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Perinatal Depression Influences on Infant Negative Affectivity: Timing, Severity, and Co-Morbid Anxiety

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Abstract

Accumulating evidence suggests that antenatal depression predicts infants' negative affectivity, albeit with variable effect sizes. With a prospective longitudinal design, we sought to explain that variability by addressing questions about timing of the depression across pregnancy and the early postpartum, the role of high symptom levels relative to diagnosed depression, comorbidity with anxiety, and the potential mediating role of neuroendocrine functioning. Primiparous women ($n = 77$) with histories of depression prior to pregnancy were assessed for cortisol levels monthly beginning by mid-pregnancy. Depression symptom levels and diagnostic status were similarly assessed monthly in pregnancy and also until infants reached three months of age, when mothers completed the Infant Behavior Questionnaire – Revised to measure infant negative affectivity. Antenatal depression symptoms and infant negative affectivity were positively associated ($r = .39$). Controlling for depression symptom levels in other trimesters, only second trimester depression symptoms predicted higher infant negative affectivity ($\beta = .44$). With postpartum depression symptom levels in the model, only antenatal depression symptoms predicted infant negative affectivity ($\beta = .45$). In the context of depression, neither antenatal anxiety symptoms nor anxiety disorder diagnosis were associated with infant NA scores. The hypothesized role of elevated maternal cortisol as a mechanism for the association between antenatal depression and infant NA was not supported. Our findings contribute to efforts to more precisely identify infants of perinatally depressed mothers who are at greater risk for elevated negative affectivity, suggesting a window of vulnerability in mid pregnancy and the need for further study of potential mechanisms.

Keywords

negative affectivity; depression; perinatal; infants; temperament

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Negative affectivity (NA) is the superordinate construct that reflects the pervasive individual differences in one's propensity to experience negative emotions (Watson & Clark, 1984). NA in infants is of particular concern for several reasons. First, NA can be reliably identified as early as three months of age (Gartstein & Rothbart, 2003) and is relatively stable over time, even from early infancy (Lee & Bates, 1985; Putnam, Rothbart, & Gartstein, 2008; Roberts & DelVecchio, 2000). Second, elevated levels of NA in infants are prospectively associated with symptoms of depression and anxiety, including internalizing symptoms at age 2 (Putnam & Stifter, 2005), internalizing and externalizing symptoms at age 4 (Gartstein, Putnam, & Rothbart, 2012), and fear, shyness, sadness, and anger/frustration at 7 years of age (Rothbart, Derryberry, & Hershey, 2000). Third, high NA in infancy is of concern because of its potential role in transactional processes (Pesonen et al., 2008; Sameroff, 1975). That is, infants high in NA may shape their environments by evoking negative responses from their caregivers, with these transactional processes in turn potentially contributing to the development of psychopathology.

Given that this measurable and stable construct has important links to the later development of psychopathology and emerges so early in development, researchers have attempted to identify its predictors. Among potential predictors, much interest has focused on pregnancy, given theory and evidence from animal and human studies that prenatal exposures may alter fetal development of neuroregulatory systems related to aspects of behavioral and emotion regulation central to the concept of temperament (DiPietro, 2012; Monk, Webb, & Nelson, 2001). Consistent with these ideas, in multiple studies, antenatal depression has been identified as a predictor of NA in infants (Austin, Hadzi-Pavlovic, Leader, Saint, & Parker, 2005; Cutrona & Troutman, 1986; Davis et al., 2007; Davis et al., 2004; Huot, Brennan, Stowe, Plotsky, & Walker, 2004). However, effect sizes have ranged broadly among the published studies, from $r = 0.11$ to $r = 0.52$. A likely factor in that variability of effect sizes is that antenatal depression is typically treated as a unitary factor, defined either as meeting diagnostic criteria or exceeding established cut scores for clinically significant levels of symptoms. Yet the construct of 'depression' comprises broad variability in terms of clinical characteristics (Boland & Keller, 2009). Thus, by taking that variability into account, we may be able to help explain for whom or under what situations antenatal depression will be associated with infant NA. We sought to understand what it is about maternal depression that matters for infant NA by testing hypotheses on theory-based aspects of antenatal depression that would be expected to be related to NA in infants, including the timing of the antenatal depression, whether depression is defined diagnostically or by high symptom levels, comorbidity with anxiety, and the role of the often correlated postpartum depression. In addition, we sought to expand on knowledge of potential mechanisms for the association between antenatal depression and infant NA by testing the potential mediating role of neuroendocrine functioning.

Greater understanding of the role of clinical characteristics of the mother's depression on infant NA has the potential to: (1) help to explain the variability in effect sizes that has been found in tests of association between antenatal depression and infant NA and (2) highlight subgroups of infants who are at greater risk for elevated NA relative to others, based on the qualities of the mothers' depression.

First, looking at the timing of antenatal depression, the literature has been somewhat mixed. Huot et al. (2004) found that depression in the first or second trimester (combined due to their small sample of women with first trimester depression) was significantly associated with NA while depression in the third trimester was not, whereas Davis et al. (2007) found significant although small associations between antenatal depression and 2-month-old infants' "negative reactivity" (measured by the Fear subscale of the Infant Behavior Questionnaire – Revised) regardless of whether depression was measured during the second or third trimester. The discrepancy in findings may be explained by Huot et al. (2004) having measured NA in offspring ranging from 6 months to 5 years of age. Further, there is some support for an increase in heritability of NA across development. In particular, a study of twin neonates found the heritability estimates of NA-like neurobehavioral indices to be no different than zero (Riese, 1990), while a longitudinal study found heritability to increase across twelve to thirty months of age (Matheny, 1989). This suggests that there might be different predictors of NA at different points in development. Therefore, we sampled infants at 3 months of age exclusively, the earliest point in development at which NA can be reliably measured (Gartstein & Rothbart, 2003), so as to delineate predictors of NA at this precise point in development. Our study further aimed to help resolve these disparate findings regarding the role of timing of antenatal depression exposure in predicting infant NA by assessing depression at multiple timepoints throughout pregnancy. In the context of the mixed findings, we also took into consideration knowledge that the neurons involved in the relevant neural circuits (e.g. limbic system and associated regions of the cortex) proliferate, differentiate, and migrate between the eighth and 24th week of gestation (Nowakowski & Hayes, 2002), and thus hypothesized that infants would be most adversely impacted by second trimester depression.

