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SEX AND GENDER ISSUES IN BEHAVIORAL HEALTH (CN EPPERSON AND L HANTSOO, SECTION EDITORS)

Does Prenatal Maternal Distress Contribute to Sex Differences in Child Psychopathology?

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Abstract

Purpose of Review Prenatal maternal psychological distress is an established risk factor for the development of psychopathology in offspring. The purpose of this review is to evaluate whether sex differences in fetal responses to maternal distress contribute to sex differences in subsequent psychopathology.

Recent Findings Male and female fetuses respond differently to stress signals. We review recent evidence that demonstrates a sex-specific pattern of association between prenatal maternal distress and pathways associated with risk for psychopathology including offspring hypothalamic pituitary adrenocortical (HPA) axis regulation, brain development, and negative emotionality.

Summary Prenatal maternal distress exerts sex-specific consequences on the fetus. These differences may contribute to the well-established sex differences in psychopathology and in particular to greater female vulnerability to develop internalizing problems.

Keywords Prenatal · Stress · Sex differences · Depression · Development · Psychopathology

Introduction

Sex differences in the rates of mental health disorders are well documented throughout the lifespan [1]. Females are diagnosed with internalizing disorders such as depression and anxiety disorders at a rate of nearly twice that of males [2, 3]. Conversely, males more often are diagnosed with externalizing disorders such as antisocial personality disorder and conduct disorder [4]. The etiology of these sex differences is poorly understood [5]; however, there is increasing evidence to suggest that these sex differences may originate during the prenatal period [6•, 7]. The intrauterine environment profoundly influences the fetal brain, shaping developmental trajectories with consequences for later psychopathology [1, 8]. We consider the possibility that sex differences in the fetal response to prenatal maternal stress contribute to these well-known sex differences in psychopathology.

The fetal period is the most rapid window of neurobiological development within the human lifespan [9]. The exceptional pace of fetal brain development renders it extremely susceptible to environmental influences, including exposure to maternal psychological stress and biological stress signals. The Fetal Programming or Developmental Origins of Adult Disease Hypothesis (DoHAD), founded in the seminal work of David Barker [10], posits that the prenatal period is a window of sensitivity where the intrauterine environment profoundly impacts the development of fetal systems. It is therefore critical to consider not only genetic risk, but also early environmental influences that shape health and development across the lifespan [11–14]. Fetal exposure to maternal psychological distress contributes to adverse developmental outcomes [15] including low birth weight [16], preterm birth [17], difficult infant temperament and negative affectivity [18], HPA axis dysregulation [19], and altered brain development [20], thus establishing a trajectory of increased risk for psychopathology, including both internalizing and externalizing problems [21–24]. Although such observational studies cannot fully rule out alternative explanations, these effects have been shown to persist after adjusting for relevant

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postnatal factors, including postnatal maternal distress and socioeconomic status [18, 25].

Maternal psychological distress, considered broadly in this literature, includes prenatal anxiety, depression, and stress. During pregnancy, the prevalence of minor depression is 16.6%, major depression is 6.6% [26], and any anxiety disorders is 15.2% [27]. Rates of mental health disorders are even more prevalent in high-risk pregnant populations (i.e., minority, low socioeconomic status) [28, 29] and women in developing countries [30–32]. Because of the high prevalence of prenatal maternal distress and the impact on mental health in the offspring, prenatal maternal distress is a global public health concern with implications for mental health and functioning across multiple generations.

Surprisingly few studies systematically examine sexually dimorphic responses to prenatal maternal psychological distress and how these responses contribute to the well-established sex differences in psychopathology. We previously hypothesized there may be a sex-dependent "viability-vulnerability" tradeoff [6•]. Specifically, under conditions of prenatal exposure to adversity (i.e., maternal psychological distress and biological stress signals), male fetuses are directly impacted via precipitous declines in their mortality and morbidity. Although females are spared this early hit to their survival, their vulnerability may be revealed later in development, and perhaps more subtly, as females with a history of prenatal distress exposure have higher levels of negative affectivity and internalizing problems and greater cortisol reactivity to challenge [6•, 33, 34•]. These sex differences are posited to strengthen reproductive success of the genetic line, such that, for male offspring, reproductive success is most likely when resources are allocated towards "a surviving cohort of the fittest" given reproductive competition encountered by males and thus the greater reproductive success of strong dominant males [35]. Reproductive success of females, on the other hand, is less variable as pregnancy is a substantial investment, and they do not encounter the same level of competition [36]. Females thus are more resilient in terms of their survival, though not unscathed, in response to early signals of stress, which may be associated with long-term consequences for neurodevelopment [1, 6•], including later risk for psychopathology.

