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Maternal parity and perinatal cortisol adaptation: The role of pregnancy-specific distress and implications for postpartum mood

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Abstract

Introduction: Compared to women who have given birth before (i.e., multiparas), those giving birth for the first time (i.e., primiparas) show higher cortisol levels. Psychological factors may play a role; hypothalamic-pituitary-adrenal activation is a well-described stress response. Primiparity also predicts greater risk for postpartum depression, which may be related to greater correspondence between cortisol and mood following prenatal cortisol elevations. The current study examined associations among parity, perinatal cortisol adaptation, pregnancy-specific distress, and postpartum mood.

Methods: This longitudinal study assayed serum cortisol levels among 137 women at early, mid-, and late pregnancy and postpartum. Pregnancy-specific distress and depressive symptoms were assessed. Maternal age, race, body mass index, sleep quality, depressive symptoms, and sampling time of day were statistically controlled.

Results: Primiparous women showed higher cortisol levels than multiparous women during mid- ($\chi^2 = 11.8, p < 0.01$), $p < 0.01$) and late pregnancy ($\chi^2 = 18.9, p < 0.01$), $p < 0.01$) and higher distress across pregnancy ($F_{1,126} = 22.1, p < 0.01$). Mediation analyses demonstrated that the association between parity and prenatal cortisol (per area under the curve; AUC) was partially accounted for by distress ($ab = 1.0, 95\%CI[0.05, 2.9]$). Prenatal cortisol (per AUC) did not predict postpartum

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Conflicts of interest

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depressive symptoms ($b^* = 0.03$, $p = 0.81$), with no difference by parity ($b^* = 0.03$, $p = 0.91$). At postpartum, a significant interaction between parity and cortisol ($b^* = 0.40$, $p = 0.03$) revealed no significant association between cortisol and mood among multiparas ($b^* = -0.11$, $p = 0.28$) but a trend toward a positive association among primiparas ($b^* = 0.24$, $p = 0.06$).

Discussion: Cortisol levels and pregnancy-specific distress are higher in primiparas versus multiparas, with pregnancy-specific distress partially mediating the association between parity and cortisol levels. Cortisol levels and mood display correspondence at postpartum in primiparous but not multiparous women. While observational studies must be interpreted with caution due to potential unmeasured confounders, these findings suggest that future studies examining mechanisms underlying perinatal and postpartum hypothalamic-pituitary-adrenal perturbations and designing interventions aimed at preventing related complications should carefully consider potential differences by parity.

Keywords

Cortisol; Parity; Postpartum; Pregnancy; Stress; Psychological; Depressive symptoms

1. Introduction

A pattern well described in humans, maternal hypothalamic-pituitary-adrenal (HPA) axis activity increases progressively across pregnancy, producing a doubling in maternal cortisol levels from early to late gestation with a return toward pre-pregnancy levels at postpartum (e.g., Conde and Figueiredo, 2014; Smy et al., 2016). Some studies suggest that, compared to women who have given birth before (i.e., multiparous women), those giving birth for the first time (i.e., primiparous women) show overall higher levels of maternal cortisol within this expected pattern of perinatal adaptation (Bouyou-Akotet et al., 2004; Conde and Figueiredo, 2014; Grajeda and Perez-Escamilla, 2002; Tu et al., 2006). Similar results have been reported across additional physiologic systems, including greater sympathetic nervous system (SNS) and cardiovascular activity among primiparous versus multiparous women (DiPietro et al., 2005; Iizuka et al., 2016; Turan et al., 2008).

Although parity is one of the most commonly included covariates in studies of perinatal health, the origins of parity-associated differences in HPA activity remain poorly defined. It is possible that the observed difference is purely biological, reflecting effects of prior pregnancy on adaptation to subsequent pregnancy. However, there is support for the role of psychological factors. Increased activation of the HPA axis and SNS is consistent with well-described physiologic responses to psychological stress. Moreover, data suggest that primiparous women report greater distress with regard to pregnancy, including concerns about physical symptoms, the health of the fetus, upcoming childbirth, and adapting to their new role as mother (Lynn et al., 2011; Takegata et al., 2017; Westerneng et al., 2017; Woods-Giscombe et al., 2010).

Of relevance in this context, while some studies report that the postpartum period presents unique stressors but is not necessarily more stressful for primiparous women (Clout and Brown, 2015; Liu et al., 2012), the bulk of evidence suggests that postpartum depression is more common following a primiparous versus multiparous pregnancy (e.g., Fiala et al.,

2017; Iwata et al., 2016; Liu et al., 2017). Mechanisms remain poorly understood, including data on the potential role of heightened HPA activity in primiparas during pregnancy (Workman et al., 2016). In addition to conferring risk for depressed mood, greater exposure to cortisol during pregnancy may alter the association between postpartum cortisol and postpartum mood. Support for this hypothesis comes from animal data showing that stress-induced hypercortisolemia can be accompanied by changing patterns of glucocorticoid receptor expression and nuclear translocation in stress-receptive regions of the brain, inducing greater susceptibility to subsequent stress exposures (Han et al., 2017; Jochems et al., 2015). During human pregnancy, some evidence also suggests that greater prenatal HPA activity predicts impaired patterns of HPA feedback at postpartum (reviewed by Glynn et al., 2013).

