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Pregnancy Distress Gets Under Fetal Skin: Maternal Ambulatory Assessment & Sex Differences in Prenatal Development

ABSTRACT: Prenatal maternal distress is associated with an at-risk developmental profile, yet there is little fetal evidence of this putative in utero process. Moreover, the biological transmission for these maternal effects remains uncertain. In a study of $n = 125$ pregnant adolescents (ages 14–19), ambulatory assessments of daily negative mood (anger, frustration, irritation, stress), physical activity, blood pressure, heart rate (every 30 min over 24 hr), and salivary cortisol (six samples) were collected at 13–16, 24–27, 34–37 gestational weeks. Corticotropin-releasing hormone, C-reactive protein, and interleukin 6 from blood draws and 20 min assessments of fetal heart rate (FHR) and movement were acquired at the latter two sessions. On average, fetuses showed development in the expected direction (decrease in FHR, increase in SD of FHR and in the correlation of movement and FHR (“coupling”). Maternal distress characteristics were associated with variations in the level and trajectory of fetal measures, and results often differed by sex. For males, greater maternal 1st and 2nd session negative mood and 2nd session physical activity were associated with lower overall FHR ($p < .01$), while 1st session cortisol was associated with a smaller increase in coupling ($p < .01$), and overall higher levels ($p = .05$)—findings suggesting accelerated development. For females, negative mood, cortisol, and diastolic blood pressure were associated with indications of relatively less advanced and accelerated outcomes. There were no associations between negative mood and biological variables. These data indicate that maternal psychobiological status influences fetal development, with females possibly more variously responsive to different exposures. © 2015 Wiley Periodicals, Inc. *Dev Psychobiol* 57:607–625, 2015.

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INTRODUCTION

Consistent with a developmental focus on the etiology of mental disorders (Insel, 2010), mounting evidence

indicates that prenatal exposure to maternal distress¹ exerts pervasive effects on infant and child physiology, behavior, and neurobehavioral trajectories (Bale et al., 2010; Charil, Laplante, Vaillancourt, & King, 2010; O'Connor, Heron, Golding, Beveridge, & Glover, 2002). This research rests on the premise that pregnant women's experiences alter fetal development, yet com-

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¹ Following Hoffman & Hatch (Hoffman & Hatch, 1996), we use the term “distress” to describe negative emotional states that may result from the perception of challenging, difficult, “stressful” experiences.

paratively few studies have assessed the fetus to substantiate this putative *in utero* process. Moreover, the limited number of fetal studies fail to identify a biological mediator between maternal psychosocial functioning and outcomes (Glynn & Sandman, 2012; Monk et al., 2004), which may reflect assessment methods that could be improved with daily ambulatory monitoring of maternal distress and biological variables acquired multiple times over pregnancy.

Neurobehavioral assessment before birth, including fetal heart rate (FHR), fetal heart rate variability (FHRV), and the cross correlation between fetal movement (FM) and FHR, "coupling," (Baser, Johnson, & Paine, 1992; DiPietro, 2005; DiPietro, Hodgson, Costigan, & Johnson, 1996b), provides an index of fetal ANS and CNS development. These parameters show consistent development patterns over pregnancy: decreasing FHR, increasing FHRV, and coupling. Maturation of the parasympathetic innervation of the heart accounts for some of these well-documented changes (Dalton, Dawes, & Patrick, 1983; Freeman, Garite, Nageotte, & Miller, 2012) while the increase in coupling reflects the development of the CNS and its coordination of the autonomic and somatic systems (Baser et al., 1992; DiPietro, Irizarry, Hawkins, Costigan, & Pressman, 2001; DiPietro et al., 2010, 1996b).

Prior studies relate maternal distress to variability in these fetal behaviors: stress to lower levels of 2nd and 3rd trimester FHRV (DiPietro, Hodgson, Costigan, & Hilton, 1996c) and coupling (DiPietro et al., 1996b); depression to slower return to 3rd trimester baseline FHR following vibro acoustic stimulation applied to the women's abdomen (Allister, Lester, Carr, & Liu, 2001; Dieter, Emory, Johnson, & Raynor, 2008). Low socio-economic status also has been associated with lower 2nd and 3rd trimester FHRV (Pressman, DiPietro, Costigan, Shupe, & Johnson, 1998). To date, maternal mood has not been examined in relation to the rate of the expected developmental changes in these fetal behaviors. For this report, both average levels of fetal parameters, and their trajectories, are studied.

The hypothesis that maternal distress is biologically transmitted to the fetus, and thereby influences fetal development finds support in studies demonstrating acute changes in FHR, FHRV, and FM to evoked maternal experience (DiPietro, Costigan, Nelson, Gurewitsch, & Laudenslager, 2008b; DiPietro, Costigan, & Gurewitsch, 2003). These data suggest that fetuses "register" women's reactions (DiPietro et al., 2003), which may, via physiological activation, serve as sensory stimuli (Novak, 2004). Throughout gestation, fetal development is thought to be shaped by these mood-associated alterations in women's biology via adaption to activation patterns and/or the direct influ-

ence of some of these biological systems (DiPietro et al., 2008a, 2003; Monk et al., 1998, 2004; Novak, 2004). The maternal ANS/cardiovascular and HPA axis systems are two primary biological effectors of emotion experiences that are potential mediators affecting fetal neurodevelopment through auditory and somatosensory stimulation, (e.g., auditory stimuli from the cardiovascular and gastrointestinal systems, somatosensory activation from changes in breathing rate and thermodynamics), changes in vascular flow and oxygenation, or cortisol exposure that targets glucocorticoid receptors in the fetal CNS and the developing HPA axis (for a review see (Owen, Andrews, & Matthews, 2005)).

In line with this biological transmission model, one report showed higher maternal cortisol was associated with greater amplitude and amount of 3rd trimester FM (DiPietro, Kivlighan, Costigan, & Laudenslager, 2009) while higher cortisol at 15 weeks predicted inadequate development of 2nd trimester FM response to stimulation (Glynn & Sandman, 2012). Higher 3rd trimester CRH (from blood assays, which reflects placenta production that can be enhanced via maternal cortisol levels (Goland et al., 1993; Robinson, Emanuel, Frim, & Majzoub, 1988)) was associated with diminished habituation in the FHR response to a series of vibro acoustic stimulations (VAS) (Sandman, Wadhwa, Chicz-DeMet, Porto, & Garite, 1999a). We found higher 3rd trimester cortisol and higher systolic blood pressure were associated with higher overall FHR (Monk, Myers, Sloan, Ellman, & Fifer, 2003). DiPietro et al. reported that average maternal and fetal heart rates were correlated from 32 weeks on (DiPietro, Irizarry, Costigan, & Gurewitsch, 2004a). Another biological effector of stress and distress, immune activation, has not yet been included in studies of fetal motor and ANS development, despite mounting evidence from animal models and human epidemiological studies demonstrating a critical role for maternal immune functioning in many neurodevelopmental disorders (Bilbo, 2012; Mehler et al., 1995; Merrill, 1992). In this report, we included assessment of maternal blood pressure, heart rate, HPA, and immune activation.

