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Impact of Maternal Stress, Depression and Anxiety on Fetal Neurobehavioral Development

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Abstract: Although postnatal psychologic distress has been widely studied for many years, particularly with a focus on postpartum depression, symptoms of maternal depression, stress, and anxiety are not more common or severe after childbirth than during pregnancy. This paper reviews the newer body of research aimed at identifying the effects of women's antenatal psychologic distress on fetal behavior and child development, and the biologic pathways for this influence. These studies are in line with the growing body of literature supporting the "fetal origins hypothesis" that prenatal environmental exposures—including maternal psychologic state-based alterations in in utero physiology—can have sustained effects across the lifespan.

Key words: fetal heart rate, fetal movement, HPA axis, neurobehavioral development, developmental psychopathology

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Introduction

Although postnatal psychologic distress has been widely studied for many years, particularly with a focus on postpartum depression, symptoms of maternal depression, stress, and anxiety are not more common or severe after childbirth than during pregnancy.[1] In a recent meta-analysis of 28 articles regarding depression during pregnancy, Gavin et al[2] found that up to 13% of women experience depressive episodes at some point during pregnancy or within the first year postpartum. Thus, a newer body of research has emerged aimed at identifying the effects of women's antenatal psychologic distress on fetal behavior and child development, and the biologic pathways for this influence. These studies are in line with the growing body of literature supporting the "fetal origins hypothesis" that

prenatal environmental exposures—including maternal psychologic state-based alterations in in utero physiology—can have sustained effects across the lifespan.

The prenatal period is a critical time for neurodevelopment and is thus a period of vulnerability during which a range of exposures have been found to exert long-term changes on brain development and behavior with implications for physical and psychiatric health. For example, maternal consumption of essential fatty acids during pregnancy is linked to lower birth weight and decrements in cognitive and motor function, whereas fetal exposure to polychlorinated biphenyls and methylmercury, through seafood in women's diet, is linked to neurocognitive deficits.[3]

Although toxins have direct effects on the processes of neurogenesis, neuronal migration, cellular differentiation and synaptic refinement that are occurring during the prenatal period, there is also evidence for the interaction between these types of prenatal exposures and maternal psychosocial health. Risk of developmental delay in children exposed prenatally to tobacco smoke has been found to be much greater among those infants whose mothers also experienced material hardship during pregnancy.[3] This finding is consistent with extensive epidemiologic research on birth cohorts from the Dutch Hunger Winter of 1944 based on offspring of women who were pregnant at the time when food intake was reduced from 500 to 1500 kcal/d during World War II. In a series of studies, Brown et al[4] have shown that fetal development during this period is associated with a 2-fold increased risk for schizophrenia, schizoid/schizoptypal personality disorder, and comparable risk for major affective disorders in adulthood. Two interpretations regarding the causal mechanisms of these effects have been suggested: (1) deficiency in many micronutrients and macronutrients, such as folate and/or overall calorie nutrition could directly alter brain development or (2) maternal stress, secondary to famine, could have neurotoxic effects on brain regions relevant to mental illness. Though these mechanisms are not mutually exclusive and could both contribute to the increased risk of psychopathology observed in these studies, there are extensive studies on prenatal stress in animals that provide support for the latter interpretation and largely rule out genetic factors for the prenatal stress effects.[5]

Clinical studies link pregnant women's exposure to a range of traumatic, as well as chronic and common life stressors (ie, bereavement, daily hassles, and earthquake), to significant alterations in children's neurodevelopment, including increased risk for mixed handedness, autism, affective disorders, and reduced cognitive ability.[6] More recently, maternal antenatal anxiety and/or depression have been shown to predict increased risk for neurodevelopmental disorders in children, and to confer risk for future mental illness. Reports show that elevated levels of antenatal depression and anxiety are associated with poor emotional adjustment in young children.[7] The impact of women's anxiety (and/or depression) during pregnancy has been found to extend into childhood and adolescence, and to affect the hypothalamic-pituitary-adrenal (HPA) axis, predicting attention deficit hyperactivity disorder symptoms in 8 to 9-years-old children[8] as well as alterations in HPA axis activation in 4-months-old in our laboratory[9] and in 10,[10] and 14 to 15-years-old.[11] The majority of these studies have controlled for women's postnatal mood, as well as other demographic factors, yet the possibility that the women's antenatal mood is a marker for qualities in the postnatal environment that affect child development cannot be ruled out. What these data suggest is that, in addition to the known pathways for the familial transmission of risk for mental illness, genetics, environment, and gene *X*

environment interactions, there is another possibility: that some of the risk is conferred prenatally through changes in women's mood-based physiology affecting the fetal neurobehavioral development.

