



Review article

Maternal Stress in Pregnancy: Considerations for Fetal Development

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A B S T R A C T

There is significant current interest in the degree to which prenatal exposures, including maternal psychological factors, influence child outcomes. Studies that detect an association between prenatal maternal psychological distress and child developmental outcomes are subject to a number of interpretative challenges in the inference of causality. Some of these are common to many types of prenatal exposures that must necessarily rely on observational designs. Such challenges include the correlation between prenatal and postnatal exposures and the potential role of other sources of shared influence, such as genetic factors. Others are more specific to this area of research. These include confounding between maternal report of child outcomes and the maternal psychological attributes under study, difficulties in distinguishing maternal stress from more ubiquitous aspects of maternal personality, and the lack of association between cortisol and measures of maternal psychological stress. This article considers these methodological issues and offers an additional methodology focused on fetal neurobehavior for discerning potential mechanisms that may mediate associations between maternal psychological functioning and the developing fetal nervous system.

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There is growing support for a central role of the prenatal period in the health and development of offspring throughout childhood and adult life. Focus on the formative role that earlier experiences and exposures can have on later periods of development, both within and across individuals, has been a central tenet of developmental sciences for much of their history, as has understanding that neither health nor development commences at birth [1]. Speculation about the influence provided by the maternal environment in general, and the emotional and psychological state of the pregnant woman in particular, permeates history, literature, and culture. The Fels Longitudinal Study of human development of the 1930s applied scientific methods to this subject. Potential prenatal maternal influences on fetal and child development that were studied include exposures such as cigarette smoking and nutritional factors, as well as maternal psychological factors of emotionality and stress [2,3]. Some 80 years later, investigators continue to pose similar questions, fa-

cilitated by newer methodologies, research design, and conceptual perspectives.

Resurgence in interest in the role of maternal psychological stress and emotions has emerged over the past several decades, focused both on pregnancy outcomes, such as timing of delivery and infant size at birth [4–6], and more persistent effects on child development, behavior, and temperament [7,8]. The current article is not meant to serve as an exhaustive review or synthesis of the abundant existing literature on prenatal maternal stress. Instead, its goals are to (1) reflect on some of the principal challenges inherent in establishing causality between prenatal psychological distress and subsequent child development outcomes, and (2) broaden the discussion by posing additional mechanisms through which the maternal psychological state may be transduced to the developing fetus.

Maternal stress as a developmental teratogen

Maternal psychological stress has essentially been conceptualized as a teratogen, an agent that can generate deleterious perinatal and/or developmental outcomes. As such, it shares the same methodological challenges that all such studies do in attempting to isolate the effects of an exposure from other con-

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founding influences because such studies are necessarily observational in design in humans [9]. In particular, as with exposure to contaminants found in the physical environment, prenatal exposures covary with postnatal exposures. That is, women who are psychologically distressed during pregnancy tend to remain so after pregnancy [10–12]. Thus, the burden of proof for investigators is to demonstrate that maternal distress, which is presumed to affect the developing fetus through physiological alterations to the intrauterine milieu, confers significant unique variance to outcomes above and beyond known associations. The known associations include the well-documented effects that maternal psychological distress (particularly depression and anxiety) and personality characteristics within the normal range have on parenting behaviors, which in turn influence child outcomes [13–15]. Inadequate measurement or control of postnatal maternal distress could result in misattribution of socially mediated mechanisms (i.e., postnatal parenting) to biological ones (i.e., physiologically inspired alterations to the developing fetal brain or other organ systems).

Although measurement reliability and validity are vital to all research, quantification of maternal psychological functioning, including perceptions of stress, is notoriously challenging, given its inherently subjective nature and individual differences in the propensity to regard circumstances as stressful [16,17]. Maternal appraisal is central to paper-and-pencil measures that are used to quantify stress during pregnancy, and there is strong empirical correspondence between measures of maternal stress, anxiety, and depression. Although these represent separate psychological constructs, empirically they are difficult to disambiguate, with correlation coefficients routinely ranging from the .50s to .70s [6,10,18,19]. As a result, we prefer to use the term “maternal distress” when characterizing the constellation of features of maternal psychological functioning that include stress appraisal, anxiety, and depressive symptomatology. More importantly, there is significant concern regarding the degree to which the questionnaires routinely used in prenatal stress research characterize true interindividual variation in stressful prenatal circumstances as opposed to expressions of maternal temperament or personality, particularly trait anxiety and neuroticism [19]. Evidence that perceived stress, as defined by these instruments, has a substantial heritable component [20] underscores these concerns. This is not simply a semantic issue but an important conceptual distinction that speaks to ultimate attribution of causality to observed associations.