There are, at best, only marginal associations between pregnant women's reports of their psychological experience and indicators of biological activation (Fink et al., 2010; Huizink, Robles de Medina, Mulder, Visser, & Buitelaar, 2003; Monk et al., 2000; Ponirakis, Susman, & Stifter, 1998; Rieger et al., 2004), which has limited the possibility of identifying a biological mediator of the maternal mood effects on the fetus. Instead, the biological and psychological variables frequently are found to be uncorrelated, or independently associated with offspring development (Baibazar-

ova et al., 2013; Davis et al., 2007; Davis & Sandman, 2010; Harville et al., 2009; Huizink, 2003). Recent research on distress during pregnancy (Entringer et al., 2012; Kaplan et al., 2012; Spicer et al., 2013) utilizes ecological momentary assessment (EMA) of emotional experiences via a personal digital assistant (PDA) multiple times a day (Entringer, Buss, Andersen, Chicz-DeMet, & Wadhwa, 2011; Giesbrecht, Campbell, Letourneau, & Kaplan, 2013) coupled with ambulatory collection of biological data. Ambulatory assessment may increase the possibility of finding mediating processes given its improved validity (in the moment responses versus the state-dependent recall of self-report questionnaires (Shiffman, 1997) and greater reliability (multiple measurements throughout the day). To that end, EMA, and ambulatory collection of cortisol, heart rate, and blood pressure are used in this study.

Two added questions in prenatal research that inform this study are the potentially differential influences related to the timing of the *in utero* distress exposure, and possible sex effects. Timing results have been somewhat variable across studies, some showing early to mid gestation as associated with a significant influence across a range of outcomes (attention, physical maturation, risk for schizophrenia) (Davis & Sandman, 2010; Ellman et al., 2008; Khashan et al., 2008; Laplante, Brunet, Schmitz, Ciampi, & King, 2008; Schneider, Roughton, Koehler, & Lubach, 1999) and others suggesting later effects, also evidenced in different results (e.g., mental development, mixed handedness) (Huizink et al., 2003) (Buss et al., 2009; Obel, Hedegaard, Henriksen, Secher, & Olsen, 2003; Sandman et al., 1991). With respect to sex, recent findings suggest that both sex-specific placental responsiveness to maternal distress, in addition to hormones related to the sex of the offspring, may contribute to greater male vulnerability and consequences (Bale et al., 2010; Clifton, 2010; Mueller & Bale, 2008; Stark, 2009), while females, according to a recently advanced perspective, initially may adapt to *in utero* adversity, though at a cost of negative health consequences later in life (Sandman, Glynn, & Davis, 2013).

Finally, two different conceptual models have guided the investigation and interpretation of maternal prenatal distress effects: maternal factors could be conceptualized as follows: (1) teratogenic and altering offspring outcomes in ways consistent with a risk phenotype; or (2) telegrams, communicating to the fetus information of an adverse postnatal environment, justified via evolutionary biology to influence development to optimize infant adaptation to it. The first approach hypothesizes that atypical fetal outcomes indicate an increased risk of future psychopathology; in the latter,

fetal development is accelerated to reduce exposure to a nonoptimal *in utero* experience and reduce maternal investment in an offspring with fewer chances for postnatal survival (Gluckman, 2005; Pike, 2005). Until recently (Sandman, Davis, & Glynn, 2012), the majority of fetal studies, including our own (Monk et al., 2000, 2004, 2010), have focused on the identification of an at-risk phenotype and that approach informed the hypotheses in this study.

The purpose of this report was twofold: (1) investigate the understudied though implicit hypothesis that maternal distress is associated with variation in key indices of fetal development and (2) consider a broad range of biological effectors of maternal distress as possible mediators transmitting maternal experience to the fetus. In this prospective research spanning the 1st to the 3rd trimesters, we studied pregnant adolescents as a sample skewed towards higher rates of psychosocial challenges and distress symptoms (Caldwell & Antonucci, 1997; Kovacs, Krol, & Voti, 1994). Based on prior research (Glynn & Sandman, 2012), we anticipated that higher maternal daily distress and elevated cortisol early in pregnancy would be associated with overall (1) higher FHR, lower FHRV, and less coupling, and, (following (Dipietro et al., 2004)) altered developmental trajectories, specifically, (2) a smaller decrease in FHR, and reduced increases in FHRV and coupling from mid to late pregnancy. Following prior research (Bale et al., 2010; Clifton, 2010; Mueller & Bale, 2008; Stark, 2009), we anticipated effects in both sexes, but predicted male versus female fetuses would show larger effects. Because there are few studies of maternal cardiovascular and immune activity in relation to human fetal behavior these variables made up exploratory aims.

METHODS

Participants

Healthy nulliparous pregnant adolescents, ages 14–19 were recruited through the Departments of Obstetrics and Gynecology at Columbia University Medical Center (CUMC) and Weill Cornell Medical College, and flyers posted in the CUMC vicinity. Adolescents were excluded if they acknowledged smoking or use of recreational drugs, lacked fluency in English or on the basis of frequent use of: nitrates, steroids, beta blockers, triptans, and psychiatric medications. Of the 325 adolescents referred to the study, 40 were not screened (15 non-English speaking, 18 unable to be reached, four declined to be screened, three other); 285 were screened and 205 enrolled following exclusion based on ineligibility ($n=27$) or failure to attend enrollment session ($n=53$). All enrolled participants provided written-informed consent, and

all procedures were approved by the Institutional Review Board of the New York State Psychiatric Institute/CUMC and Weill Cornell Medical College.

Study Procedures

There were a total of three study sessions that occurred at gestational weeks 13–16 (1st), 24–27 (2nd) and 34–37 (3rd) (see Fig. 1). One-hundred and fifty-three subjects enrolled in the 1st session and 52 enrolled in the 2nd. Each study session involved three consecutive days of assessment and included the collection of: 24 hr ambulatory blood pressure (ABP) and heart rate (HR) monitoring, 24 hr EMA of mood, and 48 hr salivary cortisol; medical data on pregnancy course (and later, birth outcomes) culled from participants' medical charts, and questionnaires about health and mood. At the 2nd and 3rd sessions, blood was drawn for immune markers and CRH, and fetal data were collected. To accommodate participants, sessions were scheduled in the late morning and afternoons; we aimed to keep the time of sessions consistent throughout study participation. There was one, randomly scheduled, urine toxicology screen to test for use of cannabinoids, amphetamines, benzodiazepines, opioids, and cotinine.

Ambulatory Blood Pressure and Heart Rate

Measures of systolic and diastolic ABP and HR were collected every 30 min for 24 hr periods using the Spacelabs Healthcare #90207 Ambulatory Blood Pressure (ABP) Monitor (Spacelabs Healthcare, Snoqualmie, WA). On the 1st day of each study session, the ABP cuff and monitor were fitted to the participant (Beevers, Lip, & O'Brien, 2001). Adjustments with ABP equipment were made until two automated readings fell within ± 10 mm Hg of two manual ones. Participants were asked not to remove the ABP monitor during each 24 hr testing period.

