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High maternal cortisol levels during pregnancy are associated with more psychiatric symptoms in offspring at age of nine – A prospective study from Nicaragua

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ABSTRACT

Maternal exposure to stress or adversity during pregnancy has been associated with negative health effects for the offspring including psychiatric symptoms. Programming of the hypothalamic–pituitary–adrenal (HPA) axis has been suggested as one mediating process. In order to investigate possible long term effects of stressors during pregnancy, we followed 70 children and their mothers from pregnancy up to nine years aiming to investigate if maternal cortisol levels and distress/exposure to partner violence were associated with child psychiatric symptoms and child cortisol levels at follow-up. Maternal distress was evaluated using The Self Reporting Questionnaire, exposure to partner violence by an instrument from WHO and child psychiatric symptoms with Child Behavior Checklist (CBCL). We adjusted the analyses for gestational week, gender, SES, perinatal data and maternal distress/exposure to partner violence at child age of nine years. Elevated maternal cortisol levels during pregnancy, as a possible marker of maternal stress load, were correlated with higher CBCL-ratings, especially concerning externalizing symptoms. Maternal cortisol levels during pregnancy were not associated with child cortisol levels at child age of nine years. Maternal distress and exposure to partner violence during pregnancy were neither associated with child psychiatric symptoms nor child cortisol levels. To conclude, intrauterine exposure to elevated cortisol levels was associated with higher ratings on offspring psychopathology at nine years of age. The lack of association between maternal cortisol levels during pregnancy and child cortisol levels does not support the hypothesis of fetal programming of the HPA-axis, but reliability problems may have contributed to this negative finding.

1. Introduction

Maternal exposure to stressors or perceived anxiety during pregnancy may have long term health effects for the offspring (O'Connor et al., 2005; Rice et al., 2007; Talge et al., 2007; Lai and Huang, 2011) including increased risks of deviating behavioral development as well as psychiatric symptoms and diagnoses like Attention-Deficit/Hyperactivity Disorder (ADHD), autism and anxiety (Charil et al., 2010; Sandman et al., 2012; Roberts et al., 2015). The findings of these kinds have inspired researchers to search for the underlying mechanisms. Since exposure to stressors like partner violence and distress have been associated with increased cortisol levels in pregnant women (Valladares et al., 2009) programming of the HPA-axis have emerged as one possible explanation (Beijers et al., 2014). Programming in this respect means changing the functioning of physiological systems in the fetus, either permanently and/or by epigenetic modification of gene expression (Lupien et al., 2009). In line with previous research, we have demonstrated from a resource constrained setting that maternal exposure to stressors during pregnancy as partner violence and low social resources were associated with reduced fetal growth, and that elevated maternal cortisol levels could be seen as a possible mechanism (Valladares et al., 2009). In order to investigate a possible programming effect on the offspring's susceptibility for psychiatric symptoms and regulation of the HPA-axis, we have now followed these children and their mothers from pregnancy up to nine years of age.

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The secretion of cortisol is regulated partly as a stress response with a peak plasma level tens of minutes after initiation, partly as a circadian fluctuation with a high morning increase and a gradual decrease until midnight (Tsigos and Chrousos, 2002; Pariante and Lightman, 2008). During pregnancy, women have elevated cortisol levels, mainly since maternal oestrogen and placental corticotrophin-releasing hormone (CRH) stimulate the maternal HPA-axis, thereby increasing the production of cortisol (Duthie and Reynolds, 2013). By the third trimester, the circulating cortisol is 2–4 times higher than before pregnancy, peaking during 3rd trimester (Allolio et al., 1990; Duthie and Reynolds, 2013). The secretion of cortisol is essential for the fetal development, but may be malicious in high concentrations (Charil et al., 2010). Excessive cortisol crosses the placenta and reaches the child and approximately 40% of the fetus cortisol levels are attributed to the mother's cortisol production (Beijers et al., 2014). The fetus is partly protected from abnormal high maternal cortisol through the placenta enzyme HSD11B2, which converts cortisol into cortisone. However, maternal exposure to stressors not only increases her own circulating cortisol, but also reduces the levels of HSD11B2 (Charil et al., 2010; Beijers et al., 2014) thereby reducing the protective capacity against high cortisol levels. Maternal cortisol levels also affect the production of placental corticotropin-releasing hormone (CRH), resulting in a progressively higher placental CRH (Charil et al., 2010).

