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Regular Article

Increases in maternal depressive symptoms during pregnancy and infant cortisol reactivity: Mediation by placental corticotropin-releasing hormone

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Abstract

Background: Maternal depressive symptoms in pregnancy may affect offspring health through prenatal programming of the hypothalamic–pituitary–adrenal (HPA) axis. The biological mechanisms that explain the associations between maternal prenatal depressive symptoms and offspring HPA axis regulation are not yet clear. This pre-registered investigation examines whether patterns of maternal depressive symptoms in pregnancy are associated with infant cortisol reactivity and whether this association is mediated by changes in placental corticotropin-releasing hormone (pCRH).
Method: A sample of 174 pregnant women completed assessments in early, mid, and late pregnancy that included standardized measures of depressive symptoms and blood samples for pCRH. Infant cortisol reactivity was assessed at 1 and 6 months of age.
Results: Greater increases in maternal depressive symptoms in pregnancy were associated with higher cortisol infant cortisol reactivity at 1 and 6 months. Greater increases in maternal depressive symptoms in pregnancy were associated with greater increases in pCRH from early to late pregnancy which in turn were associated with higher infant cortisol reactivity.
Conclusions: Increases in maternal depressive symptoms and pCRH over pregnancy may contribute to higher infant cortisol reactivity. These findings help to elucidate the prenatal biopsychosocial processes contributing to offspring HPA axis regulation early in development.

Keywords: depressive symptoms; HPA axis; infancy; placental corticotropin-releasing hormone; pregnancy

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The fetal origins model proposes that early exposures to adverse environments influence lifelong mental and physical health (Barker et al., 1993; Barker, 2007; Gluckman et al., 2010). Maternal depression is one of the most common pregnancy complications, with established risks for maternal and offspring health (Davis et al., 2018; Gavin et al., 2005; Rogers et al., 2020; Sloiman et al., 2019; Tirumalaraju et al., 2020). Exposure to maternal depressive symptoms in the prenatal period may influence offspring health through programming of the fetal hypothalamic–pituitary–adrenal (HPA) axis (Davis et al., 2011; Glover et al., 2010; Molenaar et al., 2019; Sandman, Davis, Buss, et al., 2012). For example, maternal depressive symptoms in pregnancy are associated with HPA axis dysregulation in neonates, infants, and young children (for a review, see Howland et al., 2017), which can influence susceptibility to psychopathology and stress-related diseases across the life span (Gunnar & Quevedo, 2007; Heim et al., 2000; Luby et al., 2003; McEwen, 2009; Smider et al., 2002; Snoek et al., 2004). Placental corticotropin-releasing hormone (pCRH), a stress hormone of fetal-placental origin, is a direct indicator of fetal response to maternal distress and may program the development of the fetal HPA axis (Sandman, 2018; Howland et al., 2017). Existing studies, however, have not tested pCRH as a biological mechanism explaining the association between maternal depressive symptoms and offspring HPA axis regulation.

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Maternal depressive symptoms in pregnancy and the offspring HPA axis

Individual differences in cortisol responses to acute stressors (i.e., cortisol reactivity) are observable within 24 hr of birth (Davis et al., 2011) and undergo developmental shifts until stabilizing around 6 months of age (Gunnar et al., 1996; Jansen et al., 2010; Lewis & Ramsay, 1995). The origins of offspring cortisol reactivity begin before birth as the rate of HPA axis growth in the prenatal period is unmatched by any other stage of development (Howland et al., 2017). Development of the fetal HPA axis occurs in an ordered sequence, with differentiation of the hypothalamus occurring as early as 10 weeks gestation and development of the adrenal cortex continuing through 30 weeks gestation (Howland et al., 2017).

Fetal development is guided by and responsive to maternal inputs over the course of gestation to promote survival in the postnatal environment (Bateson et al., 2014; Gluckman et al., 2005; Sandman, Davis, & Glynn, 2012). Because of the rapid and ordered HPA axis development in the prenatal period, the influence of maternal depressive symptoms on fetal HPA axis development may differ depending on timing and course of depressive symptoms (Laurent et al., 2011). Maternal depressive symptoms in pregnancy have been associated with dysregulation of the cortisol response to stressors in infants (Bleker et al., 2020; Osborne et al., 2018; Stroud et al., 2016). However, evidence of when in pregnancy depressive symptoms most strongly predict infant cortisol reactivity is equivocal (Osborne et al., 2018; Stroud et al., 2016; de Bruijn et al., 2009). This may be because single time point assessments or averages of depressive symptoms do not capture patterns of symptoms across pregnancy. Women differ not only in their levels of depressive symptoms at any given time point, but also in the degree and direction of change in symptoms over pregnancy (Baron et al., 2017; Santos et al., 2017).

Patterns of maternal psychological distress over pregnancy influence birth outcomes and offspring development. For example, increases in maternal stress and anxiety from the second to third trimester are associated with greater risk of preterm birth and increases in maternal anxiety symptoms from the first to third trimester are associated with lower language and motor development scores in infants (Doktorchik et al., 2018; Glynn et al., 2008; Irwin et al., 2020). Additionally, unpredictable changes in maternal mood over pregnancy, defined as lower entropy in maternal self-reported distress across five gestational assessments, are associated with greater negative emotionality in infancy and childhood as well as internalizing symptoms in childhood and adolescence (Glynn, Howland, Sandman et al., 2018). Notably, associations between patterns of maternal psychological distress and offspring developmental outcomes are independent of maternal mood levels during pregnancy, suggesting that patterns of maternal psychological distress exert unique influences on offspring development over and above the intensity of exposure to maternal psychological distress.

Although these studies provide evidence that patterns of maternal psychological distress over pregnancy influence offspring development, few studies have evaluated whether patterns of psychological distress relate to offspring HPA axis regulation. One key exception reported that infants of women whose depressive symptoms significantly changed from pregnancy to postpartum showed more extreme cortisol responses to a separation task at 18 months of age in a sample of 86 mother–infant dyads compared to infants of women whose depressive symptoms stayed consistently low or high (Laurent et al., 2011). Such evidence aligns with fetal programming theories proposing that less favorable offspring development occurs when changes in symptoms over time result in a mismatch between early fetal developmental adaptations and the later environment (Bateson et al., 2014; Gluckman et al., 2010). Cross-species evidence also has demonstrated that changes in maternal inputs are associated with increased excitatory synapse transmission to stress-sensitive hypothalamic neurons as well as a loss of hippocampal neurons and synapses which may contribute to HPA axis regulation (Baram et al., 2012; Gunn et al., 2013; Singh-Taylor et al., 2017). More research is necessary to elucidate how changes in maternal depressive symptoms over pregnancy specifically, a sensitive period for fetal HPA axis development, relate to infant cortisol reactivity.