EMA of Mood and Activity

Using a Personal Digital Assistant (PDA), (Palm, Inc. Tungston E2 Handheld, Sunnyvale, CA) participants com-

pleted an EMA of mood and physical activity ratings every 30 min for 24 hr periods, excluding sleeping time. Participants were instructed to complete assessments throughout the day, concurrently with automated ABP readings, using the inflation of the ABP unit as a prompt. Directions for each assessment reminded participants to report their moods and experiences at that moment. Participants completed ratings of 18 mood states, following other research using EMA mood assessment with adolescents (Adam, 2006; DeSantis et al., 2007): cheerful, lonely, nervous, cooperative, angry, responsible, frustrated, competitive, strained, worried, caring, irritated, relaxed, stressed, proud, friendly, hard working, productive (see below for the calculation of the "negative mood" variable). Participants used a four point Likert scale to complete all mood ratings, with one being "not at all (e.g., cheerful; active)" and four being "very much; the most (e.g., cheerful; active) you can imagine." Participants also provided a rating of their current physical activity level to control for its affect on ABP values as well as its possible associations with fetal outcomes. Participants were instructed to report activity on a four point scale, "with four being the most active you can imagine, and one being the least active you can imagine." At the 1st session, participants went through a practice assessment with research staff to ensure correct device use, as well as comprehension of the vocabulary, and rating scale. All EMA responses were automatically time-stamped, stored on the PDA, and uploaded to a server when participants returned devices to the lab.

Salivary Cortisol

Forty-eight hour salivary cortisol collection was timed to begin during the 1st day of each study session. Subsequent samples on the 2nd day of collection were as follows: at waking; 45 min, 2.5 hr, 3.5 hr, and 8 hr after waking; and at 10 PM or before going to bed. Cotton used for each sample was kept in a bottle with a Medication Event Monitoring System (MEMS) track cap (Aardex, Union City, CA), which records the time of opening and has been shown to help adolescents comply with sampling protocols (Adam & Kumari, 2009).

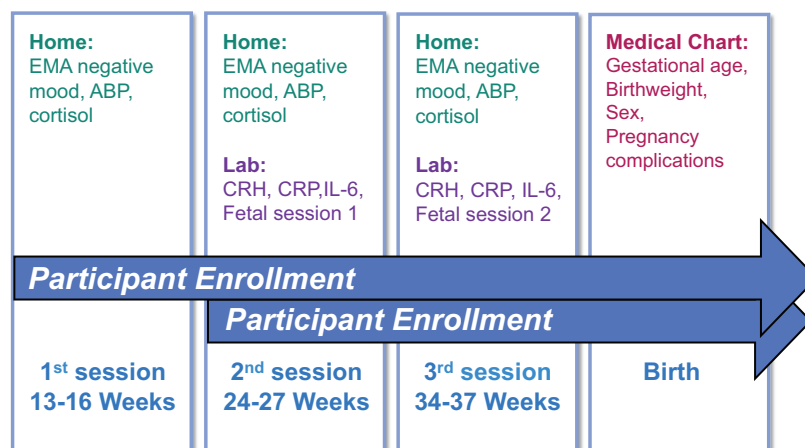


FIGURE 1 Diagram of study protocol.

Once used, the cotton was placed in a Salivette tube (Sarstedt, Newton, NC). After return to the lab, samples were kept frozen at -80°C until assayed using a commercial ELISA/EIA kit optimized for saliva (Salimetrics, State College, PA).

Immune Markers and CRH

Ten milliliter blood samples were collected in EDTA tubes. Samples were placed on ice, spun down, and frozen at -80°C within 60 min of collection. IL-6 and CRP were assayed using high sensitivity commercial ELISA kits (HS-IL-6: R + D Systems, Minneapolis, MN; Zymutest HS-CRP: Diapharma, West Chester, OH). Plasma CRH was measured by radioimmunoassay following a methanol extraction. One milliliter of each plasma sample was mixed with 4 ml ice-cold methanol in glass tubes, vortexed for 1 min and incubated on ice for 20 min. Tubes were spun at 3,500 rpm for 15 min at 4°C . The top layer was transferred to a clean glass tube on ice .5 ml of ice-cold methanol was added to the remainder pellet, vortexed and spun again at 3,500 rpm for 15 min at 4°C . The top layer was added to the first removed aliquot and dried in a vacuum centrifuge. The samples were reconstituted in 500 μl assay buffer (.063 M Na_2HPO_4 , .13 N Na_2EDTA , .02% NaN_3 , .1% Triton X-100, normal rabbit serum 1% and 25 mg/l aprotinin) incubated for 2 hr on ice and vortexed. CRF standards (Sigma-Aldrich, St Louis, MO) were prepared at 20–2,500 pg/ml. CRF antibody (Abcam, San Francisco, CA) was diluted ($1:10^7$) to produce 25–30% binding with CRH tracer and 100 μl of CRF antibody was incubated with 100 μl of standards and samples for 48 hr. CRF tracer from New England Nuclear (Boston, MA) was diluted in assay buffer to 3,000 counts per 100 μl and incubated with samples for and additional 24 hr. Fifty microliter goat anti-rabbit secondary antibody (IgG Corp, Nashville, TN) diluted 1:1 with assay buffer without normal rabbit serum, triton X or aprotinin was added for 12 hr. Then samples were centrifuged at 2,000g for 20 min, liquid aspirated and radioactivity of pellets counted in a gamma counter. Samples were run in one of two assays, with both samples from any one subject run within the same assay. A third assay was run to further dilute samples with concentrations above the standard curve. All samples were run in duplicate and standards in triplicate. Extraction efficiency was 70%. The detection limit was 20 pg/ml and intra-assay coefficient of variation was <10%. The inter-assay coefficients of variation were 4–11%.

Fetal Assessment

For the fetal assessment, participants were in a semi-recumbent position for 20 min as FM and FHR were acquired on the 1st day of the 2nd and 3rd sessions. Data were obtained using a Toitu MT 325 fetal actocardiograph (Toitu Co., Ltd, Tokyo, Japan). The Toitu detects FHR and FM via a single transabdominal Doppler transducer and processes this signal through a series of filters. The detection of FM uses these filters to remove frequency components of the Doppler signal that are associated with FHR and maternal somatic activity, and has been shown to be reliable (Besinger &

Johnson, 1989; Dipietro et al., 2004b; DiPietro, Costigan, & Pressman, 1999).

FHR and FM data were collected from the output port of the Toitu MT 325 and digitized at 50 Hz using a 16 bit A/D card (National Instruments 16XE50). Data were analyzed offline using custom Matlab programs (<http://www.mathworks.com/>) developed for this project. Three fetal variables were of interest: mean FHR; standard deviation of FHR (FHRSD, our index of FHRV); and FM/FHR cross-correlation (“coupling”). As a first step in preprocessing, FHR below 80 beats per minute (bpm) or above 200 bpm was linearly interpolated and then low-pass filtered at 3 Hz using a 16 point finite impulse response filter. Mean and standard deviation of the resulting FHR were taken over non-interpolated values. Filtered FHR was further examined for artifact in the following way: times at which the absolute sample-to-sample (20 ms) change in FHR exceeded 5 bpm were found and FHR was marked as artifact until it returned to within 5 bpm of the previous value. The resultant gaps were linearly interpolated.

