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Prenatal maternal depression is associated with low birth weight through shorter gestational age in term infants in Korea

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Abstract

Background—Maternal prenatal depression is associated with lower offspring birth weight, yet the impact of gestational age on this association remains inadequately understood.

Aims—We aimed to investigate the effect of prenatal depression on low birth weight, gestational age, and weight for gestational age at term.

Study design—Prospective cohort study.

Subject—Data were collected from 691 women in their third trimester of pregnancy who went on to give birth to a singleton at term without perinatal complications. One hundred and fifty-two

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Conflict of interest statement

There is no conflict of interest to report.

women had a Center for Epidemiologic Studies Depression Scale-10 score ≥ 10 and were classed as prenatally depressed.

Outcome measures—Low birth weight (<2500 g), gestational age at birth, and birth weight percentile for gestational age.

Results—Offspring of prenatally depressed women were more likely to be low birth weight (Odds ratio [OR] 2.94, 95% confidence interval [CI] 1.14–7.58) than offspring of prenatally non-depressed women, but the association was attenuated (OR 1.66, 95% CI 0.55–5.02) when adjusted for gestational age. Offspring of prenatally depressed women had lower gestational age in weeks (OR for one week increase in gestational age: 0.66, 95% CI 0.47–0.93) than offspring of prenatally non-depressed women. There was no association between prenatal depression and birth weight percentile for gestational age.

Conclusions—Prenatal depression was not associated with low birth weight at term, but was associated with gestational age, suggesting that association between maternal depression and birth weight may be a reflection of the impact of depression on offspring gestational age.

Keywords

Prenatal depression; Low birth weight; Gestational age; Birth weight for gestational age; Prospective study; South Korea

1. Introduction

Depressive symptoms during pregnancy are common. A metaanalysis estimated that 12.0% of women in their third trimester exhibit clinically significant depressive symptoms [1], and other study reported that 18% of women exhibit depressive symptoms antenatally [2]. Recent Korean data indicate that the prevalence of prenatal depression is as high as 20.2% [3]. In addition to depression-related disabilities in the pregnant woman, prenatal depression can have numerous adverse effects on the offspring [4]. For example, the prevalence of autism spectrum disorders [5] and emotional and behavioral problems [6] was higher among infants of mothers with prenatal depression than among infants of mothers without prenatal depression.

Neonatally, prenatal depression is associated with low birth weight and intrauterine growth restriction [7], but many studies have not assessed birth weight according to gestational age, which complicates the interpretation [8,9]. The underlying determinants and etiology of preterm birth, typically defined as birth before 37 weeks gestation, may be different to those for term births that are low birth weight. For example, parity and gestational weight gain is a risk factor for term low birth weight but not preterm delivery [10,11]. Preterm birth was more closely associated with neurodevelopmental disorders [12], whereas low birth weight was more closely associated with endocrine disorders such as metabolic syndrome [13]. Understanding whether prenatal depression influences gestational age or birth weight is thus an important distinction.

Preterm birth increases the risk of numerous adverse outcomes; however, recent research has begun to focus on potential adverse outcomes of birth between 37 and 38 weeks gestation,

namely early-term births [14]. Approximately 52% of infants are born between 37 and 39 weeks gestation [15], and these infants are at increased risk for respiratory distress syndrome [16] and autism [17], and have higher mortality [14] than infants born after 38 weeks gestation. Understanding the etiology of early-term birth is therefore an important public health priority [18].

Studies of the influence of maternal depression on gestational age and birth weight among term births are scarce, and show conflicting results [19–21]. Kelly et al. reported a two-fold increase in the odds of low birth weight in depressed women delivering at term compared to non-depressed women delivering at term [22]. Henrichs et al. and Nasreen et al. also reported a significant association between prenatal depression and low birth weight at term [20,23]. However, Evans et al. reported that, in a large sample of over 10,000 women who gave birth at term, the association between prenatal depression and low birth weight was attenuated after adjustment for health behaviors and potential confounding factors such as smoking [19], and Gawlik et al. and Lancaster et al. reported that psychosocial variables were not significant predictors of birth weight in term births [24,25]. Thus, there remains little consensus on the influence of prenatal maternal depression on birth outcomes of term births, and few investigations to date on the influence of depression on gestational age versus birth weight.

