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Practitioner Review: Maternal mood in pregnancy and child development – implications for child psychology and psychiatry

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Background: The empirical base suggesting a link between prenatal maternal anxiety, stress or depression and cognitive, behavioral, and biological outcomes in the infant and child has increased dramatically in the past 10 years. **Methods:** In this review, we consider the relevance of prenatal maternal mood for child mental health practitioners; the empirical base for a likely causal impact of the link between prenatal anxiety, depression, or stress and child outcomes; the degree to which the available evidence is sufficient for informing or altering clinical practice; and the possible role of prenatal interventions for promoting child health and development. A selective review of PubMed, Cochrane Library and other sources was undertaken. **Findings:** Clinically significant links between maternal prenatal distress and child behavioral and cognitive outcomes have been reported; predictions to stress physiology, immunology, and neurodevelopment have been reported but the effect sizes and clinical significance is less clear. Several candidate mechanisms have been proposed, with some supporting evidence. Many behavioral treatments for prenatal maternal distress exist, but their application to promoting child health is largely unknown. **Conclusions:** Research on maternal prenatal distress is a good example of translational research and offers a strong paradigm for promoting interdisciplinary clinical research on child health and development. **Keywords:** Prenatal anxiety, developmental programming, clinical trials.

Introduction

Instituted in medical practice is the view that the health of the pregnant women may affect the developing child: efforts have been underway for years to promote a healthy maternal prenatal diet and weight gain, reduce exposure to environmental toxins and viruses, and increase preparedness for the delivery and parenthood. The presumed beneficial effects of these programs constitute an evidence-based prenatal care regiment (Kirkham, Harris, & Grzybowski, 2005a,b). Accordingly, prenatal care is multifaceted, and detailed, and incorporates knowledge derived from genetics, nutrition, environmental health, and immunology, among other fields. The current practitioner review focuses on one component of pregnant women's health, maternal mood and stress, and the implications for child development.

The notion that the mother's mood disturbance or stress levels during pregnancy may influence the developing child has a robust history across cultures and is widely embedded in folk psychology. This belief or tradition has been subjected to intense empirical study in humans for about a decade. As detailed below, data indicate that greater than typical elevations in stress, anxiety, and depressive symptoms[1] are reliably associated with a wide range of behavioral, cognitive, and neurophysiological child outcomes reflective or indicative of psychopathology [though see DiPietro, Novak, Costigan, Atella, and Reusing (2006) for contradictory results]. These findings derive additional heft from nearly 50 years of experimental animal evidence, and so constitute a compelling example of translational research or the transduction of a scientific question and evidence from a basic or preclinical stage to its relevance for human health and development. The public health and clinical corollaries of this line of research for child mental health is now fittingly attracting considerable attention, and is the focus of this practitioner review. It is the relevance for child and adolescent mental health practitioners that distinguishes this review from other reviews of prenatal maternal distress in the literature (Dunkel Schetter & Tanner, 2012; Huizink, Mulder, & Buitelaar, 2004; O'Donnell, O'Connor, & Glover, 2009; Talge, Neal, & Glover, 2007).

History and context

It is first necessary to set the context for this review. One important basis is the substantial and long-standing evidence from animal studies on the impact of prenatal stress on the offspring (Ader & Plaut, 1968; Hockman, 1961; Joffe, 1965; Keeley, 1962). Furthermore, exposure to prenatal maternal stress continues to be a major paradigm for assessing the mechanisms of stress physiology and subsequent responses to environmental and pharmacological

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challenges (Wilson, Schade, & Terry, 2012) – outcomes with sizable potential value for understanding human development and pathology. Regardless of the sizable concerns in translating experimental animal results to humans (see below), the weight of the animal evidence on the impact of prenatal stress on offspring outcomes (Maccari & Morley-Fletcher, 2007; Weinstock, 2008) is simply too significant for developmentalists and clinicians to ignore. Systematic research on prenatal stress in humans is only fairly recent, but there are notable examples dating back several decades (e.g., Stott, 1973). One such example is a Finnish study showing worse outcomes of children whose fathers died prior to their birth compared with children whose fathers died in their first year of life (Huttunen & Niskanen, 1978); interestingly, this was followed 30 years later in the same journal by a Danish study linking death of a relative in the first trimester to an increased risk of schizophrenia (OR: 1.67) (Khashan et al., 2008).

There is then the matter of why prenatal maternal distress is a suitable topic for a practitioner review in this journal, that is, why would child and adolescent mental health practitioners be concerned with maternal distress during pregnancy? One reason is that a better understanding of etiology may follow from the shift emphasized by this line of research toward viewing neurobehavioral development as beginning before birth. In line with the influential findings from the perspective of fetal programming (Barker, 2007) that posits *in utero* developmental origins of future health and disease for cardiology (Gluckman, Cutfield, Hofman, & Hanson, 2005), research on maternal prenatal distress may hold clues for the characterization of novel environmental influences on child behavioral, emotional, cognitive, and neuroendocrine outcomes. Such research, in turn, may help to identify causal mechanisms and lead to effective interventions. Although the causal effect of prenatal maternal distress on child mental health outcomes has not yet been fully settled, the possibility of causal impact is gaining scientific momentum with the number and diversity of results reported (see below).

Of particular relevance to conceptual models of developmental psychopathology is the emphasis on the role of adaptation embedded in the developmental programming hypothesis. Specifically, the developmental programming hypothesis proposes that the fetus adapts to early exposures in a way that should promote (long-term, and reproductive) fitness (Gluckman & Hanson, 2005), though sometimes it fails to do so when there is discordance between the prenatal and postnatal environments (see, Glover, 2011). This concept of 'adaptation' and its failures contributing to psychopathology is significantly different from the more dominant deviance or deficit model of psychopathology, and makes some interesting and quite different predictions about childhood psychopathology (e.g., see Glover, 2011; Sandman, Davis, & Glynn, 2012). For example, a high degree of stress reactivity in the child may be promoted by maternal stress in pregnancy because it may have some adaptive value for the child in that environment (which also precipitated maternal anxiety).

A further rationale for this practitioner review is that awareness of this growing body of evidence may stimulate genuinely new preventive intervention strategies to improve child mental and physical health. There is not a surfeit of effective evidence-based interventions options for child mental health, and so new avenues are needed. The results reviewed below raise the important possibility that prenatal interventions to reduce maternal mood disturbance in pregnancy may have carryover beneficial effects for the fetus and child. If that is so, then there could be a wide range of novel practical applications, such as using prenatal interventions to promote/prevent child behavioral or other health problems. Prenatal interventions may also be quite practical, as they may be comparatively easier and cheaper to institute than interventions targeting children after the onset of documented disturbance. And, the prevention of the onset of disorder would prevent suffering and other emotional and financial burden on the family and is preferable to waiting for the problem to develop. Later in this review we consider some promising forms of prenatal interventions for preventing child mental health problems.

This area is also relevant to child mental health practitioners because of its growing popularity and public attention. Media reports on this topic are now common, as are stories and impressions in magazines, internet sites, and other opinion-influencing pressures that may shape the concerns and questions of parents of children with behavior, social, or cognitive difficulties. Understanding the nature of the research findings – what they confirm and what they do not confirm – is needed to address parental concerns that may not be tuned to the empirical evidence, and to place what is known in a broader context of factors that shape child health and behavior.

A further important aspect of history and context is that the field of perinatal psychiatry did not initially have much input from child psychology and psychiatry. This fact may now sound unusual, but it reflects a parallel separateness of obstetrics and pediatrics, and the general tendency to neglect developmental transitions from infancy, childhood, adolescence, and adulthood in many fields of science and medicine. Given the findings linking women's mental health in the perinatal period to child well--being, the field of perinatal psychiatry now has more input from child mental health. However, perinatal psychiatry remains a subdiscipline that requires still greater integration with child mental health practitioners: collaboration with perinatal psychiatrists and obstetricians could offer valuable opportunities for improved service delivery and child mental health outcomes. It also is worth noting that research on

the effects of maternal prenatal distress on the child has necessarily adopted a multidisciplinary model and research method. Such a method is followed because one of the presumed mechanisms, *in utero* programming of the child's stress response system, is relevant for neurodevelopment, metabolic disease, immune competence, and other outcomes; a corollary is that the outcomes linked with prenatal maternal distress are not particular to any organ system or medical specialty. The lesson here is that research on the prenatal maternal distress paradigm may encourage an increased emphasis in research and treatment on underlying mechanisms rather than the somewhat artificial divisions associated with disciplinary training. Movement toward etiology-focused, multidisciplinary models of child mental health – which may be illustrated through the study of prenatal maternal distress – will no doubt prove increasingly valuable as we begin to understand better the shared risks and etiologies between child mental health and physiology, immunology, and other aspects of health more broadly defined.

