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Effects of maternal cortisol during pregnancy on children's blood pressure responses

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Abstract

Background: Effects of birth weight on subsequent blood pressure are well established. Predominantly experimental studies have also reported effects of altered corticosteroid levels on subsequent cardiovascular responses. In the current study we have examined the effects of both birth weight and maternal cortisol levels in a cohort of mothers and their pre-adolescent children.

Procedure: A total of 216 women and their seven-nine year old children comprised the cohort. Women were recruited from the first (71), second (72) and third (73) trimester. Maternal cortisol was measured on a fasting sample taken between nine and 11 am. Children's blood pressure and heart rate were recorded in the resting state, in response to a ten minute video stress challenge and during recovery. Resting values, incremental responses to stress and recovery were evaluated.

Observation: Maternal cortisol levels increased with duration of pregnancy. There were inverse correlations between birth weight and all haemodynamic measures. There were positive associations between maternal cortisol and children's haemodynamic measures most evident in the first and second trimester. Birth weight was inversely related to maternal cortisol. In multiple regression analyses the effects of maternal cortisol were more consistent than those of birth weight.

Conclusion: Both birth weight and maternal cortisol are predictive of children's resting and stress modulated haemodynamic measures. The effects of birth weight may partly mediate the effects of maternal cortisol.

Introduction

Previous studies have demonstrated effects of low birth weight on the development of cardiovascular disease later in life [1]. Elevated blood pressure is a major risk factor for cardiovascular disease and effects of birth weight have been shown on subsequent blood pressure in preteen age children and adults [2,3]. Low birth weight has also been associated with increased blood pressure variability [4]. A number of studies have shown strong blood pressure tracking from childhood through to later life [5]. Furthermore both blood pressure variability in children [6] and cardiovascular reactivity to stress in young adults and school age children has been shown to predict future blood pressure [6,7]. Thus effects of birth weight on blood pressure and blood pressure response to stress in children are likely to be informative on the risk of hypertension and elevated risk of cardiovascular disease later in life.

Studies, principally from experimental animals, have also demonstrated effects of exogenous or endogenous maternal adrenal steroids on cardiovascular and stress responses amongst progeny despite the protective effect of placental 11 β hydroxysteroid dehydrogenase type 2 [8,9]. In contrast to an extensive animal literature, there are few human studies to test the potential effect of maternal corticosteroid levels on the cardiovascular responses of the offspring although studies have reported effects of prenatal maternal stress [10,11].

In the current study we have examined effects of maternal cortisol and of birth weight on children's rest and stress affected blood pressure and heart rate. In view of the known changes in circulating cortisol with duration of pregnancy and the possibility that effects may be gestation dependent, we recruited women from all three trimesters [12].

Methods

Ethics

The study was approved by the Ethics Committee, the 1st Affiliated Hospital of Xi'an Jiaotong University. Written informed consent was obtained from mothers and on behalf of their children, as approved by the Ethics Committee. Verbal consent was also obtained from children prior to their assessment.

Subjects and Biochemical Measurements

The cohort consisted of 216 mothers and children (from an initial cohort of 231 women as 15 were lost to follow up). 71 mothers were assessed for plasma cortisol during the first (≤ 16 weeks), 72 during the second (16–28 weeks) and 73 during the third (28–42 weeks) trimester. Venous blood samples were taken between nine and 11 am, in the fasting state. The samples were immediately put on ice and the obtained serum was frozen at -80°C.

Samples were subsequently thawed for determination of cortisol levels by radioimmunoassay (Jiuding Biotechnology, Tianjin, China) as in the previous study [13] at the hospital chemical pathology department and in accordance with the manufacturer's instructions. Coefficient of variation within each batch was <5%. Blood glucose was also measured using routine methodology in the hospital chemical pathology department. Children, who were all full term, were tested when aged between seven-nine years. None of the mothers or children had known cardiovascular or endocrine disorders.

