Psychoneuroendocrinology 94 (2018) 49–62

Contents lists available at ScienceDirect

Psychoneuroendocrinology

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

Review

# The effect of gestational period on the association between maternal prenatal salivary cortisol and birth weight: A systematic review and meta-analysis

Stephana J. Cherak[a,b,*], Gerald F. Giesbrecht[a,b,c,d], Amy Metcalfe[a,b,e], Paul E. Ronksley[a], Mary E. Malebranche[f]

[a] Department of Community Health Sciences, University of Calgary, 3820 Hospital Drive N.W., Calgary, AB, T2N 4Z6, Canada
[b] Alberta Children's Hospital Research Institute for Child and Maternal Health, Heritage Medical Research Building, 3330 Hospital Drive, N.W., Calgary, AB, T2N 4N1, Canada
[c] Department of Paediatrics, University of Calgary, 2888 Shaganappi Trail N.W., Calgary, AB, T3 B 6A8, Canada
[d] Department of Psychology, University of Calgary, 2500 University Drive N.W., Calgary, AB, T2N 1N4, Canada
[e] Departments of Obstetrics & Gynaecology, 1403 29 Street N.W., Calgary, AB, T2N 2T9, Canada
[f] Department of General Internal Medicine, University of Calgary, 3330 Hospital Drive N.W., Calgary, AB, T2N 4N1, Canada

ARTICLE INFO

*Keywords:*
Pregnancy
Cortisol
Birth weight
Gestational period
Maternal adaptation to pregnancy

ABSTRACT

*Background:* Studies exploring the relations between maternal stress and fetal development show an association between increased maternal stress and adverse birth outcomes. A frequently proposed mechanism linking maternal prenatal stress and adverse birth outcomes is heightened concentrations of maternal cortisol. To date, studies exploring this association have reported conflicting results because of the diverse approaches taken to measuring cortisol and the wide variety of possible birth outcomes explored. To add clarity to the growing body of literature, this systematic review and meta-analysis reports empirical findings on the association between maternal prenatal salivary cortisol and newborn birth weight.

*Methods:* Searches for relevant papers published up until November 2017 were run in MEDLINE, EMBASE, PsycINFO, and CINAHL. Non-English language papers were included and experts were contacted when necessary. We included data from human observational studies that were designed or had an underlying intention to measure maternal prenatal salivary cortisol and newborn birth weight. We only included data from measurements of salivary cortisol to prevent rendering of the review unsuitable for meta-analysis. Two independent reviewers assessed study eligibility and quality. For every maternal-fetal dyad, an area under the curve with respect to ground (AUCg) of maternal cortisol was calculated to determine a Pearson's correlation coefficient with a continuous measure of newborn birth weight. Correlation coefficients were then pooled across all stages of gestation. To examine if there are critical gestational periods in which the fetus may be more susceptible to elevated concentration of maternal salivary cortisol, a meta-analysis was performed on separate correlations calculated from gestational trimesters.

*Results:* Nine studies with a total of 1606 maternal-fetal dyads demonstrated a negative correlation between pooled maternal salivary cortisol and birth weight (−0.24, 95% CI −0.28 to −0.20), but there was a high degree of heterogeneity between studies ($I^2$ = 88.9%). To investigate heterogeneity, subgroup analysis by trimester of the pooled correlation between salivary cortisol and birth weight was performed with the following correlations found: first trimester, −0.18 (95% CI −0.32 to −0.03, $I^2$ = 97.3%); second trimester, −0.20 (95% CI −0.28 to −0.12, $I^2$ = 98.3%); and third trimester, −0.30 (95% CI −0.33 to −0.26, $I^2$ = 85.4%).

*Discussion:* A consistently negative association was observed between maternal cortisol and infant birth weight. The review highlights specific gaps in the literature on the relationship between maternal prenatal salivary cortisol and newborn birth weight. Although a significant negative correlation was found, substantial heterogeneity of effects and the likelihood of publication bias exist. The third trimester was revealed as a possible

* Corresponding author at: University of Calgary Department of Community Health Sciences 355, 3820–24 Avenue NW., 3820 Hospital Drive N.W.T2N 4Z6, Calgary, AB, Canada. T3B 2X9, Phone.: +4038600178.
*E-mail address:* sjcherak@ucalgary.ca (S.J. Cherak).

https://doi.org/10.1016/j.psyneuen.2018.04.023
Received 25 January 2018; Received in revised form 21 April 2018; Accepted 23 April 2018

critical gestational period for heightened maternal cortisol concentration to affect birth weight. Challenges faced in this body of research and recommendations for future research are discussed.

## 1. Introduction

Elevated maternal stress (e.g., psychological, physical, nutritional) during pregnancy and the accompanying changes in stress hormones are hypothesized to be key mechanisms linking early fetal development with later life disease (Alder et al., 2007). There is growing evidence suggesting that the stress hormone, cortisol, has specific and substantial effects on birth phenotype (Kivlighan et al., 2008; Obel et al., 2005; Sandman et al., 2006). Although many studies have found an association between heightened maternal cortisol levels and adverse birth outcomes, such as low birth weight and preterm birth (Diego et al., 2009; Field et al., 2008; Ghaemmaghami et al., 2014; Hodyl et al., 2010), several large studies have not (Goedhart et al., 2010; Li et al., 2012). In the present review, we critically appraise the current literature to interrogate the widely held belief that heightened maternal cortisol associates with decreased newborn birth weight.