To address the knowledge gaps in this small but important literature, the current study examined associations among parity, perinatal cortisol adaption, and pregnancy-specific distress and relationships among cortisol levels and postpartum mood. We hypothesized that primiparous women would exhibit elevations in both serum cortisol and pregnancy-specific distress during pregnancy. We also hypothesized that pregnancy-specific distress would partially mediate the association between parity and cortisol. Lastly, we examined the hypothesis that, at postpartum, maternal cortisol levels and maternal mood would show greater correspondence among primiparous versus multiparous women.

2. Methods

This longitudinal observational study was approved by The Ohio State University Biomedical Institutional Review Board. Participants were recruited from The Ohio State University Wexner Medical Center Prenatal Clinic and the surrounding community of central Ohio from 2009 to 2014. Inclusion criteria included current singleton pregnancy. Exclusion criteria included diagnosis of a fetal anomaly or a major immunological or endocrine condition of the mother (e.g., systemic lupus erythematosus, thyroid disease) and regular use of medications with implications for endocrine function (e.g., corticosteroids). Women reporting or having a medical record indicative of illicit drug use or consumption of more than two alcoholic drinks per week during pregnancy were also ineligible. At enrollment, written informed consent was obtained. Participants received modest compensation at each study visit, which occurred during early (10–14 weeks gestation), mid- (20–24 weeks gestation), and late (28–32 weeks gestation) pregnancy as well as 4–11 weeks postpartum.

2.1. Demographic, behavioral, and clinical characteristics

At first study visit, demographic characteristics, including maternal race, marital status, and annual household income, were assessed by self-report. Participants were also asked whether, at study enrollment, they were a current smoker or non-smoker. Pre-pregnancy body mass index (BMI) was calculated according to self-reported pre-pregnancy weight and height as measured at first study visit (kg/m^2). Sleep quality over the previous month was assessed during each study visit using the Pittsburgh Sleep Quality Index (PSQI). The PSQI produces a global sleep quality score by assessing subjective sleep quality, latency, duration,

efficiency, and disturbance as well as sleeping medication and daytime dysfunction, with higher scores indicating poorer sleep quality (Buysse et al., 1989). A detailed obstetric history was collected by interview and data surrounding the current pregnancy were extracted from the medical records. For the current study, women were dichotomized as primiparous if they experienced their first birth during the assessed pregnancy or multiparous if they had given birth one or more time prior to the assessed pregnancy.

2.2. Psychosocial measures

The 17-item Revised Prenatal Distress Questionnaire (NUPDQ) was administered at early, mid-, and late pregnancy and used to assess distress associated with issues specific to pregnancy, such as financial challenges, physical changes and symptoms, labor and birth, and the health of the pregnancy and baby (Lobel et al., 2008; Yali and Lobel, 1999). Example items include, “Are you feeling bothered, upset, or worried at this point in your pregnancy about the quality of your medical care during pregnancy?” and “Are you feeling bothered, upset, or worried at this point in your pregnancy about whether you might have an unhealthy baby?” Participants responded to items on a 3-point scale (not at all = 0, somewhat = 1, very much = 2) and items were summed to calculate a total score. NUPDQ Cronbach’s α ranges from 0.71 to 0.79 and test-retest reliability from 0.64 to 0.72, which is consistent with alternative measures of pregnancy-specific distress and likely reflects differences in the perception of stress as pregnancy progresses (reviewed by Alderdice et al., 2012). Prior studies have demonstrated associations among NUPDQ score and biological markers of stress during pregnancy (e.g., serum proinflammatory markers) as well as birth outcomes (e.g., Lobel et al., 2008). To determine the unique predictive value of pregnancy-specific distress within our models and to examine postpartum depressive symptoms, the Center for Epidemiologic Studies Depression (CES-D) Scale (Radloff, 1977) was also administered at prenatal study visits and at postpartum. Higher scores (with a range of 0–3 for each of 20 items) are indicative of greater depressive symptoms over the previous week and a score of ≥ 16 is consistent with clinically significant depressive symptomatology. The well-validated 14-item Perceived Stress Scale (Cohen et al., 1995) was also administered to estimate postpartum levels of psychological stress, with participants asked to describe how often they had, for example, been upset because of something that happened unexpectedly. Responses are focused on the past month and provided on a 5-point scale ranging from never to very often, with higher scores indicative of greater perceived stress.