Video stress test and measurement of haemodynamic indices

Measurement of children's cardiovascular response to a video game task was undertaken on a weekend at hospital-based offices. All studies were performed under standardized conditions, in the fasting state between nine and 11 am and at least 30 min following collection of a venous blood sample. The task involved playing video games (Breakout; Atari, Sunnyvale, CA) lasting a total of approximately ten minutes as previously described in detail [14]. Blood Pressure (BP) and heart rate (HR) were measured with an appropriately sized BP cuff connected to the children's non-dominant arm from a digital BP monitor (Omron HEM-907, Kyoto, Japan). BP and HR were measured before [rest BP (rBP) and rest HR (rHR)]; during and after video game plays. Three resting BP and HR measurements were obtained after the child had sat quietly for at least two minutes. The average of the last two measures was used in this analysis. HR and BP measurements were taken in duplicate starting two and five minutes after the onset of the video game and five minutes after its completion. The average of the two measurements was used on each occasion. Children continued playing during the measurements but without any speech or extraneous other movement. The response to stress ($\Delta_{\text{stress}}\text{HR}$ and $\Delta_{\text{stress}}\text{BP}$) was taken as the maximum increase in HR and BP between the resting values and those obtained during the video game. Recovery from stress was evaluated as the difference between the recovery and rest values (Δ_{recovery}).

Statistical Analysis

Statistical analysis was undertaken with SPSS v19. Results are given as mean $\pm$ sd or N. Associations between variables were examined by Pearson's correlation coefficient and r values are reported. Regression analyses were undertaken with forced entry. Statistical significance was defined as $p < 0.05$.

Results

All the mothers were in their first pregnancy. None smoked cigarettes during their pregnancy (and only four were smoking prior to their pregnancy). Maternal cortisol values and mothers demographics are shown in Table 1. There was a progressive increase in plasma cortisol during pregnancy with concentrations being significantly lower in trimester one than trimesters two and three.

All the children were full term and were studied when aged between seven and nine years. Children's characteristics, including birth weight are shown in Table 2. Five percent of the children had a birth weight <2.5 Kg (the usual definition of low birth weight). Correlations between maternal cortisol and birth weight were -.322 ($p=0.006$), -.229 ($p=0.043$), -.193 ($p=0.103$) for trimesters one, two and three respectively (Fig 1). Children's resting haemodynamics are shown in Table 2. Heart rate and blood pressure increased in response to the video stress as indicated in Table 2.

Birth weight was negatively related with resting HR, SBP and DBP and also with the video stress induced increments in these measures (Table 3, Fig 2). In view of the difference in maternal cortisol between the trimesters, correlations were undertaken separately for each trimester between maternal cortisol and the rest and stress haemodynamic measures. Correlations were more evident for trimesters one and two than for trimester three (Table 3, Figs 3-5).

As noted there were correlations between maternal cortisol and birth weight as well as between birth weight and the haemodynamic parameters. We therefore undertook regression analyses including both maternal cortisol and birth weight as independent variables and the haemodynamic measure as dependent variable. These were performed separately for each trimester (Tables 4–6). As can be seen significance was more evident for cortisol than birth weight in all trimesters, whilst effects were again less evident in trimester three than in trimesters one and two.

The possibility that effects of maternal cortisol were mediated by birth weight was examined by undertaking regression analyses for the effects of cortisol on birth weight (putative mediator) and, if significant, the effects of birth weight on the haemodynamic variable. In the first trimester cortisol was a predictor of birth weight with a β coefficient of -.323 ($p=0.006$). Birth weight was a significant predictor of rHR ($\beta=-.368$, $p=0.006$), $\Delta_{\text{stress}}\text{SBP}$ ($\beta=-.274$, $p=0.021$), $\Delta_{\text{recov}}\text{SBP}$ ($\beta=-.256$, $p=0.031$), $\Delta_{\text{stress}}\text{DBP}$ ($\beta=-.409$, $p<0.001$) and $\Delta_{\text{recov}}\text{DBP}$ ($\beta=-.354$, $p=0.002$). Effects on $\Delta_{\text{stress}}\text{HR}$ ($\beta=-.227$) and rSBP ($\beta=0.097$) failed to achieve statistical significance ($p=0.056$ and 0.099 respectively). In the second trimester the effects of maternal cortisol on birth weight were of borderline significance ($\beta=-.229$, $p=0.052$) and effects of birth weight limited to $\Delta_{\text{stress}}\text{SBP}$ ($\beta=-.283$, $p=0.016$).

