CLINICAL STUDY

Birthsize, gestational age and adrenal function in adult life: studies of dexamethasone suppression and ACTH_{1–24} stimulation

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Abstract

Objective: Several studies show that low birthweight is associated with long-term alterations in the function of the hypothalamic–pituitary–adrenal axis (HPAA). We recently reported that the relationship between birthweight and fasting serum cortisol concentrations differed according to the gestational age of the babies, suggesting that both hypercortisolism and hypocortisolism could be a consequence of impaired fetal growth. We have now extended these findings by examining the relationship between birthweight, gestational age and tests of adrenal suppression and stimulation.

Design: Prospective birth cohort study.

Subjects and methods: We studied 165 women (mean age 71.3 years) born at term in Helsinki, Finland, between 1924 and 1933, whose body size and gestational age at birth were recorded. These women underwent an overnight 0.25 mg dexamethasone suppression test followed by a 1 µg ACTH_{1–24} stimulation test.

Results: In all women combined, low birthweight was associated with lower total ($P = 0.03$) and free ($P = 0.02$) cortisol concentrations following dexamethasone. However, these relationships were dependent on gestational age at birth, interactions between the effects of birth size and gestational age on dexamethasone responsiveness being statistically significant. To demonstrate these interactions, we divided the study population into two groups according to gestational age. In subjects born at 40 weeks of gestation or more, low birthweight was strongly associated with enhanced dexamethasone suppression ($P = 0.003$ for total and $P = 0.0004$ for free cortisol), while in subjects born before 40 weeks of gestation there was no association. There was, however, no correlation between birth size and the adrenal response to ACTH_{1–24}.

Conclusions: These findings reinforce our suggestions that events during prenatal life may lead to both up-regulation and down-regulation of the HPAA.

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Introduction

Programming of an individual's hypothalamo–pituitary–adrenal axis (HPAA) by the *in utero* hormonal and nutritional environment may be important in linking early life events with adult disease. This hypothesis is supported by a substantial body of evidence from both animal and human studies (1), which together suggest that increased prenatal glucocorticoid exposure is linked with small size at birth and subsequent HPAA hyperactivity predisposing to cardiovascular risk factors. However, there are inconsistencies in recent observations in middle-aged men and women. In most studies, low birth weight has been associated with

higher fasting plasma (2, 3) or adrenocorticotrophin (ACTH)-stimulated (4, 5) cortisol, whereas others have shown no correlation with HPAA activity (6, 7) or even a reverse association (8). Interestingly, considerably elevated fasting plasma cortisol concentrations have been found in young adults who were born pre-term with intrauterine growth restriction (9).

In a recent study we proposed an explanation for these discrepancies by showing that the correlation between birth weight and fasting serum cortisol in elderly men and women differs according to gestational age at birth. Among subjects born at less than 39 weeks of gestational age, serum fasting cortisol concentrations fell with increasing birthweight, while among

those born at 40 weeks or more, the trend with birthweight was reversed (10). As fasting serum cortisol concentration is an imprecise measure of HPAA activity, we have conducted the present study to verify this finding by a more detailed analysis of HPAA function. We decided to focus on women because relationships between birthweight and detailed HPAA tests have previously been reported in men (5) but not in women.

Methods

Study population

The original study cohort consists of 7086 singleton individuals who were born between 1924 and 1933 at Helsinki University Central Hospital, who went to school in the city of Helsinki and were resident in Finland in 1971. Each member of the study cohort had a detailed birth record (11) which included birthweight, length and gestational age at birth. Ponderal index was calculated as birthweight (kg)/[length at birth (m)]³. Of the original study cohort, 157 men and 264 women born at term (37 weeks of gestation or more) have previously taken part in a clinical examination which included measurements of fasting plasma cortisol and an oral glucose tolerance test (10, 12).

