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Course of Ante- and Postnatal Depressive Symptoms Related to Mothers' HPA Axis Regulation

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Given high health costs of depression during pregnancy and the first postnatal year, it is important to understand mechanisms involved in the emergence and perpetuation of symptoms during this time. In a series of 2 studies, we aim to clarify bidirectional relations between mothers' physiological stress regulation—stress-related activation of the hypothalamic-pituitary-adrenal (HPA) axis—and their course of depressive symptoms. In Study 1, 230 pregnant women recruited from a women's mental health program gave 3 saliva samples in the context of psychosocial stress at 24, 30, and 36-weeks gestation. They self-reported depressive symptoms across the three trimesters of pregnancy and first year postpartum. Multilevel models revealed women with elevated salivary cortisol during pregnancy showed a course of escalating ante- and postnatal symptoms, implicating HPA hyperactivation as a precursor to worsening mood problems. In Study 2, 54 mothers from a community sample self-reported depressive symptoms at 3, 6, 12, and 18 months postnatal. At 18 months, they participated in a dyadic stress task with their infant and gave 4 saliva samples for cortisol assay. For mothers with a lifetime depression

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diagnosis, an escalating course of postnatal symptoms predicted a higher, flatter cortisol response profile. Together, the results of these studies suggest that for high-risk mothers, a trajectory of worsening depression may both follow from and give rise to neuroendocrine stress hyperactivation. These findings suggest greater attention is warranted to *course* of depressive symptoms across the ante- and postnatal period, rather than symptom levels at any given time, to characterize health risks.

General Scientific Summary

Research on the mechanisms perpetuating antenatal and postnatal depression has been limited by a focus on symptoms at a given time, rather than the course of symptoms over time. In a series of two independent but complementary studies, we investigated bidirectional associations between the course of mothers' ante- and/or postnatal depressive symptoms and their hypothalamic-pituitary-adrenal (HPA) axis activation during stress. In Study 1, we showed that women's prenatal HPA hyperactivation predicted escalating depressive symptoms from pregnancy through the first postpartum year, and in Study 2 we found that escalating postnatal depressive symptoms among mothers with a lifetime depression diagnosis predicted HPA hyperactivation during interactions with their infants; together, these findings support a role of HPA dysregulation in perpetuating depressive symptoms among at-risk mothers.

Keywords: depression, mothers, antenatal and postnatal, HPA, cortisol

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Depression in women during the period from pregnancy through the first year postpartum is both relatively common—11.5% prevalence according to the most recent Centers for Disease Control and Prevention (CDC) estimate—and harmful, increasing children's lifelong risk for mental health problems (e.g., Goodman et al., 2011; Murray et al., 2011; Stein et al., 2014). It is critically important to understand what drives this disorder and its effects on mother–child interactions. Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis—especially hyperactivation because of impaired negative feedback function—is thought to play a role in depression more generally (e.g., Gold, 2015; Juruena, Werne Baes, Menezes, & Graeff, 2015; Penninx, Milaneschi, Lamers, & Vogelzangs, 2013). However, recent reviews reveal inconsistent or null findings on associations between depression and cortisol during the ante- and postnatal period (Orta, Gelaye, Bain, & Williams, 2017; Seth, Lewis, & Galbally, 2016). Research that clarifies whether and how HPA axis dysregulation distinguishes women with persistent/worsening symptoms during this time could shed light on the pathophysiology of the disorder and the basis for ongoing dyadic dysregulation.

A failure to detect consistent associations thus far may have to do with a reliance upon cross-sectional symptom assessment, rather than *course* of symptoms (i.e., remitting or worsening over time); limited measurement of cortisol (often a simple baseline measure outside the context of psychosocial stress); and a failure to distinguish clinical-level cases from those that never cross a diagnostic threshold. The current article aims to address these gaps by testing associations between maternal HPA activation to stress and trajectories of ante- and postnatal depressive symptoms in two separate samples with varying clinical risk characteristics. These samples allow us to address separate but complementary questions about the way that HPA axis function relates to depression course. Working from a model that asserts a bidirectional association in which HPA dysregulation both gives rise to and is reinforced by the cognitive and behavioral manifestations of depression, can we discern links between (a) pregnancy HPA dysregulation and later escalation of symptoms, and (b) such symptom escalation and later HPA dysregulation during mother–infant interactions? Addressing this first point would pinpoint a contributor to worsening maternal depression during this critical period. Addressing the second point would help determine the significance of such a pattern of worsening symptoms for the ongoing stressfulness of parenting interactions. In the following set of two studies, we approach the following questions: Do cortisol levels in late pregnancy during laboratory stressors predict the course of ante- and postnatal depression? Does the course of postnatal depression predict later maternal cortisol responsiveness to infant-related stress?

Ante- and Postnatal Depression—Typical Course and Variations

Diagnostic and Statistical Manual for Mental Disorders-Fifth Edition (*DSM–5*) and *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (*ICD-10*) postpartum onset specifiers restrict depression onset to within 4 and 6 weeks after delivery, respectively; however, we have previously reported that one-third of women referred for postpartum depression experienced symptom onset either during gestation or after six postnatal weeks (Stowe, Hostetter, & Newport, 2005). This suggests a clinical construct of depression across both the ante- and postnatal time periods, rather than postpartum depression per se, may be a more appropriate clinical construct. Similarly, a comprehensive review suggests that clinically significant depression (major or minor depressive episode) occurs during both pregnancy—period prevalence 18.4%—and the first several months postpartum—period prevalence 19.2%—with peak point prevalence in the third month postpartum (Gavin et al., 2005). Although the general trend is for symptoms to decrease after this peak period, some women experience later onset (after 3 months postpartum), and a significant proportion continue to show elevated symptoms beyond the first postpartum year (Goodman,

2004). It is important to determine who will show ongoing or worsening symptoms because adverse effects on child development seem to depend on the severity/chronicity of depression rather than the occurrence of depression alone (e.g., Brennan et al., 2000; Campbell, Cohn, & Meyers, 1995; Goodman, Rouse, Long, Ji, & Brand, 2011).

Efforts to identify risk factors for ongoing or worsening ante- and postnatal depression have highlighted several broad categories of risk, but little information about specific mechanisms. A history of depression or other psychiatric disorders, situational triggers such as physical health or relationship problems, and a lack of economic and social support resources all have been found to predict depression persistence or onset beyond the first postpartum months (see Goodman, 2004; Howell, Mora, Dibonaventura, & Leventhal, 2009). Not only are these relatively nonspecific risk factors, but they also do not address the underlying processes involved. One underlying mechanism that may help to explain how these risk processes converge to lead to disorder is neurophysiological stress responding via the HPA axis (see Putnam et al., 2017).