Empirical evidence linking prenatal maternal anxiety, stress, and depression to child outcomes

Experimental animal studies on prenatal stress were instrumental in instigating and informing the human work that is herein reviewed. There are, however, sizable limitations of the animal work – or problems for translational research – as they might inform our understanding of mechanisms and applications in humans; underemphasizing these translational impediments may set up unrealistic expectations of replication and foreclose on novel explanations to do with culture or human biology. Of course, there are solid bases for some degree of extrapolating findings across species; for example, the sequence of early brain development is conserved across mammals (Finlay & Darlington, 1995). On the other hand, there remain difficulties of applying findings regarding the timing of prenatal versus postnatal stressors across species. This difficulty persists because of the differences in brain maturation at parturition (e.g., the equivalent of 3rd trimester in the human would be postnatal in the rat); what may be a prenatal stress exposure in one species may be (in terms of brain development 'equivalence') postnatal in another species (and vice versa) (Clancy, Finlay, Darlington, & Anand, 2007; Romijn, Hofman, & Gramsbergen, 1991). Another concern for cross-species comparisons are differences in stress circuitry (Sanchez, Ladd, & Plotsky, 2001). This deviation is a significant factor given the central role ascribed to the stress response system as a likely mediator of at least some of the prenatal effects on offspring behavior. An additional problem for translating animal work is the nature of the risk phenotype. Experimental animal studies typically employ various kinds of stimuli – including crowding, noise, smells (of predators), and shocks – that have a clear onset and offset at one or more stages in gestation. Alongside problems in equating periods of ontogenic vulnerability across species, this approach may have few applications because the pregnant women of greatest clinical concern are those for whom the prenatal stress is neither isolated nor conscribed but rather chronic and diffuse. The animal study was seminal, despite these limitations, yet there is now enough human evidence to sustain new programs of applied basic/clinical studies and to compose a practitioner review.

Defining the risk phenotype

In most studies the measures of prenatal anxiety or stress or depression are supplied by a self-report measure completed by the pregnant woman, typically from a questionnaire of symptoms or life events. The wide diversity of measures (in format and assessed construct) used across studies is impressive because it implies that the risk phenotype is fairly broad – extending beyond the narrow concepts denoted by anxiety, depression, or 'stress.' On the other hand, why it is that an effect on child outcome is detected for one but not another prenatal risk measure [e.g., life events stress vs. emotional stress, Tegethoff, Greene, Olsen, Schaffner, & Meinlschmidt, 2011; pregnancy-specific stress versus global assessments of distress (Buss, Davis, Hobel, & Sandman, 2011)] is not clear insofar as these distinct measures are unlikely to activate different stress circuits in the pregnant mother, and may suggest lack of a robust effect. This lack of specificity and other questions regarding the magnitude of exposure (e.g., 'how much distress is too much') point to imprecision in the research and the need for further studies (Dipietro, 2012).

What most studies have not successfully demonstrated is how maternal prenatal distress is 'communicated' to the developing fetus. This lapse is an important limitation. The need to (re-) define the risk phenotype in terms of both a psychological construct in the mother (such as anxiety, depression, or stress) and the biological effects that may shape fetal development is central to progress in research on prenatal anxiety, and parallels the general need in mental health clinical research (Insel et al., 2010).

Timing, severity, and source

The most common approach in human studies of prenatal distress is to track samples with varying degrees of exposures from pregnancy through to the postnatal period, and then connect this variation to child outcomes. The inability to experimentally introduce distress at a particular point in pregnancy (for obvious ethical reasons) means that there is limited leverage for assessing a timing effect; that is

likely why there is no consensus yet on the timing of distress for most of the outcomes assessed. The one possible exception to this is a handful of reports from naturalistic studies suggesting that early and not later gestational distress may be linked to certain neurological or more severe disturbances (Carmichael & Shaw, 2000; Glover, O'Connor, Heron, & Golding, 2004; Khashan et al., 2008). Studies that have capitalized on a natural disaster to examine timing or severity effects hypothesis, such as the Quebec ice storm (King et al., 2009) or the terrorist attacks on September 11th (Yehuda et al., 2005), or hurricane Katrina (Harville, Xiong, & Buekens, 2009) have yielded interesting findings, but in these studies duration and timing are confounded, that is, those women who experience the event earlier in pregnancy are affected by it and its consequences for a greater percentage of the pregnancy than those later exposed.

One consistent finding is that the effects of prenatal distress on child outcomes are not limited to severe maternal prenatal disturbance; rather, fairly linear or near dose-response patterns have been reported (even in studies that elect to present results using dichotomized scaling). This is an important observation insofar as it implies that the potential impact of prenatal maternal distress may be detectable at subclinical levels of distress or impairment, further raising and broadening the public health concern. One obvious implication is that interventions to reduce prenatal distress – for the benefit of the mother and child – need not be limited to or necessarily targeted on those women with clinical disorder.

Comparatively few studies have considered or differentiated the source of maternal prenatal distress. As a result, it is not clear if the increased burden or demands that may rise in pregnancy are more germane than, for example, long-standing anxiety-proneness; stressors particular to pregnancy have been discussed, including intimate partner violence and worries that may be especially salient to the pregnancy. Alternatively, it may be that routine stressors from the workplace or other settings become more burdensome in pregnancy – although available data suggest the opposite (Glynn, Wadhwa, Dunkel-Schetter, Chicz-Demet, & Sandman, 2001; Kammerer, Adams, Castelberg, & Glover, 2002). Sorting out the source of stress may provide clues to the forms that effective cognitive and psychosocial interventions may take, although each of these stressors, if they were to affect fetal development, presumably would be operating through the same stress circuits and mechanisms.

Evidence base and mechanisms of effect

The evidence base linking prenatal maternal distress to child outcomes is substantial. Minimally, that means that this now is seen as a major area for scientific inquiry, and further underscores our earlier point that there is no longer a need to rely on experimental animal investigation as an inspiration for further clinical research. Many reviews of the literature for child outcomes exist, as noted above. Our brief review of the findings highlights the more novel areas of study and illustrative findings, with a particular emphasis on clinical significance.

An interesting starting point for a research review is a recent Danish cohort study, based on over 66,000 mother-child pairings with data on mother-reported stress and health registry data in the child (Tegethoff et al., 2011). Results indicated that a measure of life stress in pregnancy was associated with modest increases in many kinds of disease and disorder, including mental and behavioral, digestive, and respiratory systems conditions. This large study demonstrates one of the more important take-home messages: the mechanisms that may be at play are not limited to child mental health (although they have attracted the most attention), and implies the somewhat artificial nature of discipline-based practices of pediatric assessment and treatment.

A second set of findings is that many of the obstetric factors that have long been associated with child health and development – birth weight, gestational age – are predicted from maternal mood and stress in pregnancy (Grote et al., 2010, but see Littleton, Breitkopf, & Berenson, 2007; Yonkers, 2013). The lesson here is that presumed established risk factors for poor future child neurobehavioral development may themselves be proxies for prenatal events and exposures. A third lesson is the real-time communication that occurs between mother and fetus. Several studies demonstrate that inducing maternal stress or relaxation activates maternal stress systems to which the fetus responds (DiPietro, Costigan, Nelson, Gurewitsch, & Laudenslager, 2008; Dipietro et al., 2006; Monk et al., 2004; Monk, Fifer et al., 2011). These findings are important in helping to establish the bona fide impact of maternal mood-based physiology on fetal development and for identifying possible strategies for intervening and demonstrating how interventions may have a salutary effect on the developing child.

A further key observation that merits further emphasis is the diverse nature of the prenatal maternal distress effects so far reported. In addition to the well-replicated associations with behavioral and emotional problems and temperament (Korhonen, Luoma, Salmelin, & Tamminen, 2012; O'Connor, Heron, Golding, & Glover, 2003; Van den Bergh, Van Calster, Smits, Van Huffel, & Lagae, 2008), are replicated findings in areas as diverse as sleep problems (O'Connor et al., 2007), neuroendocrine function and stress physiology (Davis, Glynn, Waffarn, & Sandman, 2011; Grant et al., 2009; O'Connor, Bergman, Sarkar, & Glover, 2013), atypical laterality (Glover et al., 2004; Obel, Hedegaard, Henriksen, Secher, & Olsen, 2003), immune function and autoimmune disease (O'Connor, Heron et al., 2013; Wright et al., 2010); findings

concerning neurological disorders are mixed but provocative (Li et al., 2008; Li, Vestergaard, Obel, Christensen, et al., 2009; Li, Vestergaard, Obel, Precht, et al., 2009). The diversity of outcomes linked to prenatal maternal distress is impressive, mimics the animal data, and underscores the need for research that collates methods and models from multiple disciplines.

Although there are comparatively few studies with long follow-up periods, a handful of prospective longitudinal studies suggest that the impact of maternal prenatal anxiety on the child persists at least into adolescence for behavior and physiology (O'Donnell, Glover, Jenkins, et al., 2013; Van den Bergh et al., 2008). This impact is consistent with, but does not confirm, the program-ability of these outcomes from prenatal maternal anxiety. Furthermore, there is some suggestion that the effects may be moderated, for some outcomes, by quality of early care (Bergman, Sarkar, Glover, & O'Connor, 2010). This suggestion is an important reminder that research on prenatal programming will also require careful study of the early caregiving environment (the programming window is unlikely to 'close' at birth). Finally, although there is limited relevant research, there is some suggestion that there may be important changes in the maternal brain in the perinatal period that may influence caregiving behavior (e.g., Kim et al., 2010). The extent to which these possible programming effects may be moderated by genetic factors is also an area of active study, but most studies focus on single or limited set of polymorphisms and, to date, no clear story has emerged (Braithwaite et al., 2013; Pluess et al., 2011); neither is there strong evidence yet that exposure to prenatal anxiety renders individuals more susceptible to subsequent stressors, although that is a comparatively new line of study (Laceulle et al., 2013).

