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Perinatal hypothalamic-pituitary-adrenal axis regulation among women with eating disorders and their infants

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ABSTRACT

Background: Psychiatric illness is associated with heightened hypothalamic-pituitary-adrenal (HPA) axis activity during pregnancy which may have long term effects on infant stress regulation. HPA axis regulation has not previously been investigated in women with eating disorders (ED) or their infants during the perinatal period.
Methods: Women were recruited to a prospective longitudinal study in three groups: 1) current or active ED (C-ED = 31), 2) past ED (P-ED = 29) and healthy control (HC = 57). Maternal psychopathology, diurnal cortisol levels, corticotropin-releasing hormone (CRH) and CRH binding protein (CRH-BP) were measured during the third trimester of pregnancy. At eight weeks postpartum infant cortisol was obtained before and after routine immunisations to determine infant hormonal response to a stressful situation.
Results: Women with current ED had a significantly lower cortisol decline throughout the day compared to HC, in both adjusted and unadjusted analyses. Lower cortisol decline among women with a current ED were associated with higher levels of psychopathology during pregnancy. Women's cortisol awakening response, CRH and CRH-BP levels did not differ across the three groups. Infants' stress response was also significantly higher among those in the C-ED group, although this effect was attenuated after controlling for confounders.
Conclusions: During pregnancy women with ED have lower cortisol declines, suggestive of blunted diurnal cortisol rhythms. Postnatally, their infants also have a heightened response to stress. This is the first study to identify HPA axis dysfunction in pregnancy in women with ED, and to show an intergenerational effect. Since dysfunctions in HPA activity during childhood may represent a risk factor for psychological and physical health problems later in life, further investigation of the potential long-term implications of these findings is crucial.

1. Introduction

Maternal psychiatric disorders commonly occur during pregnancy and in the postnatal period The implications are not limited to the mother, and perinatal mental illness (PNMI) can have long-term consequences for child development (Stein et al., 2014). During early pregnancy, 7.5% of women have been reported to have an eating disorder (ED) (Easter et al., 2013), and, despite some reductions women with ED continue to experience high levels of psychopathology throughout the perinatal period (Easter et al., 2014). Maternal ED have been associated with an increased risk of pregnancy and obstetric complications, in particular increased risk of miscarriage, intrauterine growth restriction and low birth weight (Micali et al., 2007; Solmi et al., 2013). There is also evidence of increased levels of emotional, conduct and hyperactivity disorders among children of women with ED (Micali et al., 2014).

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Nevertheless, ED have received substantially less research attention compared to other PNMI.

The exact mechanisms for associations between maternal psychiatric illness and childhood psychological problems are currently unknown, but are likely to involve a combination of psychological, social and biological factors (Goodman and Gotlib, 1999). The role of fetal programming (Godfrey and Barker, 2001), (i.e. the effect of the in utero environment on health and development across the lifespan) as a potential mechanism has become the focus of a great deal of research. There is a growing body of literature indicating that maternal mood and anxiety can affect the intrauterine environment, increasing the risk of obstetric complications, and have enduring effects on the psychological development of the offspring (O'Connor et al., 2002; Stein et al., 2014).

The Hypothalamic Pituitary Adrenal (HPA) axis is a major biological system involved in modulating stress and increasing research suggests that fetal exposure to excess glucocorticoids represents a critical mechanism for fetal programming (Meaney et al., 2007; Sandman et al., 2012). Under normal circumstances the HPA axis has a diurnal pattern, characterised by high levels of stress hormones in the morning, which reach a nadir in the evening. The HPA axis is programmed to respond rapidly to stressful situations and return to homeostasis once the fear of threat has passed.

Psychiatric illness appears to shape the physiology of the stress system and different psychopathology is associated with different physiological profiles. For example, whilst elevated cortisol levels have been associated with most forms of depression (Stetler and Miller, 2011), low cortisol levels are associated with post-traumatic stress disorder (Yehuda and Seckl, 2011) and have also been reported in atypical depression (Stetler and Miller, 2011).

ED have also been associated with abnormalities of the HPA axis (Ginty et al., 2012). Although findings are somewhat mixed, plasma cortisol and corticotropin-releasing hormone (CRH) levels have both been shown to be elevated in women with anorexia nervosa (AN) (Boyar et al., 1977; Hotta et al., 1986; Kaye et al., 1987; Favaro et al., 2008) and bulimia nervosa (BN) (Monteleone et al., 2001).

