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Developmental implications of maternal antenatal anxiety mechanisms and approaches to intervention

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ABSTRACT

This paper aims to examine the neurodevelopmental and psychosocial outcomes of infants born to mothers with antenatal anxiety and determine whether perinatal interventions can mitigate the negative effects of maternal anxiety.

1 Introduction

Maternal antenatal anxiety involves a spectrum of experiences including transient mood disturbance, mood change in response to a defined stress or multiple cumulative stressors, personality-based or trait anxiety, and clinical diagnoses of anxiety disorder. These various experiences of anxiety, generally measured by self-report questionnaire, have been associated with measurable effects on the infant in utero and with later emotional, cognitive, and behavioural effects on the infant/child (Glover, 2011; Talge, Neal, & Glover, 2007). This link between antenatal maternal anxiety and later infant or child outcomes persists after controlling for obstetric complications and/or depression, and also complications in the postnatal period including continuing or new onset maternal anxiety and/or depression (Van Den Bergh, Mulder, Mennes, & Glover, 2005). Importantly, when there is comorbid depression and/or obstetric complications then child developmental outcomes may be further compromised. Whilst the impact of prenatal maternal anxiety on foetal development does not occur in every case it is estimated that the attributable load of behavioural/emotional problems in the population due to maternal prenatal anxiety is 10–15% (Glover, 2015).

2 Effects of maternal antenatal anxiety on infants and children

(1) Foetal arousal and physiology: Obstetricians have long used foetal heart rate (FHR) monitoring to assess foetal well-being. Certain characteristics of foetal heart monitoring, including basal heart rate, variability, and response to stimuli and activity, have been extensively studied and are known to change with increasing gestation as the foetal nervous system matures. During normal maturation, FHR decreases linearly from 20 weeks to term and short-term FHR variability increases. There is reduced but more vigorous behaviour and increased coupling of FHR and foetal movement during gestation (DiPietro, Hodgson, Costigan, Hilton, & Johnson, 1996). Higher levels of coupling are associated with improved neural integration at birth (DiPietro et al., 2010). The effects of maternal anxiety are evident during gestation; the foetuses of anxious mothers show reduced FHR variability (DiPietro et al., 1996), higher activity levels (DiPietro et al., 2002), and reduced foetal movement–FHR coupling (DiPietro et al., 1996). These are thought to reflect delay in maturation of foetal neurological development.

(2) Preterm Birth (PTB): Antenatal maternal anxiety is associated with increased rates of spontaneous preterm births (less than 37 weeks) (Dancause et al., 2011; Glynn, Wadhwa, Dunkel-Schetter, Chicz-Demet, & Sandman, 2001; Pavlov, Steiner, Kessous, Weintraub, & Sheiner, 2014). PTB is a rising international public health problem and economic burden. Rates of PTB in Australia hover around 10% and have been rising at a rate of about 1.1% per year in the developed world (Blencowe et al., 2012) over the last two decades. Hospital care of premature infants represents half of all infant costs (on average US$32,325 compared to US$3,325 for full-term infants in 2004; Institute of Medicine (US), 2007). The prognosis for these infants is poor, with spontaneous preterm birth...
responsible for 30% of neonatal deaths (Mathews & MacDoman, 2002). An estimated 50–70% of premature infants with birth weight less than 1500g have later dysfunctions, such as learning disabilities, attention problems, autism spectrum disorders, respiratory illnesses, cognitive deficits, psychiatric disorders, neuropsychological deficits, and behavioural problems (Aylward, 2002).

(3) **Infant temperament**: Using objective measures of infant temperament, two large studies have shown a link between maternal antenatal anxiety and infant temperament. Huizink and colleagues (Huizink, De Medina, Mulder, Visser, & Buitelaar, 2002) showed an association between maternal pregnancy related anxiety and reduced attention regulation at 3 and 8 months and Bergman and colleagues (Bergman, Sarkar, O’Connor, Modi, & Glover, 2007) demonstrated a relationship between stressful life events score when the infant was 14–19 months old. More recently, Zhu and colleagues (Zhu et al., 2014) found 16–18 month old infants of mothers (exposed to stressful life events in the first trimester) showed less optimal behavioural response as measured on the Toddler Temperament Scale, than that of infants whose mothers were not exposed. However, another study (DiPietro, Novak, Costigan, Atella, & Reusing, 2006) found no relationship between maternal anxiety and infant temperament at 2 years old.