Clinical significance for child health and behavior

A question that is not routinely addressed in studies connecting prenatal maternal distress to child outcomes is whether or not the findings have 'clinical significance.' That typically is interpreted to mean that the results are positioned to inform clinical practice – because, for example, the magnitude of the effect is sizable or severe enough to detect in a routine clinical setting – rather than only inform a biological-conceptual model about development. There are several ways of calculating the clinical significance of outcomes associated with prenatal maternal distress. The most obvious way is to examine effect sizes, which are perhaps most easily understood where the scale is familiar or, there are standardized scores or norms. Tests of cognitive ability are the most obvious example. Data from Project Ice Storm indicated differences between the low, moderate, and high prenatal stress groups amounted to differences of 5–10 IQ points, depending on which groups are compared – a sizable difference relative to other known risks and important on an absolute scale given the standard deviation is 15 (Laplante, Brunet, Schmitz, Ciampi, & King, 2008). Effect sizes can be derived from statistics such as correlation coefficients, odds or relative risk ratios, or unstandardized regression coefficients, although the reporting of effect sizes remains uncommon.

Few studies assess clinical disorder in children associated with prenatal maternal distress. Data from the ALSPAC cohort, which predicted behavioral and emotional problems from prenatal anxiety, reported reasonably sizable differences in population prevalence of clinically elevated problems (composited across all clinical scales) associated with prenatal anxiety; for example, at age 13 years, the difference was approximately 7% in the low prenatal anxiety group compared with 12% in the high prenatal anxiety group (O'Donnell, Glover, Barker, & O'Connor, 2013). A smaller study using an affected sibling design reported that prenatal stress increased the risk of ADHD by a factor of greater than 6, but with wide confidence intervals (95% CI: 1.45–27.26) (Grizenko et al., 2012). In addition, findings from the Danish cohort study (described above) (Tegethoff et al., 2011) are valuable because the outcomes were derived from medical registry, that is, the clinical health outcomes were significant enough to warrant medical attention. Odds ratios from prenatal life stress ranged from about 1.2 for digestive and respiratory diseases to greater than 2 for early mental and behavioral disorders.

Many of the outcomes linked with prenatal maternal distress cannot be readily translated for clinical significance. For example, studies have linked maternal prenatal distress, or aspects of fetal neurobehavior associated with maternal prenatal distress (Werner et al., 2007), to high reactive infant temperament (Davis et al., 2004; Werner et al., 2012), a risk factor for future anxiety disorders (Biederman et al., 2001; Kagan, Snidman, Zentner, & Peterson, 1999). But, this chain of associations has not been identified in the same children longitudinally. For other outcomes, such as biological mechanisms and markers (e.g., volumetric measures from brain imaging, immune cell responses to antigen stimulation), the link between the marker and functional outcome is not sufficiently established to confirm clinical significance. The clinical impact of further research in this area will naturally depend on the translation to outcomes and metrics that have purchase in a clinical setting.

Given the number of reports linking maternal prenatal distress to child outcomes, a focus of research has shifted to identify the mechanisms of effect. The most studied candidate is the hypothalamic-pituitary-adrenal (HPA) axis (Henry, Kabbaj, Simon, Le Moal, & Maccari, 1994). The model here is that prenatal maternal mood is associated with elevated cortisol, a downstream product of the HPA

axis, that is able to cross the placenta in a limited manner to affect fetal development (Sarkar, Bergman, O'Connor, & Glover, 2008; Seckl & Meaney, 2004) or, less directly, that prenatal anxiety may alter the role of the barrier enzyme 11bHSD2 to increase fetal exposure to glucocorticoids (O'Donnell et al., 2012). Component parts of this model have been demonstrated, but the weight of the evidence is not yet convincing. So, for example, some (but by no means all) studies have reported alterations in cortisol in prenatally distressed women (Evans, Myers, & Monk, 2008; Kivlighan, DiPietro, Costigan, & Laudenslager, 2008), and prenatal cortisol exposure has been associated with child outcomes; however, there is not yet evidence that an index of cortisol exposure mediates the prenatal maternal mood effect on child outcomes (Bergman et al., 2010; Davis & Sandman, 2010). This shortcoming may be because of a myriad of challenges in assessing individual differences in cortisol particularly during pregnancy; alternatively, it may simply be that there is too much focus on an HPA-mediated effect and too little attention to complementary or competing mechanisms of stress, for example, from the sympathetic nervous system, alternative steroid hormones, immune function, or other factors; and (epi)genetics has been largely neglected in these studies.

Alternatives to an HPA axis-mediated mechanism for the prenatal distress effect are also possible and have been proposed, but none has yet attracted considerable empirical support. For example, several studies have considered uterine blood flow; adrenaline hormones which accompany distress may cause blood vessel constriction that may impair oxygen flow to the fetus, and may account for neurodevelopmental outcomes (Teixeira, Fisk, & Glover, 1999). However, recent data question this as a strong candidate (Mendelson, DiPietro, Costigan, Chen, & Henderson, 2011; Monk et al., 2012). Prenatal distress also involves the sympathetic nervous system, and alterations of the sympathetic nervous system in the mother – by experimental induction or by psychiatric characteristics – have been linked to changes in fetal behavior (Monk, Fifer et al., 2011), but it is not yet clear if this may modulate the effects on child neurodevelopment, physiology, and immunity that have been demonstrated.

Immunological mechanisms offer another alternative mechanism. In this case, maternal prenatal maternal distress may be associated with elevated inflammation [there is mixed evidence for this (Blackmore et al., 2011; Coussons-Read, Okun, & Nettles, 2007)]. Increased inflammation, which is reliably linked with increased risk of miscarriage and other obstetric complications (Culhane et al., 2001; Harris, 1919; Nepomnaschy et al., 2006; Neugebauer et al., 1996; Wadhwa, Sandman, Porto, Dunkel-Schetter, & Garite, 1993), may alter fetal development. More specifically, in animal models, inflammation in pregnancy has been repeatedly linked with disrupted brain development; perhaps related to this information are findings in human studies showing that influenza in pregnancy is associated with neuropsychiatric disorders such as schizophrenia (Brown et al., 2000). Cross-talk between the immune and stress systems (in and outside of pregnancy) underscores the difficulty in isolating a single or singular mechanism or molecule (see, for example, O'Connor, Moynihan, & Caserta, in press). Nonetheless, a number of specific molecules deserve additional investigation, such as the barrier enzyme 11bHSD2, which metabolizes cortisol in the mother to inactive cortisone, thereby reducing fetal exposure (Jensen Pena, Monk, & Champagne, 2012; O'Donnell et al., 2012; Raikkonen, Seckl, Pesonen, Simons, & Van den Bergh, 2011).

Finally, it is interesting that some of the lessons from animal studies have not transferred to human development. One of these is sex differences. Few human studies report sex differences in the link between prenatal maternal distress and child outcomes, and there are even fewer examples of sexually dimorphic outcomes; a recent study suggesting that prenatal stress may masculinize some aspects of female reproductive development is an exception (Barrett et al., 2013). This finding is in contrast with animal studies, which regularly report sex differences in effects (Zuena et al., 2008). Clearly, there are quite a number of unresolved issues about mechanisms, and it would be unlikely if there were a single mechanism involved (although this is implicitly assumed in most studies, which target one or other candidate). Identifying the mechanisms of effect is obviously valuable for identifying the most promising targets for a preventive intervention.

Threats to the causal connection

Notwithstanding the widely reported findings, it is not yet established in the human that prenatal distress has a bona fide direct *causal* impact on the fetus and child. This discrepancy occurs because the observational design in human studies is inherently limited for drawing causal conclusions. It is certainly impressive that effects in human studies have been observed in very many studies from several countries with varying measures of prenatal maternal distress and child outcome. Whether or not this kind of replication provides a 'high enough' level of evidence to institute change in practice or policy may depend less on a scientific threshold and more on clinical, cultural or institutional ones. Waiting for the definitive study will inevitably require persisting inaction given the difficulty in designing an investigation that completely accounts for the many kinds of confounds that plague this sort of research, ranging from nutrition to inflammation (e.g., Blackmore et al., 2011; Coe, Lubach, & Shirtcliff, 2007; Marques, O'Connor, Roth, Susser, & Bjorke-Monsen, 2013; Monk, Georgieff, &

Osterholm, 2013; Roseboom, de Rooij, & Painter, 2006; Schneider, Moore, Kraemer, Roberts, & DeJesus, 2002; Sullivan, Smith, & Grove, 2011).

Several studies have sought to gain some index of a genetic confound through a variety of approaches. For example, within-family study design was reported by Grizenko et al. (2012), who reported that children whose mothers were stressed during pregnancy were more likely to display ADHD symptoms than an unexposed sibling. Other investigators, who included an IVF sample indicated that a prenatal maternal stress effect was robust for child conduct problems but not for child ADHD or anxiety; however, a single item was used to index prenatal stress (Rice et al., 2010). Other data suggested that paternal prenatal anxiety may account for some of the maternal prenatal effect, implying that the proposed intrauterine effect may be overstated (Van Batenburg-Eddes et al., 2013); however, that effect appeared for attention problems but not anxiety in the child; longer term follow-up studies that controlled for prenatal paternal influences indicated no confounding effect on behavioral problems or physiology (O'Donnell, Glover, Jenkins, et al., 2013). These kinds of studies provide modest additional leverage but it is really the experimental control gained through intervention that may end up driving clinical and policy decisions.

