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Symptoms of prenatal depression are associated with raised salivary alpha-amylase levels

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Abstract
Purpose: Prenatal depression increases risk for a number of adverse offspring outcomes, however the biological mechanisms underlying this association remain unclear. It has been suggested that maternal glucocorticoids may mediate this link, though supporting evidence has been mixed. An alternative mechanism of effect may be via depression-induced changes in maternal sympathetic nervous system (SNS) function. We examined this hypothesis by determining the relationship between symptoms of maternal prenatal depression and diurnal salivary alpha-amylase (sAA) levels.
Methods: 76 pregnant women were recruited during either the second or third trimester of pregnancy. Participants self-reported depressive symptoms using the Edinburgh postnatal depression scale. Saliva samples, to be assayed for alpha-amylase activity, were collected at home over two working days.
Results: Participants with depressive symptoms in later pregnancy had elevated awakening sAA levels compared with non-depressed controls ($t_{(73)} = -2.737$, $p = 0.008$), and continued to have raised sAA throughout the day ($F_{(1)} = 10.924$, $p = 0.002$).
Conclusions: Our findings highlight that symptoms of depression during late pregnancy are associated with increased maternal SNS activity. Thus, changes in maternal SNS function, which may include increased vasoconstriction and reduced foetal blood flow, could, in part, mediate associations between prenatal depression and adverse offspring outcomes.

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1. Introduction

Prenatal psychological distress, which encompasses feelings of depression, anxiety and stress, increases risk for adverse offspring physical and psychological health outcomes. For example, prenatally distressed women are at greater risk of both preterm birth (Class et al., 2011; Copper et al., 1996; Nkansah-Amankra et al., 2010) and of having a low birth weight baby (Sable and Wilkinson, 2000; Zhu et al., 2010), which increases risk for offspring diabetes (Whincup et al., 2008) and cardiovascular disease (Barker, 1999; Huxley et al., 2007) in later life. Further, exposure to maternal psychological distress has been linked with increased rates of behavioural and emotional problems in childhood (O'Connor et al., 2002b, 2003) and increased rates of psychiatric disease in adulthood (Pearson et al., 2013; Van den Bergh and Marcoen, 2004; Van den Bergh et al., 2008). Interestingly, these effects appear to be independent of postnatal mood (O'Connor et al., 2002a; Pearson et al., 2013), and there is direct evidence to suggest that developmental changes in these offspring may begin during the prenatal period. For example, foetuses of prenatally distressed mothers show perturbed foetal heart rate responses to both maternal stress (Monk et al., 2000) and direct stimulation (Fernandes et al., 2014), and are also more active (Dieter et al., 2008), compared with foetuses of non-stressed mothers. However, despite extensive efforts, the in utero biological processes that may link prenatal disturbed mood with altered offspring development remain unclear.

In recent years, the field of perinatal psychiatry has been largely focused on alterations of the maternal and foetal hypothalamic-pituitary adrenal (HPA) axes as a potential biological mechanism that may mediate the link between prenatal disturbed mood and perturbed foetal and infant development (Braithwaite et al., 2014; Glover, 2011). This is largely because in non-pregnant populations symptoms of depression are associated with cortisol hyper-secretion (Bhagwagar et al., 2005; Cowen, 2002; Herbert, 2013). However, data linking symptoms of mood disturbance in pregnancy with changes in maternal HPA function have been mixed, with evidence both for (Giesbrecht et al., 2012; Murphy et al., 2014; O'Connor et al., 2013; Obel et al., 2005) and against (Hellgren et al., 2013; Pluess et al., 2012) cortisol hyper-secretion. One possible explanation for the disparate findings is that cortisol levels rise throughout pregnancy, regardless of mood state, due to the release of corticotrophin-releasing hormone (CRH) from the placenta. By the end of gestation, maternal serum cortisol levels are four times higher than in the non-pregnancy state (Lindsay and Nieman, 2005) and therefore detecting mood-induced changes in HPA function becomes difficult. It is possible that levels of placental CRH may be important in the onset of depressive symptoms, as raised placental CRH has been associated with both prenatal (Rich-Edwards et al., 2008) and postnatal depressive symptoms (Yim et al., 2009). However, an alternative explanation is that maternal glucocorticoids may not be as central in mediating associations between prenatal mood and foetal developmental trajectories as previously thought.

Changes in maternal sympathetic nervous system (SNS) activity have been proposed as an alternative pathway by which disturbances in prenatal mood may impact foetal development (Braithwaite et al., 2014; Talge et al., 2007). As well as the HPA axis, psychological distress also activates the SNS, which results in an increase in the circulating levels of noradrenaline. Evidence for the involvement of noradrenaline in depression is abundant, for example a number of antidepressants inhibit noradrenaline reuptake, and recent studies on neuronal pathways and depressive symptoms highlight the specific role of noradrenaline in this disorder, for review see Moret and Briley (2011). In pregnancy, noradrenaline does not directly cross the placenta (Giannakoulopoulos et al., 1999); however its release may indirectly affect the foetus by initiating vasoconstriction and disrupting uterine blood flow. The reduced or fluctuating transmission of oxygen to the foetus may perturb foetal growth, and increase risk for low birth weight or premature birth, which, as mentioned above, increases risk for poor offspring physical health (Barker, 1999; Whincup et al., 2008). Further, disruption to normal brain development resulting from the lack of oxygen or nutrients may increase the likelihood of later psychological difficulties (Morsing et al., 2011). In support of this hypothesis, animal research has shown that both acute stress and intravenous infusions of noradrenaline induce a decrease in uterine blood flow (Shnider et al., 1979; Stevens and Lumbers, 1995). Initial human investigations mirrored the animal findings, and reported associations between prenatal anxiety and decreased uterine blood flow (Sjostrom et al., 1997; Teixeira et al., 1999). However notably, there have been a number of failed replication attempts (Harville et al., 2008; Kent et al., 2002; Mendelson et al., 2011; Monk et al., 2012). Discordance in the published literature may be attributable to methodological differences in the existing studies, or because Doppler assessments of uterine blood flow are difficult to administer during pregnancy in a controlled laboratory setting.

An alternative method for assessing maternal SNS function may be via the use of the salivary biomarker, alpha-amylase. In recent years, salivary alpha-amylase (sAA) has been proposed as a sensitive biomarker of stress related changes in SNS activity, and there is a growing body of literature to support this idea (Engert et al., 2011; Nater and Rohleder, 2009; Nater et al., 2007; Rohleder and Nater, 2009). Alpha-amylase is an enzyme produced by the salivary glands, which is involved in the initiation of starch break-down in the oral cavity (Nater and Rohleder, 2009). Production of sAA is controlled by SNS innervation; therefore increased sAA concentrations are expected during periods of psychological distress, when activation of the SNS is high. Indeed, a number of studies in non-pregnant populations have found evidence to support this (Bosch et al., 1996, 2003; Chatterton et al., 1997; Skosnik et al., 2000; Takai et al., 2004, 2007). Increased sAA in response to acute stress has also been associated with the expected increase in circulating noradrenaline (Rohleder et al., 2004; Thoma et al., 2012). Further, sAA levels have also been reported to be inflated in people with depression (Ishitobi et al., 2010; Tanaka et al., 2012; Veen et al., 2013).

Studies of sAA in pregnancy are limited, however increases in sAA concentration in response to an acute stressor have been reported in a population of pregnant participants, during both the second and third trimester (Nierop et al., 2006). Just one study has assessed the effects