The association between circadian cortisol rhythm and psychosocial and socioeconomic factors experienced by pregnant women in the Peel Child Health Study

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Abstract/Introduction
There is evidence that the SAM and HPA pathways are instrumental in mediating the effect of adverse psychosocial and socioeconomic factors that are present during the early life of an individual. Known stressors that may be present during gestation include low income, poor housing, volatile partner relationship and violence; these factors are likely to be mediated via excessively increased cortisol levels. It is proposed to use blood, urine and saliva samples taken, together with questionnaires completed at 18, 26 and 34-week intervals, from 500 pregnant women enrolled into the Peel Child Health Study to study the relationship between diurnal salivary cortisol patterns and the report of maternal stress and hardship. The questionnaires were designed to elicit information about psychosocial and socioeconomic stressors present in the lives of this cohort during their pregnancy. Diurnal salivary cortisol patterns in particular, (and possibly catecholamines, CRH, DHEA-S) will be examined and statistical analyses performed to see if there is any relationship between the questionnaire stressors and the biological stress markers.

Background /Lit Review
The human stress response occurs through at least two interacting pathways or systems, one is through the SAM (sympathetic-adrenal-medullary) axis, via the release of catecholamines (noradrenaline and adrenaline), producing a rapid (within seconds) response. The other pathway, slower and of longer duration, is via the HPA (Hypothalamus-Pituitary-Adrenal Cortex) axis and is thought to play a role in human coping mechanisms. Cortisol, a glucocorticoid hormone is released from the adrenal cortex, under the stimulatory effect of ACTH (adrenocorticotrophic hormone) from the anterior pituitary, which is itself triggered by CRH (corticotropin releasing hormone) from the hypothalamus. Cortisol is released in short bursts (15-30 or so per day) and exhibits a recognisable circadian rhythm. Many factors including level of activity, time of day, medications, sleeping and eating patterns, illnesses and salivary stimulants are known to influence this rhythm of cortisol secretion and must be kept in mind when using cortisol levels as a measure of stress (Hanrahan et al., 2006).

Mammalian glucocorticoids play an important role in growth of the fetus, together with development of its tissues and maturation of its organs, hence effectively preparing the individual for life outside the uterus. The mammalian placenta serves to modulate and filter hormonal signals from the mother, including the glucocorticoid mediators of stress. Under normal circumstances placental 11β-HSD2 (an enzyme) serves to rapidly inactivate physiological glucocorticoids such as cortisol and corticosterone, through conversion to 11-keto forms e.g. cortisone, thus ensuring that the fetus is largely excluded from high glucocorticoid levels (Seckl and Megan 2007).

Excessive, non-physiological maternal and fetal glucocorticoid levels however, have been implicated in human fetal growth retardation, prematurity and low birth weight. Triggers for increased fetal cortisol levels include maternal malnutrition, restricted placental blood flow and placental insufficiency (Seckl and Holmes 2007). External factors, known to cause stress, may also lead to elevated, non-physiological cortisol levels. Some of the later life consequences of low birth weight include obesity together with those other conditions, collectively known as metabolic syndrome including stroke, coronary heart disease, hypertension, NIDDM and overall reduced life expectancy (Seckl and Megan 2007).

Maternal stressors that may be present during gestation, including low income, poor housing, volatile partner relationship and violence may lead to persistent effects throughout a child's life and thus contribute to that individual's allostatic load. The notion of allostatic load (developed by McEwen, 1998) refers to the way in which the wear and tear, experienced during a lifetime is somehow "taken on board" by an individual. McEwen and others have suggested that an organism adapts to the stresses of life by modifying aspects of its internal function (physiology) in response to demands (stresses) that are imposed upon it. In so-doing, the organism acquires an allostatic load of physiological dysregulations that may predispose it to developing pathophysiologies that will characterise its later life (the organism's disease trajectory).

Allostatic load can be predicted by measuring a number of biomarkers including neuroendocrine, immune, metabolic, cardiovascular, respiratory and anthropometric. These adverse consequences are thought to be the product of developmental or fetal programming. The molecular mechanisms thought to be responsible for this programming include permanent changes in the expression of specific transcription factors, in particular that of the glucocorticoid receptor gene. These epigenetic (inappropriate expression or silencing of genes) effects (Egger et al. 2004) are heritable and can be seen in subsequent generations (that are themselves unexposed to exogenous glucocorticoids).

Studies have produced mixed results: Ranjit, Young and Kaplan (2005) reported that diurnal cortisol rhythms were altered in poor women experiencing high levels of material hardship (based on an 8-item composite score) and that their waking cortisol surges were blunted; this supports the notion that the HPA system adapts to chronic stress by means of downregulation. A recent study by Voegtline et al. (2012) reported that levels of maternal salivary cortisol present in low-risk women were unrelated to self-reported psychological measures. The Peel Health Study sample includes many higher-risk women and the data gathered includes not only self-reported measures, but also socioeconomic and psychosocial factors that are known to be stressful.

Aims /Objectives

The aim of this study is to determine whether there is an association between circadian cortisol rhythm (taken from biological data) markers and the various psychosocial and socioeconomic factors (elicited through the questionnaire) experienced by the cohort of pregnant women in the Peel Child Health Study. A positive association may lead to the establishment of an instrument for predicting those women who may be susceptible to such stressors during pregnancy and therefore of transmitting the effects of this stress (in the form of aberrant cortisol patterns) to the developing fetus and hence exposing it to epigenetic factors.

Methodology

Circadian cortisol patterns will be established from salivary samples analysed (by other members of the research team) using LCMS (Liquid Chromatography Mass Spectrometry).
Information about family structure, housing, neighbourhood, work, financial situation, general health, physical activity, lifestyle, feelings, relationships, social support and experience of stressful life events has been gathered from the participants by means of a series of questionnaires completed at gestation intervals of 18, 26 and 34-weeks, with one year follow-up. The questionnaire used is a valid and reliable instrument, currently in use in other local, national and international studies.
This data will be analysed statistically using HLM (hierarchical linear models of regression) suitable for nested data (pregnant women, within the Peel Health area) in order to understand the functional relationships between diurnal cortisol patterns and multiple parameters (stressors) or to determine if those stressful events that a pregnant woman may be exposed to can be used to predict abnormal variations in maternal diurnal cortisol patterns which may influence fetal development and hence predict susceptibility to those disease conditions collectively known as metabolic syndrome.

Significance

If an association can be shown to exist between aberrant (hyperphysiological), salivary, circadian cortisol patterns and gestational stressors in this study, it is envisaged that an instrument or tool may be developed that could predict those women at risk during pregnancy and thus allow early interventions. This may prevent epigenetic programming via the fetal HPA axis and thus reduce the likelihood of developing the metabolic syndrome disorders associated with low birthweight.

References

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Amendment 17/12-14

In conversation with Peel Child Health Study (PCHS) Investigators Prof Brendan Waddell, Phil Stumbles, and Peter Fanklin, and Co-supervisor and Deputy Head of the School of Biomedical Sciences Cyril Mamotte, it was agreed in July 2014 that this enrolment proposal would be extended to include the analysis of blood samples to determine telomere length. An emerging literature indicates that the experience of intimate partner violence during pregnancy is associated with shortened telomere length. Approximately 10% of women enrolled in the PCHS reported at recruitment at 18 weeks in pregnancy that they had experienced being hit, kicked or punched by their partner in the previous 12 months. This violence is perceived to be a major life-stressor and shortened telomere length is believed to be a mechanism in the physiological process whereby the experience of stress during pregnancy has potential long-term harmful consequences for women and their unborn children.