In addition, results of studies of prenatal depression and offspring health outcomes are complicated by potential confounding factors. In many samples, prenatal depression is associated with increased smoking, alcohol consumption, and other unhealthy behaviors [26]. Thus, it is unclear whether prenatal depression causally increases the risk of adverse neonatal outcomes, or whether health behaviors linked to depression are the causal agents. Causal inference from observational studies will never be absolute; however, one way to mitigate the effects of confounding is to examine the association in a diverse set of populations with a different distribution of potential risk factors for birth weight and gestational age [27].

In this study, we aimed to examine the relation between maternal prenatal depression and neonatal outcomes in a large sample of term infants in Korea. We evaluated the association between maternal depression and three main outcomes: low birth weight, gestational age, and birth weight for gestational age. We drew on the strength of a large sample of pregnancies in Korea with comprehensive data on potential confounders. Women in this sample were generally quite healthy; the rate of smoking history and drinking during pregnancy was low, and no one was undergoing treatment for psychiatric disorders. Thus, the distribution of risk factors for low birth weight in this sample is likely different from samples from other geographic areas, providing a rigorous evaluation of the association between prenatal depressive symptoms and these outcomes.

2. Methods

2.1. Study subjects

Data used were collected as part of the COhort for Childhood Origin of Asthma and allergic diseases (COCOA) study, a prospective study that aims to examine the early risk factors for

childhood allergic diseases [28,29]. Women in the third trimester of pregnancy were recruited from four tertiary hospitals in Seoul, Korea between August 2007 and July 2011. For this analysis, study subjects were limited to those with depression data, who had delivery at term (later or equal to 37 weeks) and singleton births. Of 1171 women recruited, 343 women without data on prenatal depression were excluded. Women with depression data were slightly younger than those without depression data (32.2 years versus 32.8 years, $p = 0.001$) but were similar on other key demographic covariates, including educational status, occupational status, and smoking history. Additionally, 55 women with preterm delivery and 24 women who had twin births were excluded, and a further 82 women with missing data on confounders were excluded. None of the women were receiving active treatment for psychiatric disorders. Women with missing data exhibited similar demographic distribution to women without missing data. The final sample was 691 women. Written informed consent was obtained from all women, and the study was approved by the institutional review boards of Asan Medical Center (IRB No. 2008-0616), Samsung Medical Center (IRB No. 2009-02-021), Yonsei University (IRB No. 4-2008-0588), CHA Medical Center (IRB No. 2010-010), and Columbia University (IRB-AAAL4350).

2.2. Assessments

Prenatal depression was evaluated at 36th week of pregnancy using the Center for Epidemiologic Studies Depression Scale-10 (CESD-10) [30,31], a modified 10-item version of the original 20 item full-length CESD. The CESD has been validated for use during pregnancy [32]. Each item is scored in a Likert scale (0, 1, 2, 3), and the score ranges from 0 to 30, with higher scores indicating more severe depressive symptoms. Consistent with previous studies [33], a cut-off score of 10 was used to identify women with depression. The internal consistency of CESD-10 in this study indicated excellent reliability ($ICC = 0.785$).

Outcomes of interest were low birth weight, gestational age, and birth weight for gestational age. Birth data were obtained from hospital records. Low birth weight was defined as birth weight less than 2500 g [34]. Gestational age was recorded in number of days since the first day of the mother's last menstrual period. Pregnancies were categorized by weeks of gestation according to the lowest whole number of weeks of gestation, e.g., gestation of 37 weeks and 6 days was categorized as 37 weeks. Birth weight for gestational age was calculated as birth weight percentile for gestational age, according to the fetal weight equation proposed by Mikolajczyk et al. [35]. The standard deviation of birth weight was derived from the 2004 to 2008 WHO Global Survey on Maternal and Perinatal Health.