If pregnant women's distress, similar to their nutrition, is influencing children's long-term development, that is, if fetal exposure to the physiologic alterations associated with women's psychologic distress affects child outcomes, evidence of this maternal influence should be detectable during the prenatal period. This review will cover the recent studies showing associations between prenatal maternal psychologic states and alterations in fetal behavior and physiology, as well as the 2 possible pathways for the "transmission" of maternal mood to the fetus: (1) maternal-fetal HPA axis dysregulation and (2) intrauterine environment disruption because of the variations in uterine artery flow. Implications for clinical intervention will be discussed.

WOMEN'S ANTENATAL PSYCHOLOGIC STATE: INFLUENCES ON FETAL PHYSIOLOGY AND BEHAVIOR

Fetal Heart Rate

Characteristics of fetal heart rate (FHR) activity are associated with a range of dysphoric psychologic states in pregnant women, including perceived stress, lab-induced stress, self-reported depression, clinically appraised depression, anxiety disorders, state anxiety, and anxiodepressive comorbidities (Table 1). Importantly, the indices of FHR used in these studies are distinct from those of cardiac activity used by obstetricians and others in prenatal pediatrics to investigate physical disease and anomalies. Instead, common markers such as FHR reactivity to a stimulus, or heart rate variability, reflect emerging individual differences in the development of the autonomic and central nervous systems related to styles of future emotion regulation and risk for psychopathology. For example, in both child and adult psychiatry research, lower levels of high frequency heart rate variability are associated with less adaptive transitions in responding to emotion-eliciting cues[30] and (in adults) greater hostility.[31] In other studies, greater heart rate increases to novelty in infancy predicts increased fearful behavior and an increased risk for anxiety disorders in school age children.[32] That there is continuity in fetal to infant neurobehavior[29,33–35] further supports the relevance of these autonomic nervous system indices for characterizing the influence of women's antenatal distress on fetal development.

In a longitudinal study of fetal ontogeny, DiPietro et al[12] assessed fetal variables in relation to pregnant women's reports of daily stress at 6 testing sessions beginning at 20 weeks and ending at 36 to 68 weeks gestation. Fetuses of mothers who reported greater stress showed significantly lower FHR variability than the low stress group, which suggests that exposure to maternal psychologic distress may contribute to diminished parasympathetic control of the fetal heart.[12] Similarly, fetuses of women suffering from maternal depression have displayed higher baseline FHR and a delayed FHR response to stimulus. In a fetal reactivity study, Allister et al[13] monitored fetal behavior in women with untreated depression and controls at 32 to 36 weeks gestation during a baseline period, a period of fetal stimulation through a vibroacoustic stimulus administered to the mother's abdomen, and during a recovery period. Fetuses of depressed mothers displayed a higher baseline FHR, a slower FHR reaction to the external stimulus, and a longer period to return to FHR baseline levels after the stimulus compared with fetuses in a control group.[13]

In a series of studies from our group, we have shown that fetuses of mothers experiencing psychologic distress also show

TABLE 1. Women's Antenatal Psychologic State: Influences on Fetal Physiology and Behavior

