ARTICLE

Worry about worrying

Melanie Gunning examines maternal anxiety in pregnancy

The effects of anxiety in pregnancy on fetal and postnatal development are of concern for most women who are, or have been, pregnant. But how are the effects transmitted to the growing fetus, and does the research evidence actually support the media scare stories? And, intriguingly, could a moderate amount of worry actually be good for the developing baby?

question

What are the physiological and psychological routes through which relationship stress in pregnancy may impact on the developing fetus and infant?

resources

Talge, N.M., Neal, C., Glover, V. & the Early Stress, Translational Research and Prevention Science Network (2007). Antenatal maternal stress and long-term effects on child neurodevelopment: How and why? *Journal of Child Psychology and Psychiatry, 48*(3/4), 245–261.

Pregnancy tends to be a time of happy expectations, but this experience is also coloured by anxieties about the developing baby, the birth, and the changes the new arrival will bring. These normal worries may well be magnified by the media headlines maternal stress attracts: 'Stress during pregnancy harms babies' brains' (*Daily Mail*, 26 January 2006), 'Can maternal anxiety lead to ADHD?' (*The Times*, 19 June 2006), 'Hyperactivity linked to stress in pregnancy' (*The Independent*, 1 June 2002), and many more over recent years. A researcher who has published widely in this area, Janet DiPietro, has said that:

> Articles in magazines and newspapers often perpetuate this belief, thus (ironically) exacerbating stress in pregnant women...
> (DiPietro, 2002, p.1)

In a similar vein, mothers-to-be are faced with an overwhelming volume of information on the 'what not to do' of pregnancy. The possibilities for provoking anxiety and guilt are enormous. The clinician Margaret Oates, consultant in prenatal psychiatry at Queen's Medical Centre and senior lecturer in psychiatry at the University of Nottingham, has written:

> The modern Western pregnant woman must not drink more than four cups of coffee a day, drink alcohol, smoke cigarettes, change cat litter trays, eat soft cheese, uncooked eggs or packaged salads or go into the lambing sheds. They should not work too hard or too long, nor at night or be ambivalent about their pregnancies. Now it seems they must not become anxious either.
> (Oates, 2002, p.478)

I study this area of developmental psychology because I am interested in the importance of early mother–baby interactions for long-term development. In the past I have been involved in research investigating maternal postnatal depression and its impact on communication. More recently, I have begun looking into the antenatal predictors of postnatal communication patterns. This article stems from my research into fetal behaviour and postnatal development, and from my current work for the Centre for Integrated Healthcare Research (Queen Margaret University, Edinburgh). The Centre has a focus on the implications and applications of research for practice, encouraging me to think about how this research is presented to the public.

The fetal programming hypothesis

The hypothesis that the mood state of the mother or events that occur during the pregnancy may affect the fetus is not new. One quotation cited in the literature dates back to 500BC.

> The daughter of Virata...[was] exceedingly afflicted by the grief on account of the death of her husband... They all feared that the embryo in her womb might be destroyed.
> (From *The Mahabharat*, quoted in DiPietro et al., 2006, p.573)

More recently though, the number of research articles alerting us to the negative consequences of maternal anxiety in pregnancy has expanded rapidly. In fact ,the subject has warranted eight review papers published over only the last five years summarising the wealth of information that has accumulated (the most recent of which being Talge et al., 2007). Taken together the evidence

references

Barker, D.J.P. (1998). In utero programming of chronic disease. *Clinical Science, 95*, 115–128.

Benediktsson, R., Calder, A.A., Edwards, C.R. & Seckl, J.R. (1997). Placental 11 beta-hydroxysteroid dehydrogenase: a key regulator of fetal glucocorticoid exposure. *Clinical Endocrinology 46*, 161–166.

Bergman, K.,Sarkar, P., O'Connor, T. et al. (2007). Maternal stress during pregnancy predicts cognitive ability and fearfulness in infancy. *Journal of the American Academy of Child and Adolescent Psychiatry. 46*, 1454–1463.

Berkowitz, G.S., Wolff, M.S., Janevic, T. M. & Holzman, I.R. (2003). The World Trade Center disaster and intrauterine growth restriction. *Journal of the American Medical Association, 290*, 595–596.

Brouwers, E., van Baar, A. & Pop, V. (2001). Maternal anxiety during pregnancy and subsequent infant development. *Infant Behavior and Development, 24*, 95–106.