Data on confounding factors were collected at two time points, at baseline (36th week of pregnancy) and at delivery. At baseline, self-reported maternal age, pre-pregnancy body mass index (calculated from reported height and weight), number of existing children, smoking history (ever/never), and data on alcohol use during pregnancy (yes/no) were obtained. At delivery, data on sex of the baby and the delivery method (vaginal delivery/Cesarean section) were obtained from medical records.

2.3. Statistical analysis

Analyses were performed using SPSS 18.0 for Windows (SPSS Inc., Chicago, IL). Independent sample t tests and chi-square tests were used to compare demographic characteristics and neonatal outcomes between women with and without prenatal depression. Logistic regression was used to analyze the association between independent variables and low birth weight, in both an unadjusted model and a model adjusted for previously defined confounders. Gestational age was analyzed using a cumulative logit model with the outcome defined as 37, 38, 39, 40, and 41 weeks gestation (reference group 41 weeks). Birth weight percentile for gestational age was analyzed using a linear regression model. Models were adjusted for potential confounding variables including gestational age [for low birth weight only], pre-pregnancy BMI [for low birth weight only], maternal smoking history, maternal drinking during pregnancy, neonate of female sex, and delivery by cesarean section.

3. Results

3.1. Demographic characteristics and neonatal outcomes

One hundred and fifty-two women (22.0%) had prenatal depression (CESD-10 = 10). None of the women who had depression were being medically treated by physicians or used any antidepressants. About half (52.7%) of the whole sample was nulliparous. Among the whole sample, the history of smoking was low (7.5%), and for the 10.3% who reported drinking during pregnancy, the majority (96.0%) drank less than once per month.

Table 1 shows the demographic characteristics of women with and without prenatal depression. The percentage of women who reported a history of smoking was higher among women with prenatal depression than among women without prenatal depression ($\chi^2 = 22.290$, $p < 0.001$), and the percentage of women who reported having more than one existing child was also higher among women with prenatal depression ($\chi^2 = 5.779$, $p = 0.016$). Maternal age, pre-pregnancy body mass index, education status, occupation status, and drinking during pregnancy did not differ between women with and without prenatal depression (Table 1).

Table 2 shows the neonatal outcomes for offspring born to women with and without prenatal depression. Gestational age was lower in offspring born to women with prenatal depression than in offspring born to women without prenatal depression ($p = 0.005$), and the percentage of neonates with low birth weight was greater among offspring born to women with prenatal depression than among offspring born to women without prenatal depression ($\chi^2 = 5.427$, $p = 0.020$). The birth weight in grams, the sex of the baby, and the delivery mode did not differ between women with and without prenatal depression (Table 2).

3.2. Maternal prenatal depression is not associated with neonate birth weight after adjusting for gestational age

In the unadjusted model, offspring born to women with prenatal depression were more likely to be low birth weight than offspring born to women without prenatal depression (odds ratio [OR] 2.939, 95% confidence interval [CI] 1.139–7.583; Table 3). When gestational age was included in the model this association was attenuated (OR 1.788, 95% CI 0.646–4.945), and

neonates with low gestational age were more likely to have low birth weight (OR 0.209, 95% CI 0.114–0.383; Table 3). When all potential confounders (gestational age, maternal pre-pregnancy body mass index, maternal smoking history, maternal drinking during pregnancy, female sex, and Cesarean section) were included in the model, prenatal depression was not related to low birth weight (OR 1.658, 95% CI 0.548–5.017) but gestational age remained a significant predictor (OR 0.180, 95% CI 0.092–0.350; Table 3).

3.3. Maternal prenatal depression is associated with gestational age

In the unadjusted model, offspring born to women with prenatal depression were less likely to be of high gestational age (OR 0.617, 95% CI 0.446–0.855; Table 4). This association remained significant even after controlling for potential confounders (maternal smoking history, maternal drinking during pregnancy, female sex, and Cesarean section) (OR 0.658, 95% CI 0.467–0.926; Table 4). Female sex was associated with shorter gestational age (OR 1.406, 95% CI 1.060–1.865) and delivery by Cesarean section was associated with longer gestational age (OR 0.414, 95% CI 0.303–0.564; Table 4).

