such as: patient demographics, primary and secondary diagnoses, primary and secondary

procedures done, source of admission, disposition and discharge status, total charges and expected payment source. HCUP produced the Nationwide Inpatient Sample (NIS) dataset. NIS datasets represent 20% sample of all hospital admissions during any given year for patients of all ages. NIS dataset for the years 2009, 2010, and 2011 were used for this study. Variables extracted from HCUP data included age, race/ethnicity, year of admission, source of admission, clinical diagnoses and procedures done during this admission, pregnancy outcomes include whether offspring was born preterm or SGA.

Study design and population

We included hospital discharge records that had maternal-related diagnostic code specifically assigned in this database. Pregnant women diagnosed with one of the depressive disorders were identified using ICD 9 codes 296.2, 296.3, 298, 300.4, or 311. Their birth outcomes were identified using ICD 9 codes related to preterm birth (765.1, 765.2) and small for gestational age (764.0). Two study groups were created; the first for mothers with depressive disorders, and the second for mothers without depressive disorders. In addition, presence of associated maternal infection or chorioamnionitis, hypertension, diabetes mellitus, cardiovascular diseases, renal or thyroid disorder, anemia, placenta previa, and placental abruption were analyzed as potential confounders.

Statistical analysis

Frequency analysis, Chi-square and Fisher exact tests were used to examine the association of maternal depressive disorders diagnosed prior to or during pregnancy with the preterm birth or SGA in the offspring using SAS 9.1 (SAS Institute Inc., Cary, NC). Demographic and clinical characteristics of the study population were produced using the frequency procedure. Unadjusted odds ratios, 95% confidence intervals and *p* values were calculated using the chi-square and fisher exact tests for each obstetric and neonatal outcome. Multiple logistic regression analyses were performed to examine the associations of maternal depressive disorders with adverse birth outcomes while adjusting for the effect of included confounders to produce adjusted odds ratios. In this study, p values were considered statistically significant if they were <0.05. Odds ratios calculated in logistic regression models were used considering maternal depressive disorder as a rare condition, which can closely be approximated to the relative risk (RR). IRB approval was obtained from the George Washington University Hospital.

Results

The study included 2,680,437 delivering mothers; of them 3% were teenagers (13-17 years old), 82.4% were 18-34 years old, and 14.5% were of advanced maternal age (>35 years old). In this sample 45% were Whites, 13.7% were African Americans, 20.3% were Hispanics, 4.3% were Asians, 0.8% were Native Americans, and 4.2% were other races not specified. Diagnosis of depressive disorders was associated with maternal hypertension, diabetes mellitus, renal infection, severe anemia, thyroid dysfunction, cardiovascular disease, placenta previa, and placental abruption. Table 1 shows percentages and adjusted odds ratios of the demographic and clinical characteristics of the study groups.

	Mothers with depressive disorders* n = 49,980	**Mothers without depressive disorders*** n = 2,630,457	**OR**	**CI**		**P value**
				Lower 95%	**Upper 95%**	
Race						
White	55.73	44.9	1.55	1.52	1.57	<0.001
Black	11.97	13.72	0.85	0.83	0.88	<0.001
Hispanic	10.9	20.3	0.48	0.47	0.49	<0.001
Asian	1.39	4.28	0.31	0.29	0.34	<0.001
Native American	0.81	0.78	1.05	0.95	1.15	0.38
Other	2.83	4.23	0.66	0.63	0.70	<0.001
Age						
<18-year-old	2.53	3.02	0.83	0.79	0.88	<0.001
18–34-year-old	80.5	82.43	0.88	0.86	0.90	<0.001
≥35-year-old	16.95	14.45	1.21	1.18	1.24	<0.001
Hypertension	13.65	9.86	2.48	2.46	2.52	<0.001
Viral infection	6.24	2.88	1.13	1.09	1.16	<0.001

Chorioamnionitis	0.68	0.99	0.83	0.79	0.88	<0.001
Diabetes Mellitus	3.07	1.23	1.54	1.49	1.59	<0.001
Renal infection	4.41	2.63	1.26	1.23	1.30	<0.001
Anemia	16.32	10.95	1.17	1.16	1.20	<0.001
Thyroid disorder	5.73	2.41	1.17	1.14	1.21	<0.001
Placenta Previa	0.84	0.66	3.94	3.80	4.09	<0.01
Placenta Abruption	1.32	1.04	8.21	8.01	8.42	<0.001
Cardiovascular Dis.	1.51	0.7	1.17	1.11	1.23	<0.001
Preterm birth	8.14	6.45	1.18	1.14	1.22	<0.001
Small for gestational age	2.7	2.12	1.19	1.13	1.26	<0.001
*All figures are presented as percentages						

Table 1: Demographics and clinical characteristics of mothers with and without diagnosis of a depressive disorder during pregnancy.

