The relationship between cortisol concentrations in pregnancy and systemic vascular resistance in childhood

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A B S T R A C T

Objective: To assess the relationship between cortisol concentrations in the last trimester of pregnancy and systemic vascular resistance — SVR in childhood.

Materials and methods: This study is part of a cohort involving 130 Brazilian pregnant women and their children, ages 5 to 7 years. Maternal cortisol was determined in saliva by an enzyme immunoassay utilizing the mean concentration of 9 samples of saliva (3 in each different day), collected at the same time, early in the morning. SVR was assessed by the HDI/PulseWave CR-2000 Cardiovascular Profiling System®. Socioeconomic and demographic characteristics and life style factors were determined by a questionnaire. The nutritional status of the women and children was assessed by the body mass index — BMI. The association between maternal cortisol and SVR in childhood was calculated by multivariate linear regression analysis.

Results: There were statistically significant associations between maternal cortisol and SVR (p = 0.043) and BMI-z score of the children (p = 0.027), controlling for maternal BMI, birth weight, age, and gender of the children.

Conclusion: As far as we know this is the first study in the literature assessing the association between cortisol concentrations in pregnancy and SVR in childhood. Overall, the data suggest that exposure to excess glucocorticoid in the prenatal period is associated to vascular complications in childhood, predisposing to cardiovascular diseases in later life.

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1. Introduction

Prenatal overexposure to glucocorticoids may “program” a range of tissue-specific effects in the foetus, independently if the exposure is to exogenous glucocorticoids, to active steroids of maternal origin or to the foetus adrenal products. The consequences for animals and humans are consistent with a predomination of cardiometabolic and central nervous system effects [1].

The placenta establishes a barrier to maternal glucocorticoids, by the action of an enzyme — 11β-hydroxysteroid synthase (11β-HSD) which converts cortisol to its much less active form, cortisone. The placental barrier depends on the activity of the enzyme [2,3]. Apparently, small and preterm babies who suffer growth restriction in uterus have a higher chance to present low concentrations of 11β-HSD at birth [4].

The mechanisms of glucocorticoid-programmed adult cardiovascular diseases, including hypertension, are complex. Pathophysiological mechanisms regulating plasma volume, vascular resistance and cardiac output, may all be involved [5].

Exposure to glucocorticoids in the prenatal period causes increases in blood pressure in animal foetuses [6,7] and at birth in animals and preterm infants [8,9]. According to animal studies the timing of exposure to glucocorticoids in pregnancy seems to be very important, as well as the persistence of exposure [10–12].

Studies involving animals have shown that exposure to glucocorticoids in uterus affects foetal and adult vascular responses to vasoconstrictors (suggesting microvascular dysfunction), and also the renin–angiotensin system, predisposing to hypertension [13–17]. There is also evidence that prenatal exposure to glucocorticoids may affect differentially males and females [18,19].

Associations between exogenous or endogenous glucocorticoid exposure in pregnancy and increased vascular resistance have been demonstrated in animal models [20]. Nevertheless, as far as we know, there is no study assessing the association between endogenous glucocorticoid exposure in pregnancy and vascular resistance in humans.
The objective of this study was to assess the relationship between cortisol concentrations in late pregnancy and systemic vascular resistance (SVR) in childhood.

2. Materials and methods

The participants were 130 pregnant women followed from 1997 to 2000 [21], and respective children 5–7 years of age followed from 2004 to 2006 [22] in a cohort study carried out in Jundiaí City, Brazil. The women were recruited at 15 health units and 2 hospitals in the city, for assessment of risk factors for intrauterine growth restriction and prematurity. They were excluded from the study if they presented chronic infectious diseases, metabolic diseases, cardiopathy, mental diseases, hypertension/pre-eclampsia/eclampsia and multiple deliveries. All pregnant women included in the study were apparently healthy, considering that women who present any problem in pregnancy are usually referred to specialized antenatal services. Newborns with Apgar scores in the 1st and 5th minutes suggestive of severe hypoxia were excluded from the study due to the difficulty to assess their anthropometric measurements at the delivery room.

