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Prenatal depression restricts fetal growth

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ABSTRACT

Objective: To identify whether prenatal depression is a risk factor for fetal growth restriction.
Methods: Midgestation (18–20 weeks GA) estimated fetal weight and urine cortisol and birthweight and gestational age at birth data were collected on a sample of 40 depressed and 40 non-depressed women. Estimated fetal weight and birthweight data were then used to compute fetal growth rates.
Results: Depressed women had a 13% greater incidence of premature delivery (Odds ratio (OR)=2.61) and 15% greater incidence of low birthweight (OR=4.75) than non-depressed women. Depressed women also had elevated prenatal cortisol levels (p=.006) and fetuses who were smaller (p=.001) and who showed slower fetal growth rates (p=.011) and lower birthweights (p=.008). Mediation analyses further revealed that prenatal maternal cortisol levels were a potential mediator for the relationship between maternal symptoms of depression and both gestational age at birth and the rate of fetal growth. After controlling for maternal demographic variables, prenatal maternal cortisol levels were associated with 30% of the variance in gestational age at birth and 14% of the variance in the rate of fetal growth.
Conclusion: Prenatal depression was associated with adverse perinatal outcomes, including premature delivery and slower fetal growth rates. Prenatal maternal cortisol levels appear to play a role in mediating these outcomes.

Fetal growth restriction is a leading cause of infant morbidity and mortality [1,2] that is associated with adverse neurodevelopmental outcomes [3], cardiovascular disease [4] and diabetes [5,6]. A number of risk factors have been identified for fetal growth restriction including pre-existing and current medical conditions (i.e. anemia, diabetes, hypertension, etc), sociodemographic factors (i.e. age, ethnicity, SES, etc), health behaviors (i.e. substance use, diet) and maternal psychological variables including prenatal depression [2,7].

It is estimated that depression affects 18% of all pregnant women [8]. This prevalence is higher in lower SES and minority samples, with over 40% of women reporting elevated symptoms of depression during pregnancy [9]. The high incidence of prenatal depression is troubling as prenatal depression is a potential risk factor for a number of adverse pregnancy complications including spontaneous abortion [10], pre-eclampsia [11] and premature delivery [12]. Prenatal depression has also been shown to affect fetal development. Maternal symptoms of depression are related to smaller fetal head circumferences and lower fetal weights [13], and neonates born to depressed mothers are at greater risk for having low birthweight (<2500 g) [14,15]. Similarly, infants of prenatally depressed mothers are also more likely to exhibit growth retardation across the first year of life [16]. Even though studies have examined the effects of prenatal depression on prematurity, birthweight and infant growth, a review of the literature failed to identify any studies that have assessed the effects of prenatal depression on the rate of fetal growth (MEDLINE, PsycINFO; English language; Human; 1872–2007). As such, the present study examined the effects of prenatal depression on fetal growth rates.

The effects of prenatal depression on fetal development appear to be mediated by Hypothalamic Pituitary Adrenal axis (HPA) hyperactivation during pregnancy. For example, depression during pregnancy has been associated with elevated prenatal maternal cortisol levels, which have, in turn, been related to lower fetal weight, smaller fetal head circumference [13], lower birthweight [14] and premature delivery in humans [14,17]. Data from a wide range of animal studies further indicate that maternal HPA axis hyperactivation during pregnancy can lead to fetal growth restriction [18]. In the present study, elevated maternal cortisol levels during pregnancy were explored as a potential mechanism for the effects of prenatal depression on fetal growth.

