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Prenatal maternal psychopathology and stress and offspring HPA axis function at 6 years

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ABSTRACT

Objective: Intrauterine exposures such as maternal psychopathology and stress are known to influence the physical and mental health of the offspring. One of the proposed pathways underlying these associations is dysregulated hypothalamic-pituitary-adrenal (HPA) axis activity in the offspring. This study examined the relation of perinatal maternal symptoms of psychopathology and stress with offspring HPA axis activity at 6 years as measured by hair cortisol and cortisone concentrations.

Methods: The study was part of the population-based Generation R Study, a prospective population-based cohort from fetal life onwards. 2546 children and their mothers formed the study population. Perinatal maternal psychopathology and stress were assessed by questionnaires in the second and third trimester. Principal components for both psychopathology and stress were created to reduce the number of explanatory variables. Child hair samples for cortisol and cortisone measurements were collected at the age of 6. Linear regression analysis, adjusted for covariates, was used to examine associations between maternal psychopathology and stress and child hair cortisol and cortisone levels.

Results: The maternal psychopathology principal component was associated with higher child hair cortisone (adjusted B = 0.24, 95%CI 0.08;0.40, p-value < 0.01). Effect estimates of the individual dimensions ranged from 0.97 (95%CI 0.21;1.73, p-value = 0.01) for interpersonal sensitivity to 1.67 (95%CI 0.86;2.47, p-value < 0.01) for paranoid ideation. In addition, children exposed to intrauterine stress, as measured by the principal component, had higher hair cortisone levels (adjusted B = 0.54, 95%CI 0.21;0.88, p-value < 0.01). Exposure to maternal psychopathology and stress was not associated with offspring hair cortisol. Stratification by child sex resulted in associations between maternal symptoms of psychopathology during pregnancy and child hair cortisone levels in boys and associations between maternal symptoms of stress during pregnancy and child hair cortisone levels in girls.

Conclusion: Our results suggest that maternal psychopathology and stress during pregnancy are associated with long-term HPA axis activity of the offspring. The association of maternal psychopathology and stress during pregnancy with offspring hair cortisone levels is a novel finding. Future studies should examine whether these psychophysiological differences between exposed and non-exposed children underlie offspring morbidity associated with maternal psychopathology and stress during pregnancy.

1. Introduction

Many intrauterine exposures are known to influence the physical and mental health of the offspring (Barker, 2004; Van den Bergh, 2011). Maternal psychopathology and stress during pregnancy are among the most common intrauterine exposures associated with a

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negative impact on the offspring's health (Ding et al., 2014; Woody et al., 2017). Exposure to maternal psychopathology or stress during pregnancy is associated with preterm birth and low birth weight (Grote et al., 2010). In the long-term, maternal psychopathology or stress during pregnancy is related to behavioral, emotional, cognitive and motor problems in childhood (Field, 2011; Goodman et al., 2011) and psychiatric disorders in adolescence (Pearson et al., 2013; Van den Bergh et al., 2008). Inter-generational transfer of psychopathology and stress is believed to be caused by a combination of intrauterine environment, genetics and postnatal environmental factors (Braithwaite et al., 2014; Marceau et al., 2013; Pluess and Belsky, 2011). Previous research has shown associations between intrauterine maternal psychopathology and stress and child outcomes to be independent of genetics and postnatal factors (O'Connor et al., 2003; Pearson et al., 2013). This has led scientists to propose models adapted to the 'developmental programming hypothesis' (Barker, 1998, 1999, 2004). The original hypothesis was proposed to explain associations between low birth weight and later cardiovascular diseases and diabetes. According to this programming hypothesis, the fetus or infant adapts as a response to the health and physical state of the mother, thereby altering important physiological and metabolic processes that can endure into adulthood (Barker, 1998, 1999, 2004). This model has been adapted to explain associations between exposure to maternal psychopathology or stress and later behavioral, emotional and cognitive difficulties in offspring as well. Although a number of intrauterine mediation pathways have been proposed, the most widely accepted and most investigated candidate system that could be altered by adverse intrauterine exposures, is the hypothalamic-pituitary-adrenal (HPA) axis, especially since plasticity is high during early fetal development (Braithwaite et al., 2014; Talge et al., 2007). The HPA axis plays a key role in many homeostatic systems in the body and in the body's response to stress. In numerous studies, alterations in HPA axis activity have been associated with psychosomatic and psychiatric disorders, as well as with cardiovascular, infectious and inflammatory diseases (Gifford and Reynolds, 2017; Kudielka and Kirschbaum, 2005).