Biological mechanisms of prenatal programming of the fetal HPA axis: pCRH

Maternal depressive symptoms are hypothesized to influence offspring development through alterations to the intrauterine milieu and variations in fetal exposure to stress hormones (Kim et al., 2015; Shallie & Naicker, 2019). In particular, pCRH may be a key biological mechanism of prenatal programming of the fetal HPA axis. During pregnancy, the placenta expresses a gene for, synthesizes, and releases pCRH into maternal bloodstream and becomes a primary regulator of maternal and fetal stress hormone production (Kassotaki et al., 2021; McLean et al., 1995; Sandman, 2018). Compared to other maternal stress hormones that act indirectly on fetal development via the placenta, pCRH is of placental-fetal origin and therefore has a more direct influence on the intrauterine milieu, fetal exposure, and the development of the fetal HPA axis (Avishai-Eliner et al., 2002; Charil et al., 2010; Howland et al., 2017; Kassotaki et al., 2021; Lockwood et al., 1996; Sirianni et al., 2005). For example, pCRH can cross the blood–brain barrier to influence fetal neurodevelopment and the release of pCRH also stimulates fetal cortisol production thereby increasing glucocorticoid levels in the fetal compartment (Howland et al., 2016, 2017). Indeed, elevated levels of pCRH across gestation are associated with a range of less favorable offspring developmental outcomes extending through adolescence (Davis et al., 2005; Ellman et al., 2008; Howland et al., 2016; Sandman et al., 1999; Sandman, 2015).

Few studies, however, have examined associations between changes in pCRH over pregnancy and offspring developmental outcomes though levels of pCRH increase 20- to 40-fold across gestation, reaching peak levels at labor and delivery (McLean et al., 1995). In contrast to the negative feedback loop of HPA axis regulation in a non-pregnant state, detection of cortisol by CRH receptors on the placenta stimulates the release of pCRH, leading to exponential increases in cortisol and pCRH over pregnancy (McLean et al., 1995; Sandman, 2018). Whereas increases in pCRH across gestation are necessary to support fetal development and stimulate labor, greater or earlier increases in pCRH may adversely alter fetal and offspring development (Sandman, 2015, 2018; Smith & Nicholson, 2007). Higher levels of pCRH and greater accelerations in pCRH over pregnancy are associated with fetal growth trajectories and shortened length of gestation, respectively (Ramos et al., 2022; Sandman, 2015; Smith & Nicholson, 2007). Greater increases in pCRH may also influence the development of the fetal HPA axis, but this has yet to be tested. For example, greater increases in pCRH over pregnancy may program the sensitivity of the HPA axis and alter development of brain regions responsible for HPA axis regulation (Avishai-Eliner et al., 2002; Charil et al., 2010; Lockwood et al., 1996).

Maternal depressive symptoms and pCRH during pregnancy

Because the placental-fetal unit detects and responds to maternal stress signals with the synthesis and release of pCRH, higher levels of pCRH may be an indicator of fetal response to maternal stress (Sandman et al., 2018). Accordingly, maternal depressive symptoms may influence both levels of and changes in pCRH over pregnancy. Some studies report that greater maternal depressive symptoms are associated with higher levels of pCRH in mid-pregnancy (Rich-Edwards et al., 2008) whereas other studies have reported inverse associations between pCRH levels and depressive symptoms

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in pregnancy (Meltzer-Brody et al., 2011; Susman et al., 1999). Studies have yet to test whether patterns of depressive symptoms over the course of pregnancy relate to changes in pCRH. Nonetheless, modeling changes in psychological states and physiology over the course of pregnancy may be most appropriate to capture the substantial psychosocial and physiological changes that occur in pregnancy (Glynn, Howland, & Fox, 2018). In particular, prior evidence indicates that changes in depressive symptoms are associated with HPA axis regulation over the course of pregnancy in different ways than are absolute levels of symptoms at specific time points (Seth et al., 2016). For example, women whose depressive symptoms increase over pregnancy also show increases in cortisol (Giesbrecht et al., 2012; Laurent et al., 2018) whereas women with stable, high levels of depressive symptoms throughout pregnancy show lower levels of cortisol (Seth et al., 2016). This perinatal evidence is consistent with research linking transient mood changes to hypercortisolemia, thereby supporting the utility of examining changes in depressive symptoms and HPA axis function in pregnancy (Penninx et al., 2013). Other studies have also found that maternal prenatal distress is associated with distinct trajectories of cortisol across pregnancy (Peterson et al., 2020) and increases in pregnancy anxiety from mid to late pregnancy correspond to increases in pCRH over the same period (Ramos et al., 2019). Taken together, such evidence demonstrates that patterns of psychological distress during pregnancy show unique associations with changes in physiology over pregnancy. Further research is necessary to elucidate how patterns of depressive symptoms relate to changes in pCRH over the course of pregnancy.

The current study

The primary aim of the current study was to test whether patterns of maternal depressive symptoms from early to late pregnancy were associated with infant cortisol reactivity at 1 month, and if this association was mediated by changes in pCRH from early to late pregnancy. Primary analyses and hypotheses are available on the Open Science Framework, at https://osf.io/wq2hs/?view_only=6166b65adcab4d5eb99105b55ef5488b. We hypothesized that greater increases in depressive symptoms over pregnancy will be associated with greater infant cortisol reactivity at 1 month and that this association will be mediated by greater increases in pCRH from early to late pregnancy. Because there is evidence of developmental shifts in cortisol reactivity in the first 6 months of infancy (Gunnar et al., 1996; Jansen et al., 2010; Lewis & Ramsay, 1995), a parallel exploratory aim evaluated whether results were consistent when examining infant cortisol reactivity to the Still Face procedure at 6 months of age as an additional outcome.

A second exploratory aim evaluated whether there were sex differences in the association between patterns of maternal depressive symptoms and infant cortisol reactivity based on evidence of differential effects of prenatal stress on offspring development by offspring sex (Hicks et al., 2019; Kortesluoma et al., 2021; Sandman et al., 2013).

Method

Participants and procedure

A sample of 233 pregnant women were enrolled in Healthy Babies Before Birth (HB3), a longitudinal study designed to test the impact of antenatal maternal mood on birth outcomes and infant development. Participants were 18 years of age or older, with singleton intrauterine pregnancies, who gave birth to liveborn infants, and were receiving prenatal care at prenatal clinics and private practices in Denver, Colorado, and Los Angeles, California. Participants were recruited into the study before completion of their 12th week of gestation. Denver participants were included if they spoke English or Spanish as their primary language, while only English-speaking participants were included in Los Angeles. Exclusion criteria were current substance abuse diagnosis, HIV-positive status, current smoking, and multiple gestation. Participants were identified at prenatal appointments, and if eligible, invited to participate in the study. Written informed consent was obtained from all participants who expressed interest. Participants were given parking validation and $25 in cash or a gift card as compensation for each study visit.

The study was comprised of three prenatal and three postnatal visits conducted with trained research staff. Participants were evaluated in early pregnancy (8–16 weeks gestation), mid-pregnancy (20–26 weeks gestation), late pregnancy (30–36 weeks gestation), 4–8 weeks postpartum, 5–7 months postpartum, and 11–13 months postpartum. Each prenatal visit included psychosocial assessments, collection of biological samples, and collection of medical records. Postnatal visits included maternal psychosocial assessments, collection of biological samples from mothers and infants, and standardized developmental assessments. Women reported on educational attainment, income, and number of previous live births at enrollment and reported on infant age and breastfeeding status at the postnatal visits. Each institution's Institutional Review Board approved all protocols and procedures.