Recent studies have indicated that different ED subtypes might be characterised by different abnormalities of the HPA axis and dependent on the patient's stage of recovery. Cortisol Awakening Response (CAR) has been found to be significantly elevated among adult with AN (Monteleone et al., 2014, 2015), specifically during the acute phase of the illness (Monteleone et al., 2016); whereas, studies of BN have shown more contrasting findings, with evidence of both normal and increased circadian rhythm (Sauro et al., 2008).

Patients with bulimic symptoms have also shown greater cortisol suppression to the dexamethasone suppression test (DST), a frequently used test to assess adrenal gland function, compared to both controls and patients with restrictive AN (Díaz-Marsá et al., 2007). Therefore, unlike patients with AN who have been found more consistently to display hyper-reactivity, the activity in the HPA axis in BN is more varied.

Increased cortisol feedback inhibition has previously been associated with post-traumatic stress (Yehuda et al., 2004), since trauma history is common among patients with ED it has been postulated that hypersensitive DST maybe related to trauma among patients with BN (Díaz-Marsá et al., 2007).

Despite increasing understanding of HPA axis activity among patients with ED, no studies have reported the pattern of biological markers of stress among women with ED during pregnancy or the longitudinal effects on the offspring.

Although stress hormones are necessary for fetal maturation, if excessive levels reach fetal circulation they can potentially have adverse effects on development (Sandman et al., 2012) and affect their infants' ability to respond appropriately to stressful situations. Stress paradigms in humans are only recently emerging, but studies have generally indicated that high levels of self-reported stress or maternal cortisol levels in pregnancy are associated with a larger infant cortisol reaction (Gutteling et al., 2004, 2005; Tollenaar et al., 2011; Davis et al., 2011).

Micali and Treasure (2009) propose a conceptual biological model of risk of fetal programming among women with ED. This model highlights the possible mediating roles of nutrition and stress during pregnancy among women with ED and the potential interaction of these factors via hyperactivity of the maternal and fetal HPA axis. Two potential pathways are implicated in this model: poor nutrition (e.g. protein restriction) and co-morbid anxiety and depression in women with ED during pregnancy. These pathways are mediated by increased levels of maternal CRH and consequentially elevated levels of glucocorticoids in the fetal circulation. It is hypothesised that elevated levels of glucocorticoids in fetal compartments in turn increases the risk of obstetric complications and alterations in fetal development in women with ED. Micali and Treasure (2009) highlight that under-nutrition during pregnancy may be particularly relevant to HPA axis dysfunction in women with a history of AN, whereas other pathways might be more relevant to BN.

In the postnatal period, the way in which infants respond to stressful situations is indicative of how they regulate their emotions and behaviour, and is crucial for healthy psychological development. Infant stress regulation may therefore be an early risk factor for developmental problems. Recently, regulation of stress has been implicated as a risk factor for the development of AN (Favaro et al., 2008, 2010). Favaro et al. (2008, 2010) found a combined effect of obstetric complications and childhood abuse on the risk of developing an ED later in life. These preliminarily findings suggest a potential role of perinatal complications and prenatal programming of the stress response in the pathogenesis of ED.

In light of this literature the aims of this paper were threefold: 1) to investigate antenatal and postnatal biological markers of stress among women with and without ED, 2) to assess the relationship between biological markers of stress and psychopathology among women with and without ED and 3) to investigate infants' stress response at eight weeks postpartum and its relationship with maternal measures of stress and psychopathology in a longitudinal study of infants of women with ED and controls.

We aimed to investigate the effect of maternal active and past ED to try disentangling the direct effect of ED (state) on relevant outcomes, vs. any effect due to a past ED (residual effect) or that might index endophenotype/intermediate phenotype markers (trait).

2. Materials and measures

2.1. Design and participants

The Nutrition and Stress in Pregnancy (NEST-p) study is an observational prospective study of pregnant women and their infants (Easter et al., 2013).

Three groups of women were recruited for this study during the first or second trimester: women with an active ED (C-ED), women with a past ED (P-ED) and a healthy control (HC) group. Women were recruited via three recruitment methods: 1. Women attending their first or second routine ultrasound scan (see Easter et al., 2013, for further details), 2. Women referred during pregnancy to a specialist psychiatric service for treatment for an ED and 3. Recruitment posters and online information.

Inclusion criteria for the index groups were an active or past DSM-IV diagnosis of ED, ages between 18 and 45 years, and within the first or second trimester of pregnancy. Additional inclusion criteria for the HC group were no active or past full or partial psychiatric disorder including an ED. Exclusion criteria were: a