Authors	Title	Design	Results
DiPietro et al[12]	Fetal neurobehavioral development	N = 31; fetal activity and FHR digitized using fetal actocardiograph over 50 min periods at 20, 24, 28, 32, 36, and 38-39 wk gestation, whereas maternal abdomen underwent vibroacoustic stimulation; HSUP	Perceived stress was significantly inversely associated (–) with FHR variability ($P < 0.01$)
Allister et al[13]	The effects of maternal depression on fetal heart rate response to vibroacoustic stimulation	N = 20; FHR monitored using actocardiograph, whereas maternal abdomen underwent vibroacoustic stimulation between 32 and 36 wk gestation; BDI	Fetuses of depressed mothers had a significantly higher (+) mean and more (+) variable FHR during a baseline period and at the onset of vibroacoustic stimulation than fetuses of nondepressed mothers ($P < 0.05$ for both). Change in FHR after vibroacoustic stimulation was significantly higher (+) for fetuses of nondepressed mothers than depressed ($P < 0.01$). 3-6.5 min after vibroacoustic stimulation, fetuses of depressed mothers showed significantly greater (+) FHR variability than fetuses of nondepressed mothers ($P < 0.10$), suggesting that the fetuses of depressed mothers were still regulating their HR due to vibroacoustic stimulation, whereas fetuses of nondepressed mothers had returned to baseline. 3-6.5 min after vibroacoustic stimulation, fetuses of depressed mothers showed significantly greater (+) FHR variability than fetuses of nondepressed mothers ($P < 0.10$), suggesting that the fetuses of depressed mothers were still regulating their HR due to vibroacoustic stimulation, whereas fetuses of nondepressed mothers had returned to baseline
Dieter et al[14]	Maternal depression and anxiety effects on the human fetus: preliminary findings and clinical implications	N = 90; fetal activity observed via ultrasound for 5 continuous minutes between 18 and 36 wk gestation and movements were categorized; CES-D, STAI	Fetuses of depressed mothers spent a greater (+) percent of time active than nondepressed counterparts ($P < 0.01$). Fetal activity was significantly positively correlated (+) with both maternal depression ($r = 0.30$, $P < 0.01$), anxiety ($r = 0.20$, $P < 0.05$), and their

TABLE 1. (continued)

Authors	Title	Design	Results
			combined effects ($r^2 = 0.35$, $P < 0.05$)
DiPietro et al[15]	Maternal stress and affect influence fetal neurobehavioral development	N = 52; fetal activity monitored via fetal actocardiograph at 24, 30, and 36 wk gestation; AIM, DSI, PES–used to form a composite score	When analyzed groupwise using 3 strata from maternal composite stress scores, the relationship between fetal motor activity and maternal stress was significantly positive (+) ($P < 0.01$)
Monk et al[16]	Fetal heart rate reactivity differs by women's psychiatric status: an early marker for developmental risk?	N = 57; fetal activity monitored via actocardiograph and maternal EKG, BP, respiration, and salivary cortisol between 36 and 38 wk gestation during a laboratory-induced stressor; SCID and STAI during second trimester	Significant positive association (+) between maternal diagnostic group and FHR baseline reactivity from baseline to laboratory-induced stressor ($P = 0.04$). Fetuses of depressed mothers had significantly greater (+) FHR increases from baseline to laboratory-induced stressor compared with fetuses of women with anxiety disorder, healthy (no psychiatric disorder) low-anxiety women, and healthy middle-anxiety women ($P < 0.05$, $P < 0.01$, and $P < 0.05$, respectively). Fetuses of healthy high-anxiety women had significantly higher (+) FHR increase compared with fetuses of women with anxiety disorder and healthy low-anxiety women ($P < 0.05$ for both)
Monk et al[17]	Maternal stress responses and anxiety during pregnancy: effects on fetal heart rate	N = 17; fetal activity monitored via actocardiograph as well as maternal EKG, BP, and respiration between 35 and 38 wk gestation during a laboratory-induced stressor; STPI	Fetuses of above-average anxiety mothers had significantly greater (+) FHR increases from baseline to the laboratory-induced stressor than the fetuses of below-average anxiety mothers ($P < 0.05$). Fetuses of above-average anxiety mothers had a significantly higher (+) than baseline FHR during the entire laboratory-induced stressor period ($P < 0.01$), whereas fetuses of below-average anxiety mothers did not show a significantly different than baseline FHR at any point during this period
Monk et al[18]	Effects of women's stress-elicited physiological activity and chronic anxiety on fetal heart rate	N = 32; fetal activity monitored via actocardiograph as well as maternal EKG, BP, and respiration between	FHR changes during recovery from laboratory-induced stressor were significantly positively associated (+) with women's concurrently collected HR and BP changes ($r = 0.63$, $P < 0.05$).

