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

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Abstract

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.

Method—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, 2005b). Accordingly, prenatal care is multi-faceted, and detailed, and incorporates knowledge derived from genetics, nutrition, environmental health, and immunology, among other fields. The current practitioner review focuses on one component

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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 symptoms¹ 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, & Reusing, 2006) for contradictory results). These findings derive additional heft from nearly fifty 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 pre-clinical 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; K. 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 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 thirty 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 a better understanding of etiology informed by a conceptual shift that is the foundation of this research, e.g, neurobehavioral development begins 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 (P. D. Gluckman, Cutfield, Hofman, & Hanson, 2005), research on maternal prenatal distress may hold clues for the

¹To date, child outcomes have been linked to maternal prenatal stress, depression, and anxiety and there is not yet specificity, e.g., unique maternal mood associated with distinct child outcomes. 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.

characterization of novel environmental influences on child behavioral, emotional, cognitive, and neuroendocrine outcomes. That, 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 (P. Gluckman, & Hanson, M., 2005), though sometimes fails to do so when there is discordance between the pre- 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 carry-over 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. That 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. But, perinatal psychiatry remains a sub-discipline 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 multi-disciplinary model and research method. That is 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, multi-disciplinary 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; under-emphasizing 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 pre- versus postnatal stressors across species. That is 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). That 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 work 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 versus emotional stress, Tegethoff et al., 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. That 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, i.e., 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). That 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, Chic-Demet, & Sandman, 2001; Kammerer, Adams, Castelberg Bv, & 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, Greene, Olsen, Schaffner, & Meinlschmidt, 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, Bretkopf, & 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 et al., 2006; DiPietro, Costigan, Nelson, Gurewitsch, & Laudenslager, 2008; Monk, Fifer, Myers, Bagiella, Duong, Chen, Leotti, & Arman, 2011; Monk et al., 2004). 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 (E. P. 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 et al., 2013; Wright et al., 2010); findings concerning neurological disorders are mixed but provocative (Li, Vestergaard, Obel, Christensen, et al., 2009; Li et al., 2008; 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 (K.J. O'Donnell et al., in press; Van den Bergh, et al., 2008). That is consistent with, but does not confirm, the program-ability of these outcomes from prenatal maternal anxiety. Lastly, there is some suggestion that the effects may be moderated, for some outcomes, by quality of early care (Bergman, Sarkar, Glover, & O'Connor, 2010b). That 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). Furthermore, 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., in press; 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, e.g., 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 is to examine effect sizes, which are perhaps most easily understood where the scale is familiar, e.g., 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 (K.J. O'Donnell, Glover, Barker, & O'Connor, in press). 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). Additionally, 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 (A. Werner et al., 2007), to high reactive infant temperament (P. E. Davis et al., 2004) (E. 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 11 β HSD2 to increase fetal exposure to glucocorticoids (K. J. 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 (L. M. 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., 2010b; E. P. Davis & Sandman, 2010). That 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, e.g., 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, Myers, Bagiella, Duong, Chen, Leotti, & Altincatal, 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; Nepomnaschy et al., 2006; Neugebauer et al., 1996; Wadhwa, Sandman, Porto, Dunkel-Schetter, & Garite, 1993) (Harris, 1919), may alter fetal development. More specifically, in animal models, inflammation in pregnancy has been repeatedly linked with disrupted brain development; perhaps related to that 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. 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; K. J. 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). That contrasts 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. That is 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. (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 over-stated (Van Batenburg-Eddes et al., 2013); however, that 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 (K.J. O'Donnell, Glover, Jenkins, et al., in press). 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 than in the early postpartum period, e.g., (J. Evans, Heron, Francomb, Oke, & Golding, 2001). That is a significant counter-weight to the traditional focus on post-partum 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 paper, 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. That may be influenced, in part, by a predominant influence and wide-spread availability of anti-depressant 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, i.e., 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. That 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). That 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, Goodman et al., 2013) 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.

A 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, a first question to ask is if there is reason to believe that treatment success would be any different in pregnant compared to non-pregnant 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 non-supportive 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 “non-traditional” 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 non-traditional 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. That is also the basis 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 under-developed. 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 needed 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, 2010a), 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 pre or peri-natal 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, pre-term 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. That 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 interpersonal psychotherapy (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, & Joobar, 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 psychobiological 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.