The HPA Axis and Ante- and Postnatal Depression

The HPA axis is a neuroendocrine system whose activation results in the release of glucocorticoids such as cortisol from the adrenal cortex. In response to a perceived threat or challenge, HPA activation works in concert with other physiological systems to prepare the organism to manage the stressor by mobilizing energy reserves, inhibiting nonemergency processes, and enhancing vigilance and arousal (see Herman et al., 2016). Whereas moderate cortisol elevations in response to stress serve an adaptive function, marked deviations—either hyper- or hypoactivation—have been associated with mental and physical health problems (e.g., Carroll, Ginty, Whittaker, Lovallo, & de Rooij, 2017; Zorn et al., 2017). During prenatal development, maternal stress regulation is thought to influence fetal neurobehavioral outcomes via the maternal–placental-fetal neuroendocrine axis (see Wadhwa, 2005), highlighting a role for HPA axis regulation in the intergenerational transmission of health risks.

In the case of depression, researchers have typically observed HPA hyperactivation, along with blunted and/or extended reactivity to acute stress (see Burke, Davis, Otte, & Mohr, 2005; Chopra et al., 2009; de Rooij, Schene, Phillips, & Roseboom, 2010; Powers, Laurent, Gunlicks-Stoessel, Balaban, & Bent, 2016; Rao & Morris, 2015). Reasons put forward for divergent findings regarding stress responsivity in depression include differences by participant sex, depression chronicity, and comorbidities. In terms of the ante- and postnatal period, specifically, it has also been suggested that depression-related HPA profiles may vary because of normative shifts in cortisol—that is, increasingly elevated during pregnancy and abruptly reduced postpartum—as well as shifts in other hormones at this time.

Cross-sectional research on associations between cortisol and ante- and postnatal depression has yielded mixed findings. Some research has supported an association between hypercortisolism and antenatal depression, thought to be because of impaired negative feedback function of the HPA axis that is exacerbated during pregnancy (Evans, Myers, & Monk, 2008; Gelman, Flores-Ramos, López-Martínez, Fuentes, & Grajeda, 2015; Murphy et al., 2015). In particular, a positive feedforward loop involving elevated placental corticotrophin-releasing hormone (CRH) and cortisol during pregnancy may disturb the anterior pituitary's sensitivity to cortisol, leading to a prolonged postpartum HPA refractory period thought to increase risk for depression (Glynn, Davis, & Sandman, 2013). Another recent review determined that while there is some evidence for hypercortisolism in association with antenatal symptoms, and hypocortisolism with more chronic postnatal symptoms, a large number of nonsignificant results and poor-quality studies limit conclusions (Seth et al., 2016). We propose that one limiting factor in prior research that may obscure predictive associations is a reliance upon cross-sectional sampling of depression symptom severity and/or cortisol at discrete time points, rather than attention to the course of symptoms over time and relations with HPA axis regulation across the ante- and postnatal period.

It is important to understand if and how women's early HPA dysregulation before the infant is born may herald their future depression exacerbation, given the low specificity of known risk factors and serious consequences for the infant's future mental health as outlined above. Over and above the normative neuroendocrine shifts during pregnancy, an exacerbation of hypercortisolism—particularly in the context of a stress challenge—may predispose certain women to escalating symptoms across pregnancy and postpartum. In particular, prenatal cortisol during psychosocial stress may serve as a prospective predictor of depression course across the ante- and postnatal period, a possibility that has yet to be examined.

Maternal HPA Regulation With Her Infant

Beyond clarifying possible precursors to a course of persistent or worsening ante- and postnatal depressive symptoms, there is an unmet need to understand how the mother's symptom course may shape HPA dysregulation during interactions with her infant. There is evidence that greater maternal HPA hyperactivation during such interactions predicts poorer parent–child relations that negatively impact both dyad partners. For example, mothers' elevated cortisol during toddler challenge tasks has been related to harsher and more intrusive parenting, as well as insecure child attachment (Kiel & Buss, 2013; Martorell & Bugental, 2006; Roque, Verissimo, Oliveira, & Oliveira, 2012). It should be noted, though, that some studies focusing on children younger than toddlerhood have found lower maternal cortisol levels related to poorer quality interactions (i.e., disrupted communication, more neutral as opposed to positive affect—Crockett, Holmes, Granger, & Lyons-Ruth, 2013; Juul et al., 2016).

Maternal HPA dysregulation during mother–child interactions could adversely impact child development not only via problematic parenting, but also through physiological attunement, or the tendency for infant HPA activation to follow that of the mother. In fact, there is evidence that infant–mother cortisol attunement during a challenge task is heightened in dyads in which the mother has become increasingly depressed across the antenatal and postnatal period (pregnancy through 18 months postpartum), relative to mothers with low levels of depression (Laurent, Ablow, & Measelle, 2011). For these reasons, it is important to track not only whether maternal HPA activation presages a course of worsening ante- and postnatal depression, but also whether this depression

course predicts mothers' subsequent HPA regulation during interactions with their children.

The Present Studies

The studies reported here were designed to address different aspects of the knowledge gaps highlighted above. In Study 1, we test the extent to which maternal cortisol during a psychological stress task in pregnancy predicts trajectories of depressive symptoms from the first trimester of pregnancy through the first postnatal year in a high-risk sample of women recruited at the Emory Women's Mental Health Program. In Study 2, we test the extent to which the trajectory of maternal depressive symptoms from 3 to 18 months postnatal predicts women's cortisol responses to stress tasks with their toddlers in a community sample. Together, these studies aim to shed light on the role of HPA dysregulation in ante- and postnatal depression by taking a nuanced time course approach to depressive symptoms, considering cortisol in response to stress at different times in antenatal and postnatal development, and examining potential differences between clinical and nonclinical cases. As noted above, each study offers distinct but complementary information about the proposed bidirectional association between HPA dysregulation and the course of depression in mothers.

Study 1

It has been proposed that disturbance of the HPA axis in pregnant women—in particular, hyperactivation and altered sensitivity of the pituitary to corticotrophin releasing hormone—can set the stage for postpartum mood problems and, thus, that HPA activation during pregnancy could serve as a useful marker of risk for later depression (see Glynn et al., 2013). Outside of a maternal health context, there is evidence that cortisol hypersecretion predicts a course of increasing symptoms in those at risk for depression (Morris, Rao, & Garber, 2012). Guided by these considerations, we hypothesized that women with higher cortisol levels during a prenatal stressor would show an increasing trajectory of depressive symptoms across the ante- and postnatal period, from the first trimester of pregnancy to 12 months postnatal. To test this hypothesis, we sampled women with previous mood disorders, thereby increasing the likelihood of elevated depression relative to general population samples. Maternal cortisol was measured in the context of standard laboratory-based stressors previously shown to elicit physiological responses in the pregnant mother and/or fetus that differed by maternal psychopathology (Evans et al., 2008; Monk et al., 2000, 2004; Monk, Myers, Sloan, Ellman, & Fifer, 2003).