Of the 233 women enrolled in HB3, the current sample includes participants who completed prenatal assessments and the first postnatal visit ($n = 174$). A complete sample description appears in Table 1. Mean maternal age at study entry was 31.27 years ($SD = 6.19$). Mean per capita annual household income adjusted for cost of living was $31,514 ($SD = $29,688) and more than half of the sample completed college or earned a higher degree (63.8%). More than half the sample was pregnant with their first child (58.0%) and of those with a previous live birth the total number of previous births ranged from 1 (27.0%) to 4 (1.1%). Most participants were either married (71.4%) or in a relationship with the infant's father at enrollment (25.1%). Regarding racial and ethnic composition of the sample, most participants identified as White (79.2%), and slightly more than one third identified as Hispanic/Latina (35.1%). About half of the infants were female (48.8%). Infants were 1.26 months ($SD = 1.13$ months) at the first postnatal visit and 5.62 months ($SD = 1.01$ months) at the second postnatal visit.

Participants in the current sample ($n = 174$) were significantly more likely to be married, older, completed more years of education, and reported higher per capita income compared to the full sample ($n = 233$). There were no other sociodemographic differences between the current sample and full sample.

Measures

Sociodemographic and medical variables

Maternal socioeconomic status was calculated as a standardized composite of years of education and per capita income adjusted for cost of living.[1] Gestational length, birthweight, and Apgar score at 5 min (Casey et al., 2001) were abstracted from medical records.

[1]Per capita income was divided by 1.22 for participants living in Denver or by 1.42 for participants living in Los Angeles to account for cost of living at 22% and 42% higher relative to the national average at each site, respectively.

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Table 1. Sample description (n = 174)

	M (*SD*) or %
Age at enrollment (years)	31.27 (6.19)
Per capita income ($)	41,514 (29,688)
Education level	
Less than high school	4.6
Completed high school	13.2
Some college	17.8
College or higher degree	63.8
Relationship status	
Married to baby's father	71.4
In a relationship with baby's father	25.1
Single	3.5
Ethnicity	
Not Hispanic/Latina	64.9
Hispanic/Latina	35.1
Race	
White	79.2
Black or African American	6.9
Asian	8.7
Multiracial	5.2
Study site	
Denver, Colorado	59.8
Los Angeles, California	40.2

Note. Per capita income adjusted for cost of living at each study site based on Cost of Living Index.

Breastfeeding status

Women reported on breastfeeding status and updates to breastfeeding status at each postnatal visit.

Depressive symptoms

The Patient Health Questionnaire (PHQ-9) was used to assess depressive symptoms at each study visit. The PHQ-9 is a multipurpose instrument for screening, diagnosing, monitoring, and measuring the severity of depression symptoms (Kroenke et al., 2001). Participants report on the frequency of common depressive symptoms over the last 2 weeks on a scale of 0 (*not at all*) to 3 (*nearly every day*). Total scores range from 0 to 27. The diagnostic validity of the PHQ-9 has been established in studies involving several obstetrical clinics (Kroenke et al., 2001; Manea et al., 2012) and is validated for use in pregnancy (Zhong et al., 2014, 2015). The PHQ-9 demonstrated acceptable reliability at each assessment in the current sample ($\alpha = 0.67–0.83$).

Measures of depressive symptoms over the course of pregnancy were operationalized with *area under the curve* measures (Pruessner et al., 2003) selected as appropriate to model patterns of symptoms over time, as in previous studies (Phillips et al., 2013; Somers et al., 2019). Levels of depressive symptoms fluctuate throughout pregnancy and for this reason, patterns of maternal depressive symptoms were measured with *area under the curve with respect to increase* which is calculated based on changes in symptoms over time from baseline. The sign and magnitude of *area under the curve with respect to increase* represents the direction and degree of change in depressive symptoms across the three prenatal study visits. To isolate the unique effects of patterns of maternal depressive symptoms from those of cumulative exposure to depressive symptoms in pregnancy, *area under the curve with respect to ground* was also calculated and included as a covariate in statistical models. *Area under the curve with respect to ground* reflects the overall magnitude of depressive symptoms based on the levels of depressive symptoms across multiple time points in pregnancy.

Previous research demonstrates *area under the curve with respect to increase* and *area under the curve with respect to ground* measures represent distinct information about repeated measurements (fluctuations in symptoms vs. overall magnitude of symptoms) and have differential associations with outcomes, thus it is recommended to include both measures when analyzing data with repeated measures (Pruessner et al., 2003). Area under the curve measures were modestly associated in the current sample ($r = .24$).

Placental corticotropin-releasing hormone

Blood samples were obtained from women at all three prenatal assessments by nursing research staff through antecubital venipuncture. At each time point, a blood sample was collected in an aprotinin-coated vacutainer tube (BD Biosciences, San Diego, California). Immediately following collection, samples were centrifuged at 1,300–1,800 x g for 10–15 min at 4°C and 1 mL of serum was harvested and stored at −80 °C. Pregnancy serum samples from both sites were transported to a laboratory at the University of Colorado, Colorado Springs, for storage. Serum samples were shipped to Dr Roger Smith's Endocrine Lab at the University of Newcastle, Australia. Samples were extracted with methanol and pCRH was measured by using a radioimmunoassay. Extraction recovery was 82.5%. No correction of the data for extraction recoveries was made. The limit of sensitivity was 3 pg/mL. The intra- and inter-assay coefficients of variance (CVs) were 10.2% and 8.2%, respectively. Distributions of maternal blood levels of pCRH in early, mid, and late pregnancy were natural log-transformed to meet normality assumptions (skewness <3; kurtosis <7) prior to analysis as is consistent with previous studies (Ramos et al., 2019, 2022).

Infant salivary cortisol

Infant salivary cortisol was collected in standardized lab assessments administered by trained research staff. The heel stick blood draw was administered as a research procedure in the clinical settings by nurses to elicit a HPA response to mild physical pain at 1 month and the Still Face paradigm was used to assess infant cortisol reactivity to social stress at 6 months. These assessments were selected as developmentally appropriate in these age ranges and are widely used to assess cortisol reactivity at these ages (for a review, see Gunnar et al., 2009). These procedures were approved by the Human Subjects Review boards at all institutions.[2] At 1 month, infant saliva samples were collected upon arrival to the lab and again 20 min following a heel stick blood draw to assess peak cortisol response. At 6 months, infant saliva samples were collected upon arrival to the lab prior to the Still Face paradigm and again 30 min after the start of the Still Face paradigm to assess peak cortisol response.

[2]The heel stick procedure was also used to collect infant blood samples as a part of the broader study protocol.