Because the FHR/FM coupling of interest occurs on time scales fewer than 4 min, we estimated cross-correlation of FHR and FM for the entire record by averaging cross-correlations taken for 4 min overlapping (50%) segments. This is akin to averaging over FFT’s in the Welch method of power spectrum estimation (Bendat, 2000). FHR-FM cross-correlations were computed as follows: (1) FHR and FM over the entire record were first bandpass filtered between .002 and .05 Hz using a 400 point FIR filter; (2) FHR was further smoothed by subtracting a local regression of 10% span; (3) decelerations of FHR were set to zero; (4) FM was z-scored (Dipietro, Irizarry, Hawkins, Costigan, & Pressman, 2001). Before taking the cross-correlation for each 4 min segment, a Hanning window was applied. Based upon visual inspection of hundreds of similar studies, our group has developed criteria used to screen data for artifact. Specifically, individual segments were excluded from the average if any of three conditions applied: (1) total interpolated FHR exceeded 50% of segment length; (2) an interpolated gap of greater than 30 s occurred; (3) cumulative time of interpolated gaps between 2 s and 30 s exceeded 1 min. As an aid to post-processing, the mean percentage of interpolated data within each segment and the number of non-excluded segments were recorded. Finally, as a further control for artifact, any segment with maximum cross-correlation at a lag of less than -15 s or greater than 0 s was not included in the average spectral power or cross-correlation calculation because true physiological FHR-FM coupling is within this range, with FM leading FHR (DiPietro et al., 1996b).

Pregnancy Health and Birth Outcomes

Infection during pregnancy (yeast, urinary tract infections) yes/no was ascertained from the medical record and subject report at each study session. Gestational age at birth, birth-weight, pregnancy complications, C-section, and sex of the infant, were determined from the medical record. Pregnancy complications were defined as preeclampsia/hypertension, vascular issues, diabetes mellitus, and other; the number of

complications were summed and then dummy coded according to three dichotomous classifications: 0, 1–4, ≥ 5 . Gestational age at study sessions was determined based on ultrasound examinations and last reported menstrual cycle. Body mass index (BMI) was calculated using pre-pregnancy weight from self-report and measured height, both ascertained at the enrollment session.

Data Transformation and Analysis Plan

Preliminary analyses were performed to identify maternal variables that might influence fetal measures including infection status, BMI, maternal age, ethnicity, pregnancy complications, and physical activity. Pre-pregnancy BMI, pregnancy complications, and physical activity were associated with FHR and FHRSD ($p < .05$). Maternal age had a marginally significant association with FHR ($p = .13$). As other studies on fetal development have included maternal age as a covariate (DiPietro et al., 2004; DiPietro et al., 1996b), and it has been a significant covariate in another study with pregnant adolescents (despite the constricted range) (Spicer et al., 2013), it was included in statistical models, along with the other variables showing significant associations.

Of the 205 enrolled pregnant adolescents, the following data were missing from participants so that we excluded these participants from analyses: fetal data at both time points (60), pregnancy complications (15), BMI (3), maternal age (2), resulting in a sample of 125 for this study.

To create an index of EMA distress, hereafter called negative mood, all items from the mood assessments were entered into an exploratory factor analysis using maximum likelihood estimation as the fitting method. Items with loadings below .4 were excluded from further analysis. The negative mood index at each time point was calculated based on the average of the following items: angry, frustrated, irritated, and stressed. A participant's average physical activity level for each session period was calculated by summing all values reported and dividing it by the number of total responses completed over a 24 hr period. Cortisol area under the curve (AUC) (Fekedulegn, 2007), used to index HPA axis activity, was calculated from the wake up time to going to bed on the 2nd day of collection because the 2nd day included a time-based, uniform protocol. For inclusion in AUC analyses, the following was required: at least 4/6 cortisol samples, the 1st wake up collection, and ≥ 8 hr time span from first to last sample. For 1st session AUC, 10 values did not reach these criteria; for the 2nd and 3rd sessions, six did not. Cortisol AUC and CRH data from all three sessions were not normally distributed. Prior to inclusion in analyses these variables were log transformed and satisfied normality, assessed by the Kolmogorov–Smirnov test (Conover, 1971).

To evaluate if maternal and fetal variables changed across pregnancy, we used linear mixed effect analyses by treating time as both continuous (gestational week) and categorical (1st, 2nd, 3rd session) variables. To test for associations between maternal negative mood and biological variables, we used Spearman's rank-order correlation analyses. To determine which maternal variables should be included in models of fetal outcomes (in addition to our a priori ones, negative

mood, and cortisol), Spearman's rank-order correlation analyses were used to find associations between CRH, CRP, IL6, ABP, HR, and fetal outcomes.

To test the effects of maternal negative mood and biology on fetal development across pregnancy, hierarchical linear models (HLM) (Raudenbush, 2004) were used. We constructed separate two-level models to evaluate the associations between the maternal variables and fetal trajectories. First, we tested if maternal negative mood and/or biology (cortisol, etc.) variables were associated with the status, *average level*, of fetal measures across the 2nd and 3rd sessions by modeling the random intercept, and whether the timing of the maternal effect (1st or 2nd session values) was significant. Alteration of the *rate of developmental change* in fetal measures by those maternal variables was tested by modeling the random slope. Additionally, we tested the moderation effect of fetal sex. In the hierarchical models, fetal gestational age, two of the covariates (maternal age, pre-pregnancy BMI), and all predictors were centered by subtracting their overall means. To test goodness-of-fit of the models, likelihood ratio tests, and residual analyses were conducted.

All statistical analyses were performed using SAS 9.3. The residuals of the hierarchical models were normally distributed and did not show any structured pattern. All tests were two-tailed with α at .05 and only significant models are reported (Likelihood-ratio test of $p < .05$).

RESULTS

Participants

Table 1 shows descriptive data. Twelve infants had birth weights $< 2,500$ g or gestational age at birth < 37 weeks. Reported results did not change when models were re-run to exclude these fetuses. One participant included in analysis tested positive for cannabinoids during pregnancy.

Compliance With Ambulatory Assessments

As shown in Table 1, participants had good compliance with the ambulatory assessments. With respect to the diary reporting, the average of nearly 20 entries over 24 hr periods suggests almost one entry every 30 min (as requested) excluding sleeping hours. For cortisol, an average of almost six samples for the 2nd day of collection also shows overall good conformity with the study protocol.

Maternal Negative Mood and Biology Over Gestation

Table 2 shows average values for maternal negative mood and biological variables across the study sessions. Negative mood ($\beta = .02$, $p = .40$) and physical activity ($\beta = .01$, $p = .57$) and CRP ($\beta = -1.01$, $p = .12$)

Table 1. Descriptive Statistics

Variables	<i>N</i>	Mean/%	StdDev	Min	Max
<i>Maternal</i>					
Age	125	17.80	1.16	14	19
Pre-Pregnancy BMI (kg/m ²)	125	25.68	6.00	16.57	47.60
Ethnicity					
Hispanic	111	89			
Non-Hispanic	14	11			
Pregnancy					
Complications ^a					
None	65	52			
1, 2, or 3 complications	30	24			
5 complications	30	24			
C-Section					
No	93	74			
Yes	32	26			
Infection ^b					
No	71	57			
Yes	54	43			
Negative Mood—avg#of entries/24 hr ^d	125	19.75	8.12	3	59
Cortisol—avg#of samples 2nd day ^{c,d}	122	5.75	0.53	4	7
ABP—avg#of values/24 hr ^d	125	35.52	9.59	10.67	50.33
<i>Fetal</i>					
Birthweight (grams) ^e	123	3230.52	513.02	947.00	4525.00
Gestational age at Birth (weeks)	123	39.17	2.03	26.57	41.57
Sex					
Male	79	63			
Female	46	37			

StdDev, standard deviation; Min, minimum; Max, maximum; BMI, body mass index; Negative mood, ecological momentary assessment negative mood; ABP, ambulatory blood pressure.