TABLE 1. (continued)

Authors	Title	Design	Results
		35 and 38 wk gestation during a laboratory-induced stressor; STAI	Changes in FHR from baseline to laboratory-induced stressor were significantly positively correlated (+) with women's anxiety scores ($r = 0.39$, $P < 0.05$). Changes in FHR from laboratory-induced stressor to recovery were significantly inversely associated (−) with women's anxiety scores ($r = 0.39$, $P < 0.05$)
Monk et al, (In preparation)	Prenatal origins of self-regulation: fetal sensory responses differ by women's psychiatric status	N = 113; fetal activity monitored via actocardiograph as well as maternal EKG, BP, respiration, and salivary cortisol between 36 and 38 wk gestation during a laboratory-induced stressor; SCID during second trimester	Fetuses of comorbid anxiety and depression mothers displayed a significantly higher (+) FHR during laboratory-induced stressor than controls ($\beta = 4.9$, $P < 0.05$)
DiPietro et al[19]	Fetal response to induced maternal stress	N = 137; fetal activity monitored via actocardiograph as well as maternal EKG and SCL at 24 and 36 wk gestation during a laboratory-induced stressor	FHR variability significantly increased (+) during laboratory-induced stressor ($P < 0.0001$). FM significantly decreased (−) during laboratory-induced stressor ($P < 0.001$)
Groome et al[20]	Maternal anxiety during pregnancy: effect on fetal behavior at 38 to 40 weeks of gestation	N = 18; fetal activity monitored for 60 consecutive minutes using fetal actocardiograph at 38-40 wk to define in utero "sleep states"; STAI	As maternal trait anxiety increased, fetuses spent increasingly more time (+) in quiet sleep ($r = 0.627$, $P = 0.005$) and were less active (−) in active sleep ($r = -0.620$, $P = 0.006$). Significant positive linear relationship (+) between increasing maternal state anxiety scores and greater percent quiet sleep ($r = 0.633$, $P = 0.005$)
Dieter et al[14]	Maternal depression and anxiety effects on the human fetus: preliminary findings and clinical implications	N = 32; fetal activity monitored with fetal actocardiograph, whereas maternal abdomen underwent vibroacoustic stimulation at 33 wk gestation; BDI-II, BAI	Significant group effect of increased maternal depression across baseline, stimulation, and poststimulation on total FM (−) and FHR (−) ($P = 0.05$). Fetuses of depressed mothers showed a significantly lower (−) mean baseline HR than those of nondepressed mothers ($P = 0.04$). Greater proportion (+) of fetuses of depressed mothers reached habituation criterion than those of nondepressed mothers and

TABLE 1. (continued)

Authors	Title	Design	Results
			required fewer trials for habituation ($P = 0.02$). Comorbid anxiety and depression explained 34% of the variance in habituation ($P < 0.01$)
DiPietro et al[21]	Development of fetal movement—fetal heart rate coupling from 20 weeks through term	N = 31; fetal activity and FHR digitized using fetal actocardiograph over 50 min periods at 20, 24, 28, 32, 36, and 38-39 wk gestation, whereas maternal abdomen underwent vibroacoustic stimulation; HSUP	Higher maternal perceived stress was significantly inversely associated (−) with FM-FHR coupling ($P < 0.01$) Faster maternal HRs were significantly inversely associated (−) with FM-FHR coupling latency ($P < 0.05$)
Pressman et al[22]	Fetal neurobehavioral development: associations with socioeconomic class and fetal sex	N = 103; fetal activity and FHR digitized using fetal actocardiograph over 50 min period at 24, 30, and 36 wk gestation; group stratification by maternal SES	SES was significantly positively associated (+) with FHR variability ($P < 0.01$). Fetuses of low-SES mothers showed significantly less decrease (−) in FHR over gestation than those of higher SES ($P < 0.05$). SES was significantly positively associated (+) with overall FM and movement vigor ($P < 0.05$). SES was significantly positively associated (+) with degree of FM-FHR coupling ($P < 0.05$)
Sandman et al[23]	Maternal corticotropin-releasing hormone and habituation in the human fetus	N = 33; fetal activity monitored via fetal actocardiograph, whereas maternal abdomen underwent vibroacoustic stimulation and maternal plasma CRH through blood draw between 31 and 32 wk gestation	FHR response to habituation was significantly inversely related (−) to maternal CRH concentration ($r = -0.41$, $P = 0.02$). Significant positive linear association (+) between maternal CRH and FHR ($r = 0.50$, $P < 0.005$)
Field et al[24]	Prenatal maternal cortisol, fetal activity and growth	N = 131; fetal activity and estimated fetal weight coded from ultrasound, cortisol collected through urinalysis between 20 and 28 wk gestation; CES-D, STAI	Maternal cortisol levels significantly positively associated (+) with fetal activity and inversely (−) with fetal weight ($r = 0.123$, $P < 0.05$, $r = -0.01$, $P < 0.005$, respectively)
DiPietro et al[25]	Fetal motor activity is associated with maternal cortisol	N = 92; fetal activity monitoring through fetal actocardiograph and salivary cortisol	Higher maternal cortisol significantly positively associated (+) with more fetal motor vigor at 32 ($r = 0.39$, $P < 0.01$) and 36 wk ($r = 0.27$, $P < 0.05$) and, at