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Following collection, saliva samples were frozen. Frozen samples were centrifuged for 15 min at 3,000 rpm to extract sample and aliquoted into cryogenic storage vials (300–500 ml aliquots) and frozen at −80 °C until analysis. Cortisol concentrations were determined using a commercial high sensitivity EIA kit (Salimetrics) according to the directions provided by the manufacturer. Samples were run in duplicate, and optical density at 450 nm was assessed using an automatic microplate reader (BioTek). The amount of cortisol in each sample was determined using the standard curve generated with each assay. Samples were run in large cohorts utilizing the same manufacturer's lot to reduce assay drift and inter-assay variability. The mean of the duplicates were used as the unit of analysis for statistical evaluation of these data. The intra-assay CVs ranged from 7.13% to 10.72%.

Cortisol reaches peak levels between 20 and 30 min following the onset of a stressor (Davis et al., 2004; Gunnar & White, 2001). Delta (or difference) scores were used to capture infant cortisol reactivity by subtracting baseline cortisol levels from peak cortisol levels (20 min after heel stick at 1 month; 30 min after start of the Still Face paradigm at 6 months), as is standard practice in the literature to model changes in cortisol levels from baseline to peak based on two time points (Irwin et al., 2021; Noroña-Zhou et al., 2020). Cortisol data for two infants at 1 month and two infants at 6 months were extreme outliers (>5 standard deviations above the mean) and analyses were run without these cases based on prior literature (e.g., Irwin et al., 2021). Results remained the same when outliers were excluded compared to winsorized to 3 standard deviations from the mean. We present results with extreme outliers excluded.

Statistical analysis

Primary analyses

A structural equation model was conducted to model changes in pCRH and evaluate the effect of patterns of maternal depressive symptoms on infant cortisol reactivity via changes in pCRH. Given the exponential increases in pCRH over the course of pregnancy (McLean et al., 1995), latent basis growth modeling was used to capture nonlinear changes in pCRH in the structural equation model (Grimm et al., 2013). Slope loadings in latent basis growth modeling are freely estimated to model nonlinear change. The intercept estimate of the latent basis growth curve represents the average levels of pCRH in early pregnancy and the slope estimate represents the amount of change in pCRH from early to late pregnancy.

Hypothesis testing. A conceptual overview of analyses is presented in Figure 1. We modeled four sets of effects: (1) the direct effect of patterns of depressive symptoms from early to late pregnancy on infant cortisol reactivity at 1 month and 6 months; (2) the effect of patterns of depressive symptoms on changes in pCRH over the same period; and (3) the effect of changes in pCRH on infant cortisol reactivity. Finally, we evaluated the indirect effect of patterns of depressive symptoms on infant cortisol reactivity via changes in pCRH with RMediation, which produces 95% confidence intervals of the indirect effect based on the distribution of the product and an asymptomatic normal distribution (Tofighi & MacKinnon, 2011). Evidence of mediation exists if the confidence interval for the indirect effect does not contain zero.

Analyses were conducted with M*Plus* v.8.4 (Muthén & Muthén, 1998–2017) using all available values and full information maximum likelihood (FIML) to handle missing data. Thus, our analytic sample included 174 participants. FIML uses information available from other variables and iterative optimization algorithms to estimate model parameters (Enders, 2010). FIML estimates are unbiased, more efficient than other methods of adjusting for missing data (e.g., listwise deletion; complete case analysis), and recommended when missing data exceeds 10% (Enders, 2001; Little et al., 2014). The use of modern missing data handling techniques such as FIML increases precision and reduces bias in estimates compared to complete case analysis regardless of the percentage of missing data (Dong & Peng, 2013; Madley-Dowd et al., 2019). Rates of missing data in the current sample ranged from 0% (early pregnancy pCRH) to 63% (infant cortisol reactivity at 6 months). Further information on missing data is presented in the Supplementary Materials.

Exploratory analyses

To test whether associations between patterns of maternal depressive symptoms in pregnancy and infant cortisol reactivity were the same across the first 6 months of life, we added infant cortisol reactivity to the Still Face at 6 months to the structural equation model as an additional outcome (Figure 1). For the exploratory analysis examining differences by offspring sex, we added an interaction term between patterns of depressive symptoms and infant sex to the model.

Covariates

Primary and exploratory analyses adjusted for covariates based on potential confounding effects based on prior research. Consistent with an inclusive missing data approach, we also evaluated factors that could contribute to missingness for inclusion in primary models (Collins et al., 2001). Magnitude of maternal depressive symptoms in pregnancy (*area under the curve with respect to the ground* [AUCg]) and maternal depressive symptoms 1 month postpartum were included as covariates to evaluate unique associations of patterns of maternal depressive symptoms in pregnancy on pCRH changes and infant cortisol reactivity. Baseline infant cortisol levels were included as covariates to adjust for confounding effects of baseline cortisol on infant cortisol reactivity to the stressor paradigms. Gestational length was included as a covariate given associations with pCRH (e.g., Ramos et al., 2019, 2022) and infant outcomes in prior research (e.g., Anderson & Cacola, 2017; Arpi & Ferrari, 2013). Study site, parity (primiparity; no previous live births vs. one or more previous live births), birthweight, Apgar score at 5 min, infant sex, infant age, maternal socioeconomic status, time of day of the postnatal visits, and breastfeeding status were all evaluated as covariates and included in primary models if (1) associated with primary study variables or (2) associated with primary study variables and missingness on primary study variables, as is recommended to adhere to missing at random assumptions of FIML (Collins et al., 2001) ($\alpha = 0.05$).

Results

Preliminary analysis results

Descriptive results

Descriptive statistics and Pearson's correlation coefficients of maternal depressive symptoms, pCRH, and infant baseline cortisol and cortisol reactivity appear in Table 2.