2.3. Cortisol levels

Greater than 94% of blood samples were collected between the hours of 7 AM and 1 PM. After collection, samples were allowed to clot at room temperature and serum separated by centrifugation. Serum aliquots were then stored at -80°C . Batched by participant, serum was assayed for cortisol by solid-phase competitive chemiluminescence using the Immulite 1000 system per manufacturer instructions (Siemens Healthcare Diagnostics, Inc., Deerfield, IL). The immunoassay provides an analytical sensitivity of 0.2mcg/dl and coefficients of variation were 7.1% for intra-assay comparisons and 7.9% for interassay comparisons.

2.4. Statistical analyses

There were 144 women enrolled in the study, among whom 108 (75%) completed all four study visits, 24 (16.7%) completed three study visits, and 7 (4.9%) completed two study visits. Women who completed only one study visit ($n = 5$; 3.5%) were excluded, as were those for whom birth outcome data were unavailable ($n = 2$), resulting in a final analytic sample of 137.

Among the analytical sample, missing values for variables collected at early ($n = 7$), mid- ($n = 5$), and late ($n = 8$) pregnancy and postpartum ($n = 15$) study visits were addressed using multiple imputation with chained equations (5 imputations). Results were pooled across imputations to obtain final estimates for missing values.

Descriptive statistics were generated and chi-square, Fisher's exact, and Student's independent t-tests conducted to examine differences among primiparous versus multiparous women for the identification of potential confounders. Bivariate Pearson correlations were also examined for the primary variables of interest. Repeated measures ANCOVA models were built to assess associations among time, group, and time*group interactions and maternal perinatal cortisol levels and pregnancy-specific distress, adjusting for relevant covariates. The mediating role of pregnancy-specific distress in the association between primiparity and perinatal cortisol levels was assessed by applying the framework and process described by Hayes (2013). Briefly, holding relevant covariates constant, the PROCESS macro estimates the total association between a predictor and the criterion variable, the indirect association between a predictor and the criterion variable through a potential mediator, and the direct association between a predictor and the criterion variable controlling for the potential mediator. The presence or absence of an indirect (i.e., mediational) association is statistically inferred by examining the confidence interval constructed through bias-corrected bootstrapping with replacement (10,000 bootstraps). Finally, associations between prenatal maternal cortisol area under the curve and postpartum depressive symptoms as well as postpartum maternal cortisol levels and postpartum depressive symptoms were examined by multiple linear regression. To determine whether associations differed by parity, a cortisol*parity interaction term was included. As above, estimates were adjusted for relevant covariates. All models described above were also repeated with women reporting current smoking at the time of enrollment excluded.

For each model, post-estimation diagnostics were also reviewed in detail. In examining the repeated measures ANCOVA models, non-normality of criterion variables and non-constant variance were identified. Similarly, in examining the multiple linear regression models, non-normality and several instances of heteroskedasticity of error terms were identified. As such, all analyses were repeated and congruence of findings confirmed following square root transformation of criterion variables, which was largely successful in remediating violations of concern. For ease of interpretation, results are reported for the untransformed models. In addition, in examining the three outlying values that remained after appropriate transformations of the predictor and criterion variables of interest, there was no suggestion of undue influence of data points on regression estimates as evidenced by Cook's distances of ≤ 10.171 (Cook and Weisberg, 1982). Tests for mediation were completed using the Hayes

PROCESS macro within IBM SPSS Statistics 23. All additional analyses were conducted using STATA 12.1 Data Analysis and Statistical Software.

3. Results

3.1. Participant characteristics

In this sample, 33 (24.1%) women were primiparous and 104 (75.9%) were multiparous (Table 1). Groups did not significantly differ in marital status, income, pregnancy intendedness, or smoking status. Multiparous women were significantly older than primiparous women ($t(135) = 2.0, p = 0.05$) and Black women were more prevalent in the multiparous versus primiparous group ($\chi^2 = 6.2, p = 0.01$). In addition, there was a significant association between parity and pre-pregnancy BMI, with lower pre-pregnancy BMI among primiparous versus multiparous women ($t(135) = 2.1, p = 0.03$). Multiparity predicted poorer early pregnancy ($t(135) = 2.0, p = 0.05$) but not postpartum ($t(135) = 0.02, p = 0.99$) sleep quality.

Reflecting on all prior pregnancies, 2 (1.9%), 4 (3.8%), and 19 (18.3%) multiparous women reported a history of gestational diabetes mellitus, gestational hypertensive disorder, and preterm birth, respectively. As shown in Table 2, primiparous and multiparous women did not significantly differ in the occurrence of these major complications of pregnancy during the current pregnancy nor did gestational age at birth or infant birth weight differ between the groups (p values > 0.10).