Design

Of the 264 term-born women who had attended the clinical examination, 165 took part in a more detailed examination of HPAA function. We chose to study women because relationships between birth weight and detailed tests of HPAA function have previously been reported in men (5) but not in women. These women ingested 0.25 mg dexamethasone (Dexametason, Orion Pharma, Espoo, Finland) at 2200 h, fasted overnight, and attended the clinic at 0830 h the following morning. An intravenous butterfly cannula was inserted, and, after 30-min rest, a baseline blood sample was obtained before 1.0 µg freshly diluted ACTH_{1–24} (Synacthen, Novartis Pharma, Basle, Switzerland) was injected as a bolus with a 10 ml saline flush. Venous blood samples were obtained at 20, 30, 40 and 60 min after the ACTH_{1–24} administration and spun immediately; serum was frozen at –70 °C until analysis.

Anthropometric and blood pressure measurements were carried out as described (12). The 165 subjects were interviewed about their current health and use of medication. Eleven subjects reported having depression diagnosed by a physician, 22 subjects had coronary heart disease and 70 subjects hypertension. These conditions were not associated with any of the HPAA function tests. Two subjects reported receiving oral glucocorticoid treatment and were excluded from further analysis. Twelve subjects used inhaled

glucocorticoids. These subjects had lower serum cortisol concentration than those not receiving any glucocorticoid, both at baseline (geometric mean 80 vs 137 nmol/l, $P = 0.04$) and at peak after ACTH stimulation (mean 375 vs 465 nmol/l, $P = 0.01$) and were thus excluded from further analyses. This left us with a study population of 151.

The study protocol was approved by the Ethics committee of Internal Medicine at Helsinki University Central Hospital. Written informed consent was obtained from each subject.

Biochemical analyses

Plasma cortisol concentrations were measured using a direct in-house method with antiserum HPS631/1G (Guildhay, Guildford, Surrey, UK; Code S020) and a cortisol-3CMO-histamine-[¹²⁵I] tracer as previously described (13). Inter-assay imprecision (CV%) for low, medium and high quality control samples ranged from 7.4 to 10.3%. A radioimmunoassay (Medgenics Diagnostics, Fleurus, Belgium) was used to determine corticosteroid-binding globulin (CBG) concentration. Free cortisol index was calculated by the formula: FCI = [cortisol (µmol/l)/CBG (mg/ml) × 100] (14).

Data analysis

Glucose, insulin and post-dexamethasone total cortisol concentrations as well as free cortisol index were log-transformed to normality. Multiple linear regression and partial correlation analysis were used to assess associations between variables. All non-categorical data including gestational age and birth measurements were entered in the regression equation as continuous variables. Each regression or correlation analysis included current body mass index (BMI), age and the use of postmenopausal hormone replacement therapy (oestradiol or oestrogen analogue). Confidence intervals of the regression equations are presented as % increase in log-transformed or as a unit increase in non-transformed dependent variables.

Results

The 151 women were aged 71.3 (range 67.6 to 77.5) years. Table 1 shows their birth measurements and results of the clinical examination. As expected the women born after 40 weeks of gestation were heavier and longer at birth, but their ponderal index was similar. At examination, their BMI was greater ($P = 0.01$), but insulin and glucose concentrations were similar when adjusted for BMI. Neither the dexamethasone-suppressed nor ACTH-stimulated peak cortisol concentrations correlated with age or BMI. However, women with a high waist circumference had lower post-dexamethasone cortisol concentrations ($P = 0.02$). The 50

Table 1 Measurements at birth and at examination.