Animal models of prenatal stress on offspring development can circumvent this issue and also afford the opportunity to examine concomitant changes to neuronal and cellular structure and function [21,22]. Stressors used in animal models, such as periods of physical restraint or unpredictable noise, are applied in a controlled manner in terms of duration, frequency, and intensity within an experimental framework that includes essentially a random selection of animals. This degree of control is its strength but also its limitation to generalizing findings to human development. In general, for the reasons detailed in the preceding paragraph, psychological stress research in human pregnancies does not reflect systematic events applied to randomly selected individuals but rather reflects women’s appraisal of their daily lives through the lens of their mood states and personality inclinations. The exception to the nonrandomness aspect of this research can be found in studies that take advantage of naturally occurring population-based disasters [23–26]. However, because the degree to which women perceive the

same event as stressful is moderated by individual psychological differences, investigators have endeavored to distinguish objective (e.g., property damage) from subjective (e.g., ratings of distress after trauma) [25]. It is also worth noting that although exposure to disasters may be relatively random, the ability of families to mitigate the physical and psychological impact of the event is not, and corresponds to their access to resources. Given the well-known association between lower socioeconomic status and adverse child outcomes [27], strong control for socioeconomic status of participants is needed.

Measuring child behavior and developmental performance is costly and time consuming, but it is the foundation of developmental epistemology. To date, maternal report of child behavior, temperament, and developmental status, as opposed to laboratory-based measurement of these outcomes, has been the prevailing source of information in studies linking maternal psychological distress to child outcomes. Maternal report has a number of advantages (e.g., greater information regarding child behavior across time and context) and continues to play an important role in many types of developmental research. However, maternal psychological characteristics provide systematic sources of bias that color maternal perceptions of child behavior, temperament, and development [28–35]. After birth, women who report greater psychological distress during pregnancy view parenting as more stressful [36]. Because the direction of these known associations (i.e., greater maternal psychological distress is associated with more negative appraisal of child behavior or temperament) is the same as the hypothesis typically under evaluation, interpreting findings of less optimal child outcomes based on maternal reports by more distressed women is problematic, given the inherent confounding between dependent and independent measures.

Studies that show links between prenatal maternal distress and measured child outcomes reveal a complex pattern of results that can be instrument, age, or gender specific [18,37–39]. In our own work, we found that maternal psychological distress during pregnancy was associated in a dose–response manner with Bayley Scales of Infant Development scores at the age of 2 years such that greater levels of reported prenatal distress (including depressive symptoms, anxiety, and stress appraisal) were associated with higher developmental scores. Controlling for postnatal distress did not alter this association [40]. Because it is plausible that women who have these characteristics (e.g., greater anxiety) may engage in childrearing practices that may act to promote accelerated child development, we subsequently evaluated development within the second week of life using brainstem auditory evoked potentials. The speed at which the brainstem auditory evoked potential is conducted through the auditory nerve serves as a proxy for greater neural maturation [41,42]. We observed significant relations between higher maternal prenatal distress and faster conductance, suggesting that greater maternal prenatal distress was associated with accelerated neural maturation in neonates [43].

However, even studies that appropriately control for postnatal maternal distress and rely on laboratory-based measurement of development are left with a remaining interpretative challenge involving the role of shared inheritance factors in mediating both the dependent and independent measures. That is, child behavioral or temperamental outcomes that may be linked to prenatal maternal distress may be precursors or manifestations of the same characteristic expressed in adults. This concept is encountered in other types of research on prenatal exposures in