3.4. Depression is not associated with standardized birth weight for gestational age

In the unadjusted model, prenatal depression was not associated with birth weight percentile for gestational age (beta = 0.085, 95% CI –5.66–5.83; Table 5). In the adjusted model, female sex (beta = –6.799, 95% CI –11.745 to –1.852) and delivery by Cesarean section (beta = 6.519, 95% CI 1.184–11.853) were significantly associated with birth weight percentile for gestational age (Table 5).

4. Discussion

In this population-based sample of close to 700 pregnancies, maternal prenatal depression in the third trimester was not associated with low birth weight of term babies after adjustment for gestational age. By contrast, prenatal depression was associated with lower gestational age. The mean gestational age in prenatally depressed women was 0.2 weeks lower than in non-depressed women, and the association between prenatal depression and gestational age was robust and significant after controlling for confounders. This suggests that the association between prenatal depression and low birth weight reflects an underlying association with gestational age, as those infants with lower gestational ages have lower birth weights, on average. Vigorously screening for and treating prenatal depression may have an effect of reducing not only pre-term births, as previously documented [36], but also early-term births.

Results of previous studies on the association between prenatal depression and low birth weight have been mixed. Many studies have combined preterm and term births, which limits the ability to differentiate results between low gestational age and low birth weight [37,38], and many studies that found prenatal depression to be a significant predictor of low birth weight did not control for gestational age [20,39,40]. Among studies that controlled for gestational age, several found no significant association between prenatal depression and low birth weight [19,21,41], but others showed a robust association [8,22,23]. The study population has also varied across previous studies. Studies conducted in developed countries

such as the United States [25,38] and the United Kingdom [19] have shown no association between prenatal depression and birth weight, whereas studies conducted in developing countries such as Brazil [42] and Pakistan [40], or studies conducted in populations with a lower socioeconomic status [43–45], have shown a positive association. The reason for this may be that women of low socioeconomic status with prenatal depression are more likely to be vulnerable to comorbid risk factors, such as undernutrition, which is a strong predictor of low birth weight in low-income countries [46], than women of high socioeconomic status with prenatal depression. There is one previous study that has investigated the relation between prenatal depression and low birth weight in Korea [47], and the authors reported that a significant association between prenatal depression and low birth weight was attenuated after adjustment for confounding factors including gestational age. We suggest that the literature on maternal mental health and neonatal outcomes such as birth weight and gestational age would benefit from consistent examination of gestational age as a potential alternative explanation for any observed associations. Further research into the association between maternal depression and preterm as well as early-term births is critical for understanding the role of maternal depression on birth outcomes.

There are several mechanisms that have been proposed to underlie the association between prenatal depression and neonatal outcomes. The hypothesis that the association is mediated by the hypothalamic–pituitary–adrenocortical axis, which stimulates the release of stress hormones such as cortisol and catecholamines, has been most extensively investigated [48]. Emerging research suggests that prenatal maternal cortisol mediates the association between self-reported depression and gestational age at birth and fetal growth rate [8], and that glucocorticoid exposure during pregnancy resulted in a lower gestational age [49]. Other possible mechanisms include adverse health behaviors associated with depression. Depressed women are more likely to smoke and drink during pregnancy than non-depressed women [50], and these behaviors can result in low gestational age and birth weight [51]. In addition, micronutrients that are required for high birth weight and gestational age, such as iron and vitamin A [52], may be insufficient in depressed women due to lack of appetite or unhealthy diet. More broadly, the role of weight loss or gain in mediating the association between maternal depression and neonatal outcomes has received mixed support in the literature [53,54] but warrants further, more rigorous research. The use of antidepressants has also been proposed as one of the pathways linking prenatal depression and adverse neonatal outcomes [55,56]. However, none of the subjects in this study were exposed to antidepressants during pregnancy, and health behavior reports indicated low fetal exposure to tobacco, alcohol, and undernutrition, suggesting that health behaviors are unlikely to explain the observed association fully. Recently, maternal early-life risk factors, such as low socioeconomic status during childhood and low levels of social support, have also been investigated as factors that can influence both prenatal depression and the offspring's low birth weight [57,58]. Comprehensive assessments of stress exposure, health behaviors, and other potential risk factors for adverse neonatal outcomes such as pre- and early-term birth are critical to advance our understanding of the mechanisms by which maternal mental health influences fetal health.