Clinical applications: prenatal treatment as a preventive intervention

Treatment of depression and anxiety during pregnancy remains a widely discussed topic (Chaudron, 2013; Monk, Fitelson, & Werner, 2011; Yonkers et al., 2009). Several important advances are apparent in the more recent treatments of the issue. One is the recognition that depression and anxiety in pregnancy are at least as common, if not more common, in pregnancy as in the early postpartum period (e.g., Evans, Heron, Francomb, Oke, & Golding, 2001). This approach is a significant counterweight to the traditional focus on postpartum maternal depression in the child mental health area. If prenatal depression and anxiety and stress are more common in pregnancy and confer risk for child mental health, then there needs to be consequently greater attention to prenatal maternal mood. A second theme, which follows on from the evidence reviewed in this article, is the possible beneficial effects for the child for reducing depression and anxiety in pregnancy – in addition to those benefits for the mother.

From the perspective of child mental health, we see several limitations and problems with the way discussions of prenatal treatment have typically been framed. One is that many discussions focus almost exclusively on depression in pregnancy, without due regard to the broader risk phenotype of prenatal maternal distress that research says predicts poor obstetric and child outcomes. This opinion may be influenced, in part, by a predominant influence and widespread availability of antidepressant medications, especially SSRIs. It is notable, in this context, that remarkably few studies linking prenatal maternal mood to child outcomes include diagnoses; furthermore, studies showing prenatal maternal distress effects on the child have used stress and symptom measures that receive minimal attention in treatment reviews. If there is to be a child-focused attention to treating maternal prenatal distress, then there needs to be a widening of the maternal phenotypes that attract clinical attention, that is, broader than a diagnosis and broader than depression.

A second major limitation of reviews of prenatal treatment for maternal distress is the heavy focus on medication. This restriction is different from the debate about treating clinical disorders outside the perinatal period. So, for example, in the case of depression outside of the perinatal period, there remains lively debate about the comparative clinical effectiveness and comparative cost effectiveness of psychotherapy and medication (e.g., Bosmans et al., 2008; Siddique, Chung, Brown, & Miranda, 2012). Such kind of comparative effectiveness framework has not yet matured in the perinatal period; the implicit message in many reviews is a false dichotomy: treatment with medication versus no treatment. The neglect of behavioral treatments for prenatal maternal anxiety, stress, and depression is particularly problematic given resistance to medication in certain subgroups in particular (see, Jimenez-Solem et al., 2013; Kozhimannil, Adams, Soumerai, Busch, & Huskamp, 2011) and the suggestion that SSRIs may have adverse effects on the developing fetus and child (Grzeskowiak, Gilbert, & Morrison, 2012). As regards the latter point, research linking medication use such as SSRIs with obstetric and fetal outcome has been reported, with varying degrees of risk (El Marroun et al., 2012; Oberlander et al., 2010), but none of these studies had the benefit of a randomized control trial design. We focus the remainder of this review on psychological and behavioral interventions that may be delivered in pregnancy to have preventive benefits on the child.

The first point is that there is sizable evidence that anxiety and depression can be effectively treated outside the perinatal period; many specific examples of disseminated programs have been reported (e.g., Dimidjian et al., 2006; Ladouceur et al., 2000). Accordingly, the first question to ask is if there is reason to believe that treatment success would be any different in pregnant compared to nonpregnant women. Such a case might be made given the dramatic hormonal and social changes that accompany pregnancy, although there is not yet convincing evidence that this is so. Interpersonal psychotherapy (IPT) has been modified for treatment of antenatal depression in several studies (Sockol, 2011; Spinelli, 2013), and cognitive behavioral (CBT), supportive, and psychodynamic interventions have been investigated in small studies for the postpartum population,

with generally positive results and no clear differences between modalities (Brandon, 2011; Cuijpers, 2008). Nonetheless, taken as a whole, the evidence base for conventional psychological treatments for maternal prenatal distress is very limited, with some nonsupportive findings (Austin et al., 2008). There may be a case for greater inclusion of pregnant women in trials of psychological treatments for depression, anxiety, and related disorders – rather than presume that pregnancy is a defensible exclusion criterion.

What is striking in the literature is the preponderance of 'nontraditional' interventions for anxiety, depression or stress in pregnant women. These more alternative treatments may be seen as more acceptable to pregnant women, or perhaps they are simply the kinds of treatment more favored by those working with pregnant women in primary and preventive care settings. More practical research is needed to understand treatment preferences and accessibility in distressed pregnant women (Arch, Dimidjian, & Chessick, 2012; O'Brien, Schachtschneider, Koren, Walker, & Einarson, 2007).

Several lines of nontraditional prenatal treatment warrant particular attention. One uses muscle relaxation and guided imagery (Fink et al., 2011; Urech et al., 2010). For example, Urech et al. reported that guided imagery was effective for increasing relaxation in pregnant women and altering cardiovascular activity. Yoga is also popular in pregnancy and has been considered as a potential intervention for anxiety and stress. However, a recent review of this work by Curtis and colleagues (Curtis, Weinrib, & Katz, 2012) found that only a very small minority of those published would meet even basic criteria for sound methodology. This is also the basic message of a recent Cochrane review (Dennis & Allen, 2008). Massage therapy has also been suggested, and reported by Field and colleagues (e.g., Field et al., 2010) to reduce depression in pregnancy and alter cortisol levels, and acupuncture has also shown symptom reduction in antenatal depression (Manber, 2010). One potentially promising novel treatment builds on mindfulness-based stress reduction and covers both pregnancy and the early postnatal period (Duncan & Bardacke, 2010). For all of these kinds of intervention, a major consideration in judging the likely impact on the child is the degree to which the treatment alters a presumed mechanism linking maternal prenatal distress to child outcome, such as the stress hormone cortisol (e.g., Glover, Bergman, Sarkar, & O'Connor, 2009). As noted above, that issue is not yet settled, but many studies have sought to incorporate potential biomarkers of treatment response that may be relevant for obstetric and child outcomes. Collecting clinically relevant and accessible biomarkers may be one way of improving the evidence base for assessment and clinical practice. What is clear is that simply demonstrating that an intervention altered prenatal maternal distress – although important – may not be enough.

At present, probably the most important conclusion is that the evidence base for treating prenatal maternal distress is quite varied and generally underdeveloped. Several more iterations of study will be needed to know which treatment approaches are likely to benefit the mother, and if those same approaches are also likely to benefit the baby. Additional clinical intervention research is need to identify plausible strategies for preventing or reducing specific sources of distress in pregnancy, ranging from work stress and intimate partner violence to pregnancy-specific anxiety and worry.

Timing is also a lingering question for these interventions. If quality of early care does modulate or even eliminate the effects of prenatal anxiety on child cognitive, social, or emotional outcomes (Bergman, Sarkar, Glover, & O'Connor, 2008; Bergman et al., 2010), then interventions to promote child health and development need not occur solely *in utero*: interventions that are geared to the perinatal period as a whole and/or that focus on enhancing the quality of maternal-child attachment and interactions may be more effective for both relieving maternal distress and promoting child development (Forman, 2007). A further consideration in prenatal or perinatal maternal treatment is the role of fathers, which has been neglected in all but a few studies of maternal perinatal distress and child well-being (Ramchandani et al., 2008). Finally, in line with research previously reviewed, prenatal interventions that promote child development – in broad health terms – need not be psychological in nature: flu vaccine is associated with reduced risk of miscarriage, preterm birth or being born small for gestational age (Fell et al., 2012; Haberg et al., 2013). Motivating pregnant women to be vaccinated is yet another mode of prenatal preventive intervention.

Prenatal psychological interventions may confer benefit to the child even if they do not alter the prenatal hormonal milieu or screen the child during a programming window. This gain is because prenatal interventions may be one of the most effective preventive strategies for reducing postpartum depression (e.g., see Cooper, Murray, Wilson, & Romaniuk, 2003; Murray, Cooper, Wilson, & Romaniuk, 2003). A recent review of nearly 30 trials indicated that several kinds of psychological treatments in pregnancy may reduce the likelihood of postpartum depression, including home visits and individualized IPT (Dennis & Dowswell, 2013); other intervention effects may not carry over to the postnatal period (e.g., Le, Perry, & Stuart, 2011).

Finally, in most cases a clear etiology of child behavioral or emotional problems cannot be isolated. In that regard, it is notable that there is not yet evidence that prenatal maternal anxiety, depression or stress predicts a particular outcome or profile of child disturbance or that, for example, attention problems resulting from prenatal anxiety appear different or respond differently to treatment than

attention problems with a presumed alternative etiology – although evidence on this is admittedly minimal (e.g., Grizenko, Shayan, Polotskaia, Ter-Stepanian, & Joober, 2008). The implication is that no special treatment could yet be prescribed for a child health outcome thought to be linked with prenatal maternal anxiety or stress.