In this paper, we discuss evidence that sexually dimorphic responses to adversity during the fetal period contribute to sex differences in psychopathology. We first briefly review the dynamic changes in the prenatal maternal HPA axis, one of the major pathways by which maternal prenatal distress may impact the fetus. Next, we consider the sexually dimorphic responses of the placenta, a key regulator of growth and development that may contribute to sex differences in fetal programming. We then present evidence that sexually dimorphic fetal responses influence sex differences in risk trajectories (e.g., HPA axis regulation, brain development, and negative emotionality). Finally, we discuss evidence that prenatal maternal distress may contribute to sex differences in later psychopathology.

Maternal HPA and Placental Axis: a Pathway for Sex Differences in Fetal Development

The hypothalamic pituitary adrenal (HPA) axis, a key stress response system, is widely considered to be a pathway by which maternal distress may influence the development of the fetus. In the non-pregnant state, the release of corticotrophin releasing hormone (CRH) from the hypothalamus initiates a cascade of hormones, which leads to the production of cortisol from the adrenal gland. Cortisol regulates its own release via a negative feedback loop whereby increases in cortisol decrease HPA axis activity. However, during pregnancy, the development of a new fetal organ, the placenta, causes dramatic changes to the HPA axis. The placenta also produces CRH (pCRH), which is identical to hypothalamic CRH in both structure and bioactivity. However, in contrast to the negative feedback loop of cortisol on the maternal hypothalamus, cortisol stimulates the release of CRH from the placenta thereby creating a positive feedback loop. Concentrations of stress hormones including pCRH and cortisol rise dramatically over the course of a pregnancy [37]. Although this is a normative process, this positive feedback loop provides a mechanism by which the impact of maternal stress may be potentiated leading to even greater increases in stress hormones.

Fetal Sex and the Maternal HPA Axis Fetal sex may impact these critical changes in maternal HPA axis activity during pregnancy. Although very few studies have investigated this association, DiPietro and colleagues [38] show that trajectories of maternal cortisol during gestation differ based on whether the fetus is male or female. Specifically, women carrying male fetuses had higher cortisol during early third trimester, whereas women carrying female fetuses exhibit higher cortisol during late third trimester. Further, Giesbrecht and colleagues [39] demonstrate that women carrying female fetuses exhibit flatter cortisol diurnal trajectories than in those carrying male fetuses. These findings raise the intriguing possibility that fetal sex may impact the production of maternal stress hormones. How these differences in maternal stress hormones impact sex differences in fetal development is yet unknown.

Sexually Dimorphic Responses of the Placenta The placenta serves as a bidirectional interface between the mother and her fetus and profoundly impacts fetal growth and development. Not only does the placenta play a key role in the production of hormones such as pCRH, as discussed above, but it also

functions as a partially permeable barrier, regulating the passage of maternal hormones into the uterine environment. Specifically, the placental enzyme 11β-hydroxysteroid-dehydrogenase type 2 (11β-HSD2) oxidizes maternal cortisol as it crosses the placental barrier, turning 80–90% into its inactive form, cortisone [40, 41]. The placenta thus regulates normative hormonal increases over gestation (e.g., pCRH and cortisol) while also modulating fetal exposures to these hormones.

Recent evidence illustrates that the placenta responds to maternal stress signals in a sexually dimorphic pattern [34•, 42•, 43]. These findings raise the possibility that the placenta is a potential pathway that contributes to subsequent sex differences in psychopathology. The female placenta is proposed to be more responsive to signals of prenatal stress than the male placenta [42•]. Greater responsivity of the female placenta is consistent with the hypothesis that female and male fetuses implement different strategies to adapt to stressful conditions. Specifically, the female placenta makes multiple epigenetic adaptations resulting in conservation of resources and reduced growth trajectories. In contrast, the male placenta makes minimal adaptations in an effort to allocate resources towards continued growth. The consequence of these sexually dimorphic strategies is that males are more vulnerable to subsequent adversity and the investment of resources towards growth leads to greater vulnerability to morbidity and mortality during the fetal and neonatal period [42•]. However, the more subtle adaptations made by the female fetus may have consequences that are observed later in development including risk for subsequent psychopathology.