The disparate findings on timing may also be attributable to the approach to measurement of NA. Although both Huot et al. (2004) and Davis et al. (2007) measured NA with the Infant Behavior Questionnaire (IBQ) (Rothbart, 1981), Davis et al. (2007) relied on only one of the four subscales (Fear) within the IBQ-derived NA dimension. In an effort to bridge the gap between these two studies, we tested primary hypotheses with the NA dimension of the IBQ-R, but also explored associations with the subscales that comprise that dimension. We expected to replicate the Davis et al. finding on the fear subscale and examined the other three subscales in an exploratory manner.

Second, we sought to explore the extent to which clinically significant depressive symptomatology that falls short of meeting Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV) (American Psychiatric Association, 1994) Major Depressive Episode (MDE) criteria contributes to infant NA. Women with sub-clinical depression during pregnancy have been found to not differ significantly from women with diagnosed depression on stress, anxiety, and severity of depression symptoms (Goodman & Tully, 2009). In a study comparing neonatal behavioral functioning of infants, although infants of women with antenatal depression showed poorer neonatal neurobehavioral functioning than infants of women with no antenatal depression, infants of women with MDE did not differ from infants of women with sub-clinical depression (Goodman, Rouse, Long, Ji, & Brand, 2011). Consistent with this evidence, we hypothesized that infants of women with depression during pregnancy, whether defined by high depression symptoms

alone or MDE diagnosis, would have significantly higher levels of NA than infants of women who did not experience clinically-significant depression during pregnancy.

A third unanswered question about the association between antenatal depression and infant NA is the role of comorbid antenatal anxiety. In previous findings from the sample from the present study, we found that nearly forty percent of women who experienced a MDE during pregnancy also met criteria for a comorbid anxiety disorder, typically Generalized Anxiety Disorder (GAD) (CITATION REDACTED). Comorbid depression and anxiety may elevate infants' risk for NA given the finding that antenatal maternal cortisol was elevated only when both depression and anxiety disorders were co-morbid (Evans, Myers, & Monk, 2008). With this understanding, we hypothesized that NA would be highest in infants of women experiencing both depression and anxiety disorders during pregnancy, as compared to infants of women experiencing diagnosed depression only or no disorder during pregnancy. As to symptom levels, regardless of diagnosis, depression and anxiety symptom levels are typically highly correlated, with coefficients approaching .70 in population-based studies (O'Connor, Heron, & Glover, 2002). The co-occurrence of high levels of anxiety symptoms, even in the absence of a diagnosis, may represent an increased risk to the developing fetus. Thus, we predicted that symptom levels of anxiety would moderate the association between symptom levels of depression and infant NA, such that higher levels of anxiety symptoms would strengthen the association between depression symptom levels and infant NA.

Fourth and finally, it is important to consider the potential role of postnatal depression in infant NA. A large body of literature has examined postnatal depression and infant NA, even in early infancy, finding positive associations concurrently and prospectively, even after controlling for earlier level of temperament (Austin et al., 2005; for a meta-analysis, see C. T. Beck, 1996; Edhborg, Seimyr, Lundh, & Widstrom, 2000; Hanington, Ramchandani, & Stein, 2010). These findings are consistent with the idea that exposure to adverse parenting or stressors associated with postpartum depression may contribute to children's development of vulnerabilities to depression (Goodman & Gotlib, 1999). However, this interpretation fails to take into account that the strongest predictor of postnatal depressive symptoms is the presence of those symptoms during pregnancy (O'Hara & Swain, 1996), and thus findings on associations between postnatal depression and infant NA may be attributable to the prenatal depression. Therefore, we hypothesized that any association between postnatal depression symptoms and infant NA would be accounted for by the shared association with antenatal depression. In other words, we predicted that postnatal depression would not account for significant unique variance in infant NA, when antenatal depression was included in the model.

Turning to potential mechanisms, depression during pregnancy, and the often accompanying high anxiety levels (Goodman & Tully, 2009), may contribute to the development of infant NA at least partly because antenatal cortisol levels may be elevated in association with depression and anxiety (Glover, Teixeira, Gitau, & Fisk, 1999). Exposure to elevated levels of maternal cortisol may result in alterations of developing fetal neuroregulatory systems. Some animal data support the idea that the fetal hypothalamic-pituitary-adrenal (HPA) axis (Challis et al., 2001) and limbic regions that modulate fear responses (Owen, Andrews, &

Matthews, 2005) are susceptible to programming by maternal glucocorticoids. Dysfunction in these regions could contribute to both the mood dispositional tendencies and pervasive stress reactivity encompassed by the NA construct. Further, evidence from animal models reveals that fetal exposure to elevated glucocorticoids contributes to conditions resembling NA (Weinstock, 2005). Thus among infants of antenatally depressed mothers, elevated cortisol may at least partly explain the association with infant NA.

A few studies have made advances towards testing this mechanism in humans. Among women not selected for depression, higher levels of cortisol in late pregnancy were associated with more “difficult temperament” in 7-week-old infants (de Weerth, van Hees, & Buitelaar, 2003) and with 2-month-old infants’ greater “negative reactivity” (measured by the Fear subscale of the Infant Behavior Questionnaire – Revised) (Davis et al., 2007). However, de Weerth et al. (2003) did not measure maternal depression and thus were unable to test mediation, and Davis et al. (2007) found no significant association between levels of depressive symptoms and cortisol during pregnancy, and thus concluded that maternal cortisol levels did not mediate the association between antenatal depression and infant NA.

Although Davis et al. (2007) failed to support maternal cortisol levels as a mechanism for the association between depression and infant NA, several factors suggest the need for further study. First, HPA axis dysregulation is not commonly associated with depression symptoms in community samples (Peeters, Nicolson, & Berkhof, 2004). Rather, elevated cortisol is associated with more frequent and severe episodes of major depression (as reviewed by Knorr, Vinberg, Kessing, & Wetterslev, 2010). Therefore, it is not surprising that elevated cortisol was not found to be associated with depression symptoms in Davis’ community sample, unselected for depression. Thus we examined cortisol mediation in women with histories of MDEs, among whom HPA axis dysfunction would be more expected relative to general population samples. Further, Davis et al. (2007) measured afternoon cortisol, which has been recommended for capturing HPA reactivity in pregnant women (de Weerth & Buitelaar, 2005b). However for capturing baseline cortisol in pregnant women, morning cortisol is indicated (de Weerth & Buitelaar, 2005a). Baseline cortisol was our interest given our focus on chronicity of infant exposure to elevated levels of maternal cortisol, rather than on brief episodes of exposure, as are captured by studies of HPA reactivity to stressors. Thus, we measured morning cortisol, thereby expanding on the Davis et al. (2007) study. We predicted a greater likelihood of mediation by cortisol to be found during the third trimester, given the finding by Davis et al. (2007) that cortisol in the third trimester was associated with infant temperament.