Davis, E.P., Snidman, N., Wadhwa, P.D. et al. (2004). Prenatal maternal anxiety and depression predict negative behavioral reactivity in infancy. *Infancy, 6*, 319–331.

DiPietro, J. (2002). Prenatal/perinatal stress and its impact on psychosocial child development. In R.E. Tremblay, R.G. Barr & R. DeV. Peters (Eds.) *Encyclopedia on early childhood development* [online]. (pp.1–5). Montreal: Centre of Excellence for Early Childhood Development.

DiPietro, J.A., Novak, M.F.S., Costigan, K.A. et al. (2006). Maternal psychological distress during pregnancy in relation to child

suggests that stress experienced by the mother in pregnancy will have adverse developmental consequences for the fetus, newborn, child and adolescent. Gestational stress has been associated with more activity in the fetus, higher rates of premature birth and low birthweight, and increased rates of emotional regulation disturbances in children.

The theory behind this literature is that the health of offspring is influenced by processes originating in the antenatal period. These influences have been described as having 'programming' properties – a specific stimulus or insult during this critical antenatal period may lead to developmental adaptations that permanently change structure, physiology and metabolism, and may lead to pathological conditions later in life. The Barker Hypothesis (Barker, 1998) is generally considered the starting point for widespread interest in this body of research. Barker states that the ponderal index (the weight to length ratio) is determined by factors influencing the intra-uterine environment and is a risk factor for the adult onset of heart disease, diabetes and obesity.

The accumulated evidence now suggests that maternal stress and anxiety in pregnancy can also be considered a potential programming influence. As we will see, maternal stress and anxiety result in changes in the intra-uterine environment to which the fetus adapts at a neurological level, and are associated with a range of negative outcomes.

Transference of the maternal stress response to the fetus

So, how does the mother's experience of anxiety or stress affect the developing fetus? The mechanisms are not yet fully understood; however, the suggested mechanisms that are most widely cited to explain how the effects of maternal anxiety can be transferred to the fetus are clustered around the role of the maternal and fetal hypothalamic-pituitary-adrenal axis (HPA-axis). This influence may occur via transplacental transport of stress hormones; via placental production of stress hormones; or via restriction of uterine blood flow resulting in mild hypoxia (or by a combination of these routes).

Anxiety and the stress response involve both a mental and a physical component. The experience of anxiety and associated stress states in general is associated with increased activity in the HPA-axis. The body's first responses to stress include the release of the catecholamine hormones and the glucocorticoid hormones (the 'stress hormones' such as cortisol and adrenocorticotrophin, or ACTH). The interactions between the hypothalamus, pituitary gland and adrenal glands act to balance hormone release and regain homeostasis.

During pregnancy, levels of circulating maternal cortisol and ACTH rise naturally to values in the range seen in Cushing's syndrome (an endocrine disorder caused by high levels of cortisol in the blood). The causes of these increases include the placental production of corticotrophin-releasing hormone (CRH) and ACTH, desensitisation of the pituitary to the cortisol feedback system, and enhanced pituitary responses to corticotrophin-releasing factors such as CRH.

The fetus is relatively protected from the rises in circulating stress hormones by the action of 11 beta hydroxysteroid dehydrogenase 2 (11 beta-HSD 2) in the placenta, which converts active cortisol into inactive cortisone. However, despite this mechanism, the correlation between maternal and fetal cortisol levels has been reported to be $r = .63$, and the quantity of maternal cortisol reaching the fetus accounts for some 40 per cent of the variance in fetal concentrations (Gitau et al., 1998). Interestingly, there are also reports of individual differences in placental efficiency (Benediktsson et al., 1997), suggesting that there may be variations in the effectiveness of the placenta's protective function.

At the same time as the placenta produces 11 beta-HSD 2, it is also responsible for exposing the fetus to higher levels of circulating glucocorticoids via the expression of placental CRH and ACTH. A positive feedback loop acts to stimulate the placental production of CRH and ACTH in response to increased levels of these hormones at either the maternal or the fetal side of the placenta. Increases in maternal stress hormones associated with increased anxiety and stress may activate this system, increasing the fetus's exposure to high levels of stress hormones.