Method

Participants. Participants were drawn from a longitudinal study of women at high risk for depression because of previous mood difficulties (clinically significant depression and/or anxiety) who presented during pregnancy at the Emory Women's Mental Health Program (n = 279). For more information about study inclusion and exclusion criteria, see Lusby, Goodman, Yeung, Bell, and Stowe (2016). The majority of participants carried a depressive disorder diagnosis (83% major depressive disorder or depression NOS), and 61% carried an anxiety disorder diagnosis (51% carried both). See Table 1, top panel for complete sample diagnostic characteristics. Mothers were predominantly white (88%), non-Hispanic (99%), married (88%), and employed (56% full-time, 19% part-time). On average, mothers were 33.7 years old (range 20–44) at the time of study entry and had previously given birth to one child (range 0–7). The majority of women were treated with antidepressant medication during pregnancy (74%) and/or postpartum (79%; M = 55.5 weeks total on medication from first trimester pregnancy through first year postnatal).

The current study sample comprised 230 (82%) women who had any prenatal cortisol data. There were no significant demographic differences between those included in the current sample and those excluded. Self-reported depression scores across pregnancy and postpartum and the occurrence of a major depressive episode during pregnancy and the postpartum also did not differ significantly between included and excluded participants, though the former were more likely to have a lifetime major depressive disorder diagnosis at the baseline assessment, $\chi^2(1) = 6.14$, $p = .013$.

Procedure. Participating women were part of a larger longitudinal study of pathways by which infants become vulnerable to psychopathology. The study was approved by the Emory University Institutional Review Board (protocol IRB00004249). Women were consented and enrolled before 16 weeks of pregnancy and assessed at 4–6 week intervals through the first postpartum year. They completed symptom self-report questionnaires at all visits (see below). Based on prior work (Monk et al., 2000, 2004; Werner et al., 2007), mothers were also exposed to standard laboratory psychological stressors during prenatal fetal assessment sessions at 24, 30, and 36-weeks gestation (±2 weeks each time). Following a 5-min resting baseline, they completed a Stroop

Table 1
Study Sample Diagnostic Characteristics

SCID diagnosis	n	Valid percent
Study 1		
Major depressive disorder	227	81%
Depression NOS	5	2%
Bipolar disorder	19	6%
Panic disorder	79	28%
Obsessive-compulsive disorder	45	16%
Social anxiety disorder	43	15%
Generalized anxiety disorder	79	28%
Posttraumatic stress disorder	51	18%
Study 2		
Major depressive disorder	19	22%
Dysthymia	1	1%
Bipolar disorder	2	2%
Panic disorder	5	6%
Obsessive-compulsive disorder	1	1%
Social anxiety disorder	6	7%
Generalized anxiety disorder	7	8%
Specific phobia	1	1%
Anxiety NOS	7	8%
Posttraumatic stress disorder	11	13%
Substance use disorder	32	36%
Eating disorder	4	4%

Note. SCID = Structured Clinical Interview for *DSM-IV*; NOS = not otherwise specified. Lifetime diagnoses based on Structured Clinical Interview for the *Diagnostic and Statistical Manual for Mental Disorders-Fourth Edition* (*DSM-IV*) conducted at the baseline assessment for each study.

color-word test (5 min) after which they were given 5 min to recover, followed by a math task (5 min), and a final 5-min recovery period (25 min total). These tasks have been shown to elicit significant subjective stress reactivity in pregnant women (Monk et al., 2000), as well as psychopathology-related differences in physiological response (Evans et al., 2008; Monk et al., 2000). Three cortisol samples were collected at each of these sessions: The first was taken soon after arrival once the mother was settled on the ultrasound chair, the second after the mother had been hooked up to a fetal monitor and prepared for the tasks, and the third following the stressor tasks. Given the timing of the salivary cortisol response, the first two samples would thus tap any anticipatory stress and the third would tap task-related stress response. On average, samples were collected in the early afternoon (1:22–1:41 p.m. sample 1 start time across sessions), and variation in collection time was accounted for in analyses.

Measures.

Depression. Mothers completed the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) multiple times across pregnancy and the first postnatal year. This instrument has been validated for use during pregnancy (see Ji et al., 2011), and it showed good internal consistency in this sample (αs = .89–.94 across assessments). The BDI is a 21-item self-report measure of depression symptom severity in the past week, with each item rated on a 4-point scale, ranging from 0 to 3. The score is a sum across items, with higher scores indicating greater severity of depressive symptoms. Scores of 0–9 indicate no depression, 10–18 indicates mild depression, 19–29 indicates moderate-severe depression, and 30–63 indicates severe depression (Beck et al., 1961). In the current sample, based on the maximum score reported over the ante- and postnatal period, women showed substantial rates of elevated symptoms: 63% scored >9 during pregnancy and 67% during the postnatal year; 30% and 31% scored >18 during these periods; and 9 and 11% scored >29 during these periods.

Separate area under the curve (AUC) scores were calculated for each woman for each roughly 3-month time period covered in the study—that is, during each of the three trimesters of pregnancy, standardized to a 40-week pregnancy, and each of the four quarters of the first postpartum year—to represent overall depression severity across each time period. These seven AUC scores served as depressive symptom outcome measures, allowing us to capture both the total symptom elevation during specific time periods highlighted in previous ante- and postnatal depression research and change across these periods (see Lusby et al., 2016 for an example of this approach).

Cortisol. Participants' saliva samples were assayed in duplicate with the commercially available Salivary Cortisol Enzyme Immunoassay (Salimetrics, State College, PA) without modification to the manufacturer's recommended protocol. The test uses 25 μL saliva and has an assay range of .007–1.8 μg/dL. Intra-assay and interassay coefficients of variation were on average 5 and 8%, respectively. Raw scores averaged .31 μg/dL (*SD* = .23). Potential control variables—maternal age, race/ethnicity, socioeconomic status, preconception Body Mass Index (BMI), sleep problems, antidepressant medication use during pregnancy, pregnancy health complications (antiphospholipid syndrome, gestational diabetes, hydramnios, hyperemesis, and hypertension), and infant gestational age at birth—did not significantly relate to cortisol measures across sessions, so they were not included in further model testing. Cortisol values were log-transformed to correct positive skew, and standardized residuals after controlling for collection time were used in analyses.

Data analytic plan. Hierarchical linear modeling (HLM) was used to model hypothesized effects involving dependent data (i.e., multiple cortisol and depression scores clustered within mothers). This approach has the advantage of obtaining parameter estimates in the presence of missing data using full information maximum likelihood estimation. At Level 1, within-mother variation in cortisol or depressive symptoms was modeled with a participant-specific intercept and, if warranted, temporal slope/s. Level 2 captured between-mother variation in these trajectory terms, which could be explained by individual difference predictors.