We chose to operationally define infant NA with the IBQ-R, relying on mothers’ reports, instead of via a laboratory-based observational approach. Although there are strengths and weaknesses to both approaches (for a review, see Gartstein & Marmion, 2008), parent report has an advantage over laboratory assessment in that parents are able to observe their infants’ naturally occurring behaviors across settings and different times of the day. Despite their differences, the approaches are convergent (Rothbart & Bates, 2006). Although there has been some question about the reliability of child temperament reports when the parent is currently depressed (Whiffen, 1990), the IBQ-R has proven to be resistant to the potentially biasing influence of parental depression (Gartstein & Marmion, 2008). Moreover, it may be

that depression in mothers enhances their awareness of depression-related behaviors in their children. Consistent with this model, Hayden et al. (2010) found that for mothers who were high in negative emotionality (NEM) themselves, the correlation between maternal ratings of their children's temperament and laboratory measures of the children's temperament (sadness and anger/frustration) were positive and significant, whereas for mothers low in NEM, the correlation was in the negative direction and not significant (Hayden, Durbin, Klein, & Olino, 2010). That is, agreement between maternal report and laboratory measures of anger and sadness was greater among a subset of mothers high in NEM, a strong correlate of depression in adults. Finally, the IBQ-R specifically has several advantages relative to other questionnaire measures of temperament, including only asking parents to recall infant responses to concrete events that have occurred within the last 1–2 weeks and not requiring parents to make comparative judgments to other infants (Gartstein & Rothbart, 2003). Given these multiple supporting findings, we relied on maternal report with the IBQ-R to measure infant NA.

In sum, we sought to understand what it is about maternal depression that matters for infant NA, studying women who were at elevated risk for perinatal depression. First, we predicted that depression in the second trimester would be most strongly associated with infant NA relative to depression in other trimesters. We also predicted that NA would be elevated in infants of mothers with clinically significant levels of depressive symptoms during pregnancy, whether or not they met DSM-IV diagnostic criteria for a major depressive episode, relative to infants of mothers without significant depression symptoms. We tested hypotheses about the possible exacerbating role of anxiety symptom levels and disorder in associations between depression and NA. Finally, we examined contributions of antenatal depression relative to early postnatal depression in predicting NA, hypothesizing that any association between postnatal depression and infant NA would be due to a shared relationship with antenatal depression exposure. We also examined the glucocorticoid mediation hypotheses, predicting that maternal cortisol levels would mediate the associations between antenatal depression and infant NA. We tested hypotheses on prospective predictors of NA with a longitudinal design, sampling women with a history of MDE prior to pregnancy, given their heightened risk for depression recurrence during the perinatal period (O'Hara & Swain, 1996). This sampling strategy was also ideal for testing glucocorticoid mediation, given the increased likelihood of finding HPA axis dysfunction among women with depression histories relative to others.

Method

Participants

The data for the study were collected as part of a longitudinal study that followed women with histories of depression from early- to mid-pregnancy through the first year postpartum. We recruited participants from obstetrical/gynecologists' offices or through media announcements. We determined eligibility using a two-stage process. First, a brief phone screen determined if the women were likely to have ever experienced a depression episode. The screen consisted of the two gateway questions from the Diagnostic Interview Schedule (Robins, Helzer, Croughan, & Ratcliff, 1981) that inquire about at least 2 weeks of

depressed mood or anhedonia in their lifetimes. These two items have high sensitivity as screeners for depression, from .83 to .94 across samples (Rost, Burnam, & Smith, 1993). Second, eligible women were invited to the lab where, after informed consent, they were administered a diagnostic interview to determine that they met diagnostic criteria for at least one lifetime MDE, using the Structured Clinical Interview for the Diagnostic and Statistical Manual- IV Axis I Disorders – Patient Edition (SCID) (First, Spitzer, Gibbon, & Williams, 1995). Inclusion criteria for the study were selected in order to minimize the contribution of potentially confounding sociodemographic variables known to be associated with depression (e.g. teen motherhood, single motherhood, parity etc.) and were as follows: meeting DSM-IV criteria for a MDE that began prior to pregnancy, being no further along in the pregnancy than five months, being between the ages of 18 and 40, carrying their first child, being either married, cohabiting with a significant other, or some other stable living situation, and being African-American or European-American. These ethnic groups were selected to match the demographics of the metro area from which we recruited, in which these groups together comprise approximately 90% of the population (U.S. Census Bureau, 2002). Exclusion criteria included: experiencing active suicidal ideation; meeting DSM-IV criteria for an organic mental disorder, a substance use disorder, schizophrenia or other psychotic disorder or the presence of psychotic features, bipolar disorder, or delusional disorder; testing positive in a urine toxicology screen; or having a pre-existing medical condition that had not been stable for at least six months. Once infants were born, there were no exclusion criteria based on factors such as gestational age or birthweight, in order to retain as representative a sample as possible.

We enrolled 107 women through these processes, most by their fourth month of pregnancy. During pregnancy, 24% ($n = 26$) were lost to attrition; no participants explicitly declined participation once enrolled. Another four women did not withdraw from the study, but did not participate in the three-month data collection. Those women for whom we did not have three-month data did not significantly differ from the enrolled sample on amount of missing data, on any demographic variable, including ethnicity, marital status, household income, educational attainment, or age, nor on any index of psychopathology, including number of depression episodes prior to enrollment in the study, number of months since last depression episode, depression symptom severity at enrollment, or mean anxiety symptoms across pregnancy. The final sample for this study included 77 women and their 3-month-old infants ($M = 14.87$ weeks, $SD = 1.71$). Of the 77 women in the sample, 30% were African-American and 70% were European-American; 70% were college educated; 74% were married. The mean age was 30.43; the median household income group was \$71,000–\$75,000, slightly higher than the median for the area from which we sampled, \$51,349 (U.S. Census Bureau, 2002). Of the 78 infants born to these women (including one set of twins), 54% were female and 46% were male. The mean gestational age of the infants was 39.1 weeks ($SD = 0.22$, Range = 30.7 – 42.1). There were eight infants born before 37 weeks gestational age. The mean weight at birth was 3311.56 grams ($SD = 631.38$), the mean 1-minute APGAR score was 7.82 ($SD = 1.36$), and the mean 5-minute APGAR score was 8.89 ($SD = .31$). Infant NA was not significantly correlated with gestational age, birth weight, or APGAR scores, nor was the mean of antenatal maternal depression scores associated with

any infant birth indices. Finally, infant birth indices did not differ by whether or not mothers became depressed during pregnancy.