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1. Methods

1.1. Participants

The sample consisted of 40 depressed and 40 non-depressed pregnant women and their fetuses recruited from prenatal ultrasound clinics between 18 and 20 weeks gestation (M=19.0, SD=0.8). The women were on average 26.8-years-old (SD=6.5, range 18–39), predominantly lower to lower-middle socioeconomic status (SES: M=3.5, SD=1.2, Range range=1–5) on the Hollingshead index [18] and distributed 59% Hispanic, 32% African American and 9% Caucasian and had normal body mass indices (BMI: M=22.9, SD=1.2, Range range=20.9–25.6). Fetuses were distributed 48% female. 46% of the mothers were married, 34% had a partner (but were not married) and 20% were single. To avoid potential errors and confounds associated with estimating age, gestational age was estimated based on the mothers' last menstrual period (LMP) and confirmed using ultrasound measurements. Only mothers who were able to accurately recall their LMP date were included in this study. Women were recruited into the study if they met the following criteria prior to study entry: a) did not report any pregnancy complication at study entry, including: hypertensive disorders, anemia, vaginal bleeding or intrauterine growth restriction; b) did not exhibit any pregnancy complication at study entry or any pregnancy or delivery complication during previous pregnancies, including: hypertensive disorders, anemia, vaginal bleeding or intrauterine growth restriction; c) were not diagnosed with HIV or any other infectious disease; d) had normal pregnancy body mass indices as defined by Institute of Medicine criteria (BMI 19.8–26.0) and did not report having any metabolic or eating disorder (diabetes, obesity, bulimia, anorexia) or any psychiatric condition other than depression; or e) did not report smoking cigarettes, drinking alcohol or using recreational drugs during pregnancy or taking antidepressants or other psychotropic medications during pregnancy. Approximately 80% of women approached met inclusion criteria. Of these, approximately 60% agreed to participate.

1.2. Procedures

The University of Miami School of Medicine Institutional Review Board approved the study. Following informed consent, women were assessed for major depressive disorder (MDD) using the SCID, asked to provide a urine sample and complete questionnaires. During this visit, the women also received an ultrasound examination to obtain fetal biometry measurements. Shortly after delivery, birth measurements were obtained from the mothers' medical records. During the prenatal visit and shortly after delivery, medical information involving the development of any pregnancy or health complications was also collected from the mothers' medical records. Assessments were conducted during the midmorning to control for diurnal variation in cortisol levels and extremely low levels in the mid-afternoon [19].

1.3. Assessments

A *Demographic Questionnaire* was administered to the mothers after they signed an informed consent. The questionnaire included the mothers' marital status, age, ethnicity, occupation and education. Answers to the occupation and education questions were used to compute SES based on the Hollingshead Four Factor Index of Social Status [20].

1.3.1. Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-D)

Women were administered the SCID-I (Non-patient edition: research version) to determine depression during the prenatal assessment. Spanish-only speaking women were administered the Spanish version of the SCID [21]. Women diagnosed as having depression on the SCID-I were provided referral information for obtaining psychiatric care. However, none of the women who participated in this study chose to receive psychological or psychiatric treatment for depression during their pregnancy.

1.3.2. The Center for Epidemiological Studies-Depression scale (CES-D)

The CES-D [22] was administered to assess the symptoms of depression. The CES-D is a 20-item scale, with scores ranging between 0 and 60. The respondents rate the frequency (within the last week) of 20 symptoms. The symptoms include depressed mood, feelings of helplessness and hopelessness, feelings of guilt and worthlessness, loss of energy, and problems with sleep and appetite. The CES-D has adequate discriminant and convergent validity, correlates well with other depression scales, and can differentiate clinically depressed and non-depressed subjects with only a 6% false positive and 36% false negative rate [23]. In addition, this scale has been shown to be reliable and valid for diverse demographic groups [23]. Internal consistency for the CES-D is high (Cronbach's alpha=.82–.85) and test–retest reliability is satisfactory (r=.51 to .67 over a 2–8 week period; r=.32 to .54 over a 3- to 12-month period) [23].

1.3.3. Urine cortisol

Urine samples were collected from the mothers at midmorning on the day of the clinical ultrasound examination. No systematic differences were noted in the sampling or the timing of collection of urine samples between women. Urine samples were transferred to plastic vials and frozen without using acid or other preservatives and sent to Duke University Medical School where they were assayed (by S.S. and C.K.). Urinary cortisol was assayed in the stored urine samples by radioimmunoassay using a specific antiserum from Radioassay Systems Laboratories (Carson City, CA). The specificity of the assay is such that biological fluids can be assayed directly following heat inactivation of CBG, eliminating the need for time-consuming extraction into organic solvents which is usually required for this assay. Only 5–10 µl of sample is needed for triplicate assay. Specially purified 3H-cortisol from the same supplier is used as the labeled hormone. Bound and free hormones are separated by the dextran-coated charcoal technique. The sensitivity of the assay is 0.025 ng/tube. The inter-assay and intra-assay coefficient of variation is less than 10% and 5% respectively. Standards are prepared from cortisol from the same supplier, and quality control samples representing low, medium and high values are run in every assay. Cortisol values were corrected for creatinine volume.

