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Research report

Are female children more vulnerable to the long-term effects of maternal depression during pregnancy?

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ABSTRACT

Background: Female fetuses are more vulnerable to high levels of maternal glucocorticoids. We examined whether exposure to prenatal maternal depression, a condition associated with high glucocorticoids, carries greater risk for depression at 12 and 18 years in girls.

Methods: Our sample comprised 7959 mothers and children from the Avon Longitudinal Study of Parents and Children following imputation for missing data. Maternal depression was assessed pre-and postnatally, and offspring depression at ages 12 and 18. We used logistic regression models to examine the relationship between exposure to prenatal and postnatal depression and offspring depression at 18 and 12 and interactions with gender.

Results: There was an interaction between prenatal depression and gender ($P=0.027$) and between postnatal depression and gender ($P=0.027$) for offspring depression at 18. Following adjustment in prenatally depressed mothers, the odds ratio for offspring depression at 18 was 1.55 (95% c.i. 1.03–2.34) for girls and 0.54 (0.23–1.26) for boys. In post-natally depressed mothers, the odds ratio for offspring depression at 18 was 1.15 (0.70–1.89) in girls and 3.13 (1.52–6.45) in boys.

However there was no evidence for interaction between prenatal or postnatal depression and gender ($P=0.559$ and 0.780 respectively) for offspring depression at 12.

Limitations: As expected with this large cohort spanning over 18 years, there was loss-to-follow-up.

Conclusions: This is the first evidence in humans that increased vulnerability of female fetuses to maternal stress responses during pregnancy persists into adolescence. One explanation for gender differences emerging later is more depressive symptomatology is attributed to heritable risk at 12, whereas biological processes involved in brain development at 18 may be influenced by foetal programming. If replicated, this study has potential to help understand intergenerational transmission of depression, a leading cause of morbidity worldwide.

1. Introduction

Many adult diseases partly have their origins in utero as a result of foetal programming, the process by which uterine conditions lead to enduring changes in bodily structure or function that may increase risk for chronic conditions in later life. In a now landmark paper, Barker reported that human foetal undernutrition in mid to late gestation can lead to the foetus growing in a disproportionate way and a greater risk of coronary heart disease in adulthood. Babies born at a low birth weight, or who were small in relation to placental size, were at increased risk of coronary heart disease, and the mechanism underlying this is thought to be that maternal undernutrition can slow foetal cell division through altered concentrations of growth factors and hormones, particularly insulin and growth hormone (Barker, 1995). It has been shown in animal models, including primates, that if stress occurs during prenatal brain development this can lead to enduring changes in offspring behaviour, including response to stressors. Prenatal maternal stress leads to the foetal brain being exposed to excess glucocorticoids, which can lead to enduring alteration of the foetal hypothalamo-pituitary-adrenal function in the offspring throughout childhood, adolescence and adult life (Kapoor et al., 2006).

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In humans one important cause of an altered stress response is depression. The risk of depression during adolescence is thought to be increased in the offspring of mothers who were depressed during the perinatal period. A study following 151 mother–child dyads from pregnancy to the child's 16th birthday found that those children exposed to maternal depression during pregnancy were 4 times more likely to become depressed than those children never exposed to maternal depression, and episodes of depression during pregnancy were part of a wider pattern of maternal depression that often began prior to pregnancy and persisted throughout the child's life (Pawlby et al., 2009). This alone does not tell us whether the increased risk of depression in children is due to genetic inheritance, prenatal foetal exposure, or childhood environment. The mechanism for this intergenerational transmission of risk is not fully understood but there is some evidence that prenatal depression and postnatal depression are independent risk factors for offspring adolescent depression, that act via different pathways. This was demonstrated in a large population cohort study which showed that maternal prenatal depression was associated with child adolescent depression regardless of the mother's educational level, whereas postnatal maternal depression was only associated with child adolescent depression in mothers with lower educational levels, suggesting that maternal education can moderate the effect of postnatal depression on adolescent mental health, but cannot moderate the pathway for prenatal depression influencing adolescent mental health. As education can influence the impact of postnatal depression, but not of prenatal depression, this suggests that the two act via different pathways, one being modified by education and the other not (Pearson et al., 2013).