which the exposure involves a maternal behavior. A cautionary tale is provided by the widespread reports that offspring of women who smoked cigarettes during pregnancy have greater incidence of attentional and regulatory disorders, including higher rates of attention deficit hyperactivity disorder [44]. However, women who continue to smoke during pregnancy—despite widely available information on its harm to the fetus—may be systematically different from those who do not in a manner that is consistent with the observations in offspring (i.e., alterations in inhibitory or regulatory control). Refinement of the research designs used to address this issue has generated results that have begun to converge around the conclusion that the observed associations are spurious and do not reveal prenatal biological mediation of exposure to cigarette smoking on child developmental outcomes. These include comparing offspring who were conceived through assisted reproductive technologies (ART) using either genetically related or unrelated materials [45], and large-scale analyses that compare offspring of women who were smokers both within (i.e., siblings exposed to variation in exposure) and between families [46,47]. Conclusions from both types of design reveal either genetic or environmental influences on observed associations with cigarette smoking and provide strong caution against imputing prenatal causality to postnatal developmental disorders [48]. A single study using the assisted reproductive technologies design found mixed results on child outcomes with respect to maternal psychological stress (e.g., persistent associations with conduct problems but not attention deficit hyperactivity disorder or child mental health) [49]. However, this study relied on parental report of child behaviors and so generates the same concerns detailed previously in inferring causality. Nonetheless, creative approaches such as these are significant steps forward and critical to ultimately determine whether prenatal maternal psychological factors are simply markers for other processes or confer true biological mediation.

A final reflection on interpretation of studies in this area is on the prevailing notion that cortisol is the putative physiological mechanism that mediates any observed link between maternal psychological distress during pregnancy and child developmental outcomes. In general, studies have not detected significant associations between measures of maternal psychological distress during pregnancy and circulating cortisol levels detected in maternal serum or saliva [50–52]. The strength of the association is weak in those studies that do [19]. For example, in a study of maternal state anxiety preceding amniocentesis—a circumstance that can be presumed to activate the hypothalamic-pituitary-adrenal (HPA) axis—the amount of shared variance between cortisol and psychological state was approximately 3% [53]. The functioning of the HPA axis in pregnancy is complex because of the increasing role of the placenta as a neuroendocrine organ. Cortisol levels rise naturally during pregnancy as a result of elevating output of placental corticotrophin-releasing hormone [18,54–56]. The lack of influence of the maternal nervous system in this process may explain the relative imperviousness of cortisol to maternal mood or affect state [51].

We do not mean to imply that cortisol and other derivatives of the HPA axis during pregnancy are unimportant to variation in fetal development, as there is accumulating evidence that the reverse is true. For example, higher levels of maternal cortisol after 31 weeks' gestation have been associated with more advanced physical and neuromuscular neonatal maturation [57] and higher Mental Development Index scores when infants are 1 year old [18]. However, cortisol levels earlier in pregnancy

showed opposite associations with outcomes [18], and higher cortisol levels late in pregnancy have been linked to a lower intelligence quotient later in childhood [58]. Prenatal cortisol levels also seem to regulate postnatal responsiveness of the HPA axis [59,60]. Our caution is simply between equating maternal psychological distress or its appraisal with the assumption that this translates into measurable effects on prenatal cortisol production. Efforts to better understand the nuanced role of the placenta, which is of fetal origin, as an interface between HPA activity in the maternal and fetal compartments are promising [21,61].

Toward an expanded view of the influence of maternal psychological factors

Pregnancy is a complex and dynamic condition. Maternal psychological state changes produce a cascade of reactions, including changes in blood flow to the uterus and alterations to the intrauterine sensory environment experienced by the fetus. Given the intricate physiological relationship between the pregnant woman and the fetus, it would be somewhat surprising if dynamic aspects of the maternal psychological environment did *not* serve to shape neurodevelopment of the fetus and ultimately that of the child. However, because there are no direct neural connections between the pregnant woman and fetus, the fetus requires transduction of a maternal physiological signal from a psychological state to experience it. Work in our laboratory has focused on identifying whether fetal neurodevelopmental functioning is proximally affected by maternal psychological factors through the use of both observational and experimental designs, including experimental induction of both maternal stress and relaxation.

Fetal neurobehavioral development, which essentially involves measures of level and variability in fetal heart rate, motor activity, and the manner in which they interact over time, reflects the developing fetal nervous system in the same way that neonatal neurobehavioral measures both reflect maturation and reveal individual differences [62–66]. This methodology has been implemented by us and others in a developmental teratogen framework to isolate the effects of maternal substance use during the time in which these substances are pharmacologically active. Substances observed to alter fetal neurobehavior include maternal alcohol [67], methadone [68], and cocaine [69]. Studies that have extended this model to prenatal stress research have consistently indicated that maternal psychological distress appraisal, evaluated using a variety of different questionnaire methods, is associated with greater fetal motor activity [43,70,71]. Similarly, women with higher salivary cortisol levels also have fetuses that are more active [72]; although, consistent with others, we fail to detect significant associations between maternal distress and cortisol levels (K. Voegtline et al, unpublished data, 2012). Although greater fetal motor activity might be construed as an adverse effect of maternal distress, in fact, higher levels of fetal motor activity are significantly predictive of more optimal motor and reflex maturation in the first few weeks of life [43] and more advanced motor development at 6 months of age [73]. In addition, fetuses of women with higher levels of maternal distress displayed higher levels of fetal heart rate variability and a steeper incline in somatic–cardiac coupling as term approached [43], both of which are established indicators of neurologic maturation. Thus, to date, our findings can be construed as facilitative effects of maternal distress on fetal neuromaturation.