Procedure

Women took part in diagnostic interviews and completed mood questionnaires on a monthly basis from their entry into the study (typically the third or fourth month of pregnancy) through six months postpartum and then again at 12 months postpartum (Table 1). We also collected urine samples, for cortisol assays, each month from enrollment during pregnancy up to delivery. The data through infant age 3 months were the focus of this study. Women were paid \$25 at each study visit. The study was approved by the REDACTED Institutional Review Board.

Measures

The Infant Behavior Questionnaire - Revised (IBQ-R; Gartstein & Rothbart, 2003)—The IBQ-R is a 191 item, factor-analytically derived measure of infant temperament, based on the definition of temperament posited by Rothbart and Derryberry (1981). Respondents rate the infant's behavior during the past week in a variety of domains on a seven-point scale, from one (Never) to seven (Always). The questionnaire yields scores on 14 scales, with ten to 18 items per scale and scale scores being the mean of items on that scale. Scales cluster into three overarching factor scores: Orienting/Regulatory Capacity, Surgency/Extraversion, and Negative Affectivity (NA). NA, the variable of interest in this study, is calculated as the mean of four scales: Falling Reactivity, Fear, Frustration/Distress to Limitations, and Sadness, with a possible range of one to seven. Higher scores indicate higher levels of NA.

For each of the four scales that comprise NA, internal consistency within the normative sampling group of 3- to 6-month-olds was high (Gartstein & Rothbart, 2003). No equivalent data were reported for the broader factor of NA. Gartstein and Rothbart also reported high levels of inter-rater reliability between primary and secondary caregivers for three of the four scales (all but Sadness). For the present sample, the alpha coefficient(s) for NA was .94 and for the scales were as follows: Falling Reactivity (.80), Fear (.96), Frustration/Distress to Limitations (.89), and Sadness (.91).

Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; First et al., 1995)—The SCID is a semi-structured diagnostic interview designed to assess Axis I disorders of the DSM-IV. The SCID was used to assess for a lifetime history of any psychological disorders, including from conception up to the time of the initial interview in pregnancy. All interviews were conducted by master's level clinical psychologists, a psychiatric nurse, or a social worker and audio recorded. A licensed clinical psychologist, blind to other information on the participants, listened to all interviews and independently derived diagnoses. Diagnostic decisions were ultimately made by the psychologist based on discussion with the interviewer, written notes of responses to interview questions, and review of the audio-recorded interview. The full interview covering all Axis I disorders was administered only during the first visit and served as the final screener for entry into the study. The SCID screener and mood module were administered at each subsequent data

collection point. The SCID ultimately yields a diagnosis as to whether or not the women met full criteria for a Major Depressive Episode (MDE) or an Anxiety Disorder, either in the past or currently, according to criteria outlined in the DSM-IV.

Beck Depression Inventory-II (A. T. Beck, Steer, & Brown, 1997)—The BDI-II is a 21-item self-report scale assessing the intensity of depressive symptoms in the previous two weeks; higher scores reveal more severe levels of depression symptoms. In addition to evidence for reliability and consistency in clinical and nonclinical samples, the BDI-II also serves well as a screening test during pregnancy and postpartum (e.g., Boyd, Le, & Somberg, 2005; Steer, Ball, Ranieri, & Beck, 1997; Steer, Scholl, & Beck, 1990; Su et al., 2007; Whisman, Perez, & Ramel, 2000). Coefficient alpha in the current study ranged from .74 to .96. A score of 14 or higher indicates clinically significant levels of depression (A. T. Beck et al., 1997).

The State-Trait Anxiety Inventory (STAI) (Spielberger, Gorsuch, & Lushene, 1970)—The 20-item state scale of the STAI is a continuous measure of state anxiety. Scores range from 20 to 80, with higher scores indicating greater anxiety. The STAI has adequate concurrent validity and internal consistency (Spielberger et al., 1970). Coefficient alphas in the current study ranged from .89 to .97.

Cortisol—We studied morning cortisol based on findings that morning levels represent the peak in the circadian rhythm and may be the best cortisol marker of associations between antenatal stressors and infant outcomes (de Weerth & Buitelaar, 2005a). We collected urine samples at each of the monthly pregnancy visits, concurrently with the monthly SCID interview and completion of depression and anxiety rating scales (for means and standard deviations of monthly values, see Table 1). We instructed women to collect the urine in the morning, after the first voiding, until noon and refrigerate it until they brought it to the lab that day. Experienced lab technicians from the REDACTED measured urine “free” cortisol using the extracted competitive binding immunoenzymatic assay available on the Beckman Coulter Access analyzer (Beckman Coulter Access Immunoassay System Product Insert (1997): Cortisol assay 170157E, 1997). In this assay, the cortisol in urine is extracted with ethyl acetate. A portion of the ethyl acetate supernatant is evaporated to dryness and re-dissolved in assay buffer. This extraction process effectively removes the steroid metabolites and other cross-reacting steroids known to be present in urine. The extracted specimen is placed on the analyzer where the cortisol in the extract competes with a cortisol-alkaline phosphatase conjugate for binding sites on a rabbit anti-cortisol antibody. Paramagnetic particles coated with goat anti-rabbit capture antibody are then added. The captured antigen-antibody complexes are separated in a magnetic field and washed to remove unbound substances. Next, a chemiluminescent phosphatase substrate is added and the light generated measured with a luminometer. The light produced is inversely proportional to the concentration of cortisol in the sample. Recovery of cortisol from the ethyl acetate extraction averages 99% over a wide range of concentrations. The limit of detection is 0.4 µg/dL of urine. The between run imprecision is 7.9% at 6.0µg/dL and 6.0% at 24.1µg/dL. The within run imprecision is 6.7 and 4.4% at the same levels respectively. The assay has also been compared to the extracted DPC cortisol RIA and yielded a linear regression

coefficient (r) of 0.968 ($y = 0.988x + -1.10$, $n=121$). Samples are run in duplicate and three levels of quality control are included with each assay run. Duplicates are averaged unless they exceed a 10% difference in which case the analysis is repeated. Mean cortisol values showed the expected rise over the course of pregnancy (see Table 1). The number of maternal urinary cortisol sample collections during pregnancy ranged from three to eight ($M = 5.25$ ug/dL; $SD = 1.27$). For months four through nine (second and third trimesters), a total of 16.7% of values were missing. Patterns of missing values were not significantly associated with any demographic, independent, or dependent variable and thus appeared to be missing at random. Therefore we imputed values in those cases where data were missing. Following Pruessner et al. (2003), we calculated area-under-the-curve (AUC) to capture degree of fetal exposure to cortisol across the second and third trimesters (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003).