Salivary cortisol concentrations accurately reflect free plasma cortisol levels [23]. Women were assessed at home by field workers as soon as they awake, and instructed not to wash their teeth but to rinse their mouth with water before collection of the saliva samples into "salivette" tubes (Sarstedt Inc., Nümbrecht, Germany), for cortisol determination. The samples were taken in a fasting condition, and the women were not taking medications. Nine samples of saliva (3 in each different day) were collected between 8:30 and 9:00 am to control for diurnal variations in hormonal concentrations. The samples were kept on ice, centrifuged, and stored at −20 °C for a maximum of a month, until assayed. Cortisol was measured with a salivary cortisol enzyme immunoassay kit (Salimetrics, LLC, State College, PA, USA), and the results were expressed as the mean of the 9 measurements. All women were assessed during late pregnancy (mean gestational age in weeks = 35.97; SD = 4.84). Details of the collection of the saliva samples are given elsewhere [24].

Socioeconomic and demographic characteristics and life style factors were evaluated by a general questionnaire. The nutritional status of the women and respective children was assessed by the body mass index — BMI and classified according to the WHO International Classification of BMI for adults [25], and to the Centers for Disease Control and Prevention — CDC classification for children [26]. The participants were weighed on a portable Sohnle® electronic scale, with a precision of 100 g. Height was measured with a SECA wall-mounted stadiometer, with a precision of 0.1 cm. The anthropometric measurements were performed according to the recommendations of Jelliffe and Jelliffe [27]. Gestational age was determined by a combination of ultrasonography performed up to the 20th week of gestation, the Capurro method [28] (determined between 12 and 48 h of birth), and information on the date of the last menstrual period (LMP). Birth weight was collected as a known that total cortisol concentrations rise throughout pregnancy [23]. Therefore, the data are presented as quartiles, mean and standard deviation (SD).

According to Table 2, age range of the children varied from 5 years and 4 months (64 months) to 7 years and 6 months (90 months). Only 5 (3.8%) children had a low weight at birth, and the same number of children had a gestational age <37 weeks. The majority of the children showed a "normal weight", according to the CDC growth

### Table 1

<table>
<thead>
<tr>
<th>Variables</th>
<th>N</th>
<th>%</th>
<th>Mean (SD)</th>
</tr>
</thead>
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<td><strong>Age (years)</strong></td>
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<td></td>
<td>31.18 (6.3)</td>
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<tr>
<td>&lt;19</td>
<td>22</td>
<td>16.9</td>
<td></td>
</tr>
<tr>
<td>19–25</td>
<td>54</td>
<td>41.5</td>
<td></td>
</tr>
<tr>
<td>26–35</td>
<td>46</td>
<td>33.4</td>
<td></td>
</tr>
<tr>
<td>≥35</td>
<td>8</td>
<td>6.2</td>
<td></td>
</tr>
<tr>
<td><strong>Education (years)</strong></td>
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<td></td>
<td>6.1 (1.9)</td>
</tr>
<tr>
<td>≤4</td>
<td>29</td>
<td>20.8</td>
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</tr>
<tr>
<td>5–8</td>
<td>54</td>
<td>41.5</td>
<td></td>
</tr>
<tr>
<td>≥8</td>
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<td>37.7</td>
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<td></td>
<td>5.5 (5.4)</td>
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<td>10.0</td>
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</tr>
<tr>
<td>No</td>
<td>117</td>
<td>90.0</td>
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<tr>
<td><strong>Body mass index — BMI (weight/height²)</strong></td>
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<tr>
<td>20–25</td>
<td>42</td>
<td>32.3</td>
<td></td>
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<tr>
<td>25–30</td>
<td>57</td>
<td>43.9</td>
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<td>20.0</td>
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</tr>
<tr>
<td>≥35</td>
<td>5</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td><strong>Cortisol in saliva (nmol/L)</strong></td>
<td></td>
<td></td>
<td>14.24 (8.37)</td>
</tr>
<tr>
<td>≤9.10</td>
<td>33</td>
<td>25.4</td>
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<td>9.11–12.42</td>
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</tr>
<tr>
<td>≥17.12</td>
<td>31</td>
<td>23.8</td>
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</tr>
</tbody>
</table>
The results of the study point to associations between concentrations of cortisol in late pregnancy and SVR and BMI-z score in childhood, controlling for maternal BMI, birth weight, age and gender of the children.