Conclusions

Maternal prenatal distress has emerged as an excellent example of translational research – taking findings from 'basic' experimental animal studies with potential to inform human health and extend applied research to clinical practice. Furthermore, research on maternal prenatal distress and its effects on child development is a model for investigating health origins without artificial boundaries created by medical disciplines that are inconsistent with actual psycho-biological mechanisms in development. Questions remain about mediating mechanisms in the studies so far reported, and the causal case has not been unambiguously answered; however, the wealth of findings in the area is impressive for the replication across sample and diversity of outcomes assessed. Therefore, we suggest that it is adequate for promoting energetic efforts to promote child mental health outcomes *in utero*. On the other hand, the absence of a compelling evidence base from prenatal treatment studies is notable, and limiting in two important ways. First, it obviously impairs clinical decision making about which interventions may be most helpful, and for whom. Second, the lack of randomized control trials means that a potential source of experimental leverage for testing basic questions about the impact of prenatal maternal mood on child outcome has not been fully exploited. Further research is needed because genuinely novel and potentially valuable strategies for promoting child mental health may be gained from viewing prenatal maternal distress as a paradigm for clinical research.

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Key points

- Prenatal maternal anxiety, stress, and depression have been reliably associated with an increased risk for a range of biological, behavioral and cognitive outcomes in children.
- Research on prenatal maternal distress is a valuable example of translational research and a paradigm for promoting interdisciplinary clinical research in child mental and somatic health.
- Prenatal interventions to promote child health are plausible, although the empirical evidence is too limited at present.
- Key messages for practitioners include awareness of the large and expanding prenatal distress literature, and the increased opportunities for promoting child health.

Note

[1]To date, child outcomes have been linked to maternal prenatal stress, depression, and anxiety and there is not yet specificity. For this reason, going forward we will use the term 'distress' when referring in general to this research, and identify the maternal mood exposure by name when describing study-specific results.

References

Ader, R., & Plaut, S.M. (1968). Effects of prenatal maternal handling and differential housing on offspring emotionality, plasma corticosterone levels, and susceptibility to gastric erosions. *Psychosomatic Medicine*, *30*, 277–286.

Arch, J.J., Dimidjian, S., & Chessick, C. (2012). Are exposure-based cognitive behavioral therapies safe during pregnancy? *Archives of Women's Mental Health*, *15*, 445–457.

Austin, M.P., Frilingos, M., Lumley, J., Hadzi-Pavlovic, D., Roncolato, W., Acland, S., … & Parker, G. (2008). Brief antenatal cognitive behaviour therapy group intervention for the prevention of postnatal depression and anxiety: A randomised controlled trial. *Journal of Affective Disorders*, *105*, 35–44.

Barker, D.J. (2007). The origins of the developmental origins theory. [Review]. *Journal of Internal Medicine*, *261*, 412–417.

Barrett, E.S., Parlett, L.E., Sathyanarayana, S., Liu, F., Redmon, J.B., Wang, C., & Swan, S.H. (2013). Prenatal exposure to stressful life events is associated with masculinized anogenital distance (AGD) in female infants. *Physiology and Behavior*, *114–115*, 14–20.

Bergman, K., Sarkar, P., Glover, V., & O'Connor, T.G. (2008). Quality of child-parent attachment moderates the impact of antenatal stress on child fearfulness. *Journal of Child Psychology and Psychiatry*, *49*, 1089–1098.

Bergman, K., Sarkar, P., Glover, V., & O'Connor, T.G. (2010). Maternal prenatal cortisol and infant cognitive development: Moderation by infant-mother attachment. *Biological Psychiatry*, *67*, 1026–1032.

Biederman, J., Hirshfeld-Becker, D.R., Rosenbaum, J.F., Herot, C., Friedman, D., Snidman, N., … & Faraone, S.V. (2001). Further evidence of association between behavioral inhibition and social anxiety in children. *American Journal of Psychiatry*, *158*, 1673–1679.

Blackmore, E.R., Moynihan, J.A., Rubinow, D.R., Pressman, E.K., Gilchrist, M., & O'Connor, T.G. (2011). Psychiatric symptoms and proinflammatory cytokines in pregnancy. *Psychosomatic Medicine*, *73*, 656–663.

Bosmans, J.E., van Schaik, D.J., de Bruijne, M.C., van Hout, H.P., van Marwijk, H.W., van Tulder, M.W., & Stalman, W.A. (2008). Are psychological treatments for depression in primary care cost-effective? *Journal of Mental Health Policy and Economics*, *11*, 3–15.

Braithwaite, E.C., Ramchandani, P.G., O'Connor, T.G., Van Ijzendoorn, M., Bakermans-Kranenburg, M.J., Glover, V., … & Murphy, S.E. (2013). No moderating influence of the serotonin transporter polymorphism (5-HTTLPR) on the association between antenatal maternal mood and infant temperament. *Journal of the American Academy of Child and Adolescent Psychiatry*, *52*, 519–526.

Brandon, A.R. (2011). When she says "no" to medication: Psychotherapy for antepartum depression. *Current Psychiatry Reports*, *13*, 459–466.

Brown, A.S., Schaefer, C.A., Wyatt, R.J., Goetz, R., Begg, M.D., Gorman, J.M., & Susser, E.S. (2000). Maternal exposure to respiratory infections and adult schizophrenia spectrum disorders: A prospective birth cohort study. *Schizophrenia Bulletin*, *26*, 287–295.

Buss, C., Davis, E.P., Hobel, C.J., & Sandman, C.A. (2011). Maternal pregnancy-specific anxiety is associated with child executive function at 6-9 years age. *Stress*, *14*, 665–676.

Carmichael, S.L., & Shaw, G.M. (2000). Maternal life event stress and congenital anomalies. *Epidemiology*, *11*, 30–35.

Chaudron, L.H. (2013). Complex challenges in treating depression during pregnancy. *American Journal of Psychiatry*, *170*, 12–20.

Clancy, B., Finlay, B.L., Darlington, R.B., & Anand, K.J. (2007). Extrapolating brain development from experimental species to humans. *Neurotoxicology*, *28*, 931–937.

Coe, C.L., Lubach, G.R., & Shirtcliff, E.A. (2007). Maternal stress during pregnancy predisposes for iron deficiency in infant monkeys impacting innate immunity. *Pediatric Research*, *61*, 520–524.

Cooper, P.J., Murray, L., Wilson, A., & Romaniuk, H. (2003). Controlled trial of the short- and long-term effect of psychological treatment of post-partum depression. I. Impact on maternal mood. *British Journal of Psychiatry*, *182*, 412–419.

Coussons-Read, M.E., Okun, M.L., & Nettles, C.D. (2007). Psychosocial stress increases inflammatory markers and alters cytokine production across pregnancy. *Brain, Behavior, and Immunity*, *21*, 343–350.

Cuijpers, P. (2008). Psychological treatment of postpartum depression: A meta-analysis. *Journal of Clinical Psychology*, *64*, 103–118.

Culhane, J.F., Rauh, V., McCollum, K.F., Hogan, V.K., Agnew, K., & Wadhwa, P.D. (2001). Maternal stress is associated with bacterial vaginosis in human pregnancy. *Maternal and Child Health Journal*, *5*, 127–134.

Curtis, K., Weinrib, A., & Katz, J. (2012). Systematic review of yoga for pregnant women: Current status and future directions. *Evidence-Based Complementary and Alternative Medicine*, *2012*, 715942. doi: 10.1155/2012/715942.

Davis, E.P., Glynn, L.M., Waffarn, F., & Sandman, C.A. (2011). Prenatal maternal stress programs infant stress regulation. *Journal of Child Psychology and Psychiatry*, *52*, 119–129.

Davis, E.P., & Sandman, C.A. (2010). The timing of prenatal exposure to maternal cortisol and psychosocial stress is associated with human infant cognitive development. *Child Development*, *81*, 131–148.

Davis, P.E., Snidman, N., Wadhwa, P., Glynn, L.M., Schetter, C.D., & Sandman, C.A. (2004). Prenatal maternal anxiety and depression predict negative behavioral reactivity in infancy. *Infancy*, *6*, 319–331.

Dennis, C.L., & Allen, K. (2008). Interventions (other than pharmacological, psychosocial or psychological) for treating antenatal depression. *Cochrane Database Systematic Review*, *4*, CD006795. doi: 10.1002/14651858.CD006795.pub2.

Dennis, C.L., & Dowswell, T. (2013). Psychosocial and psychological interventions for preventing postpartum depression. *Cochrane Database Systematic Review*, *2*, CD001134. doi: 10.1002/14651858.CD001134.pub3.

Dimidjian, S., Hollon, S.D., Dobson, K.S., Schmaling, K.B., Kohlenberg, R.J., Addis, M.E., … & Jacobson, N.S. (2006). Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the acute treatment of adults with major depression. *Journal of Consulting and Clinical Psychology*, *74*, 658–670.

Dipietro, J.A. (2012). Maternal stress in pregnancy: Considerations for fetal development. *Journal of Adolescent Health*, *51* (2 Suppl), S3–S8.