Results

Descriptive and Preliminary Analyses

Perinatal depression and anxiety—Sample means and SDs for perinatal depression symptom levels (BDI-II), percentages of women experiencing Major Depressive Episodes, and percentages of women experiencing clinically significant depression symptom levels (BDI-II ≥ 14) are reported in Table 2. Mean antenatal anxiety symptom level (STAI-S) was 34.37 ($SD = 8.13$).

Infant NA—IBQ-R NA scores ranged from 2.72–5.66, with a mean of 3.50 ($SD = 0.57$). This mean among infants in this study was significantly higher than that of the standardization sample ($M = 2.55$), with a large effect size (Cohen's $d = 1.51$) (Cohen, 1988). NA scores were not significantly associated with the infant's gender or ethnicity or with concurrent maternal depression or anxiety symptom severity levels.

Hypothesis Testing

Depression by trimester in pregnancy and infant NA—NA scores were not significantly different between infants of women who did and did not meet diagnostic criteria for a MDE during any trimester [first trimester: $t(60) = 0.98$, $p = .33$; second trimester: $t(76) = 1.52$, $p = .14$; third trimester: $t(75) = 0.77$, $p = .45$], with small effect sizes for the differences in all three trimesters (Cohen's $d = 0.29$, 0.44 , and 0.36 , respectively). In contrast, as can be seen in Table 3, higher mean depressive symptom severity (BDI-II scores) in both the second trimester (large effect) and the third trimester (moderate effect) were significantly prospectively associated with infants' higher NA scores.

In order to test the prediction that depression in the second trimester would be most strongly associated with infant NA relative to depression experienced in other trimesters, we first regressed infant NA onto mean BDI-II scores in the second and third trimesters (Table 4), revealing that only depression symptom levels in the second trimester predicted infant NA. That is, consistent with prediction, controlling for depression symptom levels in the third trimester, only second trimester depression symptom levels accounted for significant variance in infant NA scores.

A similar regression analysis (Table 4) was conducted in which infant NA was regressed onto the MDE diagnostic status variable (depressed or not) in each trimester. This analysis revealed that MDE in any trimester, controlling for depression status in the other two trimesters, did not predict infant NA.

In an attempt to replicate the finding that antenatal depression symptoms were significantly associated with the IBQ-R Fear scale, and to explore whether the associations also extended to other three IBQ-R scales of NA, we conducted zero-order correlations between mean antenatal BDI-II score and each of the four IBQ-R scales comprising NA. All correlations were significant in the predicted direction, with effect sizes ranging from small (Fear: $r = .24$, $p = .03$, Falling Reactivity: $r = .24$, $p = .04$) to moderate (Sadness: $r = .39$, $p < .001$) to large (Distress to Limitations: $r = .50$, $p < .001$), using guidelines according to Cohen. Consistent with Distress to Limitations yielding the only association with a large effect size, partial correlations between mean antenatal BDI-II scores and each of the NA subscales, controlling for the other three subscales revealed that antenatal depression symptoms were significantly correlated only with Distress to Limitations, when controlling for the other NA subscales (partial $r = .35$, $p < .01$; all other partial r 's $< .12$). Findings were similar when limited to second trimester mean BDI-II scores predicting each of the NA subscales, controlling for the other three: only the partial correlation with Distress to Limitations was significant (partial $r = .32$, $p < .01$).

Maternal depression meeting diagnostic criteria relative to high symptom

levels and infant NA—Next, we compared NA scores in infants whose mothers had met criteria for MDE ($n = 25$, $M = 3.60$, $SD = 0.51$) with those who exceeded the BDI-II cut off but did not meet MDE criteria ($n = 17$, $M = 3.59$, $SD = 0.76$). An independent samples t-test comparing infant NA scores between the two depression groups was not significant, $t(40) = .08$, $p = .94$. We conducted a one-way analysis of variance with infant NA as the dependent variable and a planned contrast in order to test our hypothesis that the infants of the two maternal depressed groups combined would have significant elevations in NA when compared to infants of mothers who met neither criterion for depression during pregnancy ($n = 36$, $M = 3.41$, $SD = 0.50$). Contrary to our hypothesis, neither the ANOVA nor the planned contrast was significant [ANOVA: $F(2, 75) = 1.02$, $p = .37$, partial eta squared = .03; planned contrast: $t(75) = 1.40$, $p = .16$, Cohen's $d = 0.32$]. That is, we found no significant group differences in NA.

We conducted a set of post-hoc analyses in order to better understand the contrast between the findings that (1) mean BDI-II scores were significantly correlated with infant NA with a moderate effect size and (2) infant NA scores of the two depressed groups and the non-depressed group did not differ significantly. We divided the sample into two groups based on mean antenatal BDI-II score – those whose mean scores exceeded the clinical cut-off across pregnancy ($n = 17$), reflecting chronic elevated antenatal depression symptoms, and those whose mean scores did not ($n = 60$), reflecting low depression symptom levels throughout pregnancy or an occasional spike in symptoms that was not sustained. An independent samples t-test comparing infant NA scores between the two groups was significant, $t(75) = 3.90$, $p < .001$, Cohen's $d = 0.96$, a moderate effect size equivalent to $r = .43$ (Cooper, Hedges, & Valentine, 2009). As further validation, we conducted a partial

correlation between mean BDI-II score in pregnancy and infant NA, controlling for the standard deviation of individual BDI-II scores across pregnancy, and found partial $r = .51$, $p < .001$, a large effect size.

Role of comorbid antenatal anxiety in infant NA—A one-way ANOVA was conducted to determine if comorbid anxiety disorders in the context of MDE were predictive of higher infant NA than MDE alone, or no depression during pregnancy. The independent variable included three levels based on pregnancy diagnoses: no MDE ($n = 46^1$), MDE but no anxiety disorder ($n = 17$), and meeting criteria for both MDE and anxiety ($n = 7$). The ANOVA was not significant, $F(2, 67) = 2.13$, $p = .13$, partial eta squared = .06.

In order to test whether symptoms of anxiety (rather than anxiety disorder) moderated the relationship between antenatal depression symptoms and infant NA, hierarchical regression analyses were conducted. In the first step, both mean antenatal depression and anxiety symptom scores were entered. In the second step, the statistical interaction term reflecting the product of mean antenatal depression and anxiety scores was entered. Tolerance and variance inflation factor statistics were within acceptable ranges, indicating that multicollinearity was not a concern. As shown in Table 5, only antenatal depression symptom levels and not anxiety symptoms or the interaction of depression and anxiety accounted for significant variance in infant NA scores. The amount of variance in infant NA scores accounted for by antenatal depression symptoms reflected a moderate effect size.