1.3.4. Fetal growth measures

Fetal biometry measurements were performed by clinical ultrasonographers on an Aloka 5500 ultrasound machine with a 5-MHz curvilinear abdominal probe using standard clinical measurement protocols. Fetal ultrasound biometry measurements were then used to estimate fetal weight (eFW) using the Shepard et al., algorithm [24]. This formula was chosen as it results in lower estimation errors than other formulas in fetuses less than 30 weeks gestation [25] and fetuses below 2000 g [26]. Fetal weight estimation algorithms based on fetal ultrasound biometry measurements provide sufficient parametric information to allow for the accurate reconstruction of the fetal volume. Estimated fetal weight algorithms produce estimates with a 10.0% mean absolute percentage error. Fetal weight estimation is not significantly improved by the use of additional non-standard sonographic fetal measurements nor by the use of multiple assessments. There is no significant bias in fetal weight estimation introduced by differences in operator training or diagnostic setting [27]. Furthermore, fetal growth is more accurately estimated via the use of estimated fetal weight equations than with most individual ultrasound biometry measurements [28]. Fetal weight estimates were used to derive gestational age corrected fetal weight values (estimated fetal weight / gestational age at ultrasound).

Gestational age at birth and birthweight in grams, were collected from the infants' medical charts at the neonatal delivery unit and used

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to derive birthweight corrected for gestational age values (birthweight/gestational age). Estimated fetal weight, gestational age and birthweight measures were also used to compute fetal growth rates over the second half of pregnancy as follows.

1.3.4.1. Fetal growth rate

$$fG = \frac{BWT - EFWT}{GA2 - GA1}.$$

Where fG is a fetal growth rate for the second half of pregnancy, EFWT is estimated fetal weight during the first ultrasound visit, BWT is birthweight, GA1 is gestational age during the prenatal ultrasound assessment and GA2 is gestational age at birth. The difference in gestational age between assessments (i.e.GA2 − GA1) was used as the denominator in order to account for unequal measurement intervals across participants due to differences in gestational age at birth.

1.4. Statistical methods

Statistics were performed using SPSS 14.0 for Windows (SPSS Inc., Chicago, IL) and an SPSS macro developed by Preacher and Hayes [29]. Analyses of variance (ANOVAs) and χ^2 analyses were used to compare the groups on demographic and study entry characteristics including symptoms of depression. Analyses of Covariance (ANCOVAs) with Group (depressed/non-depressed) entered as the between subjects factor and marital status (married/not married), maternal age and SES entered as the covariates were used to analyze maternal cortisol levels, estimated fetal weight, estimated fetal weight corrected for gestational age, birthweight, birthweight corrected for gestational age, gestational age at birth, time between the fetal assessment and birth and fetal growth rate. Pearson correlation analyses were conducted between maternal CES-D scores, prenatal cortisol values, gestational age at birth and fetal growth rates. To explore whether elevated cortisol levels during pregnancy mediate the effects of prenatal depression on perinatal outcomes (fetal growth rate; gestational age at birth), we employed the approach proposed by Baron and Kenny [30] for testing mediation using the bootstrap method of Preacher and Hayes [29], to estimate: 1) the total effect of the independent variable (prenatal CES-D scores) on perinatal outcomes (gestational age at birth; fetal growth rate); 2) the effect of the independent variable (prenatal CES-D scores) on the mediator (prenatal maternal cortisol); 3) the effect of the mediator variable (prenatal cortisol) on perinatal outcomes (gestational age at birth; fetal growth rate) after controlling for the effects of the independent variable (prenatal CES-D scores); 4) the direct effect of the independent variable (prenatal CES-D scores) on perinatal outcomes (gestational age at birth; fetal growth rate) after controlling for the effects of the mediator (prenatal maternal cortisol). The amount of mediation as defined by the indirect effect of the independent variable (CES-D) on perinatal outcomes through the mediator (cortisol) was also estimated using both the Sobel test and bootstrap methods to assess the bias-corrected 95% confidence interval (CI) for the mediator based on 1000 bootstrap samples. Data inspection revealed one outlier (depressed woman delivered at 26 weeks gestation), which was not included in the analyses. To assess the independent variance in gestational age at birth and fetal growth rate accounted for by prenatal maternal cortisol levels, R^2_{Change} statistics were computed using two stepwise regression analyses conducted with marital status, maternal age, and SES entered on the first step and prenatal cortisol levels entered on the second step.