An initial model was run to obtain estimates (Empirical Bayes Coefficients) of each mother's HPA activation during pregnancy. Cortisol levels were modeled with an intercept, representing mean cortisol across the prenatal visits; adding a linear slope for change across the three samples within sessions did not result in improved model fit, $\chi^2(3) = .08$, *ns*, and there was not significant between-mother variability in this slope term, $\chi^2(226) = 125.28$, *ns*. However, adding a linear slope for change in cortisol across the three sessions did improve model fit, $\chi^2(3) = 449.73$, $p < .001$, and there was significant between-mother variability in these slopes, $\chi^2(184) = 794.25$, $p < .001$. Thus, estimates of each mother's overall cortisol intercept across sessions, cortisol intercept at a particular session (1–3), and slope across Sessions 1–3 were obtained in separate models, to be used in the next step of model testing.

The main explanatory models entered cortisol estimates defined by the above as Level 2 predictors of mothers' depressive symptom trajectories from the first trimester of pregnancy through the end of the first postnatal year. Both linear and quadratic symptom trajectories were considered, with temporal centering at the final (4th quarter postpartum) time point so that the intercept would reflect symptom levels at the end of the first postnatal year.

Results

Zero-order correlations among study variables can be found in supplemental Table 1.

Baseline model. The best-fitting baseline model of depressive symptom trajectories included both a linear and quadratic slope: $\chi^2(3) = 210.68$, $p < .001$ from intercept-only to linear, $\chi^2(4) = 207.16$, $p < .001$ from linear to quadratic. On average, mothers showed a significant positive quadratic curvature, reflecting a tendency to decline in symptoms across pregnancy and then increase in the early postpartum (see Figure 1, top panel for mean scores across time points). Consistent with this pattern, the average linear slope (reflecting instantaneous rate of change at the model centering point, or 4th quarter postpartum) was also positive. There was significant between-mother variability in each of the symptom trajectory terms, $\chi^2(194) = 384.53$–1347.93, $p < .001$, justifying the addition of Level 2 predictors to explain this variability.

Explanatory models. First, mothers' average prenatal cortisol was entered as a predictor of depressive symptom trajectories. Higher cortisol across sessions predicted a more positive linear slope, and marginally higher quadratic slope and symptom level by

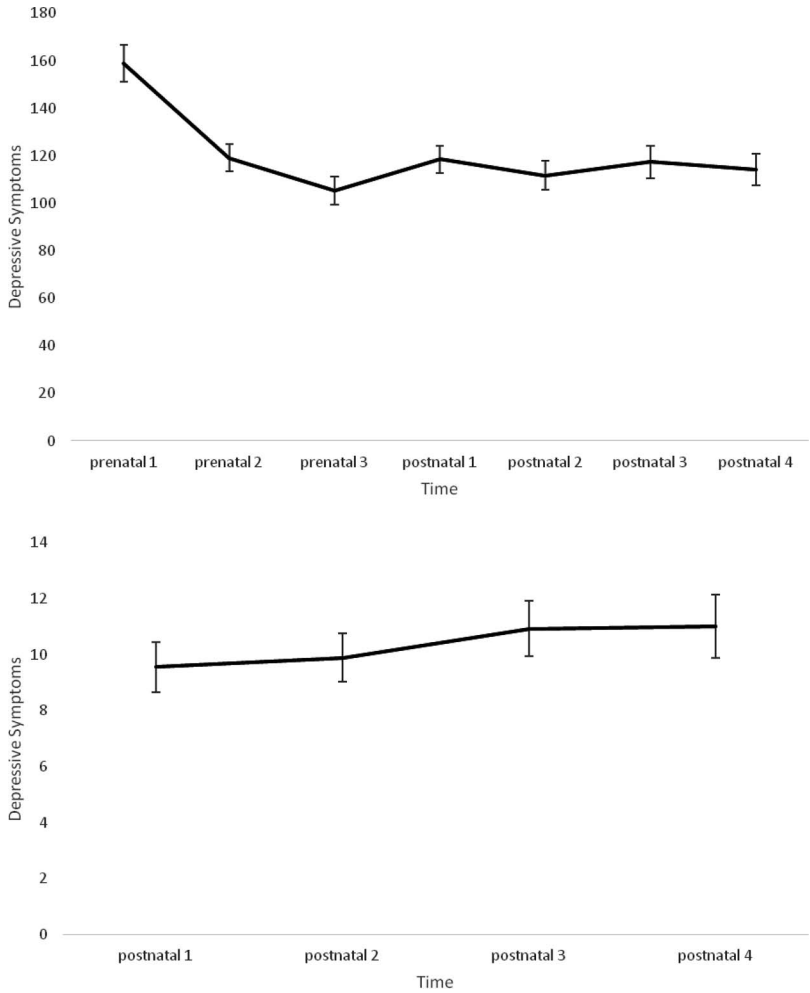

Figure 1. Mean depressive symptom scores across time in Study 1 and Study 2. Study 1 (upper panel) depressive symptoms are Beck Depression Inventory (BDI) area under the curve (AUC) scores for each trimester of pregnancy and four quarters of the postpartum year; Study 2 (lower panel) depressive symptoms are Center for Epidemiologic Studies Depression Scale (CESD) scores at 3, 6, 12, and 18 months postpartum.

the end of the postpartum year (see Table 2, panel A). Next, session-specific cortisol effects were tested by entering both the intercept (average cortisol at a given session) and slope (change in cortisol across sessions) as predictors of symptom trajectories. These models revealed a positive association between Session 2 and 3 cortisol levels and mothers' symptom intercepts, linear and quadratic slopes (see Table 2, panel B and Figure 2).[1] In other words, mothers with higher cortisol at 30 and 36 weeks gestation tended to show a more rapidly increasing postpartum symptom trajectory, resulting in higher depressive symptoms by the end of the first postnatal year.

Summary

The results of Study 1 indicate that HPA hyperactivation above and beyond the normative alterations observed during pregnancy—especially in the third trimester—predicts a pattern of escalating postnatal depressive symptoms. Elevated prenatal cortisol during psychosocial stress could serve as an important indicator of later mother (and infant) adjustment problems in high-risk samples. Whether this escalating ante- and postnatal symptom pattern predicts adverse downstream outcomes remains to be seen.

