Psychoneuroendocrinology (2015) 56, 62—78

Available online at www.sciencedirect.com

ScienceDirect

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

Prenatal maternal stress predicts stress reactivity at 2½ years of age: The Iowa Flood Study

Erin Yong Ping[a], David P. Laplante[a], Guillaume Elgbeili[a], Katharina M. Hillerer[b], Alain Brunet[a,c], Michael W. O'Hara[d], Suzanne King[a,c,*]

[a] *Psychosocial Research Division, Douglas Mental Health University Institute, Verdun, QC, Canada*
[b] *Department of Obstetrics and Gynaecology, Salzburger Landeskrankenhaus (SALK), Paracelsus Medical University, Salzburg, Austria*
[c] *Department of Psychiatry, McGill University, Montreal, QC, Canada*
[d] *Department of Psychology, University of Iowa, Iowa City, IA, United States*

Received 15 October 2014; received in revised form 19 February 2015; accepted 20 February 2015

KEYWORDS
Prenatal stress;
Cortisol reactivity;
Cortisol stress response;
HPA axis;
Child development

Summary Prenatal maternal stress (PNMS) predicts psychosocial development in offspring. It has been hypothesized that during PNMS, glucocorticoids pass the placenta, reaching the foetus, leading to a long-term reprogramming and dysregulation of the foetal hypothalamic-pituitary-adrenal (HPA) axis. However, results are inconsistent across PNMS studies. One problem may be the confounding of objective degrees of hardship due to the stressor and subjective degrees of distress in the mother. The present study investigated the association between objective and subjective PNMS due to a natural disaster, the June 2008 Iowa floods, and stress reactivity in the offspring at 2½ years of age. Women who were pregnant during the floods were recruited, on average, within three months of the floods and their stress levels assessed. Mothers and their toddlers ($n = 94$ dyads) participated in a brief mother—toddler separation to induce physiological stress responses in the offspring. Salivary cortisol samples were collected four times during the procedure. We computed absolute change in cortisol (baseline to 20-minute post-stressor; baseline to 45-minute post-stressor) and Area Under the Curve with respect to increase and ground (AUCi; AUCg). Objective and subjective PNMS were positively correlated with AUCi, as was timing in gestation: the later in pregnancy the exposure occurred, the greater the cortisol increase. Controlling for objective hardship and other covariates, sex-by-subjective PNMS interactions showed a significant and positive association between subjective PNMS and

* Corresponding author at: McGill University & Principal Investigator, Douglas Mental Health University Institute, Perry Pavillion, E-3131, 6875 LaSalle Blvd., Verdun, Quebec H4H 1R3, Canada. Tel.: +1 514 761 6131 x2353.
E-mail address: suzanne.king@mcgill.ca (S. King).

http://dx.doi.org/10.1016/j.psyneuen.2015.02.015

Absolute Increase (45 min) and AUCi in females only, with little effect in males. These results suggest that PNMS leads to long-term alterations in the functioning of the HPA axis, evident as early as 30-months of age.

1. Introduction

Prenatal maternal stress (PNMS) affects birth outcomes (Mulder et al., 2002), and subsequent cognitive and psychosocial development in infants (Buitelaar et al., 2003) and children (O'Connor et al., 2003). Studying disaster-related PNMS in Project Ice Storm, our group has replicated many of the above-mentioned findings. For example, the severity of subjective and/or objective PNMS predicts birth outcomes (Dancause et al., 2011), more immature play styles (Laplante et al., 2007), deficits in cognitive and language functioning (Laplante et al., 2008), higher rates of obesity (Dancause et al., 2012), and minor physical anomalies, such as fingerprint asymmetry (King et al., 2009). Overall, these results suggest that PNMS has long-lasting effects on infant development that persist into late childhood and early adolescence, and that objective and subjective PNMS have differential effects depending on the outcome of interest.