Maternal stress and anxiety may also act to restrict the supply of blood to the fetus via the uterine artery. This effect has been documented by Teixeira et al. (1999), who reported that women scoring high in anxiety at 28–32 weeks had a reduced arterial resistance index. Restricted blood supply to the fetus may also invoke a stress response in the fetus and fetal HPA-axis resulting in an activation of the placental feedback loop and higher circulating levels of glucocorticoids. However, a study by Kent et al. (2002), with first-time mothers

development at age two. *Child Development, 77*(3), 573–587.
Fujioka, T., Sakata, Y., Yamaguchi, K. et al. (1999). The effects of prenatal stress on the development of hypothalamic paraventricular neurons in fetal rats. *Neuroscience 92*, 1079–1088.
Gitau, R., Cameron, A., Fisk, N.M. & Glover, V. (1998). Fetal exposure to maternal cortisol. *The Lancet, 352*, 707–708.
Glover V. (2002). Response to 'Prenatal/perinatal stress and its impact on psychosocial child development' by Dr Janet DiPietro. In R.E. Tremblay, R.G. Barr & R.DeV. Peters (Eds.) *Encyclopedia on early childhood development* [online]. Montreal: Centre of Excellence for Early Childhood Development.
Glover, V. & O'Connor, T. (2006). Maternal anxiety: Its effect on the fetus and the child. *British Journal of Midwifery, 14*(11), 663–667 .
Hedegaard, M., Henriksen, T.B., Sabroe, S. & Secher, N.J. (1993). Psychological distress in pregnancy and preterm delivery. *British Medical Journal, 240*, 234–239.
Huizink, A.C., Mulder, J.H. & Buitelaar, J.K. (2004). Prenatal stress and risk for psychopathology: Specific effects or induction of general susceptibility? *Psychological Bulletin 130*(1), 115–142.
Huizink, A., Robles de Medina, P., Mulder, E. et al. (2002). Psychological measures of prenatal stress as predictors of infant temperament. *Journal of the American Academy of Child and Adolescent Psychiatry, 41*,1078–1085.
Kent, A., Hughes, P., Ormerod. L. et al.

only and using a different measure of anxiety at 20 weeks, failed to replicate this finding.

These mechanisms are not straightforward and are probably aided by sympathetic adrenal medullary (SAM) pathways with effects at the level of the vascular system. The activity of the HPA-axis and the SAM system, it is thought, may exert programming effects at the level of fetal brain development. For instance, stress hormones have been implicated in animal models showing disturbances of neurogenesis and synaptogenesis in the hippocampus and the prefrontal cortex (Roberts et al., 2004).

The evidence

The evidence for the programming effects of maternal anxiety has largely come from animal models using rodents and non-human primates, as well as from the study of human offspring and fetal development.

In brief, the evidence from rodent research has been relatively consistent, showing altered behavioural, learning and motor outcomes for pups of stressed mothers. However, the types of stressors that rats are exposed to (restraint, cold, unpredictable shocks) are generally physical in origin and may not equate well with the human experience. Research using non-human primates, however, also shows impaired behavioural, learning and motor outcomes for offspring of stressed mothers (see Huizink et al., 2004).

The evidence from human research can be broadly split into three areas, addressing (a) the fetal period, (b) perinatal outcomes, and (c) the postnatal period.

Evidence from the fetal period is somewhat equivocal and is complicated by the types of anxiety measures used and the outcomes measured. In general, studies investigating the first trimester have not tended to show any relationship between maternal anxiety and fetal behaviour. In later pregnancy, studies using measures of state and trait anxiety, or measures of perceived stress or emotional intensity, have found that fetuses of more anxious mothers tend to be more active (Van den Bergh, Mulder et al., 2005).

A large number of studies have reported a relationship between anxiety in pregnancy and perinatal outcomes such as premature birth or low birthweight (see Mulder et al., 2002). These studies vary between those which utilise questionnaire measures of stress or anxiety and those assessing the impact of exposure to stressful events. For example, Hedegaard et al. (1993) found that raised maternal stress in late pregnancy was associated with preterm delivery (<37 weeks), while Berkowitz et al. (2003) and Lederman et al. (2004) have reported reduced birthweights for infants of women near the site of the World Trade Center during the 9/11 terrorist attacks. A recent meta-analysis of the effects of general anxiety on birth outcomes, however, found only a small, unreliable effect size for the association between general maternal anxiety and perinatal outcomes (Littleton et al., 2006). While this recent analysis may temper earlier findings, it does not address the effects of marked anxiety or the longer-term associations that have been reported.

> "Could a moderate level of anxiety in pregnancy actually be beneficial?"