A recent systematic review provides compelling evidence for sex differences in epigenetic pathways linked specifically to the regulation of stress hormones in the placenta, including glucocorticoid receptor gene expression and alterations to expression and activity of 11β-HSD2 [34•]. A growing number of human studies suggest that the female placenta is broadly more responsive to early adversity. For example, maternal asthma, a stressor, is linked to the alteration of 59 genes in the female placenta, but only 6 in the male placenta [44]. Recent human studies further suggest that the male and female placentas respond differentially to maternal psychological distress [43, 45]. For example, although maternal psychological distress decreases placental 11β-HSD2 activity which increases fetal cortisol exposure [46, 47], this decrease in 11β-HSD2 activity is greater among females than males [43]. This evidence that maternal distress exerts a sexually dimorphic impact on the expression of stress-related genes in the placenta is significant because these placental mechanisms are linked to neurodevelopment in the offspring [48]. Future work is necessary to evaluate sex differences in how maternal distress impacts placental mechanisms and how this affects sex differences in subsequent psychopathology.

Sex Differences in the Effects of Prenatal Distress on Child Development

These sexually dimorphic placental and prenatal maternal HPA axis responses to stress may contribute to sex differences in offspring development, which are observed as early as the fetal period [49]. For example, maternal distress and maternal cortisol negatively impact fetal neurodevelopment [50] and fetal heart rate reactivity [51], and this effect is stronger among females as compared to males. These sexually dimorphic fetal and placental responses to prenatal distress may persist and lead to sex differences in risk pathways that contribute to later psychopathology, such as HPA axis dysregulation, aberrant brain development, and negative affectivity.

Child HPA Axis Regulation In their systematic review, Carpenter and Grecian [34•] found that the developing HPA axis is more susceptible to the impact of a variety of stressful prenatal exposures in females, leading to sex-specific risk for HPA axis dysregulation which is observed throughout infancy and childhood. For example, females who are born preterm and who were exposed prenatally to synthetic glucocorticoids exhibit a heightened cortisol response to stress in comparison to males [52, 53]. Few studies have evaluated sexually dimorphic consequences of prenatal maternal distress on the HPA axis. Two studies evaluating cortisol reactivity in response to challenge (maternal separation and a frustration task) found that prenatal maternal distress was more strongly associated with enhanced cortisol reactivity among girls as compared to boys [19, 54]. Prenatal distress has additionally been linked to diurnal cortisol regulation [55], and the impact of prenatal distress on bedtime cortisol and total cortisol production across the day differed for boys and girls [56]. Van den Bergh and colleagues did not find sex differences in diurnal cortisol regulation but did find that cortisol mediated the association between prenatal distress and offspring depression only among girls [55]. Evidence indicates that the child HPA axis responds more strongly to various types of prenatal adversity among females as compared to males [34•], although only a few studies have specifically evaluated the sex-specific impact of prenatal maternal distress. Dysregulation of the HPA axis is one of the pathways by which early experiences contribute to later psychopathology [57]. These recent studies illustrate that prenatal experiences exert sex-specific consequences for cortisol regulation and suggest that the child HPA axis may be a potential pathway by which prenatal maternal distress contributes to sex differences in offspring psychopathology.

Child Brain Development Recent evidence suggests that prenatal stress signals exert sex-specific effects on the developing brain. A focus of this research has been on evaluating the effect of prenatal distress on the structure and function of the

amygdala, as a region that is both vulnerable to early life stress and thought to play a role in development of anxiety [58]. Prenatal maternal distress and maternal cortisol are associated with greater right amygdala volume among girls, but not boys [33, 59•]. Further, prenatal distress is linked to amygdala-related circuitry in a sex-specific manner. Functional organization of the cortico-striato-amygdala circuitry, fundamental to emotional perception and regulation, is impacted by prenatal distress among girls, but not boys [60]. Relatedly, Graham and colleagues [61•] found that elevated prenatal maternal cortisol predicts stronger amygdala functional connectivity to sensory processing and integration brain regions during the neonatal period in girls only.

Consequences of prenatal stress, however, are not specific to limbic regions. Dean and colleagues [62] illustrate that the effects of prenatal maternal distress on white matter microstructure differs for males and females as early as the neonatal period. One benefit of assessing neurological outcomes within the neonatal period is that the associations between the prenatal environment and the developing brain can be assessed before postnatal influences are likely to exert an effect. Consequences of prenatal exposure to maternal distress on the female brain persist into childhood. Prenatal maternal cortisol is associated with alterations to network connectivity among girls, but not boys [63]. Further, elevated pCRH concentrations during pregnancy are associated with greater cortical thinning in girls but not boys [64•]. Recent studies evaluating prenatal influences on child brain development provide compelling evidence that prenatal maternal distress differentially impacts the male and female brain, with implications for sex differences in psychopathology.