The growing body of literature linking PNMS to negative outcomes has lead researchers to focus their attention on the biological mechanisms of PNMS. The hypothalamic—pituitary-adrenal (HPA) axis is often implicated in PNMS effects since altered HPA axis activity is commonly associated with many of the observed outcomes (Hunter et al., 2011). Maternal stress is transmitted to the foetus via high levels of glucocorticoids (GCs) (Barbazanges et al., 1996); maternal and foetal cortisol levels are positively correlated (Gitau et al., 2001). While the foetus is normally protected from maternal cortisol via 11β-hydroxysteroid dehydrogenase-2 (11β-HSD2), a placental enzyme that converts cortisol to its inactive form, cortisone, evidence of 11β-HSD2 downregulation in times of increased maternal stress has been reported (Mairesse et al., 2007).

Studies have investigated the impact of PNMS on the development of the foetal HPA axis, and how this impact presents itself throughout postnatal development. In rodents and nonhuman primates, PNMS has been associated with higher basal levels of GCs in offspring, compared to controls (Clarke et al., 1994; Fameli et al., 1994; Coe et al., 2003; Emack et al., 2008). In humans, prenatal and postnatal stress exposure, in the form of higher maternal morning cortisol levels, greater worries during pregnancy, parenting stress, and PTSD, have been associated with higher basal and diurnal cortisol levels in infants and children (Gutteling et al., 2004; Saridjan et al., 2010), as well as lower basal cortisol levels (Yehuda et al., 2005).

PNMS also affects the HPA axis with respect to stress reactivity in animal offspring (Weinstock et al., 1992); rats and nonhuman primates exposed to maternal stress in utero release more GCs in response to stress than controls (Fride et al., 1986; Takahashi and Kalin, 1991; Clarke et al., 1994; Coe et al., 2003). However, offspring whose mothers were exposed to stress prenatally have also been found to exhibit lower or blunted GC levels in response to stressful stimuli (Fameli et al., 1994; Emack et al., 2008). In humans, different experimental paradigms have been used to activate the HPA axis, with the aim of eliciting a change in cortisol levels in infants (noise burst, arm restraint, bathing, vaccination, still-face procedure, and maternal separation-reunion stress), children (vaccination), and adults (Trier Social Stress Test) (Gutteling et al., 2004; Brennan et al., 2008; Entringer et al., 2009; Grant et al., 2009; Tollenaar et al., 2011; O'Connor et al., 2013). From these studies, higher levels of prenatal anxiety, psychosocial stress, maternal cortisol levels, and pregnancy-related anxiety have been associated with increases (Brennan et al., 2008; Entringer et al., 2009; Grant et al., 2009), decreases (Tollenaar et al., 2011), dampened or blunted changes (O'Connor et al., 2013), or no change (Gutteling et al., 2004) in cortisol levels in offspring in response to stress. Collectively, these results suggest that PNMS leads to dysregulated functioning of offspring's HPA axis. Moreover, the inconsistencies across findings, possibly attributable to differing methodologies, highlight the need for further research in this field.

Timing of PNMS exposure and offspring sex have been found to affect the association between PNMS and offspring HPA axis functioning. Huizink et al. (2008) reported second trimester exposure to the Chernobyl disaster of 1986 was associated with higher basal levels of salivary cortisol in adolescent offspring, as was confirmed by Van den Bergh et al. (2008). With respect to sex differences, while female offspring have commonly been reported to be more susceptible to alterations in their physiological and behavioural development than males as a result of prenatal stress exposure (Sandman et al., 2013), little literature exists specifically examining the moderating effect of offspring sex on the relationship between PNMS and cortisol reactivity in human offspring. This is an important area of study as related findings may provide a possible mechanism for the sex difference seen in prevalence rates of psychiatric illness (Fernandez-Guasti et al., 2012). As such, the effects of timing of PNMS exposure and offspring sex were investigated in the present study.

The present study aimed to build on the existing body of literature by examining the association between PNMS and toddler cortisol reactivity. The Iowa Flood Study differentiates itself from other studies in that it examines both subjective and objective levels of PNMS associated with a natural disaster, and subsequent in utero effects that these dimensions of stress can have on the development of exposed offspring. Natural disasters provide unique opportunities to study PNMS because they are ''independent'' events that randomly distribute objective degrees of hardship to a population, irrespective of socioeconomic status, race, age, and/or maternal characteristics, thereby inherently controlling for external factors that may influence a woman's predisposition to stress. Examining stress associated with a natural disaster also allows for the study