Prospective studies examining outcomes in the newborn period, infancy, childhood and adolescence suggest impaired behavioural regulation. For instance, studies using observer-based assessments report that antenatal maternal anxiety is associated with poor scores on behavioural assessments in the newborn period (e.g. Brouwers et al., 2001; Rieger et al., 2004), ratings of difficult temperament in infancy (Davis et al., 2004; Huizink et al., 2002), teacher/observer/ mother/self ratings of attentional problems or hyperactivity in childhood (O'Connor et al., 2002; Van den Bergh & Marcoen, 2004), and impaired processing and reaction times on computerised task in adolescence (Van den Bergh, Mennes et al., 2005). This literature has been reviewed by Van den Bergh, Mennes et al. (2005) and by Talge et al. (2007), with both papers concluding that there is a consensus in the literature.

The implications of this research have been reported in particular by Vivette Glover's group at the Institute of Reproductive and Developmental Biology, Imperial College London. By one analysis, up to 11 per cent of preterm births (that's around 1500 UK births) per year may be attributed to seriously stressful events in pregnancy (Glover, 2002). Furthermore, O'Connor et al. (2002) have reported that children of mothers who scored in the top 15 per cent for anxiety during pregnancy are at double the risk for later ADHD in childhood. These striking findings have naturally led to calls for the development of antenatal interventions to reduce anxiety in pregnancy. In particular, relationship problems during pregnancy have been reported to be an important stressor and may indicate a possible route for interventions in pregnancy (Glover & O'Connor, 2006).

Taken together the data outlined do indeed provide us with something to worry about. But at the same time, the recent literature has taken a new direction. Could a moderate level of anxiety in pregnancy actually be beneficial to the developing fetus?

Moderate anxiety

A recent publication by Janet DiPietro's group (DiPietro et al., 2006) hypothesised that they would find a negative effect of maternal anxiety measured in mid-gestation on child outcomes at the age of two. In fact, the analysis of 94 mother–infant pairs found the opposite relationship, with better motor and mental scores at the age of two for the infants of their more anxious participants. When the group looked at the anxiety levels of their sample compared to those in previous studies they found that theirs

(2002). Uterine artery resistance and anxiety in the second trimester of pregnancy *Ultrasound in Obstetrics and Gynecology, 19*, 177–179.

Lederman, S.A., Rauh, V., Weiss, L. et al. (2004). Proximity to the WTC on and after 9-11-01 and its effect on birth outcomes at three lower Manhattan hospitals. *Environmental Health Perspectives, 112*, 1772–1778.

Littleton, H.L., Breitkopf, C.R. & Berenson, A.B. (2006). Correlates of anxiety symptoms during pregnancy and association with perinatal outcomes: A meta-analysis. *American Journal of Obstetrics and Gynecology, 196*, 424–432.

Lucas, A. (1998). Programming by early nutrition: an experimental approach. *Journal of Nutrition, 128*, 401S-406S.

Mulder, E., Robles de Medina, P., Huizink, A. et al. (2002). Prenatal maternal stress: Effects on pregnancy and the (unborn) child. *Early Human Development, 70*, 3–14.

Oates, M. (2002). Adverse effects of maternal antenatal anxiety on children: Causal effect or developmental continuum? *British Journal of Psychiatry, 180*, 478–479.

O'Connor, T.G., Heron, J., Golding, J. et al. (2002). Maternal antenatal anxiety and children's behavioral/emotional problems at 4 years. Report from the Avon Longitudinal Study of Parents and Children. *British Journal of Psychiatry, 180*, 502–508.

Rieger, M., Pirke, K-M., Buske-Kirschbaum, A. et al. (2004). Influence of stress during pregnancy on neonatal behavior. *Annals of the New York Academy of Science, 1032*, 1–3.

was a relatively moderate anxiety group. The animal literature has also described this type of relationship – for instance, Fujioka et al. (1999) have reported that antenatal exposure to mild stress in rats is associated with better motor outcomes in offspring.

So how can we explain this relationship? Firstly, there is the physiological explanation that the stress hormones are actually also essential to normal maturation of key organs, including the brain. Secondly, DiPietro's group have also suggested that the explanation may lie within the intrauterine environment. The hormonal, acoustic and vestibular stimulation experienced by the fetus of a markedly anxious mother may be volatile and unpredictable. The stimulation levels for a fetus of a mother experiencing moderate anxiety may be variable but may also be predictable, enabling the beginnings of classical conditioning.