Dipietro, J.A., Caulfield, L.E., Irizarry, R.A., Chen, P., Merialdi, M., & Zavaleta, N. (2006). Prenatal development of intrafetal and maternal-fetal synchrony. *Behavioral Neuroscience*, *120*, 687–701.

DiPietro, J.A., Costigan, K.A., Nelson, P., Gurewitsch, E.D., & Laudenslager, M.L. (2008). Fetal responses to induced maternal relaxation during pregnancy. *Biological Psychology*, *77*, 11–19.

DiPietro, J.A., Novak, M.F., Costigan, K.A., Atella, L.D., & Reusing, S.P. (2006). Maternal psychological distress during pregnancy in relation to child development at age two. *Child Development*, *77*, 573–587.

Duncan, L.G., & Bardacke, N. (2010). Mindfulness-based childbirth and parenting education: Promoting family mindfulness during the perinatal period. *Journal of Child and Family Studies*, *19*, 190–202.

Dunkel Schetter, C., & Tanner, L. (2012). Anxiety, depression and stress in pregnancy: Implications for mothers, children, research, and practice. *Current Opinion in Psychiatry*, *25*, 141–148.

El Marroun, H., Jaddoe, V.W., Hudziak, J.J., Roza, S.J., Steegers, E.A., Hofman, A., … & Tiemeier, H. (2012). Maternal use of selective serotonin reuptake inhibitors, fetal growth, and risk of adverse birth outcomes. *Archives of General Psychiatry*, *69*, 706–714.

Evans, J., Heron, J., Francomb, H., Oke, S., & Golding, J. (2001). Cohort study of depressed mood during pregnancy and after childbirth. *British Medical Journal*, *323*, 257–260.

Evans, L.M., Myers, M.M., & Monk, C. (2008). Pregnant women's cortisol is elevated with anxiety and depression—But only when comorbid. *Archives of Women's Mental Health*, *11*, 239–248.

Fell, D.B., Sprague, A.E., Liu, N., Yasseen, A.S. 3rd, Wen, S.W., Smith, G., & Walker, M.C. (2012). H1N1 influenza vaccination during pregnancy and fetal and neonatal outcomes. *American Journal of Public Health*, *102*, e33–e40. doi: 10.2105/AJPH.2011.300606.

Field, T., Diego, M., & Hernandez-Reif, M. (2010). Prenatal depression effects and interventions: a review. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Review]. *Infant Behavior & Development*, *33*, 409–418.

Fink, N.S., Urech, C., Isabel, F., Meyer, A., Hoesli, I., Bitzer, J., & Alder, J. (2011). Fetal response to abbreviated relaxation techniques. A randomized controlled study. *Early Human Development*, *87*, 121–127.

Finlay, B.L., & Darlington, R.B. (1995). Linked regularities in the development and evolution of mammalian brains. *Science*, *268*, 1578–1584.

Forman, D.R. (2007). Effective treatment for postpartum depression is not sufficient to improve the developing mother-child relationship. *Development and Psychopathology*, *19*, 585–602.

Glover, V. (2011). Annual Research Review: Prenatal stress and the origins of psychopathology: An evolutionary perspective. *Journal of Child Psychology and Psychiatry*, *52*, 356–367.

Glover, V., Bergman, K., Sarkar, P., & O'Connor, T.G. (2009). Association between maternal and amniotic fluid cortisol is moderated by maternal anxiety. *Psychoneuroendocrinology*, *34*, 430–435.

Glover, V., O'Connor, T.G., Heron, J., & Golding, J. (2004). Antenatal maternal anxiety is linked with atypical handedness in the child. *Early Human Development*, *79*, 107–118.

Gluckman, P.D., Cutfield, W., Hofman, P., & Hanson, M.A. (2005). The fetal, neonatal, and infant environments-the long-term consequences for disease risk. *Early Human Development*, *81*, 51–59.

Gluckman, P., & Hanson, M. (2005). *The fetal matrix: Evolution, development, and disease*. Cambridge, UK: Cambridge University Press.

Glynn, L.M., Wadhwa, P.D., Dunkel-Schetter, C., Chicz-Demet, A., & Sandman, C.A. (2001). When stress happens matters: Effects of earthquake timing on stress responsivity in pregnancy. [Research Support, U.S. Gov't, P.H.S.]. *American Journal of Obstetrics and Gynecology*, *184*, 637–642.

Grant, K.A., McMahon, C., Austin, M.P., Reilly, N., Leader, L., & Ali, S. (2009). Maternal prenatal anxiety, postnatal caregiving and infants' cortisol responses to the still-face procedure. *Developmental Psychobiology*, *51*, 625–637.

Grizenko, N., Fortier, M.E., Zadorozny, C., Thakur, G., Schmitz, N., Duval, R., & Joober, R. (2012). Maternal stress during pregnancy, ADHD symptomatology in children and genotype: Gene-environment interaction. *Journal of the Canadian Academy of Child and Adolescent Psychiatry*, *21*, 9–15.

Grizenko, N., Shayan, Y.R., Polotskaia, A., Ter-Stepanian, M., & Joober, R. (2008). Relation of maternal stress during pregnancy to symptom severity and response to treatment in children with ADHD. *Journal of Psychiatry and Neuroscience*, *33*, 10–16.

Grote, N.K., Bridge, J.A., Gavin, A.R., Melville, J.L., Iyengar, S., & Katon, W.J. (2010). A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. *Archives in General Psychiatry*, *67*, 1012–1024.

Grzeskowiak, L.E., Gilbert, A.L., & Morrison, J.L. (2012). Neonatal outcomes after late-gestation exposure to selective serotonin reuptake inhibitors. [Research Support, Non-U.S. Gov't]. *Journal of Clinical Psychopharmacology*, *32*, 615–621.

Haberg, S.E., Trogstad, L., Gunnes, N., Wilcox, A.J., Gjessing, H.K., Samuelsen, S.O., … & Stoltenberg, C. (2013). Risk of fetal death after pandemic influenza virus infection or vaccination. *New England Journal of Medicine*, *368*, 333–340.

Harris, J.W. (1919). Influenza occurring in pregnant women: A statistical study of thirteen hundred and fifty cases. *Journal of the American Medical Association*, *72*, 978–980.

Harville, E.W., Xiong, X., & Buekens, P. (2009). Hurricane Katrina and perinatal health. *Birth*, *36*, 325–331.

Henry, C., Kabbaj, M., Simon, H., Le Moal, M., & Maccari, S. (1994). Prenatal stress increases the hypothalamo-pituitary-adrenal axis response in young and adult rats. *Journal of Neuroendocrinology*, *6*, 341–345.

Hockman, C.H. (1961). Prenatal maternal stress in the rat: Its effects on emotional behavior in the offspring. *Journal of Comparative and Physiological Psychology*, *54*, 679–684.

Huizink, A.C., Mulder, E.J., & Buitelaar, J.K. (2004). Prenatal stress and risk for psychopathology: Specific effects or induction of general susceptibility? *Psychological Bulletin*, *130*, 115–142.

Huttunen, M.O., & Niskanen, P. (1978). Prenatal loss of father and psychiatric disorders. *Archives of General Psychiatry*, *35*, 429–431.

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D.S., Quinn, K., … & Wang, P. (2010). Research domain criteria (RDoC): Toward a new classification framework for research on mental disorders. *American Journal of Psychiatry*, *167*, 748–751.

Jensen Pena, C., Monk, C., & Champagne, F.A. (2012). Epigenetic effects of prenatal stress on 11beta-hydroxysteroid dehydrogenase-2 in the placenta and fetal brain. *PLoS ONE*, *7*, e39791.

Jimenez-Solem, E., Andersen, J.T., Petersen, M., Broedbaek, K., Andersen, N.L., Torp-Pedersen, C., & Poulsen, H.E. (2013). Prevalence of antidepressant use during pregnancy in Denmark, a nation-wide cohort study. [Research Support, Non-U.S. Gov't]. *PLoS One*, *8006303*, e63034. doi: 10.1371/journal.pone 0063034

Joffe, J.M. (1965). Genotype and prenatal and premating stress interact to affect adult behavior in rats. *Science*, *150*, 1844–1845.

Kagan, J., Snidman, N., Zentner, M., & Peterson, E. (1999). Infant temperament and anxious symptoms in school age children. *Development andPsychopathology*, *11*, 209–224.

Kammerer, M., Adams, D., Castelberg, B.V., & Glover, V. (2002). Pregnant women become insensitive to cold stress. *BMC Pregnancy Childbirth*, *2*, 8.

Keeley, K. (1962). Prenatal influence on behavior of offspring of crowded mice. *Science*, *135*, 44–45.

Khashan, A.S., Abel, K.M., McNamee, R., Pedersen, M.G., Webb, R.T., Baker, P.N., … & Mortensen, P.B. (2008). Higher risk of offspring schizophrenia following antenatal maternal exposure to severe adverse life events. *Archives of General Psychiatry*, *65*, 146–152.

Kim, P., Leckman, J.F., Mayes, L.C., Feldman, R., Wang, X., & Swain, J.E. (2010). The plasticity of human maternal brain: Longitudinal changes in brain anatomy during the early postpartum period. *Behavioral Neuroscience*, *124*, 695–700.