^aDefined as preeclampsia/hypertension, vascular issues, diabetes mellitus, and other(s).

^bDefined as yeast and/or urinary tract infections.

^cFour participants at the 1st session, six at the 2nd, and nine at the 3rd provided a total of seven saliva samples on the 2nd day instead of the requested six.

^dThese results are the value per assessment period (24 hr or 2nd study day) averaged over the three study sessions across pregnancy.

^eTwelve of 123 infants had birth weights <2,500 g or gestational age at birth <37 weeks. Reported results did not change when models were re-run to exclude these 12.

did not change significantly over time. All other variables showed significant increases (AUC log cortisol, diastolic ABP, HR, IL6, and log CRH ($p \leq .01$)). Finally, of note, there is significant variability in the range of negative mood scores.

Fetal Measures Over Gestation

As predicted, on average FHR decreased over pregnancy by 4 bpm from 146 to 142 bpm ($p < .0001$) while FHRSD and coupling increased (6.7 to 7.8 and .49 to .56, respectively ($p < .05$)) (see Table 2). These findings did not vary by sex.

Associations Between Negative Mood and Maternal Biology

Based on Spearman's rank-order correlation tests, there were no significant associations between negative mood and any of the maternal biological variables (all p -values $> .20$; see Supplemental Table 1).

Exploratory Variables: Associations Between Maternal Biological Variables and Fetal Measures

In Spearman's rank-order correlation tests of associations between log CRH, CRP, IL6, ABP, HR physical activity and each fetal outcome, the following exploratory variables met criterion ($p < .1$): 1st and 2nd session physical activity, and 1st session systolic and diastolic ABP. As these blood pressure variables are highly correlated, diastolic ABP was added, along with physical activity, to models predicting fetal measures.

FHR: Associations With Maternal Negative Mood and Physical Activity

There were no main effects for maternal negative mood, cortisol, diastolic ABP, or physical activity in relation to FHR. However, there were significant interactions between negative mood and physical activity, respectively, and fetal sex (*all* $p \leq .05$). For males, greater maternal 1st and 2nd session negative mood and 2nd session daily physical activity were associated with lower overall FHR (See Table 3, models 1–4). Specifically, as found in two different HLM models, for every unit increase in 1st and 2nd session negative mood, males showed 5.05 and 2.94 overall lower bpm FHR, respectively (see Fig. 2). For every unit increase in 2nd session maternal activity, males showed 2.95 bpm lower FHR (See Fig. 3). In relation to greater 1st session physical activity there was an interaction with sex ($p < .01$), though this one showing effects in the rate of change in FHR, and in females. Specifically, for females, greater 1st session maternal activity was associated with a flatter slope and less of a decrease in FHR across gestation (See Table 3, model 2). Results from models with 1st and 2nd session cortisol and 1st session negative mood showed no effects for cortisol. However, the results for negative mood were consistent

Table 2. Maternal and Fetal Variables

Variables	1st Session (13–16 weeks)				2nd Session (24–27 weeks)				3rd Session (34–37 weeks)						
	N	Mean	StdDev	Min	Max	N	Mean	StdDev	Min	Max	N	Mean	StdDev	Min	Max
Maternal															
Negative Mood	96	1.42	.43	1.00	2.89	116	1.48	.56	1.00	3.92	111	1.50	.58	1.00	3.83
Physical Activity	96	1.71	.53	1.00	4.00	116	1.74	.54	1.00	4.00	111	1.75	.63	1.00	4.00
HR	95	85.45	7.35	66.47	107.80	114	90.95	8.11	61.60	113.55	114	92.04	8.66	61.07	120.00
Diastolic BP	95	80.98	5.10	70.98	94.72	114	82.74	5.57	69.87	103.21	114	87.48	14.30	66.00	219.00
Cortisol (µg/dl) ^a	79	2.44	1.16	.56	7.84	106	2.97	1.03	1.04	6.68	97	3.50	1.34	1.53	9.45
CRH (pg/ml) ^b						99	150.63	97.86	18.00	419.00	99	1026.76	610.32	80.00	2785
CRP(mg/dL)						108	.86	.95	.03	4.65	104	.74	.60	.001	2.91
IL-6 (pg/mL)						108	1.65	1.23	.28	7.54	104	2.06	1.26	.57	7.54
Fetal^c															
FHR						95	145.86	5.48	132.94	155.39	108	142.29	6.23	128.80	155.49
FHRSD						92	6.65	2.39	3.65	17.77	104	7.79	2.28	3.26	15.23
Coupling						59	.49	.11	.26	.76	82	.56	.10	.31	.78

StdDev, standard deviation; Min, minimum; Max, maximum; HR, heart rate; CRH, corticotropin releasing hormone; CRP, C-reactive protein; IL-6, Interleukin 6; FHR, fetal heart rate; FHRSD, fetal heart rate standard deviation.

^aArea under the curve. Raw values.

^bRaw values.

^cUsing two SD, outlier fetal values were excluded from analysis: six from FHR 2nd session, six from FHR 3rd session, five from FHRSD 2nd session, eight from FHRSD 3rd session, four from coupling 2nd session, three from coupling 3rd session.

Table 3. Summary of Results From HLM Analyses: Fetal Heart Rate¹

Model Variables	Intercept					Slope				
	Main Effect		Interaction	Est. by Sex		Main Effect		Interaction	Est. by Sex	
	F Value	β	F Value	Sex	β	F Value	β	F Value	Sex	β
1 Negative Mood 1st Session	1.23	-1.92	4.16*	F	1.21	1.27	-.25	.00	F	-.26
				M***	-5.05				M	-.23
2 Negative Mood 1st Session	.76	-1.43	4.99*	F	1.99	.44	-.14	.09	F	-.08
				M***	-4.84				M	-.21
Physical Activity 1st Session	.07	.40	4.19*	F ^a	2.63	1.80	.16	7.22**	F**	.49
				M	-1.83				M	-.16
3 Negative Mood 2nd Session	.00	-.02	6.38*	F	2.90	.00	-.01	1.49	F	-.01
				M**	-2.94				M	.18
4 Negative Mood 2nd Session	.05	-.26	6.77*	F	2.66	.04	-.03	1.40	F	.15
				M***	-3.18				M	-.22
Physical Activity 2nd Session	1.44	-.88	6.34*	F	1.18	.39	.07	.14	F	.12
				M**	-2.95				M	.03

¹All models controlled for maternal age, pre-pregnancy BMI, and pregnancy complications, and are significant at a Likelihood-ratio test of $p < .001$.

^a $p < .10$.

* $p < .05$.

** $p \leq .01$.

*** $p \leq .001$.

with the others findings: higher negative mood was associated with lower FHR in males (data not shown).

FHRSD: Associations With Maternal Cortisol

For FHRSD, there were no main effects for maternal negative mood, diastolic ABP, or physical activity. Analyses did show a main effect of cortisol such that the higher the 2nd session cortisol, the greater the increase in FHRSD across gestation (Table 4, model 1). In a model also including 2nd session negative mood,

cortisol showed the same association (Table 4, model 2, and Fig. 4).