Both of these explanations suggest an inverted U-shaped association. It may be that over-exposure is toxic, but a moderate amount is beneficial. However, the new evidence of DiPietro's group is, as yet, unreplicated, and a recent analysis by Bergman et al. (2007) did not support the hypothesis, instead suggesting a linear dose effect across the range. Furthermore, DiPietro's group used a sample of well-educated, financially stable women – the results may not extend to more disadvantaged groups. At the same time, there is intuitive sense in the findings given the maturational effects of the stress hormones.

As I mentioned at the outset, the 'anxiety in pregnancy' literature is growing apace and, taken together, is compelling. However, the possibility that some anxiety may be beneficial has tended to be overlooked by the media to date, leading to an assumption that all anxiety or stress is bad. While the evidence suggests that overlooking the possible effects of severe stress in pregnancy would be a mistake, there must be some kind of balance in the messages we can take from this literature.

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The experience of life-threatening environmental situations, or the extreme trauma of loss of a loved one in pregnancy, or the ongoing stress of an abusive relationship are one thing; day-to-day stresses and strains are quite another. The explanation of an inverted U-shaped phenomenon is a useful one if we are to put this debate in the context of the fact that life is stressful, and that we actually require a level of stress to function, develop and perform well.

For instance, take the example of what seems to be a prevalent pursuit for pregnant women: moving house. Now, the literature in this area could lead us to worry further that our children are destined for, say, ADHD… but the option of not worrying about the worry is much preferable. Perhaps the experience of a moderately stimulating intra-uterine environment or exposure to moderate levels of stress hormones may mean that these babies are destined for more optimal development instead.

Neglected areas

Anxiety in pregnancy warrants further research with a new focus on the effects of moderate anxiety. At the same time, the evidence on marked anxiety and severe stress does suggest the need for interventions aimed at reducing women's experience of high levels of anxiety in pregnancy.

There also appear to be two neglected areas of investigation. The first concerns the effects of high anxiety levels on maternal eating patterns and behaviour. It is possible that these behaviours may either independently affect fetal development or may be an associated mechanism for the transference of effects. It is well known that hunger is a potent activator of the HPA-axis, and that anxiety and depression are associated with altered eating patterns. Indeed, it was Lucas (1998), studying the effects of maternal undernutrition on health outcomes, who provided the original definition of 'fetal programming'. The effects of antenatal anxiety may in fact be an expression of Lucas's hypothesis.

Secondly, there is very little research that has assessed the possibility that antenatal anxiety may act as a marker for maternal and infant communicative behaviours. It may be the case (as it appears to be in the postnatal depression research) that the early mother–baby relationship, expressed through their communication capacities, mediates the negative outcomes of marked anxiety. Perhaps antenatal anxiety begins a cycle of maternal perceptions that affect her communicative behaviours. Similarly, it is possible that high levels of anxiety may impair the young infant's ability to participate in these early interactions. If either factor, or both, significantly affects the mother–infant relationship, it could account for the long-term effects of high levels of antenatal anxiety.

In the meantime, however, although the bulk of the literature is certainly worthy of some moderate anxiety (and further research), we can at the same time alleviate at least some stress by referring readers to the possibility of an inverted-U.

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Roberts, A.D., Moore, C.F., DeJesus, O.T. et al. (2004). Prenatal stress, moderate fetal alcohol, and dopamine system function in rhesus monkeys. *Neurotoxicology and Teratology, 26*, 169–178.

Talge, N. M., Neal, C., Glover, V. & the Early Stress, Translational Research and Prevention Science Network (2007). Antenatal maternal stress and long-term effects on child neurodevelopment: How and why? *Journal of Child Psychology and Psychiatry, 48*(3/4), 245–261.

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

Van den Bergh, B.R. & Marcoen, A. (2004). High antenatal maternal anxiety is related to ADHD symptoms, externalizing problems, and anxiety in 8 and 9 year olds. *Child Development, 13*, 1085–1097.

Van den Bergh, B.R., Mennes, M., Oosterlaan, J. et al. (2005a). High antenatal maternal anxiety is related to impulsivity during performance on cognitive tasks in 14- and 15-year-olds. *Neuroscience and Biobehavioural Review, 29*, 259–269.

Van den Bergh, B.R., Mulder, E.J., Mennes, M. & Glover, V. (2005b). Antenatal maternal anxiety and stress and the neurobehavioural development of the fetus and child: Links and possible mechanisms. A review. *Neuroscience and Biobehavioural Reviews, 29*, 237–258.