Limitations of this study should be noted. First, depression was measured by self-report, and was assessed only once during pregnancy. Also, the cut-off score of 10 in the CESD-10 may

have been too low to reflect depression [59]. Further evaluation, such as structured interview, to confirm the mental health status of the studied women would have been desirable. However, the CESD-10 is a well-validated measure of depressive symptoms that is extensively used in epidemiological literature [60]; therefore, we are confident that the level of depressive symptoms was accurately assessed. Second, the dichotomization of birth weight into 'low birth weight' and 'non-low birth weight' has been criticized as being arbitrary and uninformative [61]. In this study, a further analysis was conducted using standardized birth weight for gestational age as an outcome to support the lack of intrauterine growth retardation in term babies. However, birth weight remains a well-studied neonatal outcome, and understanding how maternal mental health is related to both birth weight and gestational age can provide important information about the ways in which maternal health affects offspring. Third, further information on health behaviors in this sample, such as diet and substance use, would have increased our understanding of potential mechanisms; however, the available information indicated low prevalence of smoking and alcohol use among these women, suggesting little variation of adverse health behaviors. The relative homogeneity of the sample with respect to diet and health may limit the generalizability of the results, but this homogeneity can be considered a strength of the study regarding causal inference of the effects of maternal depression on offspring health, as there is little variation to be accounted for in our analyses. Results from this sample add to previous studies and increase the strength of the evidence on the association between prenatal depression and neonatal outcomes.

In conclusion, in this study we examined the association between prenatal depression and low birth weight, and the role of gestational age on this association. The sample was a comparatively healthy and homogenous group of women who gave birth at full term, and the results indicated that prenatal depression was not independently associated with low birth weight. Rather, women with prenatal depression were more likely to give birth at shorter gestational age, which then resulted in lower birth weight. Although the relation between prenatal depression and low birth weight has been examined in a number of studies, this study adds evidence on the mediating role of gestational age in this association. Further study of the difference between low birth weight and preterm births or shorter gestational age is needed. Furthermore, studies that examine the underlying neuroendocrinologic pathways are a critical next step in this field.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.earlhumdev.2013.11.006>.

Table 1

Demographic characteristics and health behaviors of 691 pregnant women in South Korea.

	Not depressed (n = 539)	Depressed (n = 152)	p value
Age (years)	32.7 ± 3.51	32.0 ± 3.34	0.457
Pre-pregnancy BMI (kg/m ²)	20.5 ± 2.45	20.8 ± 2.69	0.180
Education			0.390
Secondary school	39 (7.2)	12 (7.9)	
College or University	357 (66.2)	108 (71.1)	
Graduate school	143 (26.5)	32 (21.1)	
Occupation			0.157
Yes	363 (67.3)	93 (61.2)	
No	176 (32.7)	59 (38.8)	
Number of previous live births			0.016 *
None	297 (55.1)	67 (44.1)	
One or more	242 (44.9)	85 (55.9)	
History of smoking			<0.001 **
Ever	27 (5.0)	25 (16.4)	
Never	512 (95.0)	127 (83.6)	
Drinking during pregnancy			0.185
Yes	51 (9.5)	20 (13.2)	
No	488 (90.5)	132 (86.8)	

Data are mean ± standard deviation or n (%). Depressed women are those with a Center for Epidemiologic Studies Depression Scale-10 score ≥ 10 in the third trimester. BMI, body mass index.

* Indicates $p < 0.05$.