Despite the low adjusted $R^2$ (0.065) value of the multivariate linear regression model (Table 3) the association between maternal cortisol and SVR has probably a biological importance, considering the number of factors that could intervene in this association throughout prenatal life to childhood.

It is important to emphasize that maternal cortisol in pregnancy partly explains SVR in childhood, since additional genetic, epigenetic and environmental factors may also contribute to SVR [35–37].

There was no relationship between concentrations of cortisol and blood pressure of the children (data not shown), although vascular resistance, plasma volume and cardiac output may all be involved in the pathophysiology of hypertension [5].

Past or present exposure to glucocorticoid excess has been considered a condition associated to a high cardiovascular risk [1]. Animal studies have shown that even a single dose of glucocorticoid may alter detrimentally foetal cardiovascular function by causing: 1) an increase in arterial blood pressure, sometimes a transient hypertension [38]; 2) increases in central and peripheral vascular resistance [39–41]; 3) alterations in vascular sensitivity to endothelium-derived factors [13,42].

In animals there are evidence that the gestational timing of glucocorticoid exposure is important in programming arterial pressure: brief expositions in early gestation can permanently alter the arterial pressure of the offspring whereas exposures (single or repeated) in late gestation do not permanently program arterial pressure [43–45].

The long-term consequences of early prenatal cortisol or dexamethasone treatment in sheep show some differences. Both produce hypertension in the adult sheep offspring [46,47] and both produce a decrease in nephron number [48,49]. However, the hypertension in the case of prenatal cortisol exposure is dependent on increased peripheral resistance, whereas that attributable to dexamethasone is dependent upon increased cardiac output [18,50].

Schwab et al. [51] carried out a study involving pregnant sheep to examine glucocorticoid effects on umbilical placental perfusion. The sheep received 2 doses of 12 mg betamethasone (n = 6) or saline (n = 5) intramuscularly 24 h apart, and the results were examined by ultrasound. Maternal blood pressure and uterine flow did not change during glucocorticoid exposure. However, foetal blood pressure increased, and umbilical resistance showed a transient increase after each injection, followed by an increase of umbilical flow that was closely correlated to an increase in foetal heart rate which determines cardiac output of the developing heart.

To determine if early gestation corticosteroid exposure alters subsequent coronary artery reactivity, Roghair et al. [52] administered dexamethasone to pregnant ewes at 27–28 days gestation (term being 145 days). Vascular responsiveness was assessed in endothelium-intact coronary and mesenteric arteries isolated from steroid-exposed and control lambs at 4 months of age. The results demonstrated that early gestation glucocorticoid exposure programs postnatal elevations in blood pressure in pregnant ewes selectively enhance coronary artery responsiveness to second messenger-dependent vasocostricators.

A study carried out by Fletcher et al. [53] investigated the effects of treatment with dexamethasone on ovine foetal (117–120 days; term = 145 days) cardiovascular defence responses to acute hypoxaemia, occurring either during or 48 h following the period of glucocorticoid exposure. This is important because episodes of acute hypoxaemia are common in utero, particularly during labour and delivery [54]. To assess the mechanisms underlying these responses, chemoreflex function and plasma concentrations of catecholamines, neuropeptide Y (NPY) and vasopressin were measured. In control

charts for BMI in childhood [26]. Mean BMI (standard deviation — SD) was 15.67 (1.87). Mean BMI percentile (SD) and mean BMI-z score (SD) were respectively 50.7 (30.61) and −0.005 (1.12). There is no cut-off point for SVR measurements in children. Therefore, the results are presented as quartiles, mean and SD. Systolic and diastolic blood pressure are shown as percentiles, according to the National High Blood Pressure Education Program Working Group on Hypertension Control in Children, Adolescents [30]. Approximately 36% and 6.9% of the children, respectively, had high levels of systolic and diastolic blood pressure, respectively.