Study 2

Having found evidence that early (prenatal) HPA hyperactivation predicts the subsequent course of depression, we also wanted to address the other side of the proposed bidirectional association by testing whether the course of mothers' symptoms (in a separate sample) predicted their HPA regulation with their infants beyond

[1] Diagnostic status (whether women met criteria for a depressive disorder) was tested as a potential moderator of effects and found to be nonsignificant. To determine whether effects were specific to depression, mothers' anxiety symptoms were tested as an outcome in an alternative model, and potential comorbidity effects were evaluated through Depression × Anxiety Diagnosis moderators. These models did not reveal any effects on anxiety or moderation by anxiety diagnosis, supporting specificity to depression in this sample.

Table 2
Maternal Depressive Symptom Trajectories Related to Cortisol During Pregnancy

Predictor	Intercept (symptoms at fourth quarter postpartum) γ (*SE*), *p*	Linear slope (instantaneous rate of symptom change at fourth quarter postpartum) γ (*SE*), *p*	Quadratic slope (overall rate of symptom acceleration across ante- and postnatal period) γ (*SE*), *p*
A. Average prenatal cortisol	21.90 (12.78), .087	9.00 (4.36), .040	1.35 (.76), .078
B. Prenatal cortisol intercept (level at 30 weeks)	27.37 (12.88), .034	12.32 (4.64), .009	1.83 (.84), .030
Prenatal cortisol slope (growth 24–36 weeks)	17.82 (16.86), .292	9.50 (5.60), .091	1.41 (1.07), .190

Note. Symptoms are Beck Depression Inventory (BDI) area under the curve (AUC) scores measured at each trimester of pregnancy and four quarters of first postnatal year. Cortisol was measured before and after Stroop tasks at 24, 30, and 36 weeks gestation.

the first postnatal year. Given the links between parenting and HPA dysregulation highlighted earlier, such an association could tell us more about which mother–infant dyads are most likely to show ongoing harmful impacts of depression in mothers and what perpetuates pathological interaction patterns in the dyad.

There are remarkably few studies investigating relations between depression in mothers and their own (postnatal) cortisol. One study showed that mothers with elevated depressive symptoms had higher cortisol levels during a dyadic stressor (the Strange Situation) at 18 months postnatal (Laurent et al., 2011), a finding corroborated by Khoury et al. (2016). We are not aware of any research demonstrating a depression time course effect on maternal cortisol, but based on these studies we hypothesized that mothers with an increasing depression symptom trajectory across the postnatal period would show higher cortisol in response to an infant-related stressor at 18 months.

Another point of exploration is whether high-risk clinical cases—that is, mothers who have at some point crossed the threshold into a diagnosed depressive disorder—differ from lower-risk (nonclinical) cases. There is some evidence that the impact of self-reported depressive symptoms varies between these groups (see Laurent, 2017), though other research reports no significant differences between mothers with elevated depressive symptoms and those meeting diagnostic criteria (see Goodman et al., 2011; Goodman & Tully, 2009). It is important to determine when diagnostic status matters and whether there are different risk markers for HPA dysregulation in each group. Based on prior indications in this sample that adverse effects of maternal depressive symptoms are stronger in clinical cases (Laurent, 2017) and Study 1 findings relating HPA hyperactivation to depression course in a clinical sample, we hypothesized that HPA-depression course relations would be stronger in

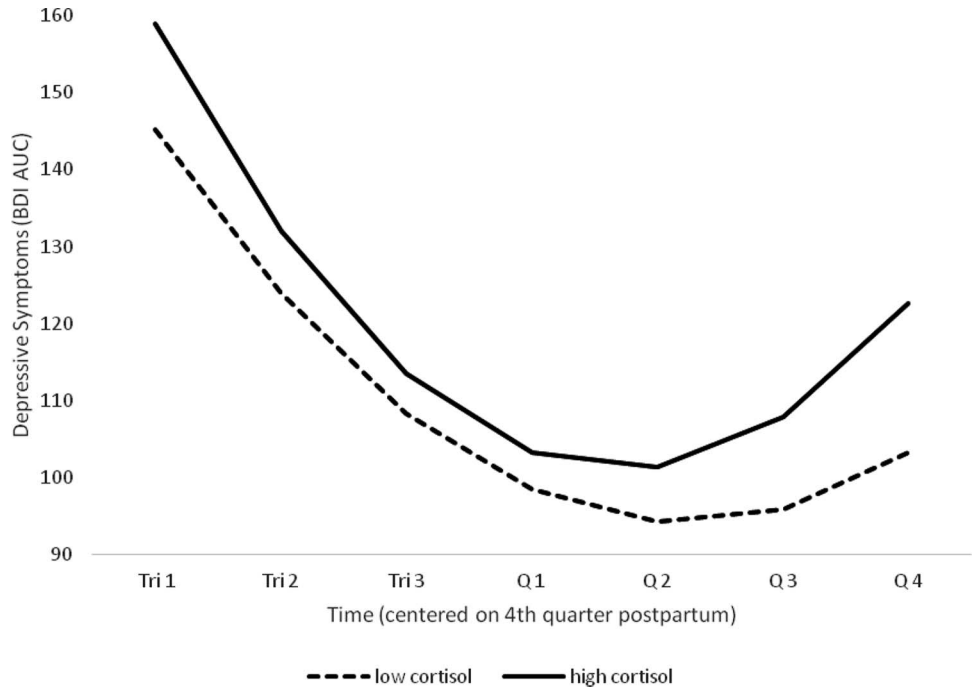

Figure 2. Maternal cortisol at 30 weeks gestation relates to depressive symptom trajectories from first trimester pregnancy to 12 months postnatal. Tri = trimester of pregnancy; Q = quarter of postpartum year.

mothers who had received a lifetime diagnosis of depression at study entry.

Method

Participants. Participants for this study were mothers of <12-week old infants recruited from community agencies serving low-income families. At the start of the study, mothers ($n = 91$) were 27 years old on average (range 18–44), predominantly White (77%) and non-Hispanic (90%), with around half (51%) married or in a legal domestic partnership. As would be expected based on the recruitment sources, a minority of mothers were employed (9% full-time, 15% part-time) and median reported household income was in the $10,000 to $19,999 range. The infant involved in the study was the first child for 49% of participating mothers (range 1–5). Even though mothers were not selected for mental health risk, a Structured Clinical Interview for *DSM-IV* (SCID) administered at the first assessment revealed that a sizable proportion met criteria for a lifetime depressive disorder (23% major depressive disorder or dysthymia) and/or an anxiety disorder (24%). See Table 1, lower panel for complete sample diagnostic information.

The current analyses are based on the 54 cases with 18-month cortisol data (see below for information about assessment times). Compared with those who were not included, these participants tended to be older, $t(89) = 2.84$, $p = .006$, report higher household income ($\chi^2[7] = 14.39$, $p = .045$), and have more biological children, $t(89) = 2.01$, $p = .047$. There were no differences on other demographic variables such as racial/ethnic identification, relationship status, education, or employment. Of a set of self-reported and diagnostic mental health variables collected at the first assessment, the only difference detected was that included cases tended to report fewer current (3-month) depressive symptoms, $t(85) = 2.58$, $p = .011$.