TABLE 1. (continued)

Authors	Title	Design	Results
		collection at 32 and 36 wk gestation; PSS, PNAS, STAI, PES	32 wk, the amount of time fetuses spent moving in 50 min observation at ($r = 0.33$, $P < 0.05$)
Sandman et al[26]	Maternal hypothalamic-pituitary-adrenal disregulation during the third trimester influences human fetal responses	N = 135; fetal activity monitored via fetal actocardiograph and maternal plasma ACTH and β-endorphin through blood draw at 32 wk gestation	Increase in maternal endocrine dysregulation (uncoupling of ACTH and β endorphin) significantly positively related (+) to FHR ($r = 0.17$, $P < 0.05$), however no significance between FHR and individual endocrine concentrations
Teixeira et al[27]	Association between maternal anxiety in pregnancy and increased uterine artery resistance index: cohort based study	N = 100; uterine artery flow assessed by color Doppler ultrasound at 32 wk gestation; STAI	Significant positive association (+) found between uterine artery resistance index and state ($r = 0.31$, $P < 0.002$) and trait anxiety ($r = 0.28$, $P < 0.005$). Presence of notched waveform was significantly positively associated (+) with state anxiety ($P < 0.02$)
Kent et al[28]	Uterine artery resistance and anxiety in the second trimester of pregnancy	N = 96; uterine artery flow assessed by color Doppler ultrasound at 20 wk gestation; HAD	No significant association between uterine artery resistance index and anxiety ($r = 0.09$, $P = 0.36$)
DiPietro et al[29]	Fetal responses to induced maternal relaxation during pregnancy	N = 99; fetal activity monitored via actocardiograph as well as maternal EKG, SCL, respiration, and uterine artery flow as assessed by color Doppler ultrasound at 32 wk gestation during a laboratory-induced maternal relaxation session; salivary cortisol collected at 6 points during session	Cortisol levels declined significantly (−) period-to-period from arrival through postrecovery ($P < 0.0001$). No significant change in uterine artery resistance from baseline to laboratory-induced relaxation. FHR significantly declined (−) over time throughout the protocol ($P < 0.05$), though decline was most pronounced from baseline to laboratory-induced relaxation ($P < 0.001$). FM significantly decreased (−) from baseline to laboratory-induced relaxation and then significantly increased (+) from laboratory-induced relaxation to recovery ($P < 0.0001$ for both). FM-FHR coupling significantly increased (+) from baseline to laboratory-induced relaxation and then significantly decreased (−) from laboratory-induced relaxation to recovery. Fetuses of women who reported greater psychologic relaxation to the procedure showed significantly greater (+) FHR

TABLE 1. (continued)

Authors	Title	Design	Results
			reactivity and recovery ($r = 0.27$, $P < 0.001$; $r = 0.20$, $P < 0.05$, respectively). Maternal HR recovery was significantly positively related (+) to both FHR and FHR variability ($r = 0.43$, $P < 0.001$; $r = 0.21$, $P < 0.05$, respectively). Significant positive association (+) between the degree of cortisol reactivity and FM suppression ($r = 0.31$, $P < 0.05$)

ACTH indicates adrenocorticotrophic hormone; AIM, affective intensity measure; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; CES-D, Center for Epidemiological Studies Depression Scale; CRH, corticotropin releasing hormone; DSI, Daily Stress Inventory; EKG, electrocardiography; FHR, fetal heart rate; FM, fetal movement; HAD, Hospital Anxiety Depression; HSUP, Hassles and Uplifts; PES, Pregnancy Experience Scale; PES, Pregnancy Experience Scale; PSS, Perceived Stress Scale; SCID, Structured Clinical Interview for DSM-IV; SCL, skin conductance level; SES, socioeconomic status; STAI, State-trait Anxiety Inventory; STPI, State-trait Personality Inventory.