Especially the prefrontal cortex, hippocampus and amygdala have been reported to be affected by abnormal maternal cortisol levels (Charil et al., 2010; Beijers et al., 2014). These regions are associated both with the regulation of the HPA-axis and with emotional and cognitive functions (Lupien et al., 2009; Beijers et al., 2014). Several studies have shown an association between higher maternal cortisol levels and shorter gestation at delivery, low birth weight and smaller size of the offspring, both in human research (Beijers et al., 2014; Duthie and Reynolds, 2013) and animal research (Grace et al., 2011; Beijers et al., 2014). Furthermore, antenatal exposure to cortisol has been associated with distractibility and inattention in teenage offspring (Duthie and Reynolds, 2013) and anxiety among preadolescents (Davis and Sandman, 2012).

Even if animal research and theoretical considerations support the hypothesis of programming of the HPA-axis as a mediator of the influence of maternal stressful exposures during pregnancy upon the development of the offspring, previous human studies have been scarce and non-conclusive. In particular, studies beyond infancy and from settings outside Northern America and Europe are lacking. Thus, in this study from Nicaragua we investigate if maternal cortisol levels, distress and exposure to partner violence during pregnancy are associated with child psychiatric symptoms and child cortisol levels at nine years of age.

2. Methods

2.1. Participants and procedure

Nicaragua is one of the three poorest countries in Latin America with half of the population in poverty. The design is a prospective study, following pregnant women identified in the demographic surveillance site of UNAN-León, Nicaragua in 2002–2003 addressing intimate partner violence (Valladares et al., 2009). A subset of 147 women had also contributed with saliva samples during pregnancy for analysis of cortisol with the aim of studying the association between exposure to partner violence during pregnancy, cortisol levels and intrauterine growth of the child (Valladares et al., 2009). The saliva collection was made during the second or the third trimester (mean week = 29; SD = 6 weeks). Nine years later, seventy (mean age = 31.8 years; SD = 5.7 years) consecutively identified mothers and their children (34 girls, 34 boys, 2 without information about gender) were recruited for follow-up including new questionnaires and saliva sampling from the children for cortisol analyses. The 70 women did not differ from the total subsample of 147 women who collected saliva during pregnancy in 2002–2003 regarding cortisol levels or perinatal data.

These women were now re-interviewed during 2012 by a trained female assistant at child age of nine years, using the same questionnaires regarding partner abuse and maternal distress as during pregnancy (for details see below). The mothers also rated their child's psychiatric symptoms using the Child Behavior Checklist (CBCL, see below). All questionnaires were reviewed by a field supervisor and the main researcher (EV).

2.2. Perinatal data

Data on gestational age, height and weight were collected from the medical record. Gestational age at birth was calculated from the date of the last menstruation period and the Capurro method was used for mothers who did not remember the date of the last menstruation. Preterm birth was considered as gestational age less than 37 completed weeks. Small for gestational age (SGA) was defined as birth weight below the tenth percentile.

2.3. Questionnaires (maternal ratings)

2.3.1. Socioeconomic status

Low socioeconomic status during pregnancy, was defined by four dimensions, scored as 0 or 1 (Pena et al., 2000): 1) Inadequate housing: Having dirtfloor or if the walls had been constructed with materials other than cement; 2) Low school enrollment: One or more children 7–14 years not attending school; 3) High dependency ratio: More than two unemployed persons for each employed person in the household; 4) Low sanitary conditions: In urban areas, sanitary conditions were considered inadequate if no piped water was available inside or outside the house or if there was no flush toilet, while in rural areas, the corresponding conditions were lack of either piped water or a well or lack of a flush toilet or latrine. The composite variable was dichotomized into high (0–1) or low (2–4) socioeconomic status (SES).

2.3.2. Maternal emotional distress

The Self Reporting Questionnaire (SRQ-20) was used to measure emotional distress during the last four weeks, both during pregnancy and at child age of nine years. It includes 20 questions (yes/no) on depression, insecurity, anxiety, fear and defenselessness. The scale is used by the national mental health program of the ministry of health which recommends a cut off at >6 points (MINSA, 1998), which was applied in this study.

2.3.3. Abuse against women

Violence was measured through a Spanish version of the questionnaire developed by the WHO Multi-Country Study on Women's Health and Domestic Violence against Women (World Health Organization, 2005; Garcia-Moreno et al., 2002) that includes different dimensions of partner violence (emotional, physical and sexual), in total 13 items (yes/no). Repeated yelling, humiliating, and threatening acts by the male partner were considered emotional abuse (in total four items). Physical abuse was defined as one or more intentional acts of physical aggression perpetrated by the male partner during the current pregnancy with the potential of causing harm, injury or death (six items). Sexual abuse was considered abuse of force, coercion or psychological intimidation by the male partner to force the woman to engage in a sex act (three items). The women were asked if they had been exposed to partner