Procedure. As described in Laurent (2017), mothers were assessed four times as part of a larger longitudinal study of stress regulation: Time 1 at 3 months postnatal, Time 2 at 6 months, Time 3 at 12 months, and Time 4 at 18 months. Time 1 was conducted in the mother's home, and Times 2–4 in the laboratory. All procedures were approved by the University of Oregon Institutional Review Board (protocol 06242013.033).

All laboratory sessions were conducted in the afternoon, a time when diurnal cortisol fluctuations should be less marked. Upon arrival at the lab, mothers answered a series of questions about factors that could affect cortisol measures, which were examined as potential control variables in analyses. They were then led through the stress tasks, followed by a 45–50 min period during which they completed questionnaires with their infant in the room. The stressor for the final (18-month) session examined in the current study involved the mother observing her infant participating in tasks from the Laboratory Temperament Assessment Battery, locomotor version (LabTAB; Goldsmith & Rothbart, 1999). The mother first left her infant alone in the lab room for 30 s (Maternal Separation episode) while watching on a computer monitor in another room. She then watched as an unfamiliar male research assistant approached, spoke to, and picked up the infant over the course of 1 min (Stranger Approach episode). Afterward, she was reunited with her infant.

Four saliva samples were collected from the mother via passive drool to index HPA axis response during the session. The first sample was collected soon after arrival at the lab, the second sample immediately after the LabTAB tasks, the third sample 20 min after the start of the Stranger Approach, and the fourth sample 30 min after the preceding sample. Given the typical 20-min lag for the HPA axis response to appear in saliva, the third sample should index peak stress related to the infant stress tasks.

Measures.

Depression. At each assessment time, mothers reported current depressive symptoms using the Center for Epidemiologic Studies Depression Scale (CESD; Radloff, 1977), an instrument that has been supported for use in the postnatal period (Campbell & Cohn, 1991). Scale reliabilities ranged from .86–.89 across assessments. Even in this community sample, a sizable minority reported clinically significant symptoms (15–21% with CESD >16 across assessments). At Time 1, they were also administered the NetSCID (TeleSage, Inc.) by a trained graduate research assistant to determine whether they met criteria for a lifetime depressive disorder according to the *DSM-IV-TR*.

Cortisol. Mothers' saliva samples were assayed in duplicate with the commercially available Salivary Cortisol Enzyme Immunoassay (Salimetrics, Carlsbad, CA) without modification to the manufacturer's recommended protocol. The test uses 25 μL saliva, has a lower limit of sensitivity of .007 μg/dL, standard curve range .012 to 3.0 μg/dL. The intra-assay coefficient of variation was on average <10%, and the interassay coefficient of variation was on average <15%. Raw scores averaged .10 μg/dL ($SD = .074$). Cortisol scores were natural log-transformed before analysis to correct positive skew. Potential control variables—that is, session start time, maternal age, race/ethnicity, socioeconomic status, sleep/wake times, recent food intake and tooth brushing, use of medications and other substances, sickness, body mass index, infant prematurity, and breastfeeding status—failed to show any consistent effects on cortisol, so they were not included in the analyses reported below.

Data analytic plan. As in Study 1, HLM was used to fit models of mothers' depressive symptoms and HPA activation over time. This time, the first step involved estimating depressive symptom trajectories from 3–18 months postnatal, with intercepts centered at the final (18-month) assessment. A linear model was found to best fit the data, $\chi^2(3) = 14.90$, $p = .002$ from intercept-only to linear; $\chi^2(3) = 6.83$, *ns* from linear to quadratic. On average, mothers showed a marginally significant ($p = .094$) increase in symptoms across the postnatal period, and there was significant between-mother variability in these slopes, $\chi^2(77) = 158.66$, $p < .001$ (see Figure 1, lower panel for mean scores across time points). Symptom intercept and slope estimates from this model (Empirical Bayes coefficients) were then entered as predictors of mothers' cortisol response trajectories with their infants at 18 months. Both linear and quadratic models were considered, centered at the third (poststress) sample to capture cortisol levels associated with peak stress.

Results

Zero-order correlations among study variables can be found in supplemental Table 2.

Baseline model. A quadratic model was found to best fit the cortisol data, $\chi^2(3) = 40.19$, $p < .001$ from intercept-only to linear, $\chi^2(3) = 45.09$, $p < .001$ from linear to quadratic. On

average, mothers showed a positive quadratic curvature, reflecting a decline in cortisol across the first three samples, followed by a slight increase from the third to the final sample. At the same time, there was significant between-mother variability in all trajectory parameters, $\chi^2(53) = 104.32–1464.63$, $p < .001$, which could be explained by adding Level 2 predictors.

Explanatory models. Mothers' depressive symptom intercept and slope estimates were entered as predictors of their cortisol response trajectories. Whereas higher (concurrent) symptoms predicted higher cortisol levels, increasing symptoms across the postnatal period predicted lower cortisol levels (see Table 3, panel A). When diagnostic status was considered as a moderator, a different pattern emerged. For mothers who had crossed the diagnostic threshold for a depressive disorder, increasing postnatal symptoms predicted higher cortisol levels and a flattened response curve (see Table 3, panel B and Figure 3).[2]

Summary

The results of Study 2 suggest that in high-risk mothers (with a diagnosed depressive disorder), a pattern of escalating postnatal symptoms relates to higher, less dynamic HPA responses to an infant-related stressor at 18 months. This type of response, associated in previous research with impaired parenting quality, could be part of a self-reinforcing cycle fueling ongoing adjustment problems in both mother and infant. By contrast, these results offer evidence for a dysregulating (hyperactivating) effect of concurrent depressive symptom levels among lower-risk (undiagnosed) mothers, suggesting researchers may need to consider different risk markers in each group.

General Discussion

Two studies that sampled differing populations of mothers offer converging evidence that a profile of escalating ante- and postnatal depressive symptoms is uniquely associated with physiological stress dysregulation. In high-risk mothers, heightened prenatal HPA activation during stress predicted a trajectory of increasing symptoms (Study 1); such a trajectory, in turn, predicted high-risk mothers' dysregulated HPA responses to stress involving their infant in a different sample (Study 2). Together, these findings have important implications for anticipating the emergence and potential sequelae of ante- and postnatal mood disturbance; they suggest that greater attention should be paid to HPA hyperactivation as a mutually reinforcing mechanism involved in the *course* of depressive symptoms across this critical period, and not simply symptom levels at any given time.