	Gestational age <40 weeks	Gestational age ≥ 40 weeks
	(Mean±S.D. (range))	(Mean±S.D. (range))
No. of subjects	78	73
Gestational age (days) ^a	272.7±5.0 (262–279)	288.1±6.5 (280–305)
Birth weight (g) ^a	3250±376 (2400–4400)	3446±376 (2700–5070)
Length at birth (cm) ^a	49.5±1.5 (46.0–54.0)	50.3±1.5 (46.0–57.0)
Ponderal index (kg/m ³) ^a	26.6±2.2 (20.8–32.4)	27.0±2.0 (21.2–32.3)
Age (years)	70.9±2.5 (67.6–77.5)	71.7±2.6 (67.9–77.5)
Height (cm)	160.7±4.7 (150.8–174.6)	160.0±5.5 (147.8–173.7)
Body mass index (kg/m ²) ^a	26.4±4.4 (16.4–38.4)	28.3±4.3 (19.7–39.5)
Waist circumference (cm) ^b	86.8±10.7 (59.0–110.0)	90.9±10.9 (62.5–119.5)
Estrogen treatment (n)	27 (35%)	23 (32%)
Systolic blood pressure (mmHg)	155±23 (105–209)	159±24 (113–239)
Diastolic blood pressure (mmHg)	87±10 (67–113)	88±9 (72–112)
Oral glucose tolerance test		
Fasting glucose (mmol/l)	5.4 ^c (3.4–8.4)	5.6 ^c (2.9–9.2)
30 min glucose (mmol/l) ^b	9.0 ^c (4.1–13.2)	9.8 ^c (4.9–15.9)
120 min glucose (mmol/l)	7.3 ^c (3.5–18.7)	8.0 ^c (2.2–20.2)
Fasting insulin (IU/l)	8.9 ^c (1.9–51.7)	10.1 ^c (0.8–115.1)
30 min insulin (IU/l)	68.1 ^c (21.0–303.0)	60.8 ^c (9.3–266.0)
120 min insulin (IU/l)	71.3 ^c (14.7–336.0)	72.3 ^c (10.1–256.9)
Fasting cortisol (nmol/l)	386±132 (132–673)	387±146 (150–973)
Dexamethasone suppression test		
Serum cortisol (nmol/l)	135 ^c (20–528)	139 ^c (25–523)
CBG (mg/l)	56.3±13.1 (16.6–114.3)	59.6±14.7 (33.2–101.3)
Free cortisol index	0.25 ^c (0.04–1.04)	0.24 ^c (0.04–1.29)
ACTH stimulation test		
Peak serum cortisol (nmol/l)	474±115 (54–804)	455±122 (64–864)

^a $P \leq 0.01$.^b $P \leq 0.05$ (unadjusted). No significant difference when adjusted for current BMI.^c Geometric means.

women taking oral oestradiol or oestrogen analogues had higher CBG ($P = 0.05$) and higher peak cortisol concentrations ($P = 0.006$), but no difference in the post-dexamethasone cortisol. The measurements of CBG, dexamethasone-suppressed and ACTH-stimulated peak cortisol concentrations did not differ by gestational age group (Table 1).

In all women the peak cortisol concentrations were associated with higher plasma glucose concentrations at 0 min ($r = 0.15$; $P = 0.06$), 30 min ($r = 0.20$; $P = 0.02$), and 120 min ($r = 0.14$; $P = 0.09$) after oral glucose challenge, but were unrelated to insulin

concentrations or blood pressure. However, the correlations with glucose concentrations were confined to subjects born before 40 weeks of gestation (Table 2). The 51 (34%) women with impaired glucose tolerance and the 22 (15%) with type 2 diabetes had similar dexamethasone-suppressed cortisol concentrations as the normoglycaemic women, but higher peak cortisol concentrations (498 vs 434 nmol/l, $P = 0.005$). Post-dexamethasone total or free cortisol concentrations were not correlated with BMI, waist circumference, glucose measurements or blood pressure, but were negatively correlated with basal and 30-min insulin

Table 2 Correlation between glucose and insulin concentrations during a 75 g oral glucose tolerance test and total cortisol concentration after dexamethasone (DEX) suppression and ACTH stimulation, according to gestational age at birth. All correlations are adjusted for current body mass index, age, and the use of oral oestrogen treatment. Results are given as correlation (r) with P value in parentheses.