2. Results

2.1. Demographics

Analyses revealed that depressed women had higher CES-D scores, were younger, lower SES and less likely to be married than non-depressed women (Table 1). No significant differences were noted in respect to the gestational age during the ultrasound assessment, ethnicity, BMI or infant gender for the depressed and non-depressed groups (Table 1).

2.2. Maternal depression, cortisol and perinatal outcomes

ANCOVAs revealed that depressed women exhibited higher prenatal cortisol levels. Further, the fetuses of depressed women had lower estimated fetal weights during midgestation and showed slower fetal growth rates during the second half of pregnancy. At birth, infants of depressed mothers showed lower birthweights both corrected and uncorrected for gestational age (Table 2). The covariates marital status, maternal age and SES were not significant in any of these analyses. Depressed women exhibited a 13% greater incidence of premature delivery (23% depressed vs. 10% non-depressed; Odds ratio = 2.61, 95% CI = 0.73 to 9.32) and a 15% greater incidence of low birthweight (20% depressed vs. 5% non-depressed; Odds ratio = 4.75, 95% CI = 0.94 to 23.99) than non-depressed women.

2.3. Prenatal maternal cortisol mediates the effects of maternal depression on perinatal outcomes

Pearson correlation analyses revealed that maternal depression scores and prenatal maternal cortisol values were significantly related to each other and to perinatal outcomes (Table 3). Mediation analyses (Table 4) revealed: 1) a significant relation between prenatal CES-D scores on gestational age at birth and fetal growth rate; 2) a significant relation between prenatal CES-D scores and the proposed mediator (prenatal maternal cortisol); 3) a significant relation between the mediator (prenatal maternal cortisol) and gestational age at birth and fetal growth rate after controlling for the effects of prenatal CES-D scores; 4) no significant direct relations between prenatal CES-D scores and gestational age at birth or fetal growth rate after controlling for the effects of the mediator (prenatal maternal cortisol); and 5) a significant reduction in the relationship between the maternal depression scores and both gestational age at birth and fetal growth rate when the mediator (prenatal maternal cortisol) was entered into the equation. Taken together these findings show that prenatal maternal cortisol meets the expanded criteria proposed by Baron and Kenny [29,30] for significant mediation for the effects of maternal depression on both fetal growth and the length of gestation. Stepwise

Table 1
Demographic characteristics

	Non-depressed	Depressed	
	N = 40	*N* = 40	
CES-D	8.33 (3.52)	25.85 (8.01)	$F(1, 78) = 160.58$, $p < .001$, $\eta^2 = .67$
Maternal age	28.03 (6.37)	25.03 (6.40)	$F(1, 78) = 4.41$, $p = .04$, $\eta^2 = .05$
SES	3.20 (1.20)	3.82 (1.26)	$F(1, 78) = 5.16$, $p = .03$, $\eta^2 = .06$
Gestational age at study entry	19.07 (.82)	18.96 (.84)	$F(1, 78) = 0.36$, $p = .55$, $\eta^2 < .01$
Maternal BMI	22.97 (1.14)	22.99 (1.16)	$F(1, 78) = 0.002$, $p = .96$, $\eta^2 < .01$
Marital status			
Married	57%	35%	$\chi^2(1) = 4.07$, $p = .04$
Not married	43%	65%	
Ethnicity			$\chi^2(2) = 0.95$, $p = .62$
Caucasian	10%	8%	
African American	28%	37%	
Hispanic	62%	55%	
Fetal gender			$\chi^2(1) = 0.05$, $p = .82$
Male	52%	50%	
Female	48%	50%	

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Table 2
Means and standard deviations (in parentheses under means) for maternal symptoms of depression (CES-D), prenatal urinary cortisol values and perinatal outcomes