Early Childhood Negative Emotionality and Internalizing Behaviors Prenatal distress has been linked to negative emotionality as well as internalizing behaviors in early childhood [65, 66], key risk factors for later psychopathology [67, 68]. Emerging evidence suggests that prenatal distress and stress signals may have a stronger impact on negative emotionality and internalizing problems among females. Several studies have shown that maternal prenatal distress and cortisol predict greater negative emotionality in female, but not male infants [6•, 69]. This pattern persists into childhood. Prenatal maternal distress is associated with internalizing behaviors [61•, 70] and emotional reactivity [71] in preschool-aged girls but not boys. In contrast to these findings, another study found that prenatal maternal distress predicts more internalizing behaviors in both preschool-aged girls and boys and increased externalizing behaviors only among girls [72]. Patterns and predictability of maternal distress over time may also be important [73] as inconsistencies in mood from pregnancy through postpartum predicts developmental outcomes including internalizing behaviors [74] more strongly among girls as compared to boys. These studies suggest that the responses of the female fetus to prenatal signals of maternal stress may lead to increased behavioral and emotional problems during infancy and early childhood among girls. Notably, these associations are observed beyond the influence of postnatal maternal psychological distress.

Do Prenatal Experiences Contribute to Sex Differences in Psychopathology?

As reviewed here, evidence supports that prenatal stress contributes to sexually dimorphic emergence of risk factors for psychopathology. Prenatal maternal distress, including depression and anxiety assessed both as elevated symptoms and diagnosed disorders, confers risk for child psychopathology [e.g. 55, 33, 75, 76•] even after accounting for postnatal maternal psychological symptoms and contextual risk factors [76•, 77–80]. Several recent studies with large sample sizes provide further evidence for the independent impact of prenatal maternal distress [25, 80, 81]. For example, in a large longitudinal birth cohort ($n = 4303$), prenatal maternal distress was associated with an increased likelihood of the offspring experiencing an anxiety diagnosis (adj. OR = 1.75), findings that persisted adjusting for postnatal distress and other postnatal influences [25]. Prenatal paternal depression was not associated with child outcomes consistent with the importance of prenatal in utero experience for transmission of prenatal maternal distress. Studies with experimental animal models [82] and research evaluating the consequences of natural disaster lend further support for the role of the prenatal environment [83]. New evidence suggests that females exposed to prenatal maternal distress are at heightened risk for depression and anxiety as compared to their male counterparts. Specifically, prenatal maternal distress more strongly predicts childhood anxiety [6•] and affective problems [33] as well as greater adolescent depressive symptoms [55] in girls as compared to boys. A strong prospective longitudinal study by Quarini and colleagues [76•] found that for girls exposed to prenatal distress, the odds of a depression diagnosis at 18 years was 1.55, whereas for boys exposed to prenatal distress, the odds of a depression diagnosis at 18 was significantly lower at 0.54 after adjusting for maternal education, parity, maternal age at birth of child, and level of maternal postpartum depression. These findings suggest that the consequences of prenatal maternal distress on internalizing psychopathology in the offspring are stronger for females.

Recent studies linking prenatal distress to increased female vulnerability have evaluated pathways mediating the association between prenatal distress and offspring psychopathology. For example, the effect of prenatal maternal cortisol on child amygdala structure and functional connectivity mediates the impact of prenatal cortisol on internalizing problems among girls [33, 61•]. Evaluation of the interconnectivity of the human brain, the connectome, illustrates that prenatal maternal

cortisol is linked to altered connectivity of brain networks among girls, and these alterations predict higher levels of internalizing problems in girls, but not boys [63]. These studies provide new evidence that the fetal programming effects of prenatal distress may impact brain development in ways that place girls at greater risk for developing internalizing psychopathology. Because of challenges of following mother-child dyads from the prenatal period through adolescence and young adulthood relatively few studies exist. Nonetheless, the existing literature suggests that the consequences of prenatal maternal psychological distress on internalizing problems are stronger among females.

Conclusions

Pervasive sex differences are well documented in psychopathology [1]. In this review, we propose that sexually dimorphic responses to prenatal maternal distress are a key pathway by which maternal mental health problems confer sex-specific risk for later psychopathology in the offspring. Internalizing problems such as anxiety and depression are more prevalent among females [3], and we suggest that maternal prenatal distress is one factor that contributes to increased prevalence of internalizing disorders among females.