Primary variable descriptive statistics and bivariate Pearson correlations are presented in Table 3, with patterns of association generally similar among primiparous and multiparous women. Of note, maternal cortisol levels were not significantly associated with postpartum depressive symptoms, with the exception of a concurrent association between postpartum parameters among primiparous women ($r = 0.34, p = 0.05$). Among the full sample, 37.2% and 30.7% of women reported clinically significant depressive symptoms at early pregnancy and postpartum, respectively. Parity was not significantly associated with depressive symptoms (measured continuously or dichotomously) at either time point (p values ≤ 0.14) nor with perceived stress at postpartum ($t(135) = -0.59, p = 0.56$). Sampling time of day at early ($M = 1037\text{h}, SD = 1\text{ h }14\text{min}$), mid- ($M = 1026\text{h}, SD = 2\text{h }5\text{min}$), and late ($M = 1030\text{ h}, SD = 2\text{h}$) pregnancy and postpartum assessments ($M = 1056\text{ h}, SD = 1\text{ h }41\text{ min}$) and days post-birth at postpartum sampling ($M = 52.9, SD = 12.3$) were also examined as potential confounders. Sampling occurred marginally later in the day among primiparous versus multiparous women at the early ($t(135) = -1.86, p = 0.06$) and mid-pregnancy assessments ($t(135) = -1.83, p = 0.07$). Primiparous and multiparous women did not differ in late pregnancy or postpartum sampling time of day nor days post-birth at postpartum sampling (p values > 0.15).

3.2. Associations among parity and perinatal cortisol levels

First, we examined associations among parity and maternal cortisol levels across pregnancy and postpartum. As expected, a main effect of time was noted ($F_{3,127} = 159.5, p < 0.01$), with cortisol levels rising from early to mid- ($\chi^2 = 108.2, p < 0.01$) and mid to late

pregnancy ($\chi^2 = 31.2, p < 0.01$) and declining at postpartum ($\chi^2 = 471.4, p < 0.01$). In addition, controlling for maternal age, race, pre-pregnancy BMI, early pregnancy sleep quality, and early and mid-pregnancy sampling time of day, primiparous women showed overall higher cortisol levels than multiparous women ($F_{1,127} = 25.7, p < 0.01$). Per post-hoc contrasts, primiparity predicted higher cortisol specifically during mid ($\chi^2 = 11.8, p < 0.01$) and late pregnancy ($\chi^2 = 18.9, p < 0.01$; Fig. 1), with no differences observed at early pregnancy or postpartum (p values = 0.13).

3.3 Associations among parity and pregnancy-specific distress

We next examined associations among parity and pregnancy-specific distress controlling for maternal age, race, pre-pregnancy BMI, early pregnancy sleep quality, early pregnancy maternal depressive symptoms, and early and mid-pregnancy sampling time of day. As shown in Fig. 2, repeated measures ANCOVA demonstrated that pregnancy-specific distress was significantly higher among primiparous compared to multiparous women ($F_{1,126} = 22.1, p < 0.01$). Post-hoc contrasts demonstrated that this association was present during early, mid, and late pregnancy (p values = 0.02).

3.4. Pregnancy-specific distress as mediator linking primiparity with elevated cortisol

Next, we examined the mediating role of pregnancy-specific distress in the association between primiparity and elevated maternal cortisol, with the pathways of analysis and findings depicted in Fig. 3. For these analyses, pregnancy-specific distress at early pregnancy was used as the predictor, given that it temporally preceded subsequent elevations in serum cortisol in mid- and late pregnancy. Cortisol levels per area under the curve (AUC) across early, mid-, and late pregnancy were used as the outcome to best capture total prenatal exposure. As above, maternal age, race, pre-pregnancy BMI, early pregnancy sleep quality, early pregnancy maternal depressive symptoms, and early and mid-pregnancy sampling time of day were included as controls. Consistent with earlier repeated measures ANCOVA, a significant total association between primiparity and maternal cortisol AUC was observed ($c = 7.8, t(128) = 3.0, p < 0.01$). Mediation analyses further demonstrated that this association was partially accounted for by pregnancy-specific distress ($ab = 1.0, 95\% CI [0.05, 2.9]$), with a direct association between primiparity and maternal cortisol levels also present ($c' = 6.7, t(128) = 2.6, p = 0.01$). As such, 13.3% versus 86.7% of the total association between primiparity and maternal cortisol AUC was mediated by pregnancy-specific distress versus directly attributable to differences by parity, respectively.