Coupling: Associations With Maternal Negative Mood, Cortisol, and Diastolic ABP

Maternal negative mood, cortisol, and diastolic ABP were associated with differences in fetal coupling; there were no significant associations with physical activity. As can be seen in Table 5, the higher 1st session negative mood, the higher the level of fetal coupling

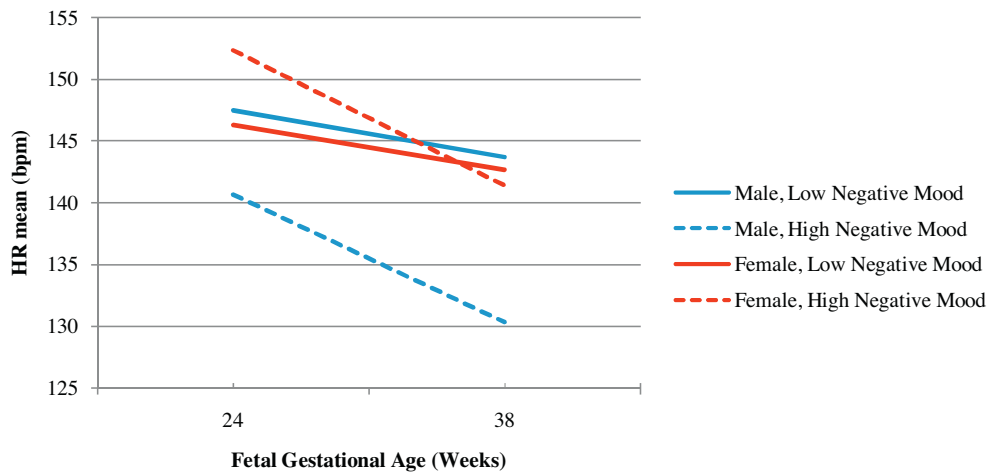


FIGURE 2 1st session maternal negative mood interacts with fetal sex to predict fetal heart rate level across gestation (Low Negative = 25th percentile and below; High Negative = 75th percentile and above).

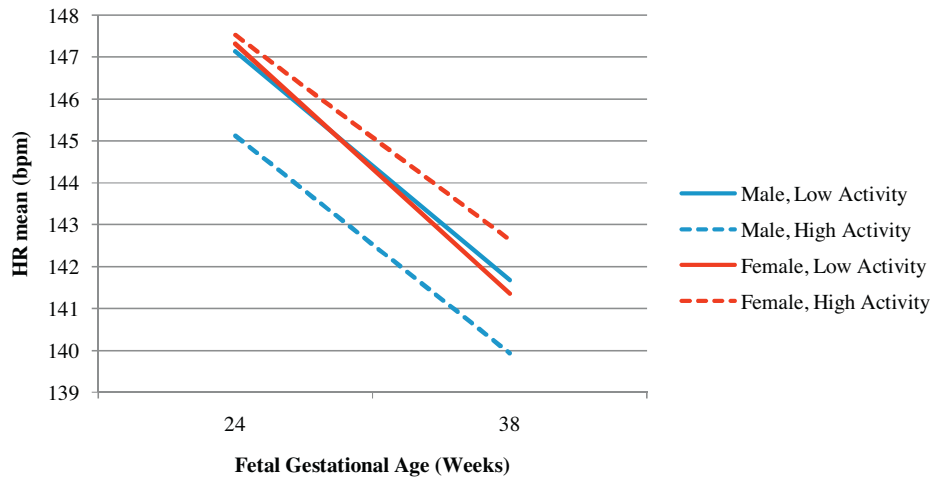


FIGURE 3 2nd session maternal physical activity interacts with fetal sex to predict fetal heart rate level across gestation (Low Activity = 25th percentile and below; High Activity = 75th percentile and above).

across gestation ($p \leq .01$). Specifically, based on results from three different models (models 1, 3, and 4), for every unit increase in 1st session negative mood, there was .09 or .11 increase, respectively, in the average level of coupling across gestation. Moreover, there was a significant interaction between negative mood and fetal sex such that in relation to negative mood, females showed greater average levels of coupling.

Also shown in two models (2 and 3) in Table 5, higher 1st session maternal cortisol was associated with less of an increase in coupling levels over gestation ($p < .01$) and there was a significant interaction with sex ($p < .05$) (model 2) such that this finding was more significant in males. In addition, in model 3, results show a significant positive association between 1st session cortisol and the average level of coupling in males, but not females (Table 5 and Fig. 5). Finally, for 1st session diastolic ABP, higher levels were associated

with lower coupling across gestation ($p < .01$), especially for females (model 4).

DISCUSSION

Similar to established neurobehavioral trajectories for early infancy (Diamond, 1995), our assessment of fetal outcomes showed development in the expected directions from mid to late pregnancy, specifically a decrease in FHR and increases in FHRSD and coupling (DiPietro, 2005; Dipietro et al., 2004). In this context of expectable development, maternal distress was associated with subtle variations in fetal measures and their rate of change. These results provide proximal evidence for the putative *in utero* shaping of children's futures in relation to maternal psychobiological status—a common premise of developmental research that is

Table 4. Summary of Results From HLM Analyses: Fetal Heart Rate Standard Deviation¹

Model Variables	Intercept					Slope				
	Main Effect		Interaction	Est. by Sex		Main Effect		Interaction	Est. by Sex	
	F Value	β	F Value	Sex	β	F Value	β	F Value	Sex	β
1 Cortisol 2nd Session	.78	.64	2.86 ^a	F	1.40 ^a	4.20*	.22	.20	F	.17
				M	-.12				M ^a	.26
2 Negative Mood 2nd Session	.00	-.01	1.69	F	-.57	.09	-.03	.75	F	-.10
				M ^a	.55				M	.05
Cortisol 2nd Session	.82	.64	3.35 ^a	F	1.46*	3.97*	.21	.18	F	.16
				M	-.18				M ^a	.25

¹All models controlled for maternal age, pre-pregnancy BMI, and pregnancy complications, and are significant at a Likelihood-ratio test of $p < .001$.

^a $p < .10$.

* $p < .05$.



FIGURE 4 2nd session maternal cortisol predicts the change in FHRV (SD) across gestation (Low Cortisol = 25th percentile and below; High Cortisol = 75th percentile and above). Contrast tests indicated that for the highest quartile value of maternal cortisol (visualized in figure 4), the FHRSD slope was significantly different from zero ($p < .01$), though it was not for the lowest value.

rarely tested directly. There were effects of exposure to maternal distress for both earlier in pregnancy (the 1st session) and from mid to later (the 2nd session), which were observed for fetal neurobehavioral trajectories across mid (the 2nd session) to late (the 3rd session) periods of gestation. Fetal sex was a significant factor. Results for male fetuses most often suggested that maternal distress lead to accelerated development, while for females, the effects differed, some showing acceleration, others a subtle deviation from what is expected and thus a potential mark of a risk phenotype. Finally, consistent with other research (Davis & Sandman, 2012; Huizink et al., 2003), despite the use of

novel, ecologically valid, ambulatory assessments, we did not find any associations between biological and psychological indices of maternal distress (negative mood), and therefore, no biological mediation of the negative mood effects on fetal measures. However, maternal cortisol, as well as diastolic blood pressure and physical activity, showed some independent associations. The results add support to a role for maternal HPA axis and vascular regulation affecting fetal development and point to the challenges in identifying the physiological pathways by which maternal prenatal psychosocial experience is related to child outcomes.