Effects on $\Delta_{\text{recov}}\text{DBP}$ failed to achieve significance ($\beta=-.277$, $p=0.056$). There were no significant effects of maternal cortisol on birth weight in the third trimester.

Discussion

There are a number of findings from the current study. Birth weight was inversely related to resting blood pressure and heart rate and also to video stress induced increments in these measures. Maternal cortisol was positively related to resting and stress haemodynamic parameters throughout pregnancy but such effects were less evident during the third trimester. There was an inverse relation between maternal cortisol and birth weight most evident for the first trimester. In multiple regression analyses including both maternal cortisol and birth weight, the effects of maternal cortisol were more consistent than those of birth weight. Finally results of mediation analysis were consistent with possibility that in early pregnancy the effects of maternal cortisol could in part be mediated by effects of cortisol on birth weight.

In keeping with other recent studies we observed significant differences amongst the trimesters in serum total cortisol [12,15,16]. Cortisol values in the first trimester were higher than those reported by Sandman C et al [16] but lower than those found by two other studies [12,15], although these studies all used different assays. Prepregnancy values were not available in the current study but a study using the same assay reported mean values of 260 and 300 nmol/l in healthy non-pregnant women aged 15 to 29, and 30 to 39 respectively [17]. The rise during pregnancy in this study was less steep than reported in other studies [12,15,16]. There do not appear to be other similar studies in Han Chinese so that is possible this reflects ethnic differences. Thus, for example, studies in Chinese men have identified a circadian pattern in serum cortisol similar to that reported in Caucasian population but with a morning peak occurring approximately two hours earlier than that seen in Western populations [18].

A number of animal studies, principally but not exclusively in rodents, have supported the hypothesis that exposure of pregnant animals to various sorts of stress can influence the cardiovascular and cortisol responses of their offspring [10,11,19,20]. Administration of dexamethasone during pregnancy has also been shown to alter the pattern of cardiovascular responses in offspring in non-human primates [8]. Exogenous dexamethasone has the advantage of being less metabolised by placental 11β hydroxysteroid dehydrogenase type 2 than is the native hormone but studies would suggest that sufficient maternal corticosteroid is able to access the foetal circulation to produce similar effects. Hydrocortisone infusion during pregnancy in sheep affects not only foetal growth but also foetal cardiac parameters and blood pressure [21]. In rats inhibition of 11β HSD with carbenoxolone is

associated with elevated blood pressure in the offspring [22]. It has been hypothesised that dysfunction of the placental glucocortisol barrier may contribute to the link between the foetal environment and adult hypertension in man [23]. Human studies have also reported effects of maternal cortisol on infant neuro and cognitive development. These studies have also identified effects of different magnitude, or indeed opposite effects, at different stages of pregnancy [24-27].

Foetal exposure to increased cortisol, as well as possibly other factors, may then exert antenatal effects on future health through alterations in the Hypothalmo-Pituitary Axis (HPA) axis [10,28-30]. Given the widespread distribution of gluco- and mineralo- corticoid receptors and the existence of both genomic and non-genomic effects, alterations in the HPA axis could be expected to exert a wide variety of effects including on central and peripheral systems relevant to BP and HR control. The observation in the current study that the effects of maternal cortisol were less evident at later stages of pregnancy is consistent with a programming effect on the developing neuro-endocrine system.