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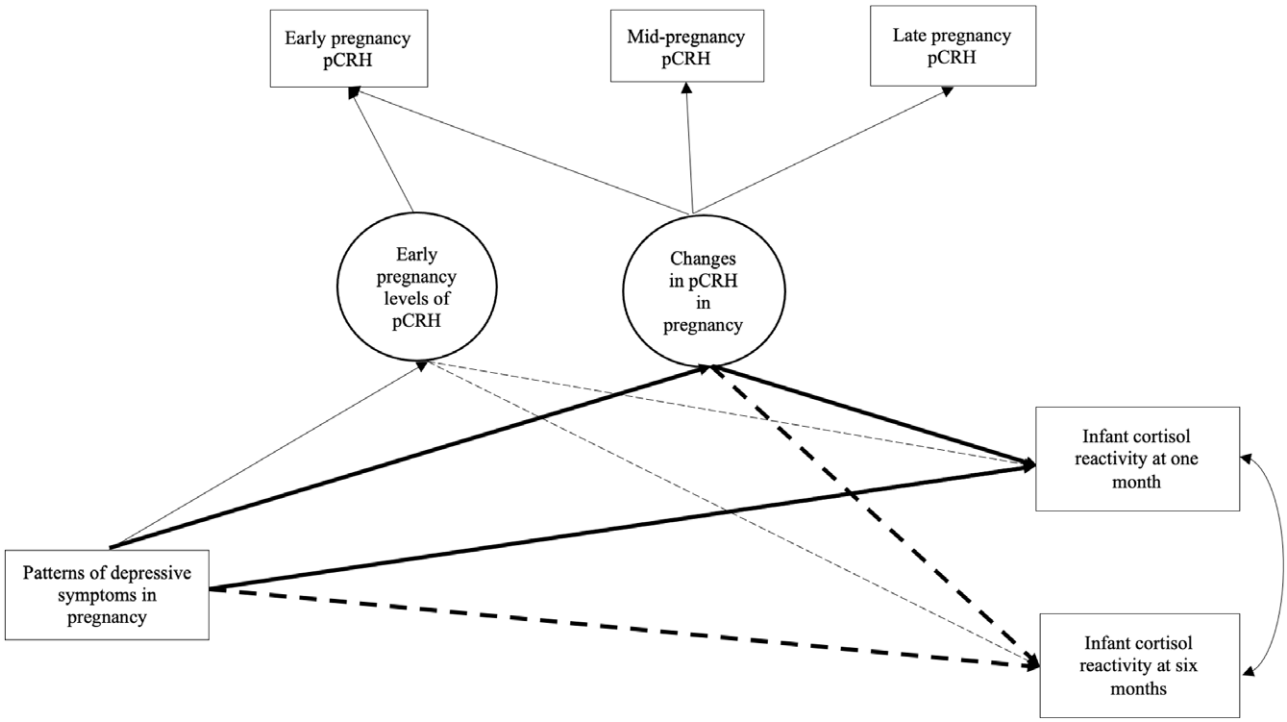

Figure 1. Structural equation model of patterns of depressive symptoms predicting infant cortisol reactivity through changes in pCRH. Note. Primary paths of interest in the current study are bolded. Paths of exploratory analysis examining infant cortisol reactivity to the Still Face paradigm at 6 months as additional outcome indicated by dashed lines. For visual clarity, covariates are not presented. pCRH = Placental corticotropin-releasing hormone.

Table 2. Descriptive statistics and bivariate associations of primary study variables

	M (*SD*)	Range	1	2	3	4	5	6	7	8	9	10	11
1. Early pregnancy depressive symptoms	4.78 (3.35)	0–17	1										
2. Mid-pregnancy depressive symptoms	3.93 (2.97)	0–14	0.36***[a]	1									
3. Late pregnancy depressive symptoms	4.38 (3.03)	0–14	0.39***[a]	0.56***[a]	1								
4. Cumulative depressive symptoms over pregnancy (AUCg)	78.71 (51.08)	5–260	0.68***[a]	0.86***[a]	0.78***[a]	1							
5. Patterns of depressive symptoms over pregnancy (AUCi)	−1.25 (44.29)	−147 to 100	−0.49***[a]	0.40***[a]	0.30**[a]	0.24*[a]	1						
6. Early pregnancy pCRH	2.81 (0.60)	1.09–3.97	0.01	0.00	−0.13	−0.13	−0.08	1					
7. Mid-pregnancy pCRH	4.05 (0.60)	2.35–5.41	−0.07	−0.01	−0.11	−0.17	−0.13	0.62***[a]	1				
8. Late pregnancy pCRH	6.16 (0.67)	0.003–1.80	−0.06	0.13	−0.11	0.14	0.16	0.35***[a]	0.53***[a]	1			
9. Infant baseline cortisol: 1 month	0.24 (0.27)	0.04–3.60	−0.05	0.25[a]	−0.10	0.10	0.15	−0.31*[a]	0.06	0.21[a]	1		
10. Infant cortisol reactivity: 1 month	0.13 (0.26)	−0.27 to 0.70	−0.41*[a]	−0.19	−0.23[a]	−0.33^[a]	0.21[a]	−0.17	0.04	−0.01	0.00	1	
11. Infant baseline cortisol: 6 months	0.11 (0.07)	0.03–0.29	−0.10	−0.18	−0.06	−0.19	0.02	0.05	−0.09	−0.09	−0.07	0.00	1
12. Infant cortisol reactivity: 6 months	0.04 (0.13)	−0.19 to 0.75	0.02	0.36**[a]	0.20[a]	0.21[a]	0.26^[a]	0.02	0.02	0.23*[a]	−0.02	−0.24[a]	−0.10

Note. pCRH natural log-transformed. Descriptive statistics and bivariate associations did not use full information maximum likelihood to handle missing data. The sample sizes are presented in the Supplemental Materials. Infant cortisol measurement units = μg/dl.

[a]Effect meets or exceeds Cohen's threshold for "small" effect size (absolute value of 0.20) (Cohen, 1988).

***$p < .001$; **$p < .01$; *$p < .05$; ^$p < .10$.

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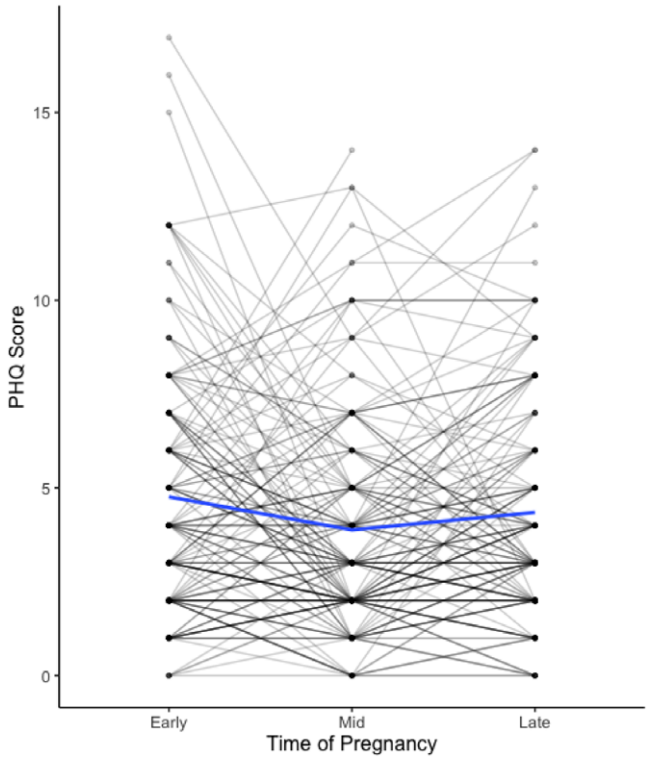

Figure 2. Fluctuations in levels of maternal depressive symptoms from early pregnancy to late pregnancy across individuals. Mean levels of depressive symptoms at each prenatal visit in the current sample are displayed in blue.