significantly different reactivity to acute maternal stress. Fetuses of depressed mothers showed a significantly higher increase in FHR when the mother was introduced to a lab-induced stressor.[16] Similar increases in FHR were found in fetuses of anxious and anxiodepressive comorbid women (Monk et al, in preparation).[17,18] In these studies, there were no group differences in baseline FHR, or in women's cardiorespiratory reactivity to the laboratory challenge, which demonstrated significant increases. We interpret these results as indicating that fetuses have group differences in their acute reactivity to changes in the intrauterine environment, that is, to changes in maternal heart rate, respiration, and blood pressure, which may function as auditory and kinesthetic stimuli to the fetus and thereby reveal variation in fetuses' central nervous system development. In a similar study of pregnant women exposed to a laboratory-based stressor, DiPietro et al,[19] found increased FHR variability (which usually is associated with lowered FHR) and reduced movement during the challenge period compared to baseline. The contrasting results between our studies and this one potentially underscore the role of chronic maternal mood in shaping fetal responses to changes in the intrauterine environment associated with maternal experience. That is, when fetal responses are examined in relation to women's psychiatric symptoms and/or chronic mood, divergent responses emerge such that the subsample of those whose mothers have symptoms have a different response from those of "controls". Consequently, when all fetuses are examined together, the FHR result of the larger "control" group is the average response, and contrasts with the finding from a clinical sample.

Another set of studies examining the effects of prenatal depression and anxiety found that fetuses of depressed and anxious mothers habituated more quickly and more fully to a vibroacoustic stimulus placed on the maternal abdomen than fetuses unexposed to maternal depression and anxiety.[14] One possible explanation for these results, which are in direct opposition to the findings of Allister et al[13] and to the greater FHR reactivity to a different stimulus in our studies,[16,17] is that, owing to methodologic differences, the fetuses in the Dieter research are not experiencing "true" habituation to the

vibroacoustic stimulus; rather, they are experiencing "receptor adaptation" or "effector fatigue"[36] such that fetuses of depressed and anxious women experience a diminished ability to react to repeated stimulation and sustain a robust response, as opposed to habituation. A better understanding of the effects of maternal psychologic state on fetal reactivity and habituation requires more research and using protocols other than vibroacoustic stimulation and laboratory stressors.[14]

Fetal Activity

In addition to FHR, fetal activity, sleep pattern, and movement have been shown to be influenced by maternal psychologic states (Table 1), suggesting that maternal mood may also affect central nervous system development. When observed with an ultrasound monitor for 5 continuous minutes between 18 and 36 weeks gestation in a study of the effects maternal anxiety and depression on fetal development, fetuses of depressed mothers spent a greater percent of time active than fetuses of nondepressed mothers. This effect of maternal mood on fetal activity was strengthened when measurements of anxiety were included concurrently with depression, explaining 35% of the variance in fetal activity.[14] Maternal stress has also been shown to have a significant association with increased fetal motor activity at 24, 30, and 36 weeks gestation.[15] In contrast, fetuses of mothers with high anxiety have also been found to spend more time in "quiet sleep" and to be less active in "active sleep" than fetuses of mothers without high anxiety, with a linear relationship emerging between maternal anxiety and percent quiet sleep over a 4 hour monitoring period.[20] The long duration of this monitoring period may serve to explain the converse findings, as most other studies have only assessed a brief snapshot of fetal behavior. This could suggest that short observation periods are capturing acute changes in fetal behavior as a result of maternal testing conditions. Further observation of prolonged fetal monitoring will help to clarify the effects of maternal psychologic distress on fetal behavior.

Finally, studies by DiPietro et al[21] have used as indices of fetal neurobehavioral the coupling of FHR and movement. They have shown that over the course of gestation, there is more often a coincidence between changes in heart rate and body movement. They interpret this finding as indicating that the coupling index is reflecting the level of integration of the central nervous system, which increases with gestational age. In several studies, they have found associations between maternal health characteristics and the coupling of FHR and movement. Fetuses of women in lower socio-economic groups, and those of women reporting greater daily stress, and who had a higher resting heart rate, had less FHR and movement coupling compared to higher socio-economic status women and those with low daily stress scores.[22]

Taken together, data from these studies, even with some contrary results, support the hypothesis that maternal psychologic distress can affect the fetal autonomic and central nervous systems. In particular, depression and multiple assessments of daily stress are chronic mood states supporting the idea that, over the course of pregnancy, repeated exposure to mood-based alterations in women's physiology shapes fetal neurobehavioral development.

