Psychoneuroendocrinology 94 (2018) 152–161

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Maternal hypothalamus-pituitary-adrenal (HPA) system activity and stress during pregnancy: Effects on gestational age and infant's anthropometric measures at birth

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ARTICLE INFO

Keywords:
Early life stress
Gestational age
Anthropometric measures at birth
Cortisol
Prenatal distress
Pregnancy

ABSTRACT

Background: Prenatal maternal stress might be a risk for the developing fetus and may have long-lasting effects on child and adult vulnerability to somatic and psychiatric disease. Over-exposure of the unborn to excess glucocorticoids and subsequent alteration of fetal development is hypothesized to be one of the key mechanisms linking prenatal stress with negative child outcome.

Methods: In this prospective longitudinal study, mothers-to-be (n = 405) in late pregnancy (36.8 ± 1.9 weeks of gestational age) and their singleton neonates were studied. We investigated the impact of different prenatal stress indices derived from six stress variables (perceived stress, specific prenatal worries, negative life events, symptoms of depression, trait anxiety, neuroticism) and diurnal maternal saliva cortisol secretion on gestational age and anthropometric measures at birth.

Results: Maternal prenatal distress during late gestation was associated with significant reduction in birth weight (−217 g; p = .005), birth length (−1.2 cm; p = .005) and head circumference (−0.8 cm; p = .001). Prenatal stress was modestly but significantly associated with altered diurnal cortisol pattern (flattened cortisol decline and higher evening cortisol), which in turn was significantly related to reduced length of gestation. No evidence for a profound interaction between maternal cortisol level in late pregnancy and infant's anthropometric measures at birth (i.e., birth weight, length, head circumference) was found.

Conclusion: Prenatal stress is associated with flattened circadian saliva cortisol profiles and reduced infant's anthropometric measures at birth. HPA system activity during pregnancy may be related to low gestational age. The effect of prenatal stress might be partly mediated by maternal-placental-fetal neuroendocrine mechanisms especially the dysregulation of diurnal cortisol profile.

1. Introduction

Accumulating evidence from animal, epidemiological, clinical and experimental studies indicates that prenatal stress can profoundly affect fetal development and may have long-lasting effects on animal offspring, as well as on child and adult vulnerability to disease (e.g., Seckl and Holmes, 2007; O'Donnell et al., 2009; Glover et al., 2010). Barker's 'fetal programming' hypothesis established a conceptual framework for prenatal stress research based on the observation that prenatal environmental conditions, low birth weight and propensity to cardiometabolic disorders in adulthood are related (Barker and Osmond, 1986; Barker et al., 1993). Adjustments to the environment during pregnancy are thought to lead to permanent changes of fetal physiology which may be maladaptive in modified circumstances postnatally and, thus, predispose for later life disease (e.g., Gluckman et al., 2005).

Reduced neonatal anthropometric measurements at birth are a

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https://doi.org/10.1016/j.psyneuen.2018.04.022
Received 31 August 2017; Received in revised form 19 April 2018; Accepted 20 April 2018

common clinical marker of an adverse intrauterine environment. For instance low birth weight, even within the normal range, is still a major issue in perinatal medicine (Wardlaw et al., 2004). It is related to negative health outcomes ranging from long-term physiological, emotional to behavioral disturbances (e.g, Glover, 2015; Harris and Seckl, 2011; Lee and Houk, 2012).

Findings from human stress research suggest a wide spectrum of prenatal stressors underlying fetal programming ranging from extreme stressors such as exposure to famine, disasters or terror (Lederman et al., 2004; Roseboom et al., 2006; Xiong et al., 2008) to minor strain caused by daily hassles or mood symptoms (Grote et al., 2010; Henrichs et al., 2010). While the impact of antenatal manifest psychiatric disorders (e.g., depression or anxiety as stress-related disorders) on negative obstetric and neonatal outcome has been demonstrated in various studies (e.g., Maina et al., 2008; Hobel et al., 2008; Loomans et al., 2013; Shapiro et al., 2013; Yedid Sion et al., 2015), the effect of moderate distress induced by subclinical psychiatric symptoms or pregnancy-related anxiety and worries is rarely investigated in this context (Rice et al., 2010; Wadhwa et al., 2011).

Prenatal stress effects are thought to be at least partly mediated by maternal-placental-fetal neuroendocrine mechanisms (Glover, 2015; Wadhwa, 2005). However, findings associating prenatal stress and mood symptoms with altered maternal glucocorticoid concentrations are controversial. In non-pregnant individuals an influence of psychosocial distress on altered HPA-function is assumed – in particular elevated diurnal cortisol patterns (e.g, Vreeburg et al., 2009). Findings on stress-induced alterations in cortisol secretion during pregnancy are still more controversial. Some studies associate psychosocial distress – such as stressful life events (Obel et al., 2005), symptoms of depression (O'Connor et al., 2014) and anxiety (Kivlighan et al., 2008)- in late pregnancy with altered diurnal cortisol concentrations, particularly decreased morning levels and flattened diurnal decline. Other studies were unable to find stress dependent alterations in maternal glucocorticoid values (Salacz et al., 2012).