3.5. The relationship between cortisol and postpartum depressive symptoms by parity

Finally, we examined whether prenatal maternal cortisol area under the curve or postpartum maternal cortisol levels were differentially associated with postpartum depressive symptoms among multiparous versus primiparous women. Regression analyses, controlling for maternal age, race, pre-pregnancy BMI, early pregnancy sleep quality, early pregnancy depressive symptoms, and early and mid-pregnancy sampling time of day as appropriate, did not provide support for an association between prenatal cortisol levels (per area under the curve) and postpartum depressive symptoms ($b^* = 0.03, p = 0.81$), with no difference by parity ($b^* = 0.03, p = 0.91$). At postpartum, however, a significant interaction between parity

and cortisol emerged in predicting depressive symptoms, indicating that the association between postpartum cortisol levels and postpartum depressive symptoms were dependent upon parity ($b^* = 0.40$, $p = 0.03$). Specifically, the model revealed no significant association between cortisol and depressive symptoms among multiparous women ($b^* = -0.11$, $p = 0.28$) but a trend toward a positive association between cortisol and depressive symptoms among primiparous women ($b^* = 0.24$, $p = 0.06$).

3.6. Sensitivity analyses

We also repeated all models, applying statistical controls as described above, and excluding women reporting current smoking status at study enrollment ($n = 19$). Results were largely consistent, including findings of a main effect of time on perinatal cortisol levels ($F_{3,108} = 143.0$, $p < 0.01$) and overall higher cortisol levels among primiparous versus multiparous women ($F_{1108} = 25.0$, $p < 0.01$). Pregnancy-specific distress was again significantly higher among primiparous versus multiparous women ($F_{1107} = 37.8$, $p < 0.01$). Mediation analyses again revealed a total association between primiparity and maternal cortisol AUC ($c = 9.0$, $t(107) = 3.2$, $p < 0.01$) and a direct association between primiparity and maternal cortisol AUC ($c' = 8.1$, $t(109) = 2.8$, $p < 0.01$). The indirect association between primiparity and maternal cortisol AUC through pregnancy-specific distress was slightly attenuated ($ab = 0.8$, 95% CI $[-0.72, 3.04]$); though, similar to above, 9.2% versus 90.8% of the total association was estimated as mediated by pregnancy-specific distress versus directly attributable to parity, respectively. Again, prenatal cortisol levels were not significantly associated with postpartum depressive symptoms ($b^* = -0.11$, $p = 0.41$), with no difference by parity ($b^* = 0.23$, $p = 0.52$). Despite the decreased sample size, results suggested the potential for effect modification by parity in the association between postpartum cortisol levels and postpartum depressive symptoms ($b^* = 0.35$, $p = 0.059$).

4. Discussion

This longitudinal study provides novel evidence that differences in pregnancy-specific distress contribute to elevations in maternal cortisol among primiparous versus multiparous women. This extends prior work identifying associations between distress related to pregnancy and maternal hypothalamic-pituitary-adrenal activity (Kane et al., 2014; Pluess et al., 2010). This finding is of importance considering that parity is commonly included as a covariate in studies aiming to identify psychoneuroendocrine contributions to perinatal complications; these data suggest that the potential moderating role of parity should be considered in statistical analyses, if appropriate to the question of interest. This finding also provides context for the consideration of prior work examining differential activity of stress response systems by parity (e.g., greater ANS and SNS activity, total peripheral resistance, and blood pressure in primiparas vs. multiparas; DiPietro et al., 2005; Iizuka et al., 2016; Turan et al., 2008). The potential role of psychological factors in parity-associated differences in cortisol adaptation during pregnancy has generally not been examined in prior studies, though some investigators have considered this possibility. For example, Ishikuro et al. (2015) proposed and found support for a greater white coat effect on blood pressure among primiparous versus multiparous women.

By assessing women at early, mid-, and late gestation and at postpartum, we were also able to generate data showing that primiparous women display early and persistent elevations in pregnancy-specific distress as compared to multiparas, with primiparity-associated elevations in cortisol first presenting at mid-pregnancy and resolving by postpartum. These findings are consistent with and extend prior work in which sampling was initiated later in pregnancy (Bouyou-Akotet et al., 2004; Conde and Figueiredo, 2014; Grajeda and Perez-Escamilla, 2002; Lynn et al., 2011; Takegata et al., 2017; Tu et al., 2006; Westerneng et al., 2017) or did not concurrently assess self-report and biological markers of pregnancy-specific distress (Woods-Giscombe et al., 2010). This report also adds to a small but important body of literature suggesting that distress specific to pregnancy is uniquely elevated among primiparas versus multiparas, an effect generally not observed using more generalized measures (Goletzke et al., 2017; Lanier and Jonson-Reid, 2014). Sources of worry that may be particularly relevant to first-time mothers and therefore targets for mental health promotion include changing finances and interpersonal relationships, newly experienced symptoms, and the perceived potential for ill health of the pregnancy or newborn (Dahlen et al., 2010; Darvill et al., 2010; Eri et al., 2010).