PHYSIOLOGIC PATHWAYS FOR TRANSMISSION OF MATERNAL DISTRESS TO THE FETUS

Though maternal psychologic distress has been shown to elicit both maternal cardiorespiratory and FHR and movement variations in baseline and lab-induced stress reactivity in many of these studies, as indicated, these physiologic changes

have been found to exist largely independent of one another. Few significant relationships between concurrent maternal autonomic measures and FHR and movement are found, with the exception of a small association between increases in maternal skin conductance reactivity and increases in fetal movement,[37] as well as an association between maternal blood pressure and FHR.[16] Researchers have looked to the HPA axis and uterine functioning as possible pathways by which maternal psychologic state is transmitted to the fetus.

Maternal-Fetal HPA Axis Dysregulation

The HPA axis is often regarded as the central regulatory system for psychologic distress.[33] The principal modulator of the HPA axis for psychologic distress is corticotropin-releasing hormone (CRH), which is primarily released by the hypothalamus into the hypothalamo-hypophyseal portal system. This portal leads CRH into the anterior of the pituitary gland, stimulating corticotropes and secreting adrenocorticotropic horomone (ACTH).[38,39] ACTH stimulates the ACTH receptors of the adrenal gland, causing the synthesis and secretion of glucocorticoids into the blood stream, primarily cortisol. Cortisol elicits physiologic responses, such as increased blood pressure and heart rate, as well as down-regulating the hypothalamic release of CRH.[38] During pregnancy, in addition to hypothalamic CRH, the placenta also generates and releases CRH into the blood stream, causing hyperactivation of the HPA axis, and a considerable rise in the ratio of free/bound cortisol, reaching values comparable to those found in Cushing's disease.[40,41] The production of placental CRH and the presence of excess cortisol begin during the second trimester and increases linearly to term, with a spike in the last 6 to 8 weeks of pregnancy. It has been demonstrated that as pregnant women progress through gestation, cortisol responses to acute stress decline, suggesting a blunting of the HPA axis owing to high levels of placental CRH.[40,42,43] In humans, by the 16th gestational week, the placental enzyme 11β-hydroxysteroid dehydrogenase-2, which converts cortisol to inactive cortisone, forms a barrier to maternal glucocorticoids. However, 10% to 20% of maternal cortisol passes through to the fetus,[44,45] which under conditions of stress-induced elevated maternal HPA activity, may be sufficient to exert long-term effects on the developing fetal brain.

In psychiatric studies, elevated reactivity of the HPA axis is commonly found in the neurobiology of depression and other psychiatric illnesses.[46] During pregnancy, the link has been less consistent. Sarkar et al[47] recently found that pregnant women's anxiety did not predict amniotic fluid cortisol and that the modest association between maternal anxiety and plasma cortisol is no longer detectable after 17 weeks gestation, likely because of the hypercortilsolemia of the HPA axis in later stages of pregnancy. However, another report from the same laboratory found that maternal plasma and amniotic fluid cortisol are correlated after 18 weeks gestation, and that state anxiety after amniocentesis collected across a range of trimesters moderated the association between maternal plasma and amniotic fluid cortisol such that there was a strong positive relationship ($r = 0.59$) for highly anxious women, and a nonsignificant correlation in the least anxious group.[45] These findings suggest that antenatal anxiety may affect placental function, which in turn, regulates fetal exposure to maternal cortisol. In another study, higher ratings of self-reported stress were associated with elevated levels of ACTH and cortisol at 28 weeks.[48] We have found that third trimester women who are comorbid for anxiety and depression have higher level of cortisol compared with healthy

controls, as well as those with only 1 psychiatric disorder.[49]

In a 2004 study of fetal activity and maternal cortisol between 20 and 28 weeks gestation, Field et al[24] found that maternal cortisol levels were significantly related to increased fetal activity and inversely related to estimated fetal weight. Similarly, DiPietro et al[25] found maternal cortisol levels were associated with fetal motor vigor and total time spent moving. In our work, maternal cortisol is positively associated with greater FHR during women's exposure to laboratory stress (Monk et al, in preparation). Furthermore, maternal CRH concentration has been evidenced to have a linear relationship with baseline FHR among women in 31 to 32 weeks gestation, whereas the inverse is demonstrated in FHR time to habituate to an abdominal vibroacoustic stimulus.[23] Interestingly, ACTH does not exhibit an association with FHR. However, dysregulated and uncoupled levels of ACTH and β-endorphin in maternal plasma displayed an effect on FHR increases.[26]