To interpret these effects, it may be useful to consider not only mechanistic links proposed between HPA axis and depression more broadly, but also factors specific to pregnancy/postpartum, including paths of influence between the mother and infant. As suggested previously (Glynn et al., 2013), excessive cortisol release during stress in pregnancy may exacerbate disturbance in the HPA negative feedback loop that contributes to the brain and behavioral characteristics of depression. In turn, the negative appraisal style characteristic of depression may heighten both subjective and neuroendocrine responses to stressors, perpetuating HPA hyperactivation during parenting interactions.

Turning to the mother–infant transaction more specifically, prenatal maternal cortisol hypersecretion has been shown to predict infant emotion dysregulation (Bolten et al., 2013; Swales et al., in press), presumably through prenatal programming biasing the infant toward heightened stress reactivity. Such infant dysregulation could feed into increasing maternal symptoms during postnatal development. Consistent with this explanation, prior research suggests elevated maternal cortisol particularly during late gestation (>27 weeks) adversely impacts child behavioral regulation (see Zijlmans, Riksen-Walraven, & de Weerth, 2015). It is thought that the convergence of elevated circulating cortisol and decreased function of the 11β-HSD2 enzyme protecting the fetus during this time makes the fetal brain particularly susceptible to maternal programming effects. An exacerbation of depression could in turn blunt mothers' neural responsiveness to their infant's emotion cues (see Laurent & Ablow, 2012; Moses-Kolko, Horner, Phillips, Hipwell, & Swain, 2014), which has been associated with mothers' HPA hyperresponse to stress involving the infant (Laurent, Stevens, & Ablow, 2011). In this way, a self-reinforcing cycle may be set up by which mothers who are having difficulties regulating their own mood are less able to respond sensitively to and soothe their dysregulated infant, which makes parenting interactions more stressful and reinforces their depression. This cycle could be further exacerbated by factors like background life stress and low social support that contribute to both hypercortisolism and depression, a possibility that should be investigated in future research.

Consistent with much of the research on ante- and postnatal depression, and depression more generally, it was a high but relatively flat/nonrecovering cortisol response that distinguished high-risk mothers with worsening mood problems in Study 2. It bears noting that rather than showing "reactivity" as defined by an increase from pre- to poststress cortisol, mothers overall tended to show a cortisol decline across the session (though this tendency was blunted in clinical cases with increasing symptoms). It may be that healthy mothers recovered from anticipatory stress while interacting with their infants across the session, whereas the mothers experiencing escalating mood difficulties were unable to modulate their already high HPA activation downward in this context. While effects on infant outcomes were beyond the scope of the present studies, research reviewed earlier suggests this pattern of HPA activation may adversely impact infants through both impaired parenting and neuroendocrine attunement during challenging interactions involving infant distress. In this way, the findings from Study 2 help contextualize the importance of Study 1 effects—they indicate that an escalating symptom course has harmful implications not only for the mother's wellbeing, but also for her ability to engage in health-promoting interactions with her infant. By demonstrating an effect of increasing symptoms, as opposed to simply high levels at a given time, these results point to intervention needs in women who may not meet a particular clinical threshold but who are experiencing growing struggles in the postpartum.

Examining a heterogeneous sample of community mothers in Study 2 revealed differing effects by risk group, with an escalating symptom profile only relating to HPA dysregulation among clin-

[2] Again, specificity to depression was evaluated by testing anxiety symptom trajectories in relation to cortisol, as well as Depression × Anxiety Diagnosis comorbidity effects. None of these models revealed significant effects involving anxiety.

Table 3
Maternal Cortisol During Infant Stressor Related to Depressive Symptom Trajectories

Predictor	Intercept (poststress cortisol level) γ (*SE*), *p*	Linear slope (instantaneous rate of cortisol change poststress) γ (*SE*), *p*	Quadratic slope (overall rate of cortisol acceleration across session) γ (*SE*), *p*
A. Depressive symptom intercept (level at 18 months postnatal)	.33 (.090), .001	−.017 (.021), .421	−.017 (.022), .426
Depressive symptom slope (growth 3–18 months postnatal)	−.16 (.078), .045	−.001 (.019), .946	.017 (.021), .423
B. Depressive disorder diagnosis	.10 (.19), .596	.002 (.047), .974	.005 (.033), .875
Depressive symptom intercept	.41 (.089), <.001	−.012 (.023), .609	−.029 (.023), .219
Depressive symptom slope	−.24 (.081), .005	.011 (.020), .592	.033 (.021), .122
Diagnosis × Symptom Intercept	−.55 (.22), .013	−.009 (.054), .873	.083 (.044), .062
Diagnosis × Symptom Slope	.56 (.23), .020	−.052 (.043), .235	−.099 (.034), .006

Note. Symptoms are Center for Epidemiologic Studies Depression Scale (CESD) scores measured at 3, 6, 12, and 18 months postnatal. Cortisol was measured before and after LabTAB Maternal Separation and Stranger Approach tasks at 18 months postnatal.

ical cases (i.e., those with a lifetime depression diagnosis). This distinction echoes another finding in this sample that the effect of maternal depressive symptoms on their infants' cortisol depended on mothers' diagnostic status (Laurent, 2017) and underlines the possibility that symptoms may carry a different meaning for women who have experienced clinically significant mood difficulties going into pregnancy and the postpartum period compared with those who have not. Opposing correlates of symptom course in the clinical and nonclinical groups could reflect different ways of responding to escalating symptoms that are more or less likely to perpetuate disorder. For example, mothers without a history of major depression may attempt to cope with mood difficulties by withdrawing from difficult interactions (and, thus, lowering cortisol), whereas mothers with major depressive disorder may find themselves becoming more enmeshed in such stressors, perpetuating the cycle of increasing symptoms and HPA axis hyperactivation. The fact that carrying a depression diagnosis did not moderate effects in Study 1 is likely attributable to limited variability—the vast majority of the sample carried a depressive disorder diagnosis, and all were classified as high-risk based on the clinical recruitment site from which they were drawn. Similarly, the lack of comorbidity effects in these studies may be because of insufficient numbers of anxious mothers in each sample, limiting our power to detect Depression × Anxiety effects.