Cortisol, the end product of the HPA system, is often used to investigate HPA axis reactivity, especially in studies on psychological stress. There are several conventional methods to measure cortisol, such as saliva, blood or urine samples. These measures reflect cortisol levels at the time of sampling and are all highly influenced by daily fluctuations due to circadian rhythms and fluctuations based on homeostatic regulation (McEwen, 2000), potentially creating methodological problems associated with collection. Conventional measures therefore reflect a 'snapshot' of HPA axis activity and may not be the most informative measure in the evaluation of long-term HPA axis activity. An increasingly used non-invasive method for detecting differences in individual's long-term stress levels is hair cortisol analysis (Liu et al., 2016; Staufenbiel et al., 2013; Vanaelst et al., 2013). Cortisol extracted from hair samples reflects accumulated concentrations and can therefore give a more stable and long-term indication of HPA axis activity than saliva, blood or urine collection. Hair grows with approximately 1 cm per month (Pragst and Balikova, 2006), enabling assessment of mean cortisol concentrations of the last couple of months (Stalder et al., 2012). Previous research showed that hair cortisol is most strongly associated with the prior 30-day integrated cortisol production measure (Short et al., 2016), or three-day average of single-day salivary level (Zhang et al., 2018), both supporting the notion that hair cortisol reflects long-term cortisol levels. Low to moderate correlations with short-term levels as single-point saliva cortisol levels were observed (Zhang et al., 2018).

With the introduction of liquid chromatography tandem-mass spectrometry (LC–MS/MS) (Noppe et al., 2015), the additional quantification of cortisone in scalp hair has become possible, which is metabolized from cortisol in the peripheral tissues by the 11ß-hydroxysteroid-dehydrogenase enzyme type 2 (11ß-HSD-2), where it might act as reserve capacity for cortisol. Adding cortisone in parallel to cortisol may give even more insight into the cumulative amount of active and inactive corticosteroids in the body. Previous research showed elevated hair cortisone concentrations in young children under psychosocial stress (Vanaelst et al., 2013). Another study even suggests salivary cortisone can provide a better reflection of systemic cortisol levels than salivary cortisol (Perogamvros et al., 2010).

A limited number of studies have related maternal psychopathology and stress during pregnancy to changes in HPA axis functioning in the offspring, mostly in the first year of life. One prospective longitudinal study assessed maternal feelings of stress and anxiety in the last trimester of pregnancy and infant cortisol reactivity, measured through saliva, at 5 and 8 weeks and at 5 and 12 months of age (Tollenaar et al., 2011); higher infant cortisol reactivity was observed at 5 and 8 weeks and at 12 months in children exposed to intrauterine anxiety. In another prospective study the association of antenatal depression with infant cortisol reactivity at 2 months of age was examined and a U-shaped relationship between antenatal depression and cortisol reactivity was observed, suggesting that infants exposed to both low and high levels of maternal depression showed greater cortisol reactivity than infants exposed to moderate levels of antenatal depression (Fernandes et al., 2015). In contrast, another prospective study among 88 mother-child dyads did not observe an association of prenatal maternal depressive symptoms with infant cortisol reactivity at 2 months (Braithwaite et al., 2016). Yet, whether symptoms of psychopathology and stress during pregnancy affect long-term HPA axis activity in the offspring is largely unknown.

The objective of the current study was therefore to investigate whether maternal psychopathology and stress during pregnancy are associated with offspring HPA axis activity at 6 years of age. We examined several dimensions of psychopathology, including depression and anxiety, as well as different forms of experienced stress during pregnancy such as stressful life events and pregnancy-related anxiety. For long-term HPA axis activity we measured both hair cortisol and the novel biomarker hair cortisone when children were 6 years of age. We hypothesized, in line with previous short-term findings, that maternal symptoms of psychopathology and stress during pregnancy are related to heightened cortisol and cortisone levels in the offspring. As previous research suggests effects on child outcomes to be sex dependent (Braithwaite et al., 2018, 2017a; Braithwaite et al., 2017b; Gifford and Reynolds, 2017; Sandman et al., 2013), we additionally examined results by child sex.

2. Methods

2.1. Setting and population

The present study was embedded in an on-going population-based cohort, the Generation R Study, designed to identify early environmental and genetic causes and causal pathways leading to normal and abnormal growth, development and health from fetal life, childhood and young adulthood (Kooijman et al., 2016). In total, n = 8880 mothers were enrolled during pregnancy with deliveries from April 2002 to January 2006. The Medical Ethics Committee of the Erasmus Medical Centre, Rotterdam, approved the study. Written informed consent was obtained from all participants.

For the present explorative analysis, only children who participated in the pre- and postnatal follow-up (n = 7510) were considered (Fig. 1). Of these, 1457 children were excluded, as they did not visit the research center in childhood, when hair samples are collected. Information on maternal psychopathology and stress parameters was missing in 338 children. Hair collection did not start immediately at onset of this data collection wave and 3161 children were not approached. The response rate for children that were approached for hair collection was 85% (Noppe et al., 2016). Cortisol concentration could be quantified in 2523 children and cortisone in 2485 children. Extreme outliers, defined as cortisol or cortisone levels > 4SD (standard deviation), indicating