King, S., Mancini-Marie, A., Brunet, A., Walker, E., Meaney, M.J., & Laplante, D.P. (2009). Prenatal maternal stress from a natural disaster predicts dermatoglyphic asymmetry in humans. *Development and Psychopathology*, *21*, 343–353.

Kirkham, C., Harris, S., & Grzybowski, S. (2005a). Evidence-based prenatal care: Part I. General prenatal care and counseling issues. [Review]. *American Family Physician*, *71*, 1307–1316.

Kirkham, C., Harris, S., & Grzybowski, S. (2005b). Evidence-based prenatal care: Part II. Third-trimester care and prevention of infectious diseases. *American Family Physician*, *71*, 1555–1560.

Kivlighan, K.T., DiPietro, J.A., Costigan, K.A., & Laudenslager, M.L. (2008). Diurnal rhythm of cortisol during late pregnancy: Associations with maternal psychological well-being and fetal growth. *Psychoneuroendocrinology*, *33*, 1225–1235.

Korhonen, M., Luoma, I., Salmelin, R., & Tamminen, T. (2012). A longitudinal study of maternal prenatal, postnatal and concurrent depressive symptoms and adolescent well-being. *Journal of Affective Disorders*, *136*, 680–692.

Kozhimannil, K.B., Adams, A.S., Soumerai, S.B., Busch, A.B., & Huskamp, H.A. (2011). New Jersey's efforts to improve postpartum depression care did not change treatment patterns for women on medicaid. [Comparative Study Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Health Affairs*, *30*, 293–301.

Laceulle, O.M., O'Donnell, K., Glover, V., O'Connor, T.G., Ormel, J., van Aken, M.A., & Nederhof, E. (2013). Stressful events and psychological difficulties: Testing alternative

candidates for sensitivity. *European Child and Adolescent Psychiatry*. Avance online publication. doi: 10.1007/s00787-013-0436-4.

Ladouceur, R., Dugas, M.J., Freeston, M.H., Leger, E., Gagnon, F., & Thibodeau, N. (2000). Efficacy of a cognitive-behavioral treatment for generalized anxiety disorder: Evaluation in a controlled clinical trial. *Journal of Consulting and Clinical Psychology*, *68*, 957–964.

Laplante, D.P., Brunet, A., Schmitz, N., Ciampi, A., & King, S. (2008). Project Ice Storm: Prenatal maternal stress affects cognitive and linguistic functioning in 5 1/2-year-old children. *Journal of the American Academy of Child and Adolescent Psychiatry*, *47*, 1063–1072.

Le, H.N., Perry, D.F., & Stuart, E.A. (2011). Randomized controlled trial of a preventive intervention for perinatal depression in high-risk Latinas. *Journal of consulting and clinical psychology*, *79*, 135–141.

Li, J., Vestergaard, M., Obel, C., Christensen, J., Precht, D.H., Lu, M., & Olsen, J. (2009). A nationwide study on the risk of autism after prenatal stress exposure to maternal bereavement. *Pediatrics*, *123*, 1102–1107.

Li, J., Vestergaard, M., Obel, C., Precht, D.H., Christensen, J., Lu, M., & Olsen, J. (2008). Prenatal stress and epilepsy in later life: A nationwide follow-up study in Denmark. *Epilepsy Research*, *81*, 52–57.

Li, J., Vestergaard, M., Obel, C., Precht, D.H., Christensen, J., Lu, M., & Olsen, J. (2009). Prenatal stress and cerebral palsy: A nationwide cohort study in Denmark. *Psychosomatic Medicine*, *71*, 615–618.

Littleton, H.L., Breitkopf, C.R., & Berenson, A.B. (2007). Correlates of anxiety symptoms during pregnancy and association with perinatal outcomes: A meta-analysis. [Meta-AnalysisResearch Support, N.I.H., Extramural-Review]. *American Journal of Obstetric Gynecology*, *196*, 424–432.

Maccari, S., & Morley-Fletcher, S. (2007). Effects of prenatal restraint stress on the hypothalamus-pituitary-adrenal axis and related behavioural and neurobiological alterations. *Psychoneuroendocrinology*, *32*, S10–S15.

Manber, R. (2010). Acupuncture for depression during pregnancy: A randomized controlled trial. *Obstetrics and Gynecology*, *115*, 511–520.

Marques, A.H., O'Connor, T.G., Roth, C., Susser, E., & Bjorke-Monsen, A.L. (2013). The influence of maternal prenatal and early childhood nutrition and maternal prenatal stress on offspring immune system development and neurodevelopmental disorders. *Frontiers in Neuroscience*, *7*, 120.

Mendelson, T., DiPietro, J.A., Costigan, K.A., Chen, P., & Henderson, J.L. (2011). Associations of maternal psychological factors with umbilical and uterine blood flow. *Journal of Psychosomatic Obstetrics and Gynaecology*, *32*, 3–9.

Monk, C., Fifer, W.P., Myers, M.M., Bagiella, E., Duong, J.K., Chen, I.S., … & Altincatal, A. (2011). Effects of maternal breathing rate, psychiatric status, and cortisol on fetal heart rate. *Developmental Psychobiology*, *53*, 221–233.

Monk, C., Fitelson, E.M., & Werner, E. (2011). Mood disorders and their pharmacological treatment during pregnancy: Is the future child affected? *Pediatric Research*, *69*, 3R–10R.

Monk, C., Georgieff, M.K., & Osterholm, E.A. (2013). Research Review: Maternal prenatal distress and poor nutrition—Mutually influencing risk factors affecting infant neurocognitive development. *Journal of Child Psychology and Psychiatry*, *54*, 115–130.

Monk, C., Myers, M.M., Sloan, R.P., Werner, L., Jeon, J., Tager, F., & Fifer, W.P. (2004). Fetal heart rate reactivity differs by women's psychiatric status: An early marker for developmental risk? *Journal of the American Academy of Child and Adolescent Psychiatry*, *43*, 283–290.

Monk, C., Newport, D.J., Korotkin, J.H., Long, Q., Knight, B., & Stowe, Z.N. (2012). Uterine blood flow in a psychiatric population: Impact of maternal depression, anxiety, and psychotropic medication. *Biological Psychiatry*, *72*, 483–490.

Murray, L., Cooper, P.J., Wilson, A., & Romaniuk, H. (2003). Controlled trial of the short- and long-term effect of psychological treatment of post-partum depression: 2. Impact on the mother-child relationship and child outcome. *British Journal of Psychiatry*, *182*, 420–427.

Nepomnaschy, P.A., Welch, K.B., McConnell, D.S., Low, B.S., Strassmann, B.I., & England, B.G. (2006). Cortisol levels and very early pregnancy loss in humans. [Research Support, Non-U.S. Gov't]. *Proceedings of the National Academy of Sciences of the United States of America*, *103*, 3938–3942.

Neugebauer, R., Kline, J., Stein, Z., Shrout, P., Warburton, D., & Susser, M. (1996). Association of stressful life events with chromosomally normal spontaneous abortion. *American Journal of Epidemiology*, *143*, 588–596.

Obel, C., Hedegaard, M., Henriksen, T.B., Secher, N.J., & Olsen, J. (2003). Psychological factors in pregnancy and mixed-handedness in the offspring. *Developmental Medicine and Child Neurology*, *45*, 557–561.

Oberlander, T.F., Papsdorf, M., Brain, U.M., Misri, S., Ross, C., & Grunau, R.E. (2010). Prenatal effects of selective serotonin reuptake inhibitor antidepressants, serotonin transporter promoter genotype (SLC6A4), and maternal mood on child behavior at 3 years of age. *Archives of Pediatrics and Adolescent Medicine*, *164*, 444–451.

O'Brien, L., Schachtschneider, A.M., Koren, G., Walker, J.H., & Einarson, A. (2007). Longitudinal study of depression, anxiety, irritability, and stress in pregnancy following evidence-based counseling on the use of antidepressants. *Journal of Psychiatric Practice*, *13*, 33–39.

O'Connor, T.G., Bergman, K., Sarkar, P., & Glover, V. (2013). Prenatal cortisol exposure predicts infant cortisol response to acute stress. *Developmental Psychobiology*, *55*, 145–155.

O'Connor, T.G., Caprariello, P., Blackmore, E.R., Gregory, A.M., Glover, V., & Fleming, P. (2007). Prenatal mood disturbance predicts sleep problems in infancy and toddlerhood. *Early Human Development*, *83*, 451–458.

O'Connor, T.G., Heron, J., Golding, J., & Glover, V. (2003). Maternal antenatal anxiety and behavioural/emotional problems in children: A test of a programming hypothesis. *Journal of Child Psychology and Psychiatry*, *44*, 1025–1036.

O'Connor, T.G., Moynihan, J.A., & Caserta, M.T (in press). The Neuroinflammation Hypothesis for Stress and Psychopathology in Children: Developmental Psychoneuroimmunology. *Journal of Child Psychology and Psychiatry*.

O'Connor, T.G., Winter, M.A., Hunn, J., Carnahan, J., Pressman, E.K., Glover, V., … & Caserta, M.T. (2013). Prenatal maternal anxiety predicts reduced adaptive immunity in infants. [Research Support, N.I.H., Extramural]. *Brain, Behavior, and Immunity*, *32*, 21–28.