In this study, we also present new evidence that postpartum cortisol levels are associated with postpartum mood among primiparas but not multiparas despite similar levels of postpartum perceived stress among the two groups. These data suggest that primiparas may be uniquely susceptible to the development of depressed mood in response to cortisol elevations during the postpartum period. These data may help to explain discordant findings in earlier studies (Corwin et al., 2015; Iliadis et al., 2015; Seth et al., 2016) and again suggest that the treatment of parity as a control variable should be carefully considered in future studies. Further, this finding may lend insight with regard to patterns of risk for postpartum depression among primiparas versus multiparas, as primiparity-associated increases in risk for postpartum mood disturbance peak at approximately two weeks and fade by eight weeks postpartum (Iwata et al., 2016; Takehara et al., 2018). Pregnancy-associated elevations in maternal cortisol levels return to baseline over the same postpartum period.

Also of clinical importance, some evidence suggests that breastfeeding offers greater protection against postpartum mood disturbance among multiparas than primiparas (Sibolboro Mezzacappa and Endicott, 2007). Greater cortisol levels, particularly at 0800 and 0830 h, have been reported among predominantly breastfeeding versus bottle feeding mothers, possibly due to more frequent waking at night and earlier rising during the day (Ahn and Corwin, 2015). Given the greater correspondence between mood and cortisol observed among primiparous women in the current study, disturbed sleep may serve as a modifiable risk factor for postpartum depression, particularly among primiparous breastfeeding mothers.

The mechanisms underlying differences by parity in the association between postpartum cortisol and postpartum mood will be an important topic of future work. The HPA hypothesis of depression posits that HPA disturbances may not only correlate with but contribute to the pathogenesis of depression (reviewed by Belmaker and Agam, 2008), suggesting that the greater HPA burden experienced by primiparas may be contributing to

our results. Indeed, susceptibility to depression appears to be dependent upon glucocorticoid signaling within stress-responsive regions of the brain, which can be influenced by prior exposures to cortisol. For example, in a study by Han et al. (2017), male C57BL/6 J mice were exposed to social defeat and subsequently classified as resilient (i.e., no social withdrawal) or susceptible (i.e., social withdrawal). While social defeat induced glucocorticoid elevations in resilient and susceptible mice, only susceptible mice showed significant elevations. Importantly, susceptible mice also demonstrated lower expression and nuclear translocation of the glucocorticoid receptor in the hippocampus, with implications for negative HPA feedback. Glynn et al. (2013) proposed and our results support that greater HPA activity during the prenatal period may increase risk for postpartum depression by promoting postpartum disturbances in HPA negative feedback.

Although we found associations between postpartum cortisol and postpartum depressive symptoms, prenatal cortisol exposure (per area under the curve) was not associated with risk for postpartum depressive symptoms. This is consistent with prior data in pregnant women (Corwin et al., 2015; Glynn and Sandman, 2014; Iliadis et al., 2015) and several prospective studies among non-pregnant populations (e.g., Grynderup et al., 2013). However, some have reported associations between early pregnancy cortisol and late pregnancy corticotropin-releasing hormone levels which, in turn, predict postpartum depressive symptoms (Glynn et al., 2007; Glynn and Sandman, 2014; Hahn-Holbrook et al., 2013). This suggests that measures of cortisol output alone are inadequate to predict risk for new onset depression and lend further support to the supposition that activity and feedback within the HPA axis following prolonged elevations in cortisol exposure may be critical determinants of risk for future mood disturbance.

Major strengths of the current study include its longitudinal design, which provided the opportunity to establish a time course. Similarly, for the quantification of serum cortisol levels, whole blood was collected at three time points across pregnancy and at postpartum and standardized according to time of day. As in the current study, prior work has demonstrated associations between psychological stress and circulating levels of cortisol during pregnancy, including under experimental conditions using animal models and per self-report during human gestation (Gillespie et al., 2017; Szenci et al., 2011). Use of the well-validated Revised Prenatal Distress Questionnaire (Lobel et al., 2008; Yali and Lobel, 1999) was also a strength of the study, as the 17-item instrument provides an estimate of pregnancy-specific distress, a unique construct.

As with any observational study, findings must be interpreted with caution. Although a number of potential confounders were assessed and statistically controlled as appropriate, there is always potential for unexplored alternate explanations. Future, sufficiently powered studies may also wish to assess the potential for effect modification by maternal factors such as race in the association between parity and perinatal cortisol adaptation. In fact, we have previously reported in a paper focused on brain-derived neurotrophic factor that Black women in this same cohort showed significantly lower serum cortisol levels at second and third trimesters than white women (Christian et al., 2016). Additional limitations of the current study include assessment at a single postpartum time point with a relatively large sampling window postbirth. Breastfeeding data was also lacking during the pilot phase of