A relation between birth weight and children's resting blood pressure, in addition to effects of low birth weight, has been observed previously [2,3]. Such a relationship has not been reported in relation to video stress induced increments in blood pressure although effects on autonomic function have been reported [31]. Blood pressure variability in young adults and children has been shown to be predictive of subsequent hypertension [6,7,32]. The mechanism responsible for the relation between birth weight and later blood pressure is not fully understood and maybe multifactorial. However, the current study raises the possibility that at least part of the effect may related to maternal cortisol elevation.

Low birth weight can result from a number of causes including maternal smoking and prematurity [33]. Neither seems responsible in the current study given the low prevalence of maternal smoking and of prematurity in the cohort. Both are in keeping with other data from China where smoking rates were 52.9% for men but only 2.4% for women [34] whilst low birth weight (<2.5 Kg) was present in five percent consistent with the overall prevalence of low birth weight reported for China [35]. Previous studies have also found a negative relation between prenatal cortisol exposure and foetal biometry measurements as well as estimated and actual foetal weight [36,37]. In contrast to the current study effects were seen both in early and late pregnancy with nearly 20% of the variance in birth weight attributable to salivary cortisol values, even after adjustment for other factors [37]. In a large cohort study examining the effects of antenatal exposure to dexamethasone it was observed that the birth weight of neonates whose mothers had received dexamethasone were lower than in those whose mothers had not [38].

The demonstration that both birth weight and maternal cortisol were predictive of children's rest and stress haemodynamic responses raised the possibility of mediation ie that the effects of maternal cortisol could be operating, partially or completely, through effects of maternal cortisol on birth weight. This possibility was examined in a series of regression analyses examining the relationship between these variables. In the first trimester there was evidence for such effects for a majority of the haemodynamic variables supporting, but not proving, the notion of mediation. This was much less evident in trimester 2 and there was no indication of such an effect in trimester 3. Thus early pregnancy effects of maternal cortisol may include effects on foetal growth which could contribute to the observed relationship between maternal cortisol and children's haemodynamics. However this mechanism is less to play a role at later stages in pregnancy. In addition it is possible that relationships between maternal cortisol and children's blood pressure responses to stress may be due, at least in part, to heritable genetic factors rather than due to pregnancy. Thus both mothers and children may share genetic predisposition to exaggerated effects of stress.

The current study demonstrates a positive association between maternal cortisol levels and children's resting and stress modulated haemodynamics. The known inverse relation between birth weight and blood pressure has been confirmed and extended to stress modulated haemodynamic measures.

Conflict of interest

We declare no competing interests.

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Table 1: Maternal Demographics and Cortisol by Trimester

	Trimester 1	Trimester 2	Trimester 3
Maternal Cortisol (nmol/l)	341±85	371±66**	411±77***
Age (y)	26.9±3.0	26.0±3.0	26.2±3.6
Pre-Pregnancy Weight (Kg)	54.4±4.3	53.3±3.7	51.7±4.4
Height (cm)	161.9±3.0	161.5±3.3	161.0±2.9
Pregnancy Duration at time of Cortisol measurement (weeks)	8.4±1.6 [#]	20.9±4.4***	33.8±3.1***, [#]
Education Level (\$)	4.2±.8	4.0±.8	4.0±.8

Values are mean±sd.

, * p<0.01, p<0.001 respectively, compared with values in trimester 1.

p<0.001 compared with values in trimester 2.

\$ Education level, 1 = not completed primary school, 2 = completed primary school, 3 = completed junior middle school, 4 = completed higher middle school, 5 = completed college or university, 6 = completed post graduate level.