O'Donnell, K.J., Bugge Jensen, A., Freeman, L., Khalife, N., O'Connor, T.G., & Glover, V. (2012). Maternal prenatal anxiety and downregulation of placental 11beta-HSD2. [Research Support, N.I.H., ExtramuralResearch Support, Non-U.S. Gov't]. *Psychoneuroendocrinology*, *37*, 818–826.

O'Donnell, K.J., Glover, V., Barker, E.D., & O'Connor, T.G. (2013). The persisting effect of maternal mood in pregnancy on childhood psychopathology. *Development and Psychopathology*. Advance online publication.

O'Donnell, K.J., Glover, V., Jenkins, J., Browne, D., Ben-Shlomo, Y., Golding, J., & O'Connor, T.G. (2013). Prenatal maternal mood is associated with altered diurnal cortisol in adolescence. *Psychoneuroendocrinology*. Advance online publication, *38*, 1630–1638.

O'Donnell, K., O'Connor, T.G., & Glover, V. (2009). Prenatal stress and neurodevelopment of the child: Focus on the HPA

axis and role of the placenta. *Developmental Neuroscience*, *31*, 285–292.

Pluess, M., Velders, F.P., Belsky, J., van IJzendoorn, M.H., Bakermans-Kranenburg, M.J., Jaddoe, V.W., … & Tiemeier, H. (2011). Serotonin transporter polymorphism moderates effects of prenatal maternal anxiety on infant negative emotionality. *Biological Psychiatry*, *69*, 520–525.

Raikkonen, K., Seckl, J.R., Pesonen, A.K., Simons, A., & Van den Bergh, B.R. (2011). Stress, glucocorticoids and liquorice in human pregnancy: Programmers of the offspring brain. *Stress*, *14*, 590–603.

Ramchandani, P.G., O'Connor, T.G., Evans, J., Heron, J., Murray, L., & Stein, A. (2008). The effects of pre- and postnatal depression in fathers: A natural experiment comparing the effects of exposure to depression on offspring. *Journal of Child Psychology and Psychiatry*, *49*, 1069–1078.

Rice, F., Harold, G.T., Boivin, J., van den Bree, M., Hay, D.F., & Thapar, A. (2010). The links between prenatal stress and offspring development and psychopathology: Disentangling environmental and inherited influences. *Psychological Medicine*, *40*, 335–345.

Romijn, H.J., Hofman, M.A., & Gramsbergen, A. (1991). At what age is the developing cerebral cortex of the rat comparable to that of the full-term newborn human baby? *Early Human Development*, *26*, 61–67.

Roseboom, T., de Rooij, S., & Painter, R. (2006). The Dutch famine and its long-term consequences for adult health. *Early Human Development*, *82*, 485–491.

Sanchez, M.M., Ladd, C.O., & Plotsky, P.M. (2001). Early adverse experience as a developmental risk factor for later psychopathology: Evidence from rodent and primate models. *Developmental Psychopathology*, *13*, 419–449.

Sandman, C.A., Davis, E.P., & Glynn, L.M. (2012). Prescient human fetuses thrive. *Psychological Science*, *23*, 93–100.

Sarkar, P., Bergman, K., O'Connor, T.G., & Glover, V. (2008). Maternal antenatal anxiety and amniotic fluid cortisol and testosterone: Possible implications for foetal programming. *Journal of Neuroendocrinology*, *20*, 489–496.

Schneider, M.L., Moore, C.F., Kraemer, G.W., Roberts, A.D., & DeJesus, O.T. (2002). The impact of prenatal stress, fetal alcohol exposure, or both on development: Perspectives from a primate model. *Psychoneuroendocrinology*, *27*, 285–298.

Seckl, J.R., & Meaney, M.J. (2004). Glucocorticoid programming. *Annals of the New York Academy of Sciences*, *1032*, 63–84.

Siddique, J., Chung, J.Y., Brown, C.H., & Miranda, J. (2012). Comparative effectiveness of medication versus cognitive-behavioral therapy in a randomized controlled trial of low-income young minority women with depression. *Journal of Consulting and Clinical Psychology*, *80*, 995–1006.

Sockol, L.E. (2011). A meta-analysis of treatments for perinatal depression. *Clinical Psychology Review*, *31*, 839–849.

Spinelli, M.G. (2013). A controlled clinical treatment trial of interpersonal psychotherapy for depressed pregnant women at 3 New York City sites. *Journal of Clinical Psychiatry*, *74*, 393–399.

Stott, D.H. (1973). Follow-up study from birth of the effects of prenatal stresses. *Developmental Medicine and Child Neurology*, *15*, 770–787.

Sullivan, E.L., Smith, M.S., & Grove, K.L. (2011). Perinatal exposure to high-fat diet programs energy balance, metabolism and behavior in adulthood. *Neuroendocrinology*, *93*, 1–8.

Talge, N.M., Neal, C., & Glover, V. (2007). Antenatal maternal stress and long-term effects on child neurodevelopment: How and why? *Journal of Child Psychology and Psychiatry*, *48*, 245–261.

Tegethoff, M., Greene, N., Olsen, J., Schaffner, E., & Meinlschmidt, G. (2011). Stress during pregnancy and offspring pediatric disease: A national cohort study. *Environmental Health Perspectives*, *119*, 1647–1652.

Teixeira, J.M., Fisk, N.M., & Glover, V. (1999). Association between maternal anxiety in pregnancy and increased uterine artery resistance index: Cohort based study. *British Medical Journal*, *318*, 153–157.

Urech, C., Fink, N.S., Hoesli, I., Wilhelm, F.H., Bitzer, J., & Alder, J. (2010). Effects of relaxation on psychobiological wellbeing during pregnancy: A randomized controlled trial. [Randomized Controlled TrialResearch Support, Non-U.S. Gov't]. *Psychoneuroendocrinology*, *35*, 1348–1355.

Van Batenburg-Eddes, T., Brion, M.J., Henrichs, J., Jaddoe, V.W., Hofman, A., Verhulst, F.C., … & Tiemeier, H. (2013). Parental depressive and anxiety symptoms during pregnancy and attention problems in children: A cross-cohort consistency study. *Journal of Child Psychology and Psychiatry*, *54*, 591–600.

Van den Bergh, B.R., Van Calster, B., Smits, T., Van Huffel, S., & Lagae, L. (2008). Antenatal maternal anxiety is related to HPA-axis dysregulation and self-reported depressive symptoms in adolescence: A prospective study on the fetal origins of depressed mood. *Neuropsychopharmacology*, *33*, 536–545.

Wadhwa, P.D., Sandman, C.A., Porto, M., Dunkel-Schetter, C., & Garite, T.J. (1993). The association between prenatal stress and infant birth weight and gestational age at birth: A prospective investigation. *American Journal of Obstetrics and Gynecology*, *169*, 858–865.

Weinstock, M. (2008). The long-term behavioural consequences of prenatal stress. *Neuroscience and Biobehavior Review*, *32*, 1073–1086.

Werner, A., Myers, M.M., Fifer, W.P., Cheng, B., Fang, Y., Allen, R., & Monk, C. (2007). Prenatal predictors of infant temperament. *Developmental Psychobiology*, *49*, 474–484.

Werner, E., Zhao, Y., Evans, L., Kinsella, M., Kurzius, L., Altincatal, A., … & Monk, C. (2012). Higher maternal prenatal cortisol and younger age predict greater infant reactivity to novelty at 4 months: An observation-based study. *Developmental Psychobiology*. Advacnce online publication. doi: 10.1002/dev.21066.

Wilson, C.A., Schade, R., & Terry, A.V., Jr (2012). Variable prenatal stress results in impairments of sustained attention and inhibitory response control in a 5-choice serial reaction time task in rats. *Neuroscience*, *218*, 126–137.

Wright, R.J., Visness, C.M., Calatroni, A., Grayson, M.H., Gold, D.R., Sandel, M.T., … & Gern, J.E. (2010). Prenatal maternal stress and cord blood innate and adaptive cytokine responses in an inner-city cohort. *American Journal of Respiratory and Critical Care Medicine*, *182*, 25–33.

Yehuda, R., Engel, S.M., Brand, S.R., Seckl, J., Marcus, S.M., & Berkowitz, G.S. (2005). Transgenerational effects of posttraumatic stress disorder in babies of mothers exposed to the World Trade Center attacks during pregnancy. *Journal of Clinical Endocrinology and Metabolism*, *90*, 4115–4118.

Yonkers, K.A. (2013). The possible effects of depressive symptoms on risk of preterm birth are clouded by lack of control over confounding factors. *Evidence Based Medicine*. Advanced online publication. doi: eb-2012-101136 [pii]10.1136/eb-2012-101136.

Yonkers, K.A., Wisner, K.L., Stewart, D.E., Oberlander, T.F., Dell, D.L., Stotland, N., … & Lockwood, C. (2009). The management of depression during pregnancy: A report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. *General Hospital Psychiatry*, *31*, 403–413.

Zuena, A.R., Mairesse, J., Casolini, P., Cinque, C., Alema, G.S., Morley-Fletcher, S., … & Maccari, S. (2008). Prenatal restraint stress generates two distinct behavioral and neurochemical profiles in male and female rats. *PLoS ONE*, *3*, e2170.

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