Relative contributions of antenatal and postnatal depression to infant NA—In order to test our hypothesis that antenatal depression (symptom level or diagnosis) is more predictive of infant NA than postnatal depression (symptom level or diagnosis), we conducted multiple regression analyses, entering antenatal depression (mean symptom levels or diagnostic status) into the equation at the first step, and postnatal depression through three months at the second step (Table 6). Tests of collinearity indicated that the regression models were not unduly influenced by multicollinearity.

With depression symptom levels, consistent with our hypothesis, when both mean antenatal BDI-II scores and mean postnatal BDI-II scores were included together in the model, only antenatal BDI-II scores significantly predicted NA scores. Contrary to our hypothesis, neither antenatal nor postpartum MDE status explained significant variance in infant NA scores.

Cortisol mediation hypothesis—In order to examine the hypothesis that maternal cortisol levels during the second and third trimesters mediate the association between antenatal depression and infant NA, we followed the steps of mediational analysis suggested by Fairchild and McKinnon (2009) and an SPSS macro developed by Preacher and Hayes (2008). In a mediational analysis, three path coefficients among variables are calculated. For this study, those three coefficients were for paths 1) between mean antenatal depression symptom severity and infant NA; 2) between mean antenatal depression severity and

¹Four participants who did not experience a MDE during pregnancy and met criteria for an anxiety disorder were excluded from this analysis, reducing the size of the no MDE group from $n = 50$ to $n = 46$.

maternal cortisol levels, either in the second or third trimester (AUC); and 3) between maternal cortisol (AUC) and infant NA. Only the path coefficient for the direct effect between mean antenatal depression severity and infant NA was significant. Neither of the indirect path coefficients was significant (for zero-order correlations, see Table 3). Therefore, mediation was not supported.

To further understand the failure to support mediation, we examined whether antenatal maternal cortisol level in either the second or third trimester (AUC) was significantly higher among women who experienced a MDE during pregnancy ($n = 23$) compared to those who did not ($n = 54$). There were no significant group differences in cortisol AUC in the second trimester, $t(75) = .77, p = .44$, Cohen's $d = .20$, or in the third trimester, $t(75) = -.52, p = .60$, Cohen's $d = .13$. Further, contrary to the findings of Evans, Myers, and Monk (2008), antenatal cortisol AUC in either the second or third trimesters was not significantly higher among women who experienced both a MDE and a co-morbid anxiety disorder (most frequently generalized anxiety disorder) during pregnancy ($n = 7$) relative to those experiencing only a MDE without co-morbid anxiety ($n = 18$) and those not experiencing a MDE ($n = 52$), second trimester: $F(2, 74) = 0.38, p = .68$, partial eta squared = .01, third trimester: $F(2, 74) = 2.31, p = .11$, partial eta squared = .06.

Discussion

In an effort to account for variability in reported effect sizes of the association between antenatal maternal depression and infant NA, this study sought to understand what it is about perinatal depression that matters in the prediction of 3-month-old infants' NA. In our sample of women with a history of at least one major depressive episode prior to pregnancy, as expected, we found a moderately-sized positive association between mean depression symptom levels across pregnancy and infant NA. Depression symptoms during both the second and third trimesters were significantly associated with higher NA scores, with moderate and small effect sizes respectively. However, controlling for one another, only depression symptoms during the second trimester significantly predicted higher infant NA, with a moderate effect size. We found that infant NA did not differ based on how depression during pregnancy was defined. However, nor did the NA scores of the infants of mothers who experienced at least one episode of clinically significant depression symptoms, whether or not the episode met MDE criteria, differ significantly from those of infants whose mothers depression symptom levels remained low during pregnancy. We failed to support our hypothesis that infant NA would be highest in the context of comorbid depression and anxiety disorders or that higher levels of anxiety symptoms would moderate the association between depression symptom levels and infant NA. In contrast, we found that although antenatal anxiety symptoms were moderately associated with higher infant NA, when considered in the context of antenatal depression symptom levels, only depression was significantly predictive of infant NA scores, with a moderate effect size. We supported our prediction that postnatal depression would not account for significant unique variance in infant NA beyond the contribution of antenatal depression. Only antenatal depression symptoms explained unique variance in infant NA, with a moderate effect size. Finally, we failed to support a mediational role of maternal antenatal cortisol levels in the association

between antenatal depression and infant NA: cortisol levels were neither significantly associated with depression symptom levels nor with infant NA.

Our finding that higher depression symptom levels during the second trimester were associated with elevated infant NA suggests that, relative to exposure in the third trimester, there may be greater sensitivity in the development of infant NA during the second trimester, consistent with what is known about fetal brain development (Herlenius & Lagercrantz, 2001). Further, although MDE status in any trimester did not statistically significantly predict NA, the effect size for the second trimester association was the largest of the three, consistent with the finding of second trimester depression symptom levels being associated with infant NA.

Suggestive of the potential benefit of examining component constructs within NA in addition to the broader construct, we found that one of the four NA subscales, Distress to Limitations, was driving the association with second trimester depression symptoms. Although we found no published study to report having examined the IBQ-R NA subscales related to antenatal depression, one study found both Distress to Limitations and Sadness to be associated with antenatal anxiety symptoms (Henrichs et al., 2009). Those two scales are typically highly correlated, as they represent two different behavioral responses, frustration or withdrawal, to blocked goal-directed behavior (Putnam, Ellis, & Rothbart, 2001). In fact, the two subscales were also highly correlated in our sample ($r = .70$), but it was uniquely Distress to Limitations that was significantly predicted by antenatal depression when controlling for the other subscales. This finding suggests that antenatal depression symptoms during the second trimester are predictive of a certain subset of the repertoire of infant behaviors that comprise NA. Future studies might expand on this finding to understand the nature of the association between antenatal depression and the type of frustrated infant behaviors tapped by the Distress to Limitations construct.

In contrast to our strong support for mean antenatal depression symptom levels, particularly in the second trimester, predicting infant NA, we did not find support for our hypothesis that infants of mothers with any antenatal MDEs would fare worse than infants whose mothers remained low in depression. That is, it was the fetus's exposure to their mothers' antenatal depression symptoms over the course of the pregnancy, and not their exposure to discrete episodes of MDE per se, that significantly predicted NA. If replicated, this finding suggests the importance of the full antenatal exposure relative to discrete episodes of depression.

Our failure to find significant group differences in infant NA based on maternal antenatal MDEs led us to pose additional questions about the course and severity of antenatal depression exposure. Post-hoc analyses revealed that chronic exposure to high levels of maternal depression was associated with elevated infant NA. This suggested that our failure to find an association with antenatal MDEs might have been due to some women having had only brief episodes. After controlling for variability of depression symptom scores, the effect size for the association between antenatal depression symptoms and infant NA became greater in magnitude than the zero-order effect size lending support to our supposition that chronicity and severity of depression symptoms are both important factors to consider.