A more effective, but methodologically challenging, way to evaluate whether maternal psychological state affects the developing fetus is to manipulate maternal state and observe whether there is a fetal response. Maternal challenge using the Stroop color–word task was associated with increased variability in fetal heart rate and suppression of motor activity, with return to baseline levels at termination of the stressor [74]. We have also used maternal viewing of a labor and delivery documentary as a maternal manipulation; fetuses responded with decreased motor activity and, in contrast to the Stroop intervention, also with decreased heart rate variability [75]. Analysis of the fetal response to a specific component of the documentary—the first graphic birth scene—revealed a somewhat different pattern of responsiveness. Fetuses of women who had not given birth before showed a transient increase in motor activity during this scene. Reactivity and regulation are core constructs of temperament and important characteristics of child behavior. We have reported moderate stability over gestation in the degree of both the maternal physiological response and the degree of fetal reactivity [74] and prediction to response patterns in infancy from response patterns in the fetus [75]. Together these suggest that maternal reactivity to stressors may serve to entrain the developing fetal response.

Unexpectedly, we have observed that fetuses respond similarly to both induced maternal stress and relaxation. Maternal relaxation induced through a guided-imagery audiotape generated the expected reduction in maternal psychological and physiological tension. The fetal response included decreased heart rate and increased heart rate variability during the relaxation segment, but attributing these to the relaxation procedure itself could not be distinguished from simple maternal rest and changes in umbilical blood flow. However, as with both stress interventions, fetal motor activity was suppressed during the manipulation but recovered after the relaxation protocol concluded [76].

We have been fairly unsuccessful in determining the mechanisms through which maternal manipulations are transmitted to the fetus. The rapidity of the onset of fetal responsiveness to maternal physiological alterations exceeds the temporal response curve of products of the HPA axis. Efforts to link specific changes in concurrently measured maternal physiological indicators of autonomic responsiveness (e.g., electrodermal activity, heart rate) to commensurate changes in fetal variables have been minimally successful. Instead, our interpretation of these and related findings has focused on fetal detection of and response to changes in the intrauterine milieu inspired by the manipulation. Fetal heart rate responses have been observed within seconds of disruptions of the maternal environment in the investigations of the development of fetal sensory capacities including maternal postural changes [77] and auditory stimuli, [78] and it is clear that sounds generated by maternal vasculature and the digestive tract are prominent in the uterine auditory environment [79]. Specifically, we suspect that at least the initiation, if not the maintenance, of the fetal response to some maternal manipulations may be mediated by fetal perceptual detection of changes in the intrauterine milieu. The possibility of a sensory-oriented fetal response to maternal stressors has also been offered previously in nonhuman primate models [80]. It is possible that after a certain point in gestation, when the fetal brain is sufficiently mature, any maternal manipulation elicits an acute phasic response that includes a rapid sensory-mediated component as the fetus detects a change, followed by a more tonic secondary response with more complex neuroendocrine, autonomic, or vasodilatory maternal input that may account for more chronic activation.

A biphasic fetal response could also serve to reconcile the observed association between higher levels of fetal motor activity and psychological distress, as described in the previous section, with the transient suppression of fetal motor activity observed in response to acute maternal state changes. Such observations suggest that women who express greater psychological lability, including indicators of distress, provide more varied—and perhaps more stimulating—intrauterine environments to the fetus with implications for the developing fetal brain.

A number of studies have documented blunted autonomic or neuroendocrine responsiveness in pregnancy to stressful manipulations [81,82], including the Stroop task [83]. Although it has been suggested that the adaptational significance of this phenomenon is directed at buffering against potentially deleterious effects of stress, pregnant women also exhibit blunted responsiveness to induced relaxation [84]. As such, it may be more accurate to suggest that maternal physiological adaptation during pregnancy is geared toward conserving the homeostasis of the intrauterine milieu, perhaps in service of energy conservation.