Uterine Artery Resistance

Another mechanism by which maternal psychologic state might affect the fetus is through the alteration of blood flow to the fetus through the uterine arteries. Uterine blood flow can be assessed by using a color Doppler ultrasound to measure uterine artery resistance and to detect the presence of notches in the ultrasound waveform pattern. The presence of a notch denotes a very high resistance to blood flow. Measures of high uterine artery resistance have been previously associated with underweight for gestational age babies and preeclampsia.[50,51]

This potential maternal-fetal psychologic pathway remains largely unresearched, with only 2 conflicting studies. Teixeira et al[27] investigated uterine artery resistance among women experiencing anxiety versus controls at 32 weeks gestation. A significant positive association was discovered between both maximum artery resistance scores and mean artery resistance and anxiety levels. There was also a significant dichotomous relationship between women with high anxiety and the presence of waveform notching. In a similarly designed study, though with women in the 20th week of gestation, Kent et al[28] could not repeat these findings, discovering no associative relationships between anxiety and uterine blood flow.

Although the HPA axis may be involved with increasing uterine artery resistance, it has been suggested that noradrenaline is a likely mediator through sympathetic-adrenal activation.[27] Previous studies have shown a linear relationship between plasma noradrenaline concentration and anxiety.[52] Animal research has linked noradrenaline levels and decreased uterine blood flow.[53,54] More research on this association using a wider body of psychologic, physiologic, and neuroendocrine measurements is necessary.

Environmental Imprinting?

Recently, DiPietro et al[37] used the notion of transmitting maternal state to the fetus in a lab-induced relaxation study. During the 32nd week of gestation, maternal-fetal pairs were monitored for maternal electrocardiography, skin conductance, and respiration as well as FHR and movement for 18 minutes of baseline, 18 minutes of guided relaxation, and 18 minutes of recovery. Salivary cortisol was collected at 6 different times during the study period including immediately following: subject arrival, ultrasound, baseline, relaxation, postrelaxation, and just before the subject departs.

All maternal physiologic measures, except for respiration, declined significantly from baseline to relaxation, as well as their salivary cortisol levels. FHR and movement also declined significantly

from baseline to relaxation, whereas FHR variability increased. Although maternal skin conductance level and respiration were significantly associated with FHR, the associations, as previously described, were small ($r_s = 0.22$ and -0.21, respectively). Moreover, induced relaxation elicited a decline in fetal movement and an augmentation in FHR variability similar to the inducement of maternal stress.[37] Taken together, DiPietro et al consider that these unexpected results as suggesting that the fetal responses to both situations may, in part, reflect fetal perception of changes in the intrauterine environment resulting from the laboratory and relaxation manipulations. Because FHR decreases, they consider the possibility that the fetuses are showing an orienting response. This interpretation is similar to the previously discussed interpretation by Monk et al, in which group differences in FHR reactivity reflect group differences in fetal autonomic and central nervous system regulation in response to cardiorespiratory reactivity in women. It is possible that over the course of gestation, fetuses are conditioned by the stimuli in their prenatal environment to be better prepared for what they will encounter postnatally. Thus, some of the transmission of women's psychologic distress-based changes in physiology may shape fetal behavior as a result of in utero perception and learning.

CLINICAL IMPLICATIONS

Studies discussed here, all of which are ongoing, indicate that pregnant women's psychologic health may have consequences for fetal neurobehavioral development, and consequently, child outcomes. These findings underscore the importance of considering the effects of women's mental health on child development during the prenatal, as well the postnatal, periods. Although gestational diabetes is far less common than depression during pregnancy, women are routinely screened for this disorder, but not for depression, any psychiatric illness, nor even experiences of life stress. This is a short coming of public health policy, as it is an optimal time to perform mental health screenings as women most often are under regular care and thus available for referrals and follow-up interventions, and because there is, potentially, more than 1 patient. Some forms of psychotherapy, and psychopharmacologic medications have been shown to be effective for depression and anxiety during pregnancy.[55,56] Further research likely will lead to targeted interventions for this population. For now, the first aim should be improved surveillance of women's mood and mental health during pregnancy.

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