(4) **Child emotional and behavioural development**: Studies following up children of mothers with antenatal anxiety have shown an association between antenatal anxiety and total problem behaviour at 27 months (Gutteling et al., 2005), 4 years (O’Connor, Heron, Goldberg, Beveridge, & Glover, 2002), and at 81 months (O’Connor, Heron, Goldberg, & Glover, 2003). Maternal anxiety has also been linked to hyperactivity/inattention (in boys only) (Loomans, Van Der Stelt, Van Eijsden, Gemke, & Vrijkotte, 2012) and externalizing problems at 8–9 years (Van Den Bergh & Marcouen, 2004); anxiety in children aged 6–9 years (Davis & Sandman, 2012), internalizing difficulties in 7–8-year-olds (Barker, Jaffee, Uher, & Maughan, 2011), and depressive symptoms in adolescence (Huizink et al., 2007). In addition, Betts and colleagues (Betts, Williams, Najman, & Alati, 2014) have shown that the combination of maternal antenatal depressive, anxiety, and stress symptoms are associated with greater levels of internalizing problems in offspring when aged 14 years.

(5) **Impact on caregiving and parenting**: There is an emerging understanding of the significant changes that occur during brain functioning during the transition to parenting and their importance for the quality of attachment (Kim, Strathearn, & Swain, 2016). Enquiry into the neurobiological impact of antenatal anxiety and maternal psychopathology on parenting behaviour is also an emerging field of study. At a brain level, caregiving involves a complex interactions of systems mediating attachment behaviours, affective processing and response, and processes involved in affect regulation. Neurobiological changes post-delivery, including both hormonal and neurotransmitter changes, impact directly on brain circuitry in sensitivity of maternal response. There is also emerging evidence that maternal psychopathology, particularly the impact of stress related hormones on circuitry central to hormonal regulation, may have a disruptive impact on caregiving behaviours (Moses-Kolko, Homer, Phillips, Hipwell, & Swain, 2014). Postnatal depression as a form of maternal psychopathology has been widely studied, with brain imaging studies indicating a dampened or reduced neural response in the emotional regulation circuits in depressed mothers (Moses-Kolko et al., 2014). Similarly, in studies of PTSD, associations have been found with heightened neural response to infants in the emotion regulation circuits. Inslicht and colleagues (Inslicht et al., 2013) found heightened sub-cortical responses in the fear circuitry in the brains of women with PTSD secondary to adult interpersonal violence. These reports suggest that there is a need to be more mindful of the complex interplay between antenatal and postnatal factors in modelling the functioning of the maternal brain and caregiver behavioural system. The study of the neurobiology of parenting disturbance, particularly the transgenerational transmission of impaired caretaking behaviours (Newman, Harris, & Allen, 2011; Swain, Dayton, Kim, Tolman, & Volling, 2014), is of potentially considerable importance in elucidating these patterns.

(6) **Developmental problems and cognitive functioning**: Studies have shown a relationship between maternal anxiety and lower mental development index (MDI) and psychosocial development index (PDI) scores on the Bayley Scales of Infant Development at 8 months (Buitelaar, Huizink, Mulder, De Medina, & Visser, 2003); stressful life events and lower MDI score at 14–19 months (Bergman et al., 2007); stressful life events and lower MDI
3 How does antenatal maternal anxiety affect developmental outcomes?

The mechanisms underlying the association between maternal antenatal anxiety and developmental outcomes are not fully elucidated. Many propose that this is an example of the developmental origins of health and disease (DOHaD) hypothesis (Gluckman, Hanson, & Mitchell, 2010), which suggests that adaptations made by the developing foetus to a detrimental intra-uterine environment (e.g. resulting from maternal anxiety) lead to permanent changes in structure and function. Increasingly, interest has focused on whether the effects of maternal stress-related hormones on foetal development either through direct effects on brain cells, or through effects on programming of certain biological systems responsible for the regulation of foetal development, explain these developmental outcomes. It is suggested that the mechanisms underlying these effects are associated with or mediated by epigenetic regulation (Babenko, Kovalchuk, & Metz, 2015), i.e. alterations in gene function in the absence of changes in the DNA sequence (due to DNA methylation, histone modifications, or non-coding RNAs).