Our findings indicate that anxiety in the context of depression does not increase the risk for infant NA. Further, although we had no specific hypothesis about the relative contribution of depression and anxiety symptoms in predicting NA, antenatal depression symptoms accounted for almost all of the variance in infant NA when anxiety symptoms were included in the model, suggesting something unique about the influence of antenatal depression, relative to anxiety, on infant NA. The tripartite model of anxiety and depression posits that low positive emotionality, manifest as anhedonia, is what distinguishes depression from anxiety (Clark & Watson, 1991). Therefore, there may be a biological correlate of anhedonia that differentially influences the development of infant NA, relative to the general affective distress that anxiety and depression share. Future studies should continue to explore biological mechanisms or symptom patterns that might uniquely be associated with depression relative to anxiety in order to further elucidate the risk posed to the developing fetus and the associated vulnerabilities to the development of psychopathology.

Our finding that postnatal depression did not account for unique variance in infant NA has implications for those studies that have examined postnatal depression exclusively, in the absence of measures of prenatal depression, and infant NA. Specifically, we found an instance of statistical suppression in our analyses, revealing that the small association between postnatal depression and infant NA was attributable to their shared association with antenatal depression. Typical cross-sectional studies of postnatal maternal depression and infant NA, which fail to consider antenatal depression, may be coming to erroneous conclusions.

Our finding that cortisol does not mediate the association between antenatal depression symptoms and infant NA corroborates the findings from the only other study we found to have reported testing cortisol as a potential mediator of the association between antenatal depression and infant NA, Davis and colleagues (2007). They found that maternal antenatal cortisol levels were not significantly associated with symptoms of either depression or anxiety during pregnancy. Further, they found that total cortisol across pregnancy, calculated by adding three cortisol values collected during pregnancy, was not predictive of infant fear. We expanded upon their finding in important ways. Namely, we sampled women with elevated depression risk due to histories of depression, we selected a broad, dimensional measure of NA, we calculated area under the curve scores for each trimester, and we measured urinary cortisol in the morning. Even with these methodological advantages, our data failed to support mediation.

An important difference between our study and other studies finding associations between antenatal depression and cortisol (Evans et al., 2008; Lundy et al., 1999) is that our sample of pregnant women was selected for having histories of MDE prior to pregnancy. Given that the neurobiology of HPA axis dysregulation during depressive episodes changes over time (Parker, Schatzberg, & Lyons, 2003), it is possible that the individual differences in history of MDE (e.g. severity, course, age of onset, number of episodes) may introduce error variance, thereby masking a 'true' effect. It will be important for future studies to test whether the elevated antenatal cortisol associated with depression may be moderated by characteristics of depression history.

Our lack of support for mediation by cortisol has implications for the glucocorticoid mediation hypothesis, a leading hypothesis to explain how depression during pregnancy might impact fetal development (Goodman & Gotlib, 1999; O'Donnell, O'Connor, & Glover, 2009). Accumulating evidence suggests that mechanisms other than cortisol are more likely to be involved (DiPietro, 2012). For example, there are polymorphisms in genes regulating the expression of glucocorticoid transporter proteins in the placenta, thereby altering its permeability to maternal stress hormones (Audus, Soares, & Hunt, 2002; O'Donnell et al., 2009). Thus, although antenatal cortisol may not be directly related to antenatal depression symptoms or infant NA, as we found in our sample of 3-month old infants, it continues to be an important focus of research, as it has been found to be directly related to a number of infant outcomes and also may predict postpartum depression (DiPietro, 2012).

The unexpected finding that the mean NA score for our sample of infants was significantly greater than the mean for the standardization sample suggests that infants born to women with history of MDE prior to pregnancy may have a shared liability related to NA. Consistent with a diathesis-stress model (Monroe & Simons, 1991), infants born to women with histories of depression prior to pregnancy may be vulnerable to higher NA, the diathesis, relative to infants of mothers with no such history; subsequently, extent of antenatal exposure to depression, the stressor, may direct infants on a pathway to even higher NA. Studies might test this idea by comparing infants of women with and without histories of depression along with testing the role of antenatal depression exposure.

Strengths and Limitations

The design of this study had many strengths, which allowed for a robust examination of the hypotheses. Our sample of mothers was selected to be socio-demographically low-risk, in order to eliminate the possibility that the stressors known to be associated with poverty or single- or teenaged-parenting, for example, might explain our findings. At the same time, 30% of the women were African-American, commensurate with their representation in the geographic region from which we sampled. We prospectively measured maternal depression and anxiety, and obtained cortisol data at multiple time points through pregnancy and continued to prospectively measure depression at multiple times during the postpartum period up to the infants' age of 3 months. This strategy allowed us to assess the effects of timing of depression on infant NA. It also allowed us to benefit from being able to create mean and area under the curve scores that reflect cumulative exposure over multiple time points rather than relying on a single or a few scores reflecting depression, anxiety, or cortisol at discrete points in time. We also were able to examine a specific point in infant development by uniformly assessing all of the infants at 3 months of age, rather than a range of ages. In contrast to other studies, we did not exclude based on infant factors, such as gestational age at birth or birthweight. As these factors are associated with greater negative temperament (Gennaro, Tulman, & Fawcett, 1990; Medoff-Cooper, 1986) this sampling strategy allowed us to retain a more representative sample than if we had excluded on these factors. Finally, our design allowed us to extend the findings of other studies in order to hone in on questions of the roles of timing, cortisol as a mechanism, and clinical characteristics of depression in relation to infant NA.

One primary limitation of this study is the relative unavailability of depression symptom level measures collected in the first trimester of pregnancy, due to many women not enrolling in the study until the second trimester. Because of this, we were constrained to retrospectively reported diagnostic data for our analyses of first trimester depression, albeit from only a few months later, and such data are subject to underreporting (Newport et al., 2008). Thus it is possible that depression symptom levels in the first trimester might have also been associated with infant outcomes, which we were unable to detect.

A second set of limitations relate to our approach to analyses. Some of our hypotheses relied on analyses of group differences, e.g. diagnostic status. Knowledge that analyses of continuous data are generally more powerful than analyses of categorical data (MacCallum, Zhang, Preacher, & Rucker, 2002) may help explain the discrepant findings in our depression symptom data versus our depression diagnosis data. Further, we conducted multiple independent statistical tests, which may have increased the likelihood of Type I error. Finally, for some of our exploratory analyses of group differences, some of the subgroup samples sizes were small (e.g. $n = 7$), thereby limiting the power to detect group differences and the generalizability of those findings.