This distinction between clinical and nonclinical cases contrasts with other maternal depression research highlighting similarities between women with elevated depressive symptoms not reaching diagnostic criteria and those with a depression diagnosis (Good-

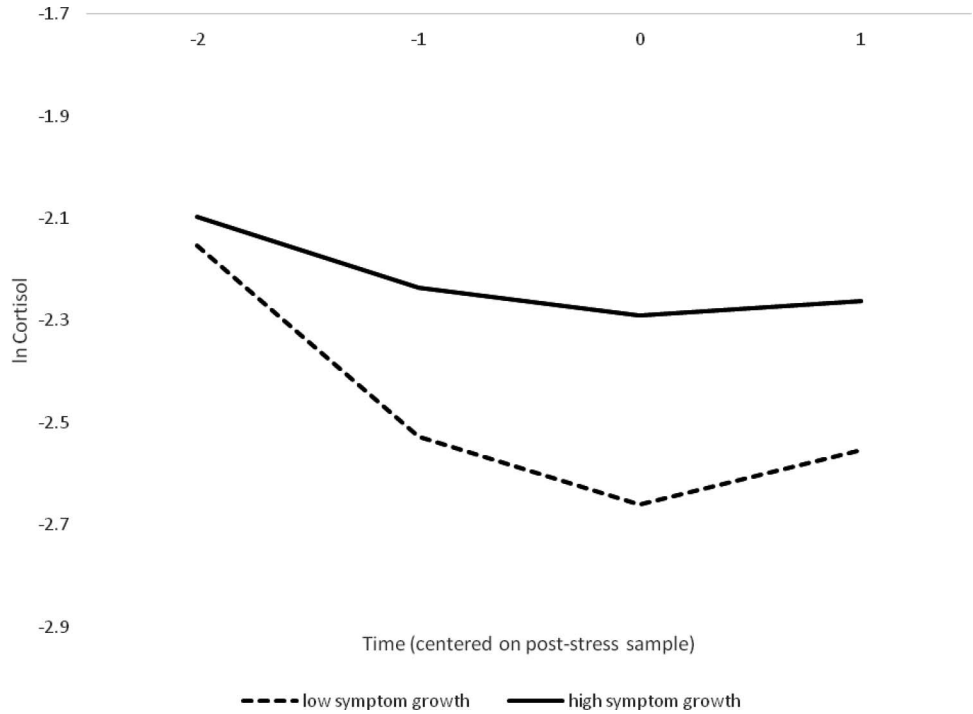

Figure 3. Course of depressive symptoms from 3–18 months postnatal predicts cortisol response trajectories at 18 months postnatal for mothers with a depression diagnosis.

man et al., 2011; Goodman & Tully, 2009). One point of divergence between these studies is the type of outcome under investigation; those showing differences by diagnostic status involve neuroendocrine (cortisol) outcomes, whereas those showing similarities involve psychosocial outcomes. It is possible that the divide between clinical and nonclinical cases is not evident at the behavioral level, but it is at the physiological level. It should also be born in mind that the analytic approaches in these studies differ, and two variables with similar main effects could *also* moderate the effect of one another—that is, saying that highly symptomatic women resemble those with a diagnosis does not exclude the possibility that the effect of those symptoms varies across diagnostic groups. Further work will need to be done to disentangle the conditions under which diagnostic status matters, and research should continue to probe risk dimensions that shape when and how ante- and postnatal depressive symptoms adversely impact mother and infant outcomes.

Beyond helping to illuminate the nature of HPA axis-depression associations during the ante- and postnatal period, this research points to intervention priorities that could improve on current models. If mothers' prenatal HPA activation during stress can prospectively predict symptom trajectories, there may be value in prenatal screening of cortisol response to challenge among high-risk mothers to determine which ones require extra support during the transition to parenting their infant. The current findings further support targeting two groups for early intervention to prevent ongoing stress dysregulation: higher-risk mothers with escalating depressive symptoms and lower-risk mothers with elevated current symptom levels. Other research demonstrating parenting intervention effects on maternal HPA regulation (Toth, Sturge-Apple, Rogosch, & Cicchetti, 2015) suggests that such early stress regulation interventions should focus not solely on the mothers' mental health, but rather should include the mother–infant relationship.

Limitations in the design of the current studies should be used to guide next steps in this line of research. Cortisol measures at three different times from late second trimester to late third trimester of pregnancy indicated stronger effects in the third trimester; this should be followed up with further investigation of the predictive value of maternal cortisol across different periods of pregnancy, and of cortisol in response to different types of stressors—that is, not simply a performance task, but also interpersonal challenges that may involve infant cues. As one example of the latter, the viewing of a labor and delivery documentary was found to evoke physiological (autonomic) reactivity in both pregnant women and their fetuses, which in turn predicted later infant emotional reactivity (DiPietro, Ghera, & Costigan, 2008). Similarly, more fine-grained assessment of the bidirectional associations between maternal symptoms and HPA responsiveness with her infant during early postnatal development would help to clarify when maladaptive patterns become entrenched and what an optimal intervention window might be.

It will also be critical to test mediators of the reported effects, including infant emotion regulation, parenting efficacy and effectiveness, and perceived stressfulness of parent–infant interactions. Prospective effects of maternal symptom trajectories and HPA regulation during parenting interactions on child adjustment outcomes should be tested to establish the potential role of these patterns in intergenerational transmission of mental health risks. Although we did not find evidence that other factors previously associated with HPA function, such as PTSD, anxiety, and psychiatric treatment (weeks of antidepressant use during pregnancy), impacted the reported findings, future studies designed to address these factors in greater depth (e.g., randomized-controlled-trials in samples with varying comorbidities) could further probe such possibilities. It is noteworthy that the majority of women in Study 1 were followed clinically in a treatment program. It is likely that if depressive symptoms increased in the postpartum period, there may have been alterations in treatment to reduce such symptoms. This would have potentially decreased our ability to detect the predictive association of prenatal cortisol with later depression, underscoring the relative strength of the association demonstrated.

Finally, although a strength of the study was the two samples representing varied sets of risk characteristics—that is, higher-SES with serious mental health risks and lower-SES not selected for mental health risk—it will be important to test these effects in larger samples that encompass a range of these and other characteristics to better characterize risk groups. One relevant dimension on which the current samples were fairly homogenous was race/ethnicity, with the majority of women in both studies describing themselves as White and non-Hispanic. Given evidence that women of color typically experience more stress during pregnancy and adverse perinatal outcomes that may be related to stress dysregulation (Alhusen, Bower, Epstein, & Sharps, 2016), it will be critical to evaluate whether the HPA axis-symptom associations detected here apply to these groups. Selection bias may also have impacted results; whereas Study 1 included more participants with a diagnosed depressive disorder, Study 2 included participants with higher income and fewer depressive symptoms, compared with excluded participants. Thus, we might expect Study 1 to better detect effects that apply to a high-risk group, whereas Study 2 would be limited in the detection of such effects. Each set of effects—that is, of earlier cortisol on later depression course, and of earlier depression course on later cortisol—should be tested across a balanced range of diagnostic status including relevant comorbidities.

For now, the studies reported here take a critical step toward understanding who among a high-risk pool of mothers are at greatest risk for ongoing mood difficulties and why. By highlighting identifiable risk trajectories, we hope to inform targets of ante- and postnatal screening and intervention that could interrupt cycles of psychophysiological dysregulation both within and across generations.

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