Research has focused on the placenta, in particular on the function of the glucocorticoid genes in the placenta, as the placenta plays an important role in protecting the foetus from the mother’s cortisol through the expression of the inactive enzyme 11-beta hydroxysteroid dehydrogenase type 2 (11β-HSD2). It has been suggested that reduced enzyme expression in this pathway, leaving the foetus vulnerable to the mother’s circulating stress hormones, is the key epigenetic mechanism explaining neurodevelopmental outcomes of infants of mothers with antenatal anxiety.

Studies have demonstrated that maternal anxiety does effect placental 11β-HSD2 expression. One study showed increased placental 11β-HSD2 methylation following exposure to maternal anxiety (Conradt, Lester, Appleton, Armstrong, & Marsit, 2013) and another has shown an association between maternal trait and state anxiety and reduced placental 11β-HSD 2 expression (O’Donnell et al., 2012). Most recently, Monk and colleagues (Monk et al., 2016) have not only demonstrated a relationship between maternal mood and placental DNA methylation of the gene that codes for 11β-HSD2 but have also shown a link

score at 16–18 months (Bergman et al., 2007); maternal anxiety and lower MDI at 1 and 2 years old (Brouwers, Van Baar, & Pop, 2001); maternal exposure to catastrophic event during pregnancy and lower productive language scores, less time in productive play, and more time in stereotyped play at 2 years old (Laplanche et al., 2004); poorer verbal intelligence and language skills at 5 1/2 years old (Laplanche, Brunet, Schmitz, Ciampi, & King, 2008); maternal anxiety and altered cognitive control in 5 year olds (Loomans et al., 2012); maternal anxiety, lower visual working memory performance, and (in girls only) lower inhibitory control at 6–9 years old (Buss, Davis, Hobel, & Sandman, 2011); maternal anxiety and impulsive response pattern on cognitive tasks and lower scores on two intelligence subtests at 14/15 years old (Seebach et al., 2005); maternal anxiety and lower scores on tasks of cognitive control (Mennes, Stiers, & Lagae, 2006); and less efficient pattern of decision making on endogenous control tasks at 17 years old (Mennes, Van Den Bergh, Lagae, & Stiers, 2009).
with foetal coupling, an index of foetal neurodevelopment. Greater methylation of the gene, and so more foetal cortisol exposure, was significantly associated with less foetal coupling. These researchers also demonstrated an effect of maternal distress on a second placental glucocorticoid-related gene FKBP5 which decreases the binding of cortisol to its receptor. Maternal distress was associated with increased placental DNA methylation of FKBP5 and this, in turn, predicted reduced foetal coupling.

Whilst cortisol is essential for normal brain development, exposure to excessive amounts may have profound effects on the developing brain; it can modify cell proliferation and differentiation and synaptic development in various brain regions. Foetal brain exposure to elevated levels of glucocorticoids transmitted across the placenta, at these early stages of brain change and adaptation, may be an important factor in explaining neurodevelopmental outcomes of infants exposed to maternal anxiety when in utero.

Excess cortisol present during specific sensitive developmental periods may disturb the programming of certain biological systems important to regulation of the infant stress response and social cognition and engagement. For example, animal and human studies have shown that DNA methylation at birth in the cortisol-binding glucocorticoid receptor (NR3C1) and the cortisol-inactivating enzyme 11B-HSD2 – genes central to the stress response pathway – can be influenced by maternal anxiety and depression (Conradt et al., 2013; Hompes et al., 2013; Oberlander et al., 2008; Radtke et al., 2011). Increased methylation of these genes is correlated with increased saliva cortisol stress response in infants (Oberlander et al., 2008) in infants. If the stress response pathway (the HPA axis) is programmed in response to early exposure to cortisol in the antenatal period, this may account for the persistent effects into adulthood (O’Connor et al., 2003).

Maternal anxiety may have a powerful effect on parenting, and this can further contribute adversely to a child’s development. Anxiety during pregnancy is often focused on the experience of pregnancy itself, with concerns about foetal well-being and the forthcoming tasks of parenting. In obsessive compulsive disorder for example, the pregnant woman may experience specific concerns about harm and contamination of the developing foetus and these may further develop when she attempts to care for the newborn. Anxiety is commonly experienced about the capacity to parent and to tolerate the dependency of the infant. These anxieties will clearly impact on the attachment relationship with the infant and the quality of early emotional interaction. It is this pathway that appears to be particularly significant when considering neonatal outcome in cases of maternal antenatal anxiety.