	Non-depressed	Depressed	
	$N=40$	$N=39$[a]	
Prenatal cortisol	134.01 (72.68)	197.04 (111.25)	$F(1, 74)=7.92$, $p=.006$, $\eta^2=.10$
Estimated fetal weight	323.90 (48.44)	284.63 (72.38)	$F(1, 74)=9.06$, $p=.004$, $\eta^2=.11$
Estimated fetal weight (corrected for GA)	16.89 (3.22)	14.95 (2.00)	$F(1, 74)=11.25$, $p=.001$, $\eta^2=.13$
Birthweight	3437.22 (436.63)	3105.18 (480.88)	$F(1, 74)=6.47$, $p=.013$, $\eta^2=.08$
Birthweight (corrected for GA)	89.14 (9.62)	81.38 (10.67)	$F(1, 74)=7.35$, $p=.008$, $\eta^2=.09$
Gestational age at birth	38.48 (1.17)	38.04 (1.65)	$F(1, 74)=0.97$, $p=.336$, $\eta^2=.01$
Time between fetal assessment and birth	19.40 (1.41)	19.07 (1.69)	$F(1, 74)=0.17$, $p=.679$, $\eta^2<.01$
Fetal growth rate	160.20 (16.53)	147.41 (19.10)	$F(1, 74)=6.76$, $p=.011$, $\eta^2=.08$

Marital status, maternal age and SES entered as covariates.
[a] Data inspection revealed one outlier (depressed woman delivered at 26 weeks gestation), which was not included in these analyses.

regression analyses further revealed that prenatal maternal cortisol levels independently predicted 30% of the variance in gestational age at birth ($R^2_{Change}=.30$, F (1, 74)=35.35, $p<.001$) and 14% of the variance in the rate of fetal growth ($R^2_{Change}=.14$, F (1, 74)=13.32, $p<.001$).

3. Discussion

Depressed women exhibited a higher incidence of prematurity and low birthweight than non-depressed women. This is consistent with previous research documenting that women who exhibit elevated depression symptoms during pregnancy are at increased risk for delivering premature and low birthweight infants [14,31]. Fetuses of depressed women also exhibited lower estimated fetal weights during midgestation (18–20 weeks GA) and lower birthweights than fetuses of non-depressed women. These findings are consistent with a recent study documenting that maternal distress (anxiety, depression, stress) during pregnancy was associated with lower estimated fetal weight [13] and research documenting that women exhibiting elevated symptoms of depression have lower birthweight infants [14,15].

Fetal growth restriction is among the leading causes of fetal morbidity and mortality and has been associated with adverse long-term health outcomes [32]. Inasmuch as early diagnosis of fetuses at risk for fetal growth restriction can reduce perinatal morbidity and mortality, it is important to identify factors that place fetuses at risk for fetal growth restriction. Previous studies have attempted to indirectly estimate the effects of maternal depression on fetal growth by assessing birthweight corrected for gestational age [33]. None, however, have assessed the effects of prenatal depression on the rate of fetal growth. In the present study, we found that fetuses of depressed women exhibited slower fetal growth rates across the second half of pregnancy than fetuses of non-depressed women, suggesting that maternal depression is a potential risk factor for fetal growth restriction.

As has been noted before [13,14], depressed women exhibited elevated urinary cortisol levels during midgestation which appeared to mediate the effects of maternal depression on both fetal growth rates and the length of gestation. These findings are consistent with several lines of evidence, which suggest that prenatal depression may affect perinatal outcomes, including premature delivery and fetal growth restriction, through complex mechanisms including elevated maternal cortisol levels during pregnancy. For example, elevated prenatal maternal cortisol may affect fetal growth by both directly reaching the fetus and by changing the placental environment. From 10% to 20% of maternal cortisol can readily cross the placenta [34,35], where it has been shown to stimulate the fetal HPA axis [34,36] resulting in elevated fetal cortisol levels which may in turn affect fetal growth by dysregulating fetal autonomic nervous system activity [37] and mobilizing fetal energy stores via glycogenolysis (the conversion of glycogen to glucose) resulting in a high degree of calorie expenditure. Alternatively, elevated maternal cortisol, which has been shown to induce vascular constriction [38,39] and potentiate norepinephrine-induced uterine artery contractions during mid-pregnancy [40], may also lead to reduced uterine artery blood flow, which has been associated with the development of perinatal complications including fetal growth restriction [41,37] and premature delivery [42] possibly as a result of placental hypoxia and the restriction of oxygen and nutrient delivery to the fetus. Elevated maternal cortisol levels during the second trimester may also lead to

Table 3
Pearson correlation analyses

	CES-D	Prenatal cortisol	Gestational age at birth
Prenatal cortisol	.37**		
Gestational age at birth	−.24*	−.59**	
Fetal growth rate	−.27*	−.39**	.43**

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

Table 4
Mediation effects of prenatal cortisol (Cortisol) on the relationship between prenatal symptoms of depression (CES-D) and gestational age at birth (GA) and fetal growth rates (FG)