Third, although our strategy for sampling cortisol improved on the literature in multiple ways, we were limited to a single sample on a single day for each month of pregnancy. Given that cortisol varies on a day-to-day basis (e.g. Hellhammer et al., 2007), future studies would improve on our approach by collecting samples on multiple days. Fourth, we did not conduct a lab-based assessment of temperament, which, although limited in external validity, could have added convergent validity to our mother-reported measure of infant temperament. Thus, despite the strengths of the IBQ-R, the validity of our construct may have suffered from the use of a single approach to measurement.

Finally, in an effort to focus on history of depression as the primary risk factor for perinatal depression and minimize the potentially confounding influence of demographic factors known to be associated with depression (greater parity, single motherhood, etc.), we selected a sample that was fairly low-risk demographically. This selection strategy likely limits the extent to which our findings can be generalized. Specifically, our findings need to be replicated in samples of women with elevated socio-demographic risks.

Clinical Implications

The higher reported NA in the infants of mothers with elevated depression symptoms in pregnancy may have implications for subsequent maladaptive behaviors in the children, both as a function of NA being a stable construct and transactional processes. A longitudinal validation study of the IBQ-R has shown that the NA factor, as measured between 4–12 months of age, has moderate and statistically significant ($r = .36$) stability with the child version of the measure (CBQ) administered at child age 6 years (Putnam et al., 2008). A study of convergent validity found that, among 4- and 5-year-olds, the CBQ NA factor was significantly correlated with the Child Behavior Checklist (CBCL) Total, Internalizing, and Externalizing scales as well as all of the DSM-oriented scales, with the largest effect size ($r = .51$) found for the correlation with the Anxiety scale (De Pauw, Mervielde, & Van Leeuwen, 2009). Further studies are needed to identify the likely multiple alternative

pathways that young infants with elevated NA levels may follow, as well as protective and exacerbating factors and transactional processes that are likely to play significant roles in developmental pathways to psychopathology (Cicchetti & Toth, 2009). Nonetheless, our results contribute to a model in which NA is a common factor in many forms of maladaptive behaviors in children, is moderately stable throughout childhood, and has origins in the antenatal environment. Consistent with the conclusions from an Academy of Medicine report (National Research Council and Institute of Medicine, 2009), the findings underscore the urgency of thorough empirically based assessment, prevention, and treatment of depression during pregnancy, each of which should be the standard of care. Finally, researchers should test potential secondary benefits to the infants of either the prevention or treatment of antenatal depression, such as has been found in studies of treatment for postpartum depression (Goodman, Broth, Hall, & Stowe, 2008).

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Table 1

Mean and SD Values for Maternal Pregnancy Assessments

Assessment month in pregnancy	1	2	3	4	5	6	7	8	9
Gestational age in weeks	7.33 (1.16)	9.83 (1.64)	14.46 (1.02)	18.65 (1.32)	22.47 (1.25)	26.59 (1.03)	30.48 (1.21)	34.46 (1.14)	37.72 (1.04)
Cortisol (ug/dL)	4.76 (3.72)	6.22 (3.43)	5.53 (5.13)	8.99 (7.44)	11.55 (7.67)	12.60 (10.49)	12.69 (10.40)	11.69 (8.51)	9.35 (6.94)
Cortisol (ug/dL) – including imputed values	-	-	-	9.23 (6.11)	11.27 (7.35)	12.21 (10.09)	12.73 (9.87)	11.77 (7.94)	9.61 (5.51)
<i>n</i>	3	12	37	51	70	69	71	72	47

Table 2

Descriptive Data for the BDI-II and Major Depressive Episodes (MDE) During Pregnancy and Postpartum

	BDI-II		% of mothers experiencing MDE	% of mothers experiencing clinically significant depression symptoms (≥ 14 BDI-II score)
	Mean	SD		
Pregnancy	9.64	5.45	32.5%	49.4%
1st trimester ^I	-	-	19%	-
2nd trimester	9.51	6.29	20.3%	32.9%
3rd trimester	8.36	5.25	6.3%	24.1%
Postpartum (through 3 months)	8.43	5.14	12.7	32.5

^I BDI-II data were not available for most women in the first trimester given their point of entry into the study, whereas the SCID yielded data on the first trimester, in some cases retrospectively.

Note: BDI-II = Beck Depression Inventory, Second Edition

Table 3

Intercorrelations Among Maternal Variables and Infant Negative Affectivity

Measure	1	2	3	4	5	6	7	8
1. Mean antenatal BDI-II	-	.91***	.89***	.65***	-.16	-.05	.60***	.39***
2. Mean 2nd trimester BDI-II		-	.69***	.59***	-.07	.08	.47***	.43***
3. Mean 3rd trimester BDI-II			-	.54***	-.11	-.14	.72***	.29*
4. Mean antenatal STAI-S				-	-.03	.05	.51***	.31**
5. Antenatal cortisol AUC – 2 nd trimester					-	.60***	-.21	-.07
6. Antenatal cortisol AUC – 3 rd trimester						-	-.19	-.11
7. Mean postnatal BDI-II							-	.18
8. IBQ-R Negative Affectivity								-

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

Table 4

Summary of Multivariate Regression Analysis for Maternal Antenatal Depression Variables by Trimester
Predicting Infant Negative Affectivity

Predictor	<u>Method of characterizing maternal depression by trimester</u>			
	<u>Mean BDI-II scores</u>		<u>Major Depressive Episode</u>	
	R^2	β	R^2	β
Full model	.19***		.05	
1st trimester		-		.12
2nd trimester		.44**		.12
3rd trimester		-.01		.07

**
 $p < .01$;

 $p < .001$

Table 5

Summary of Hierarchical Regression Analysis for Maternal Depression and Anxiety Variables Predicting Infant Negative Affectivity

Predictor ^I	R^2	β
Step 1	.19***	
Mean antenatal BDI-II		.31*
Mean antenatal STAI-S		.06
Step 2	.01	
Interaction term		.14
Total R^2	.20***	

^I Centered predictor variables.

* $p < .05$;

*** $p < .001$

Table 6

Summary of Multivariate Regression Analysis for Maternal Depression Variables Predicting Infant NA

Predictor	Method of characterizing maternal depression			
	Mean BDI-II scores		Major Depressive Episode	
	R^2	β	R^2	β
Step 1	.19***		.01	
Antenatal depression		.43***		.11
Step 2	.01		.001	
Antenatal depression		.49***		.11
Postnatal depression		-.10		-.02
Total R^2	.20***		.01	

 $p < .001$