The neuroendocrine feedback system between the hypothalamus, pituitary and adrenal glands, can be altered in depression resulting in persistently raised cortisol (Antonijevic, 2008; Min et al., 2012). The effect of this alteration in the maternal stress response during pregnancy on the neural development of the foetus could explain how exposure to prenatal depression increases risk of depression in offspring (Douglas, 2005).

One of the mechanisms by which maternal depression during pregnancy could affect the developing foetus is through altered cortisol transmission across the placenta, and there is accumulating evidence from animal and human studies that this is the case. Maternal prenatal anxiety is associated with the foetus being exposed to higher levels of maternal cortisol when the mother is stressed (O'Donnell et al., 2012). A recent study using the same cohort that we investigate here has shown that maternal prenatal anxiety and depression have an impact on diurnal cortisol variation in adolescent offspring, and the authors suggest that the mechanism for this may be through prenatal programming of the hypothalamopituitary adrenal axis resulting from exposure to high maternal cortisol (O'Donnell et al., 2013).

There is increasing evidence from animal studies that female foetuses are more vulnerable both to high levels of glucocorticoid exposure and prenatal stress than male foetuses (Richardson et al., 2006). Animal studies have shown there are differences in the biology of placental function between male and female foetuses. Female foetuses are more susceptible to anxiety, stress and depression responses in adulthood if they were exposed to maternal prenatal stress, whereas males exposed to prenatal stress are more likely to have learning and memory problems (Glover and Hill, 2012). In mice, more corticosterone crosses from the maternal bloodstream to the placenta in female compared to male foetuses following a stress response in the mother (Montano et al., 1993). If the effect of prenatal depression operates through this mechanism in humans, we would expect to find differences in risk arising from prenatal exposure according to offspring gender.

Understanding the mechanisms of developing depression, particularly in young people, provides an important first step and opportunity for developing methods for prevention. This is an important public health priority as depression is now the leading cause of disability worldwide according to the World Health Organisation (World Health Organisation). Adolescents with depression are at increased risk of depression and anxiety disorders in adulthood, and have increased rates of unemployment, educational underachievement, alcohol abuse, and early parenthood (Fergusson and Woodward, 2002). A large cohort study has demonstrated that frequent depressive episodes in adolescence are followed by poor adult mental health outcomes including major depression, anxiety disorder, suicidal ideation and suicide attempt, as well as greater levels of unemployment and dependence on welfare, even when confounding factors were controlled for (Fergusson et al., 2007).

We have previously demonstrated that both prenatal and postnatal depression is associated with increased risk of depression in offspring at age 18 using data from a large longitudinal UK cohort (Pearson et al., 2013). However, the moderating role of offspring gender was not investigated. Here we investigate whether maternal prenatal depression confers a greater risk of developing adolescent depression on girls than on boys in this cohort. We tested the hypotheses that, at 18 years, girls of prenatally depressed mothers would be more susceptible to depression than boys of prenatally depressed mothers. We also wanted to test children at age 12 to ascertain whether any gender differences were present from early adolescence and persisted into early adulthood, or whether differences emerged during adolescence. We were interested in looking at these two time points, at the beginning and end of adolescence, as different biological processes are involved in brain development (myelination and synaptic pruning) at age 18 compared to age 12, and these processes may be influenced by foetal or early life programming so be more subject to gender influences and timing of maternal depression than earlier in life, when genetic influences alone are likely to be stronger.

We examined evidence for these hypotheses using data from a large longitudinal cohort with 7959 mother–child pairs (after data imputation) followed up until the children were 18 years of age.

2. Methods

Our sample comprised participants from the Avon Longitudinal Study of Parents and Children (ALSPAC) which recruited the children of 14,541 pregnancies born between 1990 and 1992 (Fraser et al., 2013). This is an ongoing population-based study which has been running for over 20 years and is investigating the effects of a wide range of variables on the physical and emotional development of children.

Pregnant women living in the area of the former Avon Health Authority in South-West England with an expected delivery date between 1 April 1991 and 31 December 1992 were invited to take part, and the children of 14,541 pregnancies were recruited. Regular objective measurements made in research clinics as well as self-report questionnaires on aspects of health and lifestyle have been collected on the cohort of mothers since early pregnancy and on them and their children since.

Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. After complete description of the study to the subjects, written informed consent was obtained.