Table 2: Baseline Characteristics of the Children and their Rest and Stress Induced Haemodynamics

Age (years)	7.97±1.12
Gender (M/F)	110/115
Birth Weight (Kg)	3.34±.40
Child's BMI (Kgm ⁻²)	22.88±3.00
rHR (bpm)	78.14±7.04
Δ_{stress} HR (bpm)	16.27±3.22
Δ_{recov} HR (bpm)	4.51±8.57
rSBP (mmHg)	96.25±2.95
Δ_{stress} SBP (mmHg)	17.49±2.49
Δ_{recov} SBP (mmHg)	5.33±5.73
rDBP (mmHg)	67.53±4.50
Δ_{stress} DBP (mmHg)	13.71±2.62
Δ_{recov} DBP (mmHg)	5.73±4.34

rHR, rSBP and rDBP refer to the rest heart rate, systolic and diastolic blood pressure whilst Δ_{stress} values refer to the maximum increase in these variables above resting values in response to the video stress and Δ_{recov} to the difference between rest and recovery.

Table 3: Correlations between birth weight, maternal cortisol and children's haemodynamic measures

	Heart Rate			Systolic BP			Diastolic BP		
	rest	Δ_{stress}	Δ_{recov}	rest	Δ_{stress}	Δ_{recov}	rest	Δ_{stress}	Δ_{recov}
Birth Weight N=216	-.293***	-.180**	-.048	-.203**	-.242***	-.264***	-.180**	-.196**	-.231**
Mat Cortisol (T1) N=71	.388**	.284*	.380**	.220	.436***	.564***	.233	.405***	.643***
Mat Cortisol (T2) N=72	.603***	.344**	.238*	.286*	.612***	.651***	.237*	.397**	.659***
Mat Cortisol (T3) N=73	.259*	.336**	.458***	.218	.263*	.379*	.169	.230	.438***

Correlations for each trimester between maternal cortisol and children's haemodynamic measures. T1, T2 and T3 refer to trimesters one, two and three. Correlations between birth weight and haemodynamic parameters were for all trimesters combined.

r values (Pearson) are shown with statistical significance shown in brackets.

*, **, *** $p < 0.05$, $p < 0.01$, $p < 0.001$ respectively.

Table 4: Results of Multiple Regression Analyses for Trimester 1

	Cortisol		Birth Weight		Overall r
	β	Partial Correlation	β	Partial Correlation	
rHR	.301*	.307	-.271*	-.278	.465***
Δ_{stress} HR	.235	.229	-.152	-.150	.318*
Δ_{recov} HR	.382**	.364	.004	.004	.380**
rSBP	.175	.169	-.141	-.192	.257
Δ_{stress} SBP	.388**	.382	-.149	-.157	.438***
Δ_{recov} SBP	.538***	.527	-.083	-.095	.570***
rDBP	.197	.189	-.113	-.110	.257
Δ_{stress} DBP	.306**	.317	-.311**	-.327	.501***
Δ_{recov} DBP	.591***	.598	-.164	-.203	.662***

The Table shows results of regression analyses with each specified haemodynamic variable as the dependent variable and including both maternal cortisol and birth weight as independent variables. No other independent variables were included. The standardized β coefficient, partial correlation and overall r are shown.

*, **, *** p<0.05, p<0.01, p<0.001 respectively.

Table 5: Results of Multiple regression Analyses for Trimester 2

	Cortisol		Birth Weight		Overall r
	β	Partial Correlation	β	Partial Correlation	
rHR	.610***	.597	-.030	-.036	.604***
Δ_{stress} HR	.323**	.319	-.089	-.093	.354*
Δ_{recov} HR	.236	.230	-.100	-.100	.238
rSBP	.236*	-.260	-.098	-.100	.301*
Δ_{stress} SBP	.577***	.586	-.151	-.186	.629***
Δ_{recov} SBP	.656***	.632	-.082	-.105	.656***
rDBP	.215	.214	-.096	-.096	.255
Δ_{stress} DBP	.381**	.375	-.070	-.074	.402**
Δ_{recov} DBP	.663***	.652	.018	.023	.660***

The Table shows results of regression analyses with each specified haemodynamic variable as the dependent variable and including both maternal cortisol and birth weight as independent variables. No other independent variables were included. The standardized β coefficient, partial correlation and overall r are shown.