Although the discussion so far has been limited to a unidirectional relationship from pregnant woman to fetus, the fetus is an active contributor to its own epigenesis within the uterine environment [85]. Previously, we demonstrated in two economically and ethnically diverse samples (in Lima, Peru, and Baltimore, MD), measured longitudinally from the 20th to the 38th week of gestation, that spontaneous fetal motor activity transiently stimulates maternal sympathetic arousal [86]. These findings were based on time-series analyses of contemporaneous maternal–fetal recordings during undisturbed periods of maternal rest during which time fetal movements were observed to generate an increase in maternal heart rate and electrodermal activity within 2–3 seconds after the spontaneous fetal movement. Recently, we have demonstrated the same phenomenon using an experimental model in which a fetal motor response was elicited by an external stimulus and generated a maternal physiological response consistent with an orienting response (J. DiPietro et al, unpublished data, 2012). Despite the ubiquity of the stimulus (i.e., fetuses move, on average, about once per minute in pregnancy), the indication is that women do not physiologically habituate or become desensitized to fetal movements. Although we have speculated that such fetal signaling prepares pregnant women for infant caretaking, we include it here as a reminder that the maternal–fetal interface is bidirectional with largely unknown repercussions. Could, for example, natural variation in levels of fetal motor activity generate variation in feelings of psychological stress in pregnant women?

Concluding reflections

The existing literature on whether and how maternal psychological stress during pregnancy affects the developing fetal brain, as measured by indicators of developmental functioning during childhood, is subject to a number of interpretative cautions in establishing causality. In part, these are no different from establishing causality between any prenatal exposure and postnatal outcome in which the exposures cannot be randomized across individuals. However, design features that are particular challenges to this line of research include the influence of prenatal distress characteristics on postnatal parenting practices; difficulty in distinguishing prenatal stress from more ubiquitous aspects of maternal psychological functioning; confounding between aspects of maternal psychological factors under study with maternal report or infant outcome;

and the potential of shared genetic contribution to both prenatal and postnatal variables.

We wonder whether the conceptualization of maternal stress originally as a developmental teratogen, and subsequently within a programming framework originally used to examine the role of prenatal undernutrition on adult metabolic disorders [87], may have canalized research toward a search for adverse outcomes in lieu of a broader perspective on the interplay between the maternal environment and the developing fetal brain. There is long-standing theoretical and empirical support for an inverted U-shaped association between stress and performance, as described by Yerkes and Dodson more than a century ago [88], consistent with the current view that the human brain requires sufficient, but not overwhelming, stress to promote optimal neural development both before [89] and after birth [90]. This perspective is consistent with the model of the role of early postnatal stress in the promotion of developmental adaptation as reflected by arousal regulation and resilience stress in nonhuman primates [91]. This has implications for data analysis, as it suggests nonlinear associations, which can be obscured by standard analytical techniques. Among the most provocative recent reports of a nonlinear relation between maternal distress (in this case, depressive symptoms) and infant development is a finding that individuals exposed to maternal depression both before and after birth showed comparable developmental outcome with those exposed at neither time but better outcomes than those exposed only at either time [92]. These findings were interpreted within a predictive adaptive response framework and highlight the value of novel constructions of data.

The inverted U model also has implications for sample selection to the extent that maternal distress is differentially present. Our own research findings showing increased maternal distress to be facilitative to both prenatal and postnatal development, for example, are based on samples composed predominantly of mentally healthy well-educated women who are most likely to participate as volunteers in longitudinal research. As such, they may not generalize to populations of disadvantaged women who face chronic socioeconomic stressors. Similarly, clinically depressed or anxious women may also experience prenatal distress beyond the mild-to-moderate range, and there is supportive evidence that the fetal response to the maternal Stroop stressor interacts with maternal psychiatric status [93,94].

Ultimate understanding of the influence of maternal psychological distress during pregnancy on child outcomes is likely to reveal a complex story. Issues of timing, intensity, mediation, and population are likely to be paramount. Incorrect attribution of causal models has consequences for pregnant women [95]. Incorporating methods of studying the fetus into research on this topic provides the opportunity to examine the intrauterine milieu as the developmental niche of the fetus and to better understand mechanisms through which maternal psychological factors may have implications for development after birth.

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