this study ($n = 62$), prohibiting related analyses. Future studies with repeated measures across the postpartum period and detailed accounts of the breastfeeding experience among primiparous and multiparous mothers may provide greater insight into the pathways contributing to the development of postpartum depressive symptoms, including the consideration of breastfeeding status as a potential confounder. In addition, longitudinal assessment of diurnal cortisol profiles and/or hair cortisol could provide more complete estimates of total cortisol exposure in future work. Moreover, assessment of neural glucocorticoid signaling using animal models and more complete assessment of HPA hormones (i.e., corticotropin-releasing hormone and adrenocorticotrophic hormone in addition to cortisol) in human studies will be critical to determining whether our findings are suggestive of the development of transient postpartum HPA dysregulation following the greater prenatal HPA burden associated with primiparity. Lastly, 37.2% and 30.7% of our sample exhibited clinically significant depressive symptoms at prenatal and postpartum assessments, respectively. These rates are higher than those reported in other U.S. studies using comparable screening tools and cut-points (e.g., 24.8% and 18.2%, respectively; Meltzer-Brody et al., 2011), which must be considered in terms of generalizability.

The findings of this study hold several important implications. First, they suggest that all women, particularly first-time mothers who account for 1.5 million annual births in the U.S. alone (Martin et al., 2017), may reap benefit from societal and clinical support systems aimed at reducing pregnancy-specific distress and resultant increases in maternal cortisol levels. While it is premature to offer specific recommendations, further research in this area is certainly warranted. Indeed, prior studies have implicated greater maternal prenatal HPA activity in complications of pregnancy such as the development of shortened gestation (Gillespie et al., 2017; Hoffman et al., 2016), gestational hypertensive disorders (Harville et al., 2008), and postpartum depression (Glynn et al., 2013; Glynn and Sandman, 2014). Further, while it remains unclear whether depression is less or more common among perinatal (estimates of 9.1%–13.0%) versus reproductive aged women (estimates of 9.1%–13.1%) in U.S. and other high-income countries (Guo et al., 2018; Hahn-Holbrook et al., 2018; Hoertel et al., 2015; Woody et al., 2017), it is certainly possible that the biology underlying depressive symptomatology differs as a function of the presence and features of perinatal adaptation. Specifically, the findings from this study suggest that postpartum depressive symptoms may be driven by different biological pathways among primiparous versus multiparous women, with primiparous women perhaps uniquely susceptible to depressed mood associated with the hormonal fluctuations of the early postpartum period. This possibility deserves further attention, particularly in the pursuit of precision approaches to health promotion.

In conclusion, the current study provides novel data indicating that primiparity-associated elevations in pregnancy-specific distress precede elevations in maternal cortisol levels among primiparous versus multiparous women and partially mediates the association between parity and perinatal cortisol adaptation. Correspondence between cortisol levels and mood at postpartum was also uniquely identified among primiparous women, who had recently experienced a greater prenatal HPA burden. These findings suggest that future studies examining mechanisms underlying perinatal HPA perturbations and designing

interventions aimed at preventing related complications should carefully consider potential differences by parity.

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Fig. 1.

Maternal cortisol levels across pregnancy and postpartum by parity. Primiparity predicted higher cortisol during mid ($\chi^2 = 10.7, p < 0.01$) and late pregnancy ($\chi^2 = 17.4, p < 0.01$), with no differences at early pregnancy or postpartum (p values = 0.18).

Fig. 2.

Pregnancy-specific distress across pregnancy by parity. Pregnancy-specific distress was elevated among primiparous compared to multiparous women across pregnancy ($F_{1,129} = 20.9$, $p < 0.01$).

Fig. 3.

Mediation model assessing the association between parity and prenatal cortisol area under the curve through pregnancy-specific distress. A significant total effect of primiparity on prenatal cortisol AUC was observed (c). This effect was partially accounted for by pregnancy-specific distress at early pregnancy (ab), with a direct effect of primiparity on prenatal cortisol area under the curve also present (c'). Analyses adjusted for maternal age, race, prepregnancy body mass index, early pregnancy sleep quality, early pregnancy depressive symptoms, and early and mid-pregnancy sampling time of day. AUC = area under the curve.

Table 1Demographic and behavioral characteristics (Count (%) or Mean $\pm$ SD).