*, **, *** p<0.05, p<0.01, p<0.001 respectively.

Table 6: Results of Multiple regression Analyses for Trimester 3

	Cortisol		Birth Weight		Overall r
	β	Partial Correlation	β	Partial Correlation	
rHR	.216	.220	-.222	-.226	.264*
Δ_{stress} HR	.333**	.328	-.014	-.015	.336*
Δ_{recov} HR	.478***	.469	.106	.117	.470***
rSBP	.190	.190	-.141	-.142	.258
Δ_{stress} SBP	.266*	.261	.018	.018	.263
Δ_{recov} SBP	.343**	.347	-.191	-.203	.433**
rDBP	.145	.144	-.116	-.125	.209
Δ_{stress} DBP	.250	.246	.102	.103	.251
Δ_{recov} DBP	.441***	.434	.018	.019	.438**

The Table shows results of regression analyses with each specified haemodynamic variable as the dependent variable and including both maternal cortisol and birth weight as independent variables. No other independent variables were included. The standardized β coefficient, partial correlation and overall r are shown.

*, **, *** p<0.05, p<0.01, p<0.001 respectively.

Figure Legend

Figure 1: Scatterplot and linear regression between birth weight and maternal cortisol shown separately for each trimester.

** $p < 0.01$

Figure 2: Scatterplot and linear regression of the relation between maternal cortisol and childrens haemodynamic responses for trimester 2.

*, **, ***, $p < 0.05$, $p < 0.01$, $p < 0.001$

Figure 1

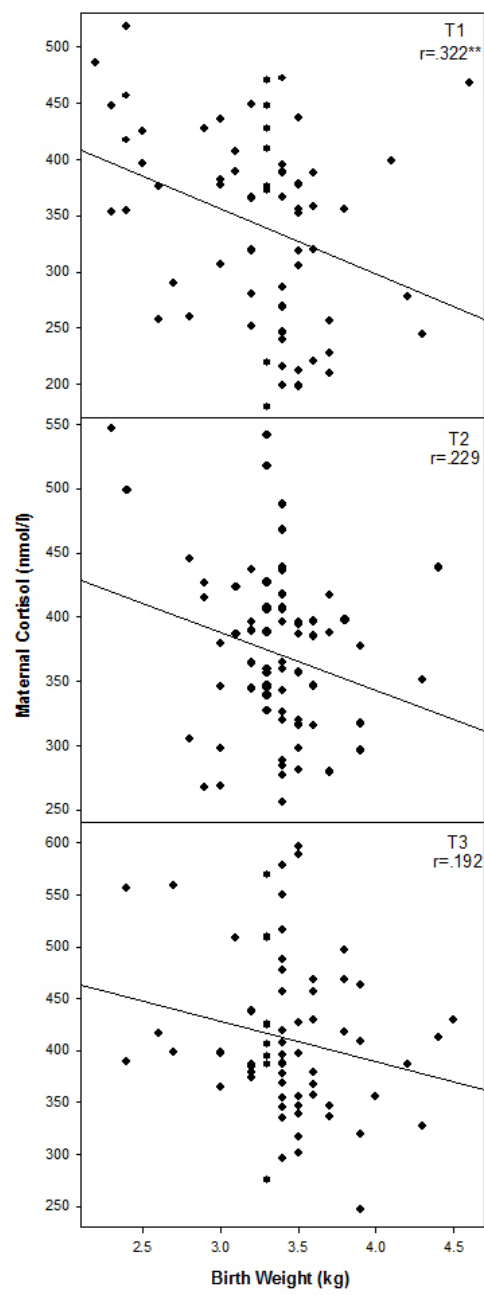


Figure 2