Table 5. Summary of Results From HLM Analyses: Fetal Coupling¹

Model Variables	Intercept					Slope				
	Main Effect		Interaction		Est. by Sex	Main Effect		Interaction		Est. by Sex
	F Value	β	F Value	Sex	β	F Value	β	F Value	Sex	β
1 Negative Mood 1st Session	7.22**	.09	9.53**	F**	.19	2.32	.01	.08	F	.01
				M	-.01				M	.01
2 Cortisol 1st Session	3.63	.03	1.42	F	.01	8.20**	-.01	5.14*	F	-.01
				M ^a	.05				M**	-.02
3 Negative Mood 1st Session	9.21**	.11	5.21*	F*	.22	.60	.01	.21	F	.01
				M	.03				M	.00
4 Cortisol 1st Session	3.32	.03	2.22	F	.00	9.20**	-.02	.17	F	-.01
				M*	.05				M**	-.02
4 Negative Mood 1st Session	12.43***	.11	15.93***	F***	.23	3.87 ^a	.02	.52	F	.02
				M	-.01				M	.01
Diastolic BP 1st Session	6.43**	.00	4.13*	F**	-.01	.02	.00	1.53	F	.00
				M	.00				M	.00

¹All models controlled for maternal age, pre-pregnancy BMI, and pregnancy complications, and are significant at a Likelihood-ratio test of $p < .001$.

^a $p < .10$.

* $p < .05$.

** $p < .01$.

*** $p \leq .001$.

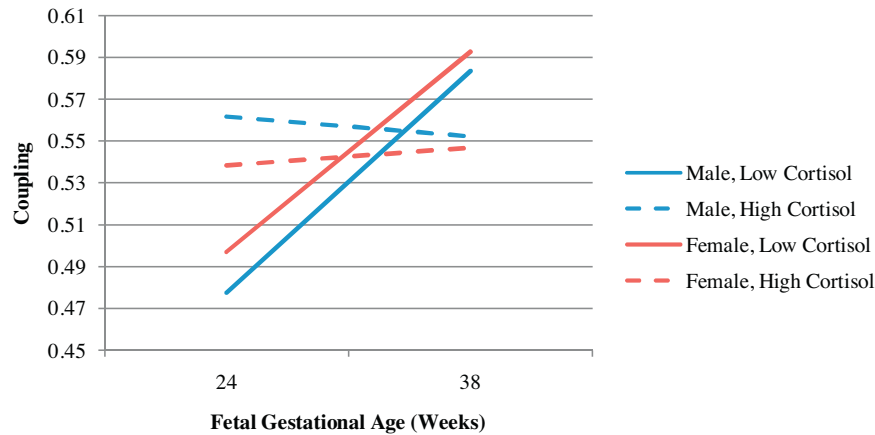


FIGURE 5 1st session maternal cortisol interacts with fetal sex to predict fetal coupling across gestation (Low Cortisol = 25th percentile and below; High Cortisol = 75th percentile and above). Contrast tests show that for the lowest quartile value of maternal cortisol, the coupling slope was significantly different from zero ($p < .01$), though it was not for the highest value.

The two a priori hypothesized variables, maternal negative mood and cortisol, showed associations with fetal measures moderated by sex. For male fetuses, a higher level of maternal negative mood, ascertained from multiple ambulatory assessments throughout a 24 hr period from earlier (1st session) as well as middle (2nd session) pregnancy was related to lower FHR across gestation, a mark of accelerated development. Finally, greater negative mood earlier in pregnancy (1st session) was associated with higher levels of fetal coupling across time points—indicative of accelerated development given the normative trajectory for this fetal outcome. In addition to this main effect, there was a sex effect such that this result was largely driven by findings with females.

Rather than maternal negative mood altering fetal development in ways that primarily mark a risk phenotype (lower levels of expected fetal measures as we had predicted and others have found (Allister et al., 2001; Dieter et al., 2008; DiPietro et al., 1996a,b; Pressman et al., 1998)), frequently the data indicated that maternal distress was associated with accelerated fetal development (seen fairly consistently in males, see below for discussion on sex differences). These results can be interpreted in two ways, which are not mutually exclusive.

Mild to moderate levels of psychological distress may enhance fetal maturation based on the opportunity to sample additional stimulation resulting from women's psychologically induced physiological reactivity and variability (DiPietro, Novak, Costigan, Atella, & Reusing, 2006). Throughout gestation, fetal development may be shaped by these alterations in women's biology (e.g., auditory stimuli from the cardiovascular

and gastrointestinal systems, somatosensory activation from changes in breathing rate, and thermodynamics) with heightened opportunities for conditioning enhancing neural development (Costigan et al., 2008; DiPietro et al., 2003, 2008; Monk et al., 2000, 2004; Novak, 2004). Higher maternal distress has been associated with advanced postnatal motor and cognitive development (DiPietro, 2004, 2010). It also has been associated with greater fetal coupling (DiPietro et al., 2010), as shown in the current study, which in turn, predicts more mature neural integration at birth (DiPietro et al., 2010). These findings are in line with an animal model showing that in pregnant rats exposure to mild stress is associated with offspring having enhanced learning abilities (Fujioka et al., 2001). Previously, we reported maternal prenatal distress, including frank psychiatric symptoms of mood disorders, was associated with greater FHR reactivity when women underwent a laboratory stressor, and interpreted the findings using a risk-model as indicating a potential marker for future stress-based psychopathology (Monk et al., 2000, 2004, 2010). Possibly these results instead index accelerated development and more mature ANS control of the cardiac system.

These results also are in line with a theoretical model suggesting that maternal distress facilitates accelerated development to shape neurobehavioral systems to reduce time in the adverse *in utero* environment and promote survival in the non-optimal postnatal one to come (Glover, 2011; McLean et al., 1995; Pike, 2005). In this perspective, whether this precocity is beneficial to long-term health trajectories depends on the correspondence or “fit” between the neurobiological profile established *in utero* and the demands of the

postnatal world (Ellis, 2011; Frankenhuis & Del Giudice, 2012; Glover, 2011; Sandman et al., 2012). Alternatively, another view supported by recent data suggests that there is a detrimental trade off to long-term health of early accelerated development (Sandman et al., 2013).

The other a priori predictor variable, higher cortisol, based on AUC of daily samples, was associated with an accelerated rate of change over gestation in fetal parameters. Specifically, higher 2nd session cortisol was associated with a steeper increase in FHRSD over gestation. In addition, higher 1st session maternal cortisol was associated with a slower increase in coupling over time, and this tended to be more true for males. However, this relative elevation in cortisol also showed a sex finding such that higher cortisol was associated with greater couplings in males. Taken together these coupling findings related to maternal cortisol suggest accelerated development: males may be at higher levels sooner and increase less as gestation goes on.