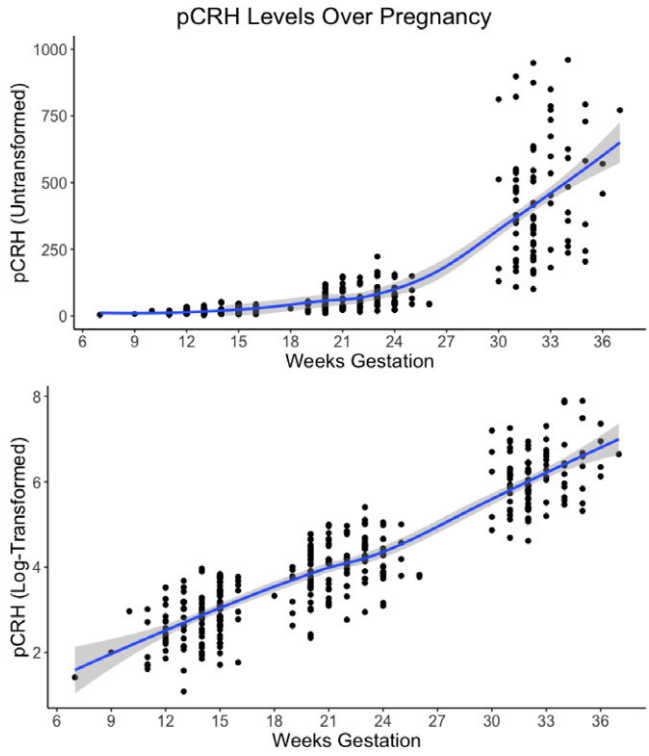

Figure 3. Placental CRH from early to late pregnancy. Blue line represents locally estimated scatterplot smoothing (LOESS) line and shaded region represents 95% confidence interval.

Depressive symptoms. On average, the sample reported low to moderate levels of depressive symptoms at each prenatal time point with considerable variability in the sample. Depressive symptoms fluctuated across individuals over the course of pregnancy and the direction and degree of change varied (see Figure 2). Over half of the sample reported symptoms that increased from early to late pregnancy (55%) and the rest reported symptoms that decreased (45%). Of those that reported symptoms that increased, 6.6% of the sample reported statistically significant increases whereas 14.0% of the sample reported symptoms that significantly decreased (more than 1.65 standard deviations above or below the sample mean, respectively). Changes in depressive symptoms (area under the curve with respect to increase [AUCi]) were positively associated with infant cortisol reactivity at 1 month and 6 months such that greater increases in depressive symptoms from early to late pregnancy were associated with higher infant cortisol reactivity.

Placental CRH levels. Levels of pCRH at each assessment were modestly to moderately intercorrelated (r's = .35–.62). Mean levels of pCRH (transformed and untransformed) increased over the course of pregnancy, as would be expected (see Figure 3). Mean levels of pCRH were lowest in early pregnancy ($M_{transformed}$ = 2.81, SD = 0.68; $M_{untransformed}$ = 19.56, SD = 12.29) and increased in mid-pregnancy ($M_{transformed}$ = 4.05, SD = 0.69; $M_{untransformed}$ = 68.12, SD = 42.57) and late pregnancy ($M_{transformed}$ = 6.16, SD = 0.77; $M_{untransformed}$ = 597.80, SD = 452.00). Late pregnancy pCRH was significantly positively associated with infant cortisol reactivity at 6 months.

Infant cortisol reactivity. Mean levels of infant cortisol at 1 month significantly increased from baseline (M = 0.24, SD = 0.27) to 20 min after the heel stick (M = 0.31, SD = 0.27), $t(144) = 3.52$, $p = .001$, $M_{difference}$ = 0.13 [0.07, 0.21]. Mean cortisol levels at 6 months increased from baseline (M = 0.11, SD = 0.07) to 30 min after the Still Face paradigm (M = 0.14, SD = 0.12), $t(99) = 1.70$, $p = .095$, $M_{difference}$ = 0.04 [−0.01, 0.08]; however, this increase was not statistically significant. This is consistent with prior evidence documenting a dampening of cortisol response to stressors with increasing infant age (hyporesponsivity; Jansen et al., 2010) that onsets between 2 and 6 months of age (Gunnar et al., 1996, 2009).

Covariates

Final models controlled for overall magnitude of depressive symptoms (AUCg) over pregnancy, maternal postpartum depressive symptoms, baseline infant cortisol levels, gestational length, maternal socioeconomic status, Apgar scores, primiparity, and study site based on associations with primary study variables and/or missingness on primary study variables. Socioeconomic status was positively associated with pCRH in mid (r = .24) and late pregnancy (r = .26). Maternal depressive symptoms were positively associated with infant cortisol reactivity at 1 month (r = .26) and Apgar score was inversely associated with infant cortisol reactivity at 6 months (r = −.27). First-born infants had significantly higher cortisol reactivity at 6 months. Study site was associated with early pregnancy pCRH such that participants at the Los Angeles site had higher levels of pCRH in early pregnancy. Socioeconomic status was associated with missingness on patterns of depressive symptoms. Socioeconomic status and study site were associated with missingness on infant cortisol reactivity at both time points. Primiparity was associated with missingness on mid-pregnancy pCRH (all p's < .05).

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Results of primary analysis

The structural equation model testing whether changes in maternal depressive symptoms predicted infant cortisol reactivity at 1 month via changes in pCRH showed acceptable fit, χ^2 (21) = 29.06, $p = .11$, RMSEA = 0.05 (90% CI: 0.00, 0.09), CFI = 0.95, SRMR = 0.04 (Hox & Bechger, 1999). The average level of pCRH (log-transformed) was 2.91 (SE = 0.06, $p < .001$) in early pregnancy after adjusting for depressive symptoms and covariates. The slope was estimated as 3.26 units ($SE = 0.08$, $p < .001$), indicating an average increase of 112% in pCRH from early to late pregnancy. The change between early and mid-pregnancy was estimated as 36% of the overall change between early and late pregnancy such that most of the increases in pCRH occurred from mid to late pregnancy. That is, there was a 40% increase in pCRH between early and mid-pregnancy and an additional 72% increase mid- and late pregnancy.

Hypothesis testing

First, we found that changes in maternal depressive symptoms from early to late pregnancy predicted infant cortisol reactivity to the heel stick procedure at 1 month of age ($\beta = 0.20$, $SE = 0.10$, $p = .05$) such that greater increases in maternal prenatal depressive symptoms were associated with greater infant cortisol reactivity. Second, changes in maternal depressive symptoms significantly predicted increases in pCRH from early to late pregnancy ($\beta = 0.25$, $SE = 0.11$, $p = .02$). Greater increases in maternal depressive symptoms predicted greater increases in pCRH over pregnancy. Third, increases in pCRH significantly predicted infant cortisol reactivity at 1 month ($\beta = 0.29$, $SE = 0.12$, $p = .01$). Greater increases in pCRH were associated with greater infant cortisol reactivity. Finally, the indirect effect of changes in maternal depressive symptoms and infant cortisol reactivity at 1 month via changes in pCRH was significant ($b = 0.072$, $SE = 0.046$, 95% CI of indirect effect: [0.002, 0.178]). Greater increases in depressive symptoms were associated with greater increases in pCRH which were in turn associated with greater infant cortisol reactivity.