### 1.1. Developmental origins of health and disease (DOHaD) hypothesis

The Developmental Origins of Health and Disease (DOHaD) hypothesis posits that variations in the quality of fetal development play a significant role in establishing vulnerabilities for chronic disease later in life (Barker, 1998, 2000; Godfrey et al., 2010). The term 'developmental programming' was popularized by David Barker in the 1990s to describe a conceptual framework based on his epidemiological studies, such that adverse perinatal environments can affect the function of various fetal tissue and organ systems, and consequently, the way they develop (Barker, 1998; Godfrey and Barker, 2000). Since then, numerous studies consisting of basic research, clinical and epidemiological studies have revealed that various mechanisms that regulate disease susceptibility can be traced back to fetal life and early infancy (Delisle and Simard, 2002; Hochberg et al., 2011; Shukla et al., 2014). The importance of development during these early periods of life is now well established and is considered a strong predictor for non-communicable disease in adulthood (Godfrey and Barker, 2000).

The DOHaD hypothesis argues that there are critical periods of rapid development during which the fetus is particularly vulnerable to intrauterine exposures. Exposures during these critical periods of gestation can therefore alter the developmental trajectory of the fetus, resulting in structural and functional changes in its cells, tissues and organ systems (Barker and Osmond, 1986; Berge et al., 1996; Gluckman et al., 2010).

### 1.2. The hypothalamic pituitary adrenal (HPA) axis

The hypothalamic pituitary adrenal (HPA) axis is a complex signaling system involving three endocrine glands: the hypothalamus, the pituitary gland and the adrenal gland. In humans, upon activation of the HPA axis, the hypothalamus releases corticotrophin releasing hormone (CRH), which in turn stimulates the pituitary gland to release adrenocorticotrophin hormone (ACTH) (Arafah, 2006; Stratakis and Chrousos, 1995). ACTH acts on the adrenal cortex to release cortisol into the bloodstream, which is the end product of the HPA axis. The hypothalamus is sensitive to circulating concentrations of cortisol which inhibits further release of CRH, thus forming a negative feedback loop that allows the system to return to baseline (Gunnar and Quevedo, 2007). Cortisol concentrations may become chronically heightened with repeated exposures to stressors (de Weerth et al., 2013).

### 1.3. Changes in maternal HPA axis during pregnancy

Adverse maternal stress during pregnancy is believed to contribute to fetal growth restriction (Entringer et al., 2011). Because the hypothalamic-pituitary-adrenal (HPA) axis is an important player in maternal stress physiology, it is thought that dysregulation or frequent activation of this system during pregnancy is one of the mechanisms that link maternal stress during pregnancy with poor fetal development (Alder et al., 2007). Several studies have shown that the HPA axis remains responsive to stress during pregnancy (Giesbrecht et al., 2013; Giesbrecht et al., 2012; Schulte et al., 1990), however, gestation initiates several additional tightly coordinated processes to enable proper fetal development and gestational success in the face of maternal stress (Huizink et al., 2003; Zijlmans et al., 2013). One of the most extensive alterations is the development of the placenta, which plays essential roles in fetal nourishment, support and protection, as well as in production of several hormones and hormonal mediators (Mulders et al., 1987). Importantly, CRH is secreted by the placenta and is identical to hypothalamic CRH in structure, immunoreactivity and bioactivity (Challis et al., 2013; Mulders et al., 1987). Interestingly, however, the regulation of placental CRH and hypothalamic CRH is tissue specific. Whereas glucocorticoids elicit an inhibitory effect on hypothalamic production of CRH, placental CRH is stimulated by glucocorticoids in a positive feedback loop (Economides et al., 1987). This stimulatory effect results in dramatic increases in cortisol concentrations during pregnancy, peaking in the third trimester at levels three times non-pregnancy levels (Allolio et al., 1990; Jung et al., 2011). Despite these increases in cortisol concentration, the normal diurnal pattern of higher levels in the morning and lower levels in the afternoon and evening is maintained during pregnancy (Allolio et al., 1990; Gutteling et al., 2005a; Kirschbaum and Hellhammer, 1989a; Pruessner et al., 1997a).

### 1.4. The present review

There is significant variability in cortisol measurements during pregnancy across studies, such as inconsistencies in sampling times during the day and gestational week, and several biological materials from which cortisol is measured (e.g., blood, saliva, urine, hair). This variability has rendered earlier systematic reviews unsuitable for conducting meta-analyses (Orta et al., 2017; Seth et al., 2016; Zijlmans et al., 2015). To mitigate the potential heterogeneity in data, a clear primary objective was defined for the present review – to explore the association between maternal prenatal salivary cortisol, expressed as an area under the curve with respect to ground (AUCg), and newborn birth weight expressed as a continuous variable.

Salivary cortisol has frequently been used as a tool for physiologic and diagnostic studies (Clements et al., 2013) Salivary cortisol measures reliably reflect serum levels of unbound cortisol, the biologically active form of cortisol for up to five days Salivary cortisol is a useful and attractive approach to researching cortisol in developmental research.

Computation of an area under the curve (AUC) is a frequently used method in endocrinologic research to estimate circadian changes of hormones and to assess the overall secretion of cortisol over a specific time period (Pruessner et al., 1997b). Two indicators of HPA axis function are commonly used in the literature (Khoury et al., 2015). The 'area under the curve with respect to increase' (AUCi) and the 'area under the curve with respect to ground' (AUCg). With endocrinologic data, it is usually assumed that an AUCg will result in a measure that is more related to total hormonal output. In fact, a recent review characterizing 15 cortisol indices of the HPA axis concluded that an AUCg