Maternal HPA axis regulation is the distress-linked biological parameter most consistently associated with differences in fetal, infant, and child outcomes. The majority of findings relate exposure to elevated maternal cortisol to a neurobehavioral risk profile including greater stress reactivity at birth and infant fussiness in the first months of life (Davis, Waffarn, & Sandman, 2010; de Weerth, van Hees, & Buitelaar, 2003; Werner et al., 2013). In the few fetal studies considering maternal cortisol as a possible influence on fetal development, associations were found between concurrently tested elevations and greater movement at 32–36 gestational weeks (DiPietro et al., 2009) and higher overall FHR at 36–38 weeks (Monk et al., 2004). Using a longitudinal study design, Glynn and Sandman (2012) showed lower cortisol early in pregnancy was associated with precocious development indexed by mounting a motor response to a vibro acoustic stimulus (Glynn & Sandman, 2012). To our knowledge, our current study is the only report showing higher maternal cortisol associated with indicators of accelerated fetal development, though it is consistent with evolutionary perspectives on maternal distress effects (see below), as well as the biological role cortisol plays in regulating fetal development. Glucocorticoids are critical to the maturation of the human fetal lungs (Ballard & Ballard, 1974), CNS, and brain (Uno et al., 1994). Synthetic glucocorticoids such as dexamethasone have provided a model for the effects of maternal cortisol levels on offspring development, showing prenatal exposure to elevated levels of dexamethasone alters the normal developmental trajectory of CNS and brain (Uno et al., 1990) at multiple levels, including accelerated trajectory of neuronal maturation (Slotkin et al., 1992).

Two other maternal variables that showed associations with fetal measures were diastolic blood pressure and physical activity. Consistent with our original hypothesis, higher diastolic blood pressure in early pregnancy (1st session) was associated with lower levels of coupling, particularly for females. Greater physical activity early in pregnancy (1st session) was associated with higher FHR across gestation and a less of a decrease in slope in females whereas in mid pregnancy (2nd session) it was associated with lower overall FHR levels in males. Physical activity as an independent predictor of fetal measures was unexpected, though the results are consistent with those showing that physical exercise during pregnancy influences fetal ANS development (Gustafson, May, Yeh, Million, & Allen, 2012; May, Glaros, Yeh, Clapp, & Gustafson, 2010; May, Suminski, Langaker, Yeh, & Gustafson, 2012), and point to yet another lifestyle characteristic through which women may shape fetal development. However, our index of physical activity was not very rigorous; future research exploring this maternal factor for fetal development should use other approaches, such as more objective systems using an accelerometer worn on the wrist (Troost, Loprinzi, Moore, & Pfeiffer, 2011; Ward, Evenson, Vaughn, Rodgers, & Troiano, 2005).

Fetal sex significantly moderated the associations between maternal factors and the range of fetal measures. In the context of greater maternal negative mood, elevated cortisol, more physical activity, and higher maternal diastolic blood pressure, female fetuses showed deviations from expected behavior (slower decrease in FHR, less coupling) as well as accelerated development (greater coupling). Under similar conditions, male fetuses evidenced accelerated development (decrease in FHR, slower increase in coupling in the context of a positive association between cortisol and overall coupling levels). Clifton (Clifton, 2010) has proposed that sex differences in the function and structure of the placenta may play a role in sex differences in maternal distress-related fetal and child outcomes. In Clifton's view, female fetuses make multiple adaptations in placental gene and protein expression in response to intrauterine adversity (e.g., maternal asthma and preeclampsia). Similar to Glynn et al. (2012), our results suggest that the female fetus is variously responsive to signals from the prenatal context. For males, Clifton suggests they have a "minimalist" approach and show fewer signs of adapting to their context, which may put them at risk in the future, consistent with the higher levels of neurodevelopmental disorders seen in male children (Clifton, 2010; Clifton, Stark, Osei-Kumah, & Hodyl, 2012). We found that male fetuses *did* alter their development in

the face of maternal distress, though with a uniform response of accelerated development.

The questions of *when* distress exposure has effects on shaping *which* outcomes are key issues concerning two changing systems over the course of pregnancy: fetal development and maternal psychobiology. Some studies show effects of late pregnancy distress (Ellman et al., 2008; Huizink et al., 2003), many others find effects early on, these largely consistent with the risk phenotype model (Davis & Sandman, 2010; Ellman et al., 2008; Davis & Sandman, 2010; King & Laplante, 2005; Laplante et al., 2008). In this report, maternal factors assessed at 13–16 (1st session) and at 24–27 weeks (2nd session) were associated with variation in fetal behavior. Neuronal migration peaks between gestational weeks 12–20 and the architectural framework and functional capacities of the major neurotransmitter systems are established early in gestation. Factors that alter the neurotransmitter physiology, such as glucocorticoids or variation in oxygenation, may affect the development of neural circuits and neurotransmitter systems in subtle though significant ways that are as yet poorly understood (Tau & Peterson, 2010). Clearly, future studies, with more fine grained time frames, are needed to begin to characterize the specificity of timing effects.

Despite the inclusion of multiple potential biological effectors of maternal distress reflecting different physiological systems—cardiovascular, HPA, immune, and ecologically valid daily sampling, we did not find associations between maternal negative mood and these biological variables, and few associations with fetal variables. Similar to other research (Davis & Sandman, 2012; Huizink et al., 2003; Ponirakis et al., 1998; Rieger et al., 2004), our results do not identify a biological, mediating pathway by which maternal psychological distress affects the fetus. Instead, results underscore the need to consider a complex series of transmissions, e.g., maternal anxiety affects placental gene expression (O'Donnell et al., 2012), which, in turn, influences fetal exposure to maternal stress hormones, as well as indirect effects, e.g., maternal distress is a marker variable for nutrition, which influences the fetus (Monk, Georgieff, & Osterholm, 2012a). EMA is a sensitive method of assessing perceived psychological distress (Entringer et al., 2011) though within subject, event-related approaches (Giesbrecht, Campbell, Letourneau, & Kaplan, 2013) or those tracking mood-based differences in biological trajectories over gestation (Kane, Dunkel Schetter, Glynn, Hobel, & Sandman, 2014), and not using a composite value such as ours, may be needed to characterize the co-variation of mood and biology, and to relate them to fetal development. Finally, though we

modeled our EMA approach to mood dysregulation in adolescents on similar studies with this age group (Adam, 2006; DeSantis et al., 2007), and used an empirically validated method to produce a composite score that we labeled negative mood (consisting of angry, frustrated, irritated, and stressed), this distress index did not target depression and anxiety, which may have contributed to our null findings.

CONCLUSION

There are developmental origins to almost all forms of psychopathology (Cicchetti & Rogosch, 1996; Sroufe & Rutter, 1984), with strong evidence supporting the role of neurodevelopmental pathways (Insel, 2014; Insel & Wang, 2010). Increasingly, maternal prenatal distress is accepted as contributing to these neurobehavioral outcomes based on extensive data showing associations between it and at-risk infant, child, and adult mental health profiles (Beydoun & Saftlas, 2008). Here we show evidence for the premise underlying these prenatal programming studies: proximal associations between maternal distress and variation in fetal development. However, our measures suggesting relative decrements as well as acceleration in expected fetal outcomes, and significant moderation by sex, indicate that this relatively brief neurodevelopmental period—*in utero*—encompasses heterogeneous pathways and complex processes to arrive at the individual differences present at birth.

NOTES

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