From a psychological perspective, high levels of maternal anxiety may be seen as disrupting parental reflective functioning which is defined as the capacity to focus on and understand the inner world and mental states of the infant in an empathic way (Fonagy, Gergely, Jurist, & Target, 2002). Anxious parents are more likely to misinterpret infant emotional communication in a negative fashion and to lack confidence in their own ability to understand their infant’s signals. This in turn results in the infant experiencing the carer as misattuned or non-validating which, for the infant, is a high-stress situation. Longitudinal developmental studies of maternal anxiety find increased levels of anxiety and stress-related disorders in children and also in broad symptoms related to attachment insecurity. In parents with higher levels of sensitivity, the impact of prenatal anxiety on infant outcome is moderated when compared to low-sensitivity mothers. Maternal sensitivity moderates the impact of antenatal anxiety on infant outcomes (Grant, McMahon, Reilly, & Austin, 2010a, 2010b; Kaplan, Evans, & Monk, 2008).

There is currently limited longitudinal data exploring the mechanism around the buffering effect of parental sensitivity when looking at child outcomes. The capacity of the more sensitive parent to recognise and respond appropriately to the infant’s distress, and to interact with the infant in a way that contains the infant’s anxiety, appears to be an important early mechanism in understanding variation in developmental outcome (Grant et al., 2010a). The quality of early interaction and care of the infant is a major factor in promoting emotional and stress regulation and establishes the basis for the organisation of the attachment relationship (Conradt & Ablow, 2010).

4 What can be done to mitigate the effects of maternal antenatal anxiety on the foetus?

Current clinical guidelines (Australian Health Ministers’ Advisory Council, 2014; National Institute for Health and Care Excellence (NICE), 2014) suggest that both maternal anxiety and depression when present during pregnancy should be the subject of targeted support and intervention. Whilst it is clear that clinical levels of depression may respond to and warrant biological treatment such as antidepressants, there are no randomized controlled trials (RCTs) demonstrating the efficacy of these medications for the treatment of prenatal depression. Rather, it has been assumed that antidepressants have similar benefits for the treatment of women who are depressed when pregnant as for those who are depressed at other periods during their life. Furthermore, it has been shown that relapse rates amongst pregnant women who discontinue antidepressants are far greater than those who maintained their pre-pregnancy antidepressant
treatment (68 vs 26%) (Cohen et al., 2006) and these rates are similar to those reported in non-gravid samples (Kupfer et al., 1992).

A similar situation exists for anxiety. There are no RCTs examining the benefits of anxiolytic and antidepressant medications for clinical levels of anxiety as inclusion of pregnant women in such studies is not considered to be ethical. But, as with depression, clinicians expect that response rates would be similar in pregnant and non-gravid women. The use of psychological and psychosocial treatments in prenatal anxiety disorders is currently under-researched. The available literature supports a variety of approaches aimed at improving the mother’s anxiety tolerance and teaching anxiety regulation techniques. Approaches that have been used include mindfulness-based therapy (Woolhouse, Mercuri, Judd, & Brown, 2014), meditation approaches (Chan, 2014), and cognitive behaviour therapy (Austin et al., 2008).

There are small-scale studies looking at neonatal outcomes following these supportive and psychological interventions which are suggestive of improved neonatal outcome where treatment is offered compared to control groups (Chan, 2014). Further research in this area is urgently needed, particularly to more clearly determine the beneficial effects of these interventions for both mother and for neonatal outcomes.

The findings of Monk and colleagues (Monk et al., 2016) suggest that one focus of interventional research should be to determine whether early effective therapies for maternal anxiety can mitigate the methylation patterns of stress-regulating genes in the placenta and, in turn, the developmental outcomes of children. Research is currently being developed to trial brief interventions for antenatal anxiety with the important component of linking service delivery to routine antenatal care (Wilkinson et al., 2016). This is an RCT using cognitive behaviour therapy principles focused on transition to parenthood and the management of antenatal anxiety symptoms. This will be a valuable contribution to thinking about appropriate ways of supporting women who might be identified as suffering from significant levels of antenatal anxiety.

Disclosure statement
No potential conflict of interest was reported by the authors.

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Angela Komiti is a research psychologist and Project Coordinator of the Building Early Attachment and Resilience (BEAR) study which is researching effective early interventions for parents at risk of attachment difficulties with their infants. The study is joint project between the Centre for Women’s Mental Health, Royal Women’s Hospital, the Department of Psychiatry University of Melbourne and The Mental Health Foundation of Australia. She has worked in the field of anxiety and depression research over the last 20 years.

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