Over-exposure of the developing fetus to glucocorticoids is hypothesized to be one of the key mechanisms linking prenatal stress with negative child outcome (Cottrell et al., 2012; Edwards et al., 1993). The placental barrier enzyme 11ß-hydroxysteroid-dehydrogenase type 2 (11ß-HSD 2) converts about 80–90% of the biological active cortisol into its inactive metabolite cortisone (Murphy et al., 1974) and physiologically protects the developing fetus from the ten-fold higher maternal cortisol concentrations (Edwards et al., 1993).

To provide an appropriate intrauterine environment for the developing fetus the maternal hypothalamic-pituitary-adrenal (HPA) system undergoes crucial alterations. Throughout pregnancy maternal cortisol concentrations in serum rise up to three-fold non-pregnant level (Jung et al., 2011).

This is partly due to the release of large quantities of placental corticotropin-releasing hormone (CRH) (Campbell et al., 1987), which stimulates cortisol secretion from maternal adrenal gland directly and via maternal pituitary and subsequent adrenocorticotropic hormone (ACTH) release.

Thus, circadian cortisol rhythmicity (peaking in response to awakening and consecutive decline over the day) remains stable over the course of pregnancy (Entringer et al., 2010). These high levels of maternal cortisol during pregnancy drop postpartum, although it takes several weeks (up to 3–4 month postpartum) until level establish at normal values (Kirschbaum and Hellhammer, 1989).

About 10–20% of intact maternal cortisol crosses the placental barrier (Benediktsson et al., 1997). This doubles fetal concentrations at mid to late gestation (Gitau et al., 1998) although human placental 11ß-HSD2 increases according to the rising levels of maternal cortisol throughout gestation (McTernan et al., 2001).

Due to the large gradient in concentration between both compartments (maternal/fetal-ratio 11:4), the fetus is directly dependent on maternal cortisol values, depending on the time of gestation. The fetus is more dependent on the maternal cortisol early in gestation and less so toward the end of gestation, with fetal HPA activity beginning at midgestation (e.g., Gitau et al., 2001; Mastorakos and Ilias, 2003). The placental CRH also stimulates fetal hormone output and is linked with the activation of the fetal HPA (Challis et al., 2001). The fetal HPA activity begins at midgestation and fetal stress responses are independent of maternal responses (Gitau et al., 2001). However, minor changes in maternal cortisol concentrations and placental 11ß-HSD2 function might be able to profoundly influence fetal glucocorticoid exposure and may play a crucial role in transmitting prenatal early life stress (ELS) to the fetus (Gitau et al., 1998).

Evidence for the glucocorticoid hypothesis mostly results from animal studies which allow experimental stress induction using various manipulations (e.g., inhibition of 11ß-HSD2, administration of exogenous steroids) to induce fetal exposure to glucocorticoids. Lower birth weight and alterations of neuroendocrine function were linked with increasing glucocorticoid levels (Cottrell et al., 2012; Harris and Seckl, 2011). Human studies link impaired placental barrier function with negative birth outcomes moderated by prenatal maternal distress and symptoms of depression or anxiety (O'Donnell et al., 2012). Research on prenatal stress effects and mediating maternal-placental-fetal neuroendocrine mechanism underlying fetal programming cannot draw firm conclusion yet.

Here, we studied a large cohort of women during their 3rd trimester of pregnancy as well as their neonates in order to test the hypothesis that distress during pregnancy is related to HPA system dysfunction as well as anthropometric variation in the neonate.

2. Materials and methods

2.1. Study participants

Data were obtained from a cohort of mothers-to-be (n = 405) and their neonates (n = 405), recruited in the 3rd trimester of pregnancy (4–8 weeks prior to term) from the Rhine-Neckar Region of Germany. All mothers were informed about the 'POSEIDON' (Pre-, Peri- and Postnatal Stress: Epigenetic Impact on Depression) study and provided written informed consent prior to participation. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Medical Faculty Mannheim of the University of Heidelberg as well as the Ethics Commission of the State Chamber of Medicine in Rhineland-Palatinate.

The study protocol included structured interviews, questionnaires and saliva samples of the mothers-to-be in the third trimester of pregnancy as well as birth-related characteristics of the infants collected immediately after delivery. The following inclusion criteria for mothers were applied: main caregiver; German-speaking; age 16–45 years. Exclusion criteria for mothers were: hepatitis B or C or human immunodeficiency virus (HIV) infection; any current psychiatric disorder requiring inpatient treatment; any history or current diagnosis of schizophrenia/psychotic disorder; or any substance dependency other than nicotine during pregnancy. Exclusion criteria for neonates were: birth weight < 1.500 g; gestational age < 30 weeks; or presence of any congenital diseases, malformations, deformations, and/or chromosomal abnormalities.

All data were obtained at two points of time: in the third trimester and at birth, encompassing a broad range of environmental and sociodemographic risk factors, prenatal medical risk factors and general medical characteristics. Prenatal risk factors were assessed by structured interviews and questionnaires. Furthermore, peri- and postnatal risk factors as well as birth characteristics including anthropometrical data and gestational age were collected from maternity records and obstetric records immediately after delivery (for more information about the cohort see Supplementary material).

Six main prenatal stressor scores were derived from psychological questionnaires: Edinburgh postnatal depression scale [EPDS], Perceived