Depressive disorders were diagnosed in 49,980 of mothers representing 1.86% of the sample. In comparing the two groups, 8.14% of mothers with depressive disorders delivered preterm newborns compared to 6.45% of mothers with no depressive disorder, adjusted odds ratios (aOR) 1.18 (CI:1.14-1.22, p < 0.001) after adjusting for demographic and clinical risk factors, table 1 and figure 1. On examining preterm delivery in each race category, mothers of Caucasian race (Whites) with depressive disorders had more preterm infants born compared to White mothers with no depressive disorders, aOR 1.35 (CI:1.33-1.37, p < 0.001). African Americans, Native Americans, Hispanics, and others, similarly, had significant aOR; 1.05 (CI:1.04-1.07, p < 0.001), 1.10 (CI:1.07-1.13, p < 0.001), 1.04 (CI: 1.02-1.07, p = 0.002), and 1.11 (CI:1.09-1.13, p < 0.001), respectively. Preterm delivery associated with Asian race were not significant; aOR 1.05 (CI: 0.99-1.11, p = 0.11) after adjusting for demographic and clinical risk factors, table 2.

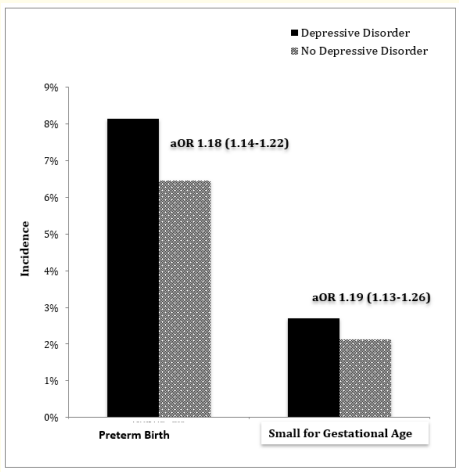

Figure 1: Preterm birth and small for gestational age birth outcomes in mothers with depressive disorders compared to those without depressive disorders.

Preterm birth in mothers with depressive disorder in each race/ethnicity group compared to Whites				
	OR	**Lower 95% CI**	**Upper 95% CI**	**P value**
African American vs. Whites	1.05	1.04	1.07	<0.001
Hispanic vs. Whites	1.04	1.02	1.07	0.002
Asian vs. Whites	1.05	0.99	1.11	0.11
Native Amer. vs. Whites	1.10	1.07	1.13	<0.001
Other vs. Whites	1.11	1.09	1.13	<0.001
Small for gestational age in mothers with depressive disorder in each race/ethnicity groups compared to Whites				
	OR	**Lower 95% CI**	**Upper 95% CI**	**P value**
African American vs. Whites	0.70	0.68	0.71	<0.001

Hispanic vs. Whites	1.27	1.22	1.32	<0.001
Asian vs. Whites	0.88	0.80	0.98	0.017
Native Amer. vs. Whites	1.06	1.02	1.11	0.004
Others vs. Whites	1.05	1.02	1.08	<0.001

Table 2: Odds ratios to have preterm birth or small for gestational age in mothers with depressive disorders compared to mothers without in each racial/ethnic groups compared to Whites.

Of those mothers diagnosed with depressive disorders, 2.7% delivered infants who were SGA compared to 2.12% with no depressive disorders; aOR 1.19 (CI:1.13-1.26, p < 0.001) after adjusting for demographic and clinical risk factors, table 1 and Figure 1. Comparing racial groups, mothers of Whites, Hispanics, Native American and other race category with depressive disorders had more infants born SGA compared to mothers with no depressive disorders in the same racial group, aOR 1.31 (CI:1.28-1.34, p < 0.001), 1.27 (CI:1.22-1.32, p < 0.001), 1.06 (CI:1.02-1.011, p = 0.004) and 1.05 (CI:1.02-1.08, p < 0.001), respectively, after adjusting for demographic and clinical risk factors. African American and Asian newborns had less incidence of being born SGA, aOR 0.70 (CI:0.68-0.71, p < 0.001) and 0.88 (CI:0.80-0.98, p = 0.17), table 2.