Although the current literature supports the hypothesis that prenatal maternal distress may contribute to sex differences in psychopathology, several limitations are evident. First, many studies of prenatal distress and child psychopathology do not include sex as a variable of interest or report it as a main effect, without evaluating how males and females respond differently to prenatal exposures. Second, human research primarily relies on observational study designs limiting the ability to draw causal conclusions or to fully rule out alternative explanations such as shared genes or postnatal influences. Cross-species research [84], quasi-experimental designs evaluating stressors such as natural disasters [85, 86], and implementation of randomized controlled trials are methods to address this challenge [87]. Third, variability in the type and timing of prenatal stress exposures across studies limit the ability to make cross-study comparisons. Fourth, the majority of the studies evaluating sex differences focus on a limited range of outcomes. It is therefore unclear whether greater female vulnerability is specific to internalizing problems. Fifth, few studies consider the consequences of prenatal maternal distress in both the prenatal and the postnatal period to investigate their joint or synergistic role in contributing to sex differences and later outcomes. Finally, we know little about possible interventions or protective factors, which could ameliorate the consequences of prenatal maternal distress and whether response to intervention could differ by sex of the offspring. These gaps in the literature suggest several directions for future research. We discuss the last three gaps in more detail below.

There is a need for research that considers the impact of sexually dimorphic responses to prenatal distress on a broader range of outcomes. There is robust evidence that male and female fetuses and placentas differentially respond to maternal stress and stress signals. These different adaptive strategies may render the male fetus more susceptible to morbidity and mortality, while the more subtle adaptations made by the female fetus to stress signals may increase both viability and subsequent vulnerability to psychopathology. Tests of this hypothesis have primarily focused on development of internalizing problems. It is possible, however, that males retain vulnerability in other domains, such as externalizing problems. Consistent with this possibility, Glasheen and colleagues [88] found that that boys of mothers with high levels of pre- and postnatal anxiety were 5.6 times more likely to meet criteria for conduct disorder than boys of mothers with low levels of pre- and postnatal anxiety; the opposite pattern was found for girls. Similarly, boys of mothers with elevated prenatal distress exhibit significantly higher antisocial behavior scores than girls [89]. In contrast, Soe and colleagues found that prenatal maternal distress increased externalizing problems among girls, but not boys [72]. There is a clear need for research examining sexually dimorphic consequences of prenatal distress that considers both internalizing and externalizing disorders to determine whether the greater susceptibility to prenatal maternal distress observed among females is specific to internalizing psychopathology and whether a similar vulnerability to externalizing psychopathology exists for males.

The majority of research in this area focuses on demonstrating consequences of the prenatal environment above and beyond the postnatal environment [90]. There is a need for research considering the sex-specific impact of exposure to maternal distress during both the prenatal and the postnatal period. Adaptations the fetus makes to maternal stress signals in utero may prepare the fetus to be better suited certain types of postnatal environments [91, 92]. Glover and Hill [8] propose that evolutionary pressures have led males and females respond differently to prenatal stress signals given sex-specific adaptive demands in the postnatal environment. For example, increased vigilance and anxiety among females in a stressful environment may be adaptive for rearing and protecting offspring. Thus, the consequences of prenatal maternal distress for males and females may be dependent on the postnatal environment into which they are born. Future studies should investigate the interplay of the prenatal and postnatal environment on sexual dimorphism in children's psychopathology.

Finally, in concert with continued investigation of the sex-specific consequences of prenatal maternal distress for child, psychopathology is the need for investigation of interventions and protective factors that can mitigate the impact of prenatal maternal distress. We are currently implementing a randomized controlled trial (RCT), thus employing an experimental design to evaluate the impact of a prenatal intervention to

reduce maternal distress on risk factors for psychopathology in the offspring [87]. Such prospective investigations, powered to test sex differences, will provide new insight into the benefits of reducing prenatal maternal depression for child outcomes and whether the impact of these interventions differ by sex. There is evidence that postnatal factors such as positive paternal engagement [93], maternal-child attachment [94, 95], and family cohesion [22] can reduce the consequences of prenatal maternal distress on child risk for psychopathology. However, whether the impact of these protective factors differs by sex remains unclear. Research evaluating sex-specific responses to both the prenatal and postnatal environments (both adverse and promotive) will directly inform intervention through considering sex-specific benefits of the intervention and timing of delivery.

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