There was a positive correlation between maternal cortisol and SVR in children (Spearman correlation = 0.23; p = 0.016). Table 3 shows a multivariate linear regression analysis considering SVR of the children as the dependent variable. There were statistically significant associations between maternal cortisol and SVR (p = 0.043) and BMI-z score of the children (p = 0.027), controlling for maternal BMI, birth weight, age, and gender of the children.

4. Discussion

As far as we know this is the first study in humans assessing the relationship between concentrations of endogenous glucocorticoids in pregnancy and systemic vascular resistance in childhood.
foetuses, acute hypoxaemia led to transient bradycardia, femoral vasoconstriction and significant increases in plasma concentrations of catecholamines, vasopressin and NPY. In foetuses subjected to acute hypoxaemia during dexamethasone treatment, the increase in plasma NPY was enhanced, the bradycardic response was prolonged, and the plasma catecholamine and vasopressin responses were diminished. In foetuses subjected to acute hypoxaemia 48 h following dexamethasone treatment, femoral vasoconstriction and plasma catecholamine and vasopressin responses were enhanced, whilst the prolonged bradycardia and augmented plasma NPY responses persisted. These data show that foetal treatment with dexamethasone modifies the pattern and magnitude of foetal cardiovascular responses to acute oxygen deprivation. Modifications of different mechanisms mediating the foetal defence responses to acute hypoxaemia that occur during dexamethasone treatment may reverse, persist or even become enhanced by 48 h following treatment period.

Molnar et al. [17] was the first researcher to carry out a 5 month follow-up study assessing the effect of antenatal glucocorticoids on vascular resistance. The authors demonstrated that exposure of the foetus to three courses of dexamethasone administered to the pregnant ewe at weekly intervals has persistent effects on the peripheral vasculature of the offspring at 5 months of age, but no change in blood pressure. The results of the study showed an increased sensitivity to endothelin-1 (ET), increased acetylcholine-induced relaxation, abolished N-nitro-L-arginine methyl ester (L-NAME) suppressible vasodilatory response to ET, no changes in endothelial-dependent vasodilatation and in endothelial nitric oxide synthase RNA and protein levels, compared to controls. The authors speculated that the offspring, later in life, probably have a limited ability to increase compensatory vasodilatation, perhaps similar to the exhaustion atrophy seen in other systems that are hyperactive for a long period. As a result vascular tone increases and hypertension consequently supervenes.

In this study besides the positive association between maternal cortisol and SVR in childhood, there was a negative association between maternal cortisol and BMI-z score in childhood, contrary to what we expected. A possible explanation for the finding is the observation of a significant correlation between birth weight and actual weight (r = 0.25; p < 0.001) suggesting that children who are born small probably gained less weight up to 5–7 years of age. The percentage of overweight children (9.2%) was higher than the percentage of overweight children (6.2%) implying that obesity is less important than malnutrition in this paediatric population. These data should be analyzed with caution since both obesity and malnutrition may cause vascular changes secondary to oxidative reactions [55,56], possibly altering SVR.

Overall, the data suggest that exposure to excess glucocorticoid in the prenatal period is associated to vascular complications in childhood.

We advise the development of further large cohort epidemiological studies to assess the concentrations of cortisol in mothers and respective babies/children and its relationship to vascular complications in childhood and cardiovascular diseases in later life. It would also be very interesting to assess 11β-HSD in babies with a wide range of birth weight and gestational age and its relationship with maternal cortisol concentrations.

**Conflict of interest statement**

None declared.

**Ethical consent**

The research has been carried out in accordance with the Declaration of Helsinki of the World Medical Association, and has been approved by the Ethics Committee of the School of Public Health, University of São Paulo.

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**References**

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