	Full Sample (N = 137)	Primiparous (n = 33)	Multiparous (n = 104)	p value
Maternal age	24.6 $\pm$ 4.1	23.4 $\pm$ 3.9	25.0 $\pm$ 4.1	0.05
Race				0.01
Black	76 (55.5%)	12 (36.4%)	64 (61.5%)	
White	61 (44.5%)	21 (63.6%)	40 (38.5%)	
Marital status				0.30
Married	40 (29.2%)	13 (39.4%)	27 (26.0%)	
In a relationship	72 (52.6%)	14 (42.4%)	58 (55.8%)	
Single	25 (18.2%)	6 (18.2%)	19 (18.3%)	
Annual household income				0.29
< \$15,000	64 (46.7%)	12 (36.4%)	52 (50.0%)	
\$15,000 – 29,999	35 (25.5%)	8 (24.2%)	27 (26.0%)	
\$30,000 - \$49,999	19 (13.9%)	6 (18.2%)	13 (12.5%)	
\$50,000 - \$74,999	8 (5.8%)	2 (6.2%)	6 (5.8%)	
\$75,000 - \$99,999	7 (5.1%)	4 (12.1%)	3 (2.9%)	
\$100,000	4 (2.9%)	1 (3.0%)	3 (2.9%)	
Smoking status				0.14
Smoker	19 (13.9%)	2 (6.1%)	17 (16.3%)	
Non-smoker	118 (86.1%)	31 (93.9%)	87 (83.7%)	
Pre-pregnancy BMI	27.9 $\pm$ 7.0	25.6 $\pm$ 5.2	28.6 $\pm$ 7.4	0.03
Sleep quality (PSQI score)				
Early pregnancy	6.8 $\pm$ 3.8	5.6 $\pm$ 2.9	6.8 $\pm$ 4.2	0.05
Postpartum	7.5 $\pm$ 3.4	7.5 $\pm$ 3.0	7.5 $\pm$ 3.6	0.99

Note. Comparisons by parity made using Student's independent *t*-test, χ^2 test, or Fisher's exact test as appropriate. BMI = Body Mass Index; PSQI = Pittsburgh Sleep Quality Index.

Table 2Clinical characteristics for current pregnancy (Count (%) or Mean $\pm$ SD).

	Full Sample (N = 137)	Primiparous (n = 33)	Multiparous (n = 104)	p value
Gestational diabetes mellitus (yes)	6 (4.4%)	1 (3.0%)	5 (4.8%)	0.66
Gestational hypertensive disorder (yes)	8 (5.8%)	0 (0.0%)	8 (7.7%)	0.10
Preterm birth (yes)	12 (8.8%)	4 (12.1%)	8 (7.7%)	0.43
Gestational age at birth (days)	272.0 $\pm$ 15.5	270.7 $\pm$ 23.8	272.5 $\pm$ 11.8	0.58
Birth weight (grams)	3251.8 $\pm$ 609.5	3158.0 $\pm$ 777.0	3281.5 $\pm$ 547.1	0.31

Note. Comparisons by parity made using Student's independent *t*-test or χ^2 test as appropriate.

Table 3

Primary variable descriptive statistics and Pearson correlations.

	Mean ± SD	1a	1b	1c	1d	2a	2b	2c	3
Primiparous (n = 33)									
1. Maternal cortisol level (meg/dL)									
1a. Early pregnancy	17.2 ± 6.2	1.0							
1b. Mid-pregnancy	27.2 ± 9.8	0.40*	1.0						
1c. Late pregnancy	32.5 ± 8.3	0.31	0.56*	1.0					
1d. Postpartum	12.6 ± 6.5	-0.03	0.12	0.42*	1.0				
2. Pregnancy-specific distress (NUPDQ score)									
2a. Early pregnancy	9.9 ± 4.1	0.12	0.07	0.02	0.11	1.0			
2b. Mid-pregnancy	8.4 ± 3.4	-0.04	-0.04	-0.17	-0.20	0.49*	1.0		
2c. Late pregnancy	8.8 ± 3.3	0.11	0.14	0.06	-0.01	0.61*	0.69*	1.0	
3. Postpartum depressive symptoms (CES-D score)	10.2 ± 7.6	-0.12	-0.01	0.18	0.34*	0.49*	0.05	0.11	1.0
Multiparous (n = 104)									
1. Maternal cortisol level (meg/dL)									
1a. Early pregnancy	14.2 ± 5.1	1.0							
1b. Mid-pregnancy	21.7 ± 7.7	0.33*	1.0						
1c. Late pregnancy	25.8 ± 8.2	0.29*	0.52*	1.0					
1d. Postpartum	9.7 ± 4.7	0.22*	0.13	0.28*	1.0				
2. Pregnancy-specific distress (NUPDQ score)									
2a. Early pregnancy	7.5 ± 5.7	0.10	0.20*	0.19*	-0.01	1.0			
2b. Mid-pregnancy	6.9 ± 5.4	0.01	0.11	0.09	0.06	0.71*	1.0		
2c. Late pregnancy	6.6 ± 4.9	0.02	0.12	0.09	-0.04	0.65*	0.68*	1.0	
3. Postpartum depressive symptoms (CES-D score)	12.4 ± 10.2	-0.06	-0.01	-0.05	-0.09	0.28*	0.47*	0.33*	1.0

Notes. Pearson correlation coefficients presented; NUPDQ = Revised Prenatal Distress Questionnaire; CES-D = Center for Epidemiologic Studies Depression Scale;

*
p < 0.05.