Results of exploratory analyses

The structural equation model testing whether changes in maternal depressive symptoms predicted infant cortisol reactivity at to the heel stick at 1 month and to the Still Face at 6 months via changes in pCRH showed acceptable fit, χ^2 (28) = 30.96, $p = .32$, RMSEA = 0.03 (90% CI: 0.00, 0.07), CFI = 0.98, SRMR = 0.05. The results remained consistent when examining infant cortisol reactivity at 1 month of age and 6 months of age. Complete path coefficients are presented in Table 3. First, changes in maternal depressive symptoms from early to late pregnancy significantly predicted infant cortisol reactivity to the heel stick procedure at 1 month and cortisol reactivity to the Still Face paradigm at 6 months such that greater increases in depressive symptoms were associated with higher infant cortisol reactivity at both time points. Second, changes in maternal depressive symptoms significantly predicted increases in pCRH from early to late pregnancy; greater increases in depressive symptoms were associated with greater increases in pCRH. Furthermore, increases in pCRH significantly predicted infant cortisol reactivity to the heel stick at 1 month and to the Still Face paradigm at 6 months such that greater increases in pCRH were associated with higher infant cortisol reactivity at both time points. However, the indirect effect of changes in maternal depressive symptoms and infant cortisol reactivity via changes in pCRH was not statistically significant ($\alpha = 0.05$) at 1 month ($b = 0.062$, $SE = 0.043$, 95% CI of indirect effect [−0.001, 0.162], $p = .062$) or 6 months ($b = 0.074$, $SE = 0.052$. 95% CI of indirect effect [−0.003, 0.196], $p = .071$).

Sex did not significantly modify the association between patterns of depressive symptoms and pCRH or between changes in pCRH and infant cortisol reactivity at 1 month or 6 months (all p's > .05).

Discussion

The current study examined whether patterns of maternal depressive symptoms over the course of pregnancy were associated with infant cortisol reactivity and evaluated whether changes in pCRH from early to late pregnancy mediated the association between patterns of depressive symptoms and infant cortisol reactivity. Results indicated that greater increases in maternal depressive symptoms from early to late pregnancy were associated with higher infant cortisol reactivity to heel stick at 1 month and to the Still Face procedure at 6 months of age. Notably, greater increases in depressive symptoms were associated with greater increases in levels of pCRH in maternal plasma during pregnancy, which were in turn associated with higher infant cortisol reactivity at 1 month and 6 months. Furthermore, there was a significant indirect effect of increases in depressive symptoms on infant cortisol reactivity at 1 month via increases in pCRH. These associations were independent of confounding variables of socioeconomic status, gestational length, Apgar scores, parity, study site, maternal postpartum depressive symptoms, and overall levels of maternal depressive symptoms in pregnancy. Results did not differ by offspring sex.

This study advances our current understanding of biopsychosocial mechanisms of prenatal programming by modeling aspects of psychological and physiological changes that occur over the course of pregnancy and testing how these changes relate to one another and to infant cortisol reactivity. Overall, these findings help to elucidate the prenatal maternal factors contributing to offspring HPA axis regulation. These results have potentially important implications for offspring health and development because HPA axis regulation early in life is associated with susceptibility to mental and physical health problems over the life span (Heim et al., 2000; Luby et al., 2003; McEwen, 2009; Smider et al., 2002; Snoek et al., 2004).

Maternal prenatal depressive symptoms are prevalent and associated with less favorable offspring mental and physical health over the life span (Davis et al., 2018). Although several fetal programming models argue that changes in maternal depressive symptoms over time (as compared to absolute levels at specific times) predict less optimal development (Bateson et al., 2014; Conradt et al., 2018; Gluckman et al., 2005), few studies have examined patterns of depressive symptoms in pregnancy in relation to offspring development (Laurent et al., 2011). Levels of depressive symptoms fluctuated over the course of pregnancy in the current sample, and both the direction and degree of change varied across individuals. Most individuals reported symptoms that slightly increased or decreased from early to late pregnancy whereas some reported significant increases or decreases. Within this context, greater increases in depressive symptoms over the course of pregnancy predicted greater infant cortisol reactivity at 1 month and 6 months old. Moreover, increases in maternal depressive symptoms over gestation may contribute to an adverse in-utero environment and signal that the postnatal environment will be stressful. Because fetal development is responsive to maternal inputs to promote survival in the anticipated postnatal environment (Bateson

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Table 3. Structural equation model of analyses evaluating infant cortisol reactivity 1 month and 6 months as outcomes

Factor loadings			
Effect	**Est**	***SE***	
Early pregnancy	0.000	0.000	
Mid-pregnancy	0.361***	0.012	
Late pregnancy	1.000	0.000	
Latent factor intercepts			
Effect	**Est**	***SE***	
Early pregnancy pCRH	2.913***	0.062	
Changes in pCRH	3.262***	0.083	
Beta coefficients			
Outcome	**Predictor**	**Est**	***SE***
Early pregnancy pCRH	Patterns of depressive symptoms (AUCi)	−0.017	0.127
	Overall depressive symptoms (AUCg)	−0.180	0.110
	Primiparity	0.025	0.109
	Socioeconomic status	0.093	0.108
	Study site	−0.197	0.100
Changes in pCRH	Patterns of depressive symptoms (AUCi)	0.239*	0.108
	Overall depressive symptoms (AUCg)	0.355***	0.100
	Primiparity	−0.140	0.104
	Socioeconomic status	0.200	0.102
Infant cortisol reactivity at 1 month	Patterns of depressive symptoms (AUCi)	0.203*	0.102
	Changes in pCRH	0.263*	0.120
	Early pregnancy pCRH	0.090	0.123
	Overall depressive symptoms (AUCg)	−0.385*	0.157
	Baseline cortisol at 1 month	−0.240*	0.106
	Primiparity	0.428***	0.113
	Socioeconomic status	−0.206	0.129
	Postpartum depressive symptoms (1 month)	0.300*	0.126
	Apgar score	−0.087	0.100
	Gestational length	0.219	0.119
Infant cortisol reactivity at 6 months	Patterns of depressive symptoms (AUCi)	0.304*	0.123
	Changes in pCRH	0.306*	0.147
	Early pregnancy pCRH	0.070	0.144
	Overall depressive symptoms (AUCg)	−0.013	0.248
	Baseline cortisol at 6 months	−0.101	0.135
	Infant cortisol reactivity at 1 month	−0.294	0.202
	Primiparity	−0.061	0.153
	Socioeconomic status	−0.078	0.171
	Postpartum depressive symptoms (1 month)	−0.103	0.187
	Apgar score	−0.235*	0.120
	Gestational length	0.062	0.132
Covariances			
		Est	***SE***
Early pregnancy pCRH	Changes in pCRH	−0.425**	0.101

***$p < .001$; **$p < .01$; *$p < .05$.

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et al., 2014; Gluckman et al., 2005; Sandman, Davis, & Glynn, 2012), fetal developmental trajectories may shift in response to changes in maternal symptoms to accelerate development of stress response systems and enhance ability to respond to a stressful postnatal environment (Howland et al., 2017). This finding is also consistent with cross-species evidence that changes in maternal inputs early in development are associated with heightened excitatory input to the hypothalamus and hippocampal neuronal loss as compared to stable maternal inputs (Baram et al., 2012; Gunn et al., 2013; Singh-Taylor et al., 2017). Thus, greater increases in maternal depressive symptoms in pregnancy may alter fetal developmental trajectories and neurodevelopment in a manner that contributes to higher cortisol reactivity in infancy.