Discussion

Mental disorders, especially depression, are a worldwide public health issue. It has a negative impact on all aspects of an individual's life and can lead to many adverse outcomes [1,2]. Maternal depression negatively impact the health and development of children even before they are born [3-10]. One in every eight pregnant women develops an illness that poses the risk of preterm birth or having a LBW newborn [14]. Although, approximately 12% of women may experience depression in a given year, it is estimated that rates of depression among pregnant, postpartum and parenting women may range from 5% to 25% [15,16].

Our study results suggest that the risk of preterm birth is increased in women experiencing symptoms of depression during pregnancy. In addition, higher rates of SGA birth were observed among women with depressive disorders during pregnancy. Our results are consistent with eth findings of other studies [20-24]. A meta-analysis of 20 studies examined the risk of preterm birth in relation to maternal depression reported that antepartum depression is associated with modest but statistically significant increased risk of preterm birth [20].

Another review found relatively large effects of maternal depressive disorders on infant birth weight with the largest effects for low-income women and women of color [21,22]. Maternal depression has been linked with smaller head circumference and lower Apgar scores in offspring [23]. One study reported that mothers with a depressive disorder had 1.8 times greater risk of giving birth to a LBW infant than mothers without [21,24].

Our study is consistent with Goedhart., *et al*. who observed that maternal depression was associated with preterm birth and SGA where the odds of preterm birth and SGA increased 1.2-fold for mothers with depressive symptoms (OR 1.21, p = 0.10) and (OR 1.25, p = 0.004), respectively [7]. Interestingly, studies from developing countries reported much higher impact where pregnant women with depression had 3.4 times more likely to deliver preterm and 4 times as likely to deliver a LBW infant than non-depressed women [25]. This association was stronger than our results and sheds more light on the serious impact of maternal depressive disorders in low resource settings.

Racial/ethnic minorities have a high prevalence of both prenatal depression and adverse perinatal health outcomes. In the U.S., compared to white women, black women are more susceptible for stress-induced neuroendocrine and inflammatory pathways that leads into adverse perinatal outcomes, possibly as a result of higher vascular activity [23]. In contrast to previous studies, our results shows that white women were more likely than other race/ethnic groups to be diagnosed with depression or have preterm birth or SGA infants.

Some limitations were observed in this study. Although using a national database that identified specific ICD-9 diagnostic codes for depression, preterm birth, and small for gestational age, it is impossible to account for variations in the diagnostic practices of physicians. The study may also be limited due to the inability to identify some demographic characteristics in the analysis;

socioeconomic status or maternal educational levels. Similarly, this study did not control for maternal use of psychotropic medications during pregnancy which has been shown to pose risk of preterm birth [26,27].

Despite these limitations, this study had several advantages. The study included hospital discharge records from a national mega dataset that spread across more than 40 States and the District of Columbia that encompasses several level care and diverse participation of different size hospitals of academic and non-academic medical institutions in contrast to some previous studies that were limited to only one center or state level databases. The study also included obstetrical risk factors that were not included in previous studies, allowing to control for several additional potential confounders.

Conclusion

In conclusion, maternal depression is associated with preterm birth and/or SGA newborns. Future research efforts are warranted to confirm potential biological pathways and examine approaches for early identification and proper intervention of maternal depression to avoid its side effects. Enhancements in the collaboration between maternal child health and mental health programs is warranted and researchers, and practitioners, are needed to make mental health screening an integral component of primary health care and establish referral mechanisms. The American Congress of Obstetricians recently suggested an objective for Healthy People 2020 targeted at increasing the proportion of pregnant and postpartum women who receive screening for maternal depression and referral for evidence-based theory.[11] Further work is needed to understanding whether negative outcomes in the developing fetus are attributable to the mental illness or its treatment.

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None.

Conflicts of Interest

None.

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