Regression path	*b*	s.e.	*t*	*p*
Gestational age at birth ($R^2=.35$, adjusted $R^2=.33$, $F(2, 76)=20.09$, $p<.001$)				
Total effect *c* (CES-D on GA; Cortisol *not* included)[a]	−.032	.015	2.15	.035
Mediation path *a* (CES-D on Cortisol)[a]	3.39	.979	3.46	<.001
Mediation path *b* (Cortisol on GA)[a]	−.008	.001	5.79	<.001
Direct effect *c′* (CES-D on GA; Cortisol *is* included)[a]	−.003	.013	0.25	.801
Indirect effect tests			95% confidence intervals	
Sobel	−.029	.009	(−.047 to −.009) $Z=2.94$, $p=.003$	
Bootstrap ($z=1000$)			(−.050 to −.010)[c]	
Fetal growth rate ($R^2=.17$, adjusted $R^2=.15$, $F(2, 76)=7.78$, $p<.001$)				
Total effect *c* (CES-D on FG; Cortisol *not* included)[a]	−.472	.195	2.42	.018
Mediation path *a* (CES-D on Cortisol)[a]	3.39	.979	3.46	<.001
Mediation path *b* (Cortisol on FG)[a]	−.065	.022	3.01	.035
Direct effect *c′* (CES-D on FG; Cortisol *is* included)[a]	−.252	.199	1.26	.210
Indirect effect tests *c*–*c′*[ab]			95% confidence intervals	
Sobel	−.214	.093	(−.414 to −.026) $Z=2.22$, $p=.026$	
Bootstrap ($z=1000$)			(−.421 to −.055)[c]	

b = unstandardised coefficient; s.e. = standard error.
[a] Effects that need to be significant to meet the criteria for mediation according to Baron and Kenny [30].
[b] If this coefficient is reduced to zero then we have perfect mediation, if it is reduced significantly but not to zero then we have partial mediation, (Baron and Kenny [30]). The effect of CES-D on both GA and FG is significantly reduced when cortisol is introduced as a mediator.
[c] If the 95% confidence interval produced by the bootstrap does not include zero then criteria for mediation has been meet (Preacher and Hayes [29]).

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premature delivery by acting on the placental clock via increases in placental CRH [17].

The role for the timing of prenatal depression on influencing perinatal outcomes remains unknown. In our study, the lower fetal weight exhibited by fetuses of depressed women at 18–20 weeks gestation, suggests that maternal depression may begin to impact fetal development as early as the second trimester. While it is possible that maternal depression can begin to impact fetal development at an even earlier stage, the low maternal blood flow to the placenta [43,44] and oxygen tension within the fetoplacental unit [45] observed during the first 7 weeks of gestation suggests that during early gestation, the embryo remains relatively isolated and protected from the maternal biochemical environment during the beginning of the first trimester [46]. Similarly, the threefold increase in maternal cortisol [17], the increase in the placental cortisol metabolizing enzyme 11β-hydroxysteroid dehydrogenase type 2 [47] and the attenuated HPA axis responses to stress observed during late pregnancy [48] may help to buffer negative effects of maternal distress and elevated cortisol levels on the fetus and intrauterine environment during late gestation. This is consistent with the relationship observed between preterm birth and elevated cortisol levels at 15 and 19 weeks gestation but not at 25 or 30 weeks gestation [17]. However, the slower fetal growth rates observed across the second half of pregnancy (mid second trimester to delivery) in fetuses of depressed women, suggest that maternal depression continues to impact fetal development through the third trimester to at least some extent. Future research should attempt to evaluate the timing associated with the impact of maternal depression on perinatal outcomes.

Because prenatal depression has been associated with poorer diet and eating habits early in pregnancy [49], we only included women with normal pregnancy body mass indices who did not report having any metabolic or eating disorder. While midgestation body mass indices (BMI) for depressed and non-depressed women did not differ, we did not collect information on maternal nutrition during pregnancy, which plays a critical role in fetal development [50]. Future research should evaluate maternal nutrition as a potential moderator for the effects of maternal depression on fetal development.

In conclusion, prenatal depression was associated with adverse perinatal outcomes, including premature delivery and slower fetal growth rates. Depressed women also exhibited elevated cortisol levels midgestation. Results from our mediation analyses suggest that maternal depression may lead to adverse perinatal outcomes via increased prenatal maternal cortisol levels.

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