Although there is increasing evidence that different patterns of maternal psychological distress during pregnancy are associated with offspring developmental outcomes, the biological mechanisms explaining these associations are unclear (Doktorchik et al., 2018; Glynn et al., 2008; Glynn, Howland, Sandman, et al., 2018; Glynn & Baram, 2019). In the present study, increases in maternal depressive symptoms predicted infant cortisol reactivity indirectly through greater increases in pCRH from early to late pregnancy. As expected based on prior work (Howland et al., 2017; McLean et al., 1995; Smith & Nicholson, 2007), in the present sample, on average, levels of pCRH increased 112% from early to late pregnancy and a greater proportion of these changes occurred between mid and late pregnancy. That women who reported greater increases in depressive symptoms showed greater increases in pCRH suggests the fetal-placental unit is detecting and responding to maternal stress signals with greater release of pCRH, consistent with previous literature suggesting that pCRH is an indicator of fetal response to maternal stress signals (Sandman et al., 2018).

Results of prior studies examining associations between maternal depressive symptoms and pCRH in pregnancy are mixed, likely because measures at single time points or means over the course of pregnancy do not capture important changes in mood and physiology that occur during this time (Glynn, Howl, Fox, 2018; Meltzer-Brody et al., 2011; Rich-Edwards et al., 2008; Susman et al., 1999). Notably, these results add to small but growing evidence that profiles of psychological and physiological change over pregnancy may better capture the links between psychological distress and prenatal stress physiology (e.g., Peterson et al., 2020), thus supporting calls for comprehensive measurement of stress physiology during pregnancy (Giesbrecht et al., 2015; Howland et al., 2016). This study advances our understanding of how prenatal programming of the fetal HPA axis may occur by examining how patterns of maternal psychological distress relate to changes in pCRH as well as infant cortisol reactivity. The current results indicate assessment of patterns of depressive symptoms and changes in pCRH over the course of pregnancy.

Previous studies examining the prenatal biological predictors of offspring HPA axis regulation have often examined maternal physiological stress indicators such as cortisol (Davis et al., 2011; Gutteling et al., 2005, 2009; Irwin et al., 2021; Osborne et al., 2018; Simons et al., 2019; Swales et al., 2018), the effects of which act indirectly through the placenta (Zijlmans et al., 2015) and may depend on timing (Swales et al., 2018). However, CRH of placental-fetal origin may be a more direct indicator of changes in the intrauterine milieu and fetal exposure to stress hormones (Howland et al., 2016, 2017; Sandman et al., 2018). Prior studies indicate that fetal exposure to maternal depressive symptoms and higher levels of pCRH are associated with cortical thinning in children (Sandman et al., 2015, 2018). Thus, structural alterations to fetal neurodevelopment may be a central pathway by which fetal exposure to maternal depressive symptoms and pCRH influence infant HPA axis regulation.

To our knowledge, this study is the first to examine associations of changes in pCRH with offspring cortisol reactivity. There are several ways that greater increases in levels of pCRH from early to late pregnancy may contribute to fetal programming of the HPA axis and higher offspring cortisol reactivity (Kassotaki et al., 2021). Greater increases in pCRH over gestation may upregulate ACTH receptor sensitivity of the fetal HPA axis, thereby enhancing offspring HPA axis responsiveness to ACTH and promoting adrenal cortisol production in infancy (Lockwood et al., 1996; Sirianni et al., 2005). Moreover, greater CRH exposure in-utero can contribute to loss of hippocampal neurons integral to inhibitory regulation of the HPA axis (Avishai-Eliner et al., 2002). Placental CRH may also act indirectly on the developing fetal HPA axis by stimulating fetal cortisol production and increasing glucocorticoid levels in the fetal compartment (Howland et al., 2017). Higher levels of glucocorticoids the fetal compartment can alter glucocorticoid receptor density and function in the hippocampus and amygdala thus calibrating feedback mechanisms and inhibitory control of the HPA axis (Matthews, 2002). Future research should elucidate the epigenetic and neurodevelopmental processes that explain the association between increases in pCRH and infant cortisol reactivity.

Strengths and Limitations

The current study has notable strengths including that all assessments took place during prenatal visits or lab assessments with trained research staff and validated procedures and measures. Additionally, the current study included two assessments of infant cortisol reactivity 6 months apart with two different age-appropriate standardized lab tasks. Early assessment of cortisol reactivity at 1 month of age minimizes the effects of postnatal environmental factors. However, cortisol responses do not stabilize until 6 months of age (Jansen et al., 2010). That the same associations were found at both time points improves confidence in the current results. Furthermore, repeated measures of both maternal depressive symptoms and pCRH at three prenatal assessments allowed for examination of associations between changes in symptoms and physiology over the course of pregnancy. The indices used to examine patterns of change over time in depressive symptoms and nonlinear increases in pCRH were selected to be sensitive to patterns of change in each measure in pregnancy and are another strength of the current investigation.

There are also limitations in the present study. First, the two standardized lab assessments used to measure infant cortisol reactivity included one which was nonsocial (heel stick) and one that was social (Still Face). Differences in the nature of the stressors used at 1 month and 6 months may influence infant cortisol response (Jansen et al., 2010). For example, response to Still Face may depend on unmeasured factors such as attachment security or parenting behaviors. Nonetheless, the same pattern of results was observed at both assessments. Given the extended longitudinal nature of the study design, there was missingness on some study variables, including infant cortisol reactivity; however, the current analyses used an inclusive missing data handling method based on modern missing data recommendations that increase precision and reduce bias (Collins et al., 2001; Enders, 2010) and results were robust to sensitivity analyses assessing the impact of missing data. Finally, the size of the current sample may have limited the power to detect sex differences in our secondary analyses.

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Conclusions

HPA axis regulation early in life can influence susceptibility to psychiatric disorders and stress-related diseases over the life span (Heim et al., 2000; Luby et al., 2003; McEwen, 2009; Smider et al., 2002; Snoek et al., 2004). The current study helps to elucidate the prenatal biopsychosocial factors that influence offspring HPA axis regulation in the first 6 months of life and adds to a growing literature modeling changes in psychological states and physiology over the course of pregnancy. In this study, greater increases in depressive symptoms were associated with greater infant cortisol reactivity at 1 month and 6 months, and notably, this association was mediated by greater increases in pCRH in maternal blood over the course of pregnancy. Future assessment of maternal patterns of psychological distress over pregnancy and changes in stress physiology is indicated to elucidate the biopsychosocial processes of prenatal programming.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0954579422000621

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Conflicts of interest. None.

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