** Indicates $p < 0.01$.

Table 2

Neonatal outcomes of offspring from 691 pregnant women in South Korea.

	Not depressed (n = 539)		Depressed (n = 152)		p value
	M	SD	M	SD	
Gestational age (weeks)	39.0	1.07	38.8	1.11	0.005**
Birth weight (g)	3237.8	346.85	3202.5	389.12	0.313
	n	%	n	%	
Sex					
Male	274	50.8	85	55.9	0.268
Female	265	49.2	67	44.1	
Delivery mode					
Vaginal delivery	338	68.7	101	69.7	0.827
Cesarean section	154	31.3	44	30.3	
Low birth weight (<2500 g)					
Yes	10	1.9	8	5.3	0.020*
No	529	98.1	144	94.7	

Depressed women are those with a Center for Epidemiologic Studies Depression Scale-10 score 10 in the third trimester.

* Indicates $p < 0.05$.** Indicates $p < 0.01$.

Table 3

Results of logistic regression for low birth weight^a in 691 pregnancies in South Korea.

	Unadjusted	Model 1	Model 2
Prenatal depression ^b	2.939 (1.139–7.583)	1.788 (0.646–4.945)	1.658 (0.548–5.017)
Gestational age	–	0.209 (0.114–0.383)	0.180 (0.092–0.350)
Maternal pre-pregnancy body mass index	–	–	0.774 (0.585–1.024)
Maternal smoking history	–	–	1.475 (0.271–8.032)
Maternal drinking during pregnancy	–	–	0.995 (0.199–4.982)
Female sex	–	–	1.835 (0.627–5.368)
Cesarean section	–	–	1.164 (0.384–3.523)

Data are odds ratio (95% confidence interval). Model 1: adjusted for gestational age. Model 2: adjusted for gestational age, maternal pre-pregnancy body mass index, maternal smoking history, maternal drinking during pregnancy, female sex of the offspring, and delivery by Cesarean section. Dashes indicate that the variable was not included in the model.

^aLow birth weight was defined as birth weight <2500 g.

^bPrenatal depression was defined as a Center for Epidemiologic Studies Depression Scale-10 score ≥ 10 in the third trimester.

Table 4

Results of ordered polytomous regression^a for gestational age^b in 691 pregnancies in South Korea.

	Unadjusted	Adjusted
Prenatal depression ^c	0.617 (0.446–0.855)	0.658 (0.467–0.926)
Maternal smoking history	–	0.862 (0.498–1.489)
Maternal drinking during pregnancy	–	0.711 (0.449–1.125)
Female sex	–	1.406 (1.060–1.865)
Cesarean section	–	0.414 (0.303–0.564)

Data are odds ratio (95% confidence interval). Adjusted model is adjusted for maternal smoking history, maternal drinking during pregnancy, female sex of the offspring, and delivery by Cesarean section. Dashes indicate that the variable was not included in the model.

^aCumulative logit model.

^bGestational age was analyzed using a cumulative logit model with the outcome defined as 37, 38, 39, 40, and 41 weeks gestation (reference group 41 weeks).

^cPrenatal depression was defined as a Center for Epidemiologic Studies Depression Scale-10 score ≥ 10 in the third trimester.

Table 5

Results of linear regression for birth weight percentile for gestational age in 691 pregnancies in South Korea.

	Unadjusted	Adjusted
Prenatal depression ^a	0.085 (−5.66–5.83)	0.275 (−5.715–6.265)
Maternal smoking history	–	−5.400 (−15.019–4.218)
Maternal drinking during pregnancy	–	−1.493 (−9.548–6.562)
Female sex	–	−6.799 (−11.745 to −1.852)
Cesarean section	–	6.519 (1.184–11.853)

Data are beta coefficient (95% confidence interval). Adjusted model is adjusted for maternal smoking history, maternal drinking during pregnancy, female sex of the offspring, and delivery by Cesarean section. Dashes indicate that the variable was not included in the model.

^aPrenatal depression was defined as a Center for Epidemiologic Studies Depression Scale-10 score ≥ 10 in the third trimester.