	Gestational age <40 weeks		Gestational age ≥ 40 weeks	
	Cortisol after DEX suppression	Peak cortisol after ACTH stimulation	Cortisol after DEX suppression	Peak cortisol after ACTH stimulation
Glucose 0 min	0.16 (0.2)	0.29 (0.01)	−0.01 (1.0)	0.06 (0.6)
Glucose 30 min	0.09 (0.4)	0.27 (0.02)	−0.06 (0.6)	0.15 (0.2)
Glucose 120 min	−0.01 (0.9)	0.26 (0.02)	−0.10 (0.4)	0.10 (0.4)
Insulin 0 min	−0.25 (0.03)	0.10 (0.4)	−0.04 (0.8)	0.08 (0.5)
Insulin 30 min	−0.23 (0.05)	0.08 (0.5)	−0.02 (0.8)	−0.12 (0.3)
Insulin 120 min	−0.12 (0.3)	0.13 (0.3)	−0.25 (0.04)	−0.05 (0.7)

concentrations in subjects born before 40 weeks of gestation and negatively correlated with 120-min insulin concentrations in subjects born after 40 weeks of gestation. The difference between fasting cortisol and post-dexamethasone cortisol was associated with BMI ($r = -0.17$; $P = 0.04$) but not with waist circumference, glucose concentration or blood pressure.

Table 3 shows that in all women combined, low birthweight was associated with lower cortisol concentrations after dexamethasone suppression. One kilogram increase in birthweight corresponded to a 37% increase (95% confidence interval (CI) 3 to 82%; $P = 0.03$) in dexamethasone-suppressed total cortisol. However, this effect was dependent on gestational age at birth, being stronger in subjects born at a more advanced gestational age; in other words, the interactions between birthweight and gestational age were significant (Table 3). To demonstrate these interactions, we divided the subjects into two groups according to gestational age at birth. We chose the limit of 40 weeks which represents approximately the median gestational age and was the gestational age at which the relationship between birthweight and cortisol reversed in our previous study (10). In subjects born after 40 weeks of gestation, 1 kg increase in birthweight was associated with an 84% increase (95% CI 23 to 175%; $P = 0.003$; Fig. 1) in dexamethasone-suppressed total cortisol. This association was not seen in

subjects born before 40 weeks of gestation, in whom 1 kg increase in birthweight was associated with a 6% increase (95% CI -30 to 62%, $P = 0.8$; Fig. 1) in dexamethasone-suppressed total cortisol. Similar correlations were observed with ponderal index at birth. By contrast, peak cortisol after ACTH stimulation was not associated with birth weight (1 kg increase in birthweight corresponding to 3.9 nmol/l, 95% CI -46 to 54 nmol/l increase in peak cortisol, $P = 0.9$) or with any other birth data. Neither was there any association with ACTH-stimulated cortisol in the subgroups defined according to gestational age at birth. Allowing for primiparity and maternal height or BMI did not alter any of the results.

Discussion

In our previous study we showed that fasting plasma cortisol concentrations were high in men and women who were born with low birthweight at less than 39 weeks of gestation, whereas among those born with low birthweight at more than 40 weeks this trend was reversed (10). In the present study, our aim was to assess whether this interactive effect of gestational age and birth weight is sustained when HPAA activity is assessed with more detailed methods. We found that this is indeed the case regarding the response of

Table 3 Mean cortisol concentration and free cortisol index after overnight low-dose (0.25 mg) dexamethasone suppression, according to birth weight, ponderal index and gestational age. Numbers are geometric means, with numbers of cases in parentheses.

	All women	Gestational age <40 weeks	Gestational age $\geq$ 40 weeks
Total cortisol (nmol/l)			
Birth weight (g)			
– 3000	116 (26)	128 (19)	89 (7)
– 3500	130 (81)	130 (41)	129 (40)
> 3500	166 (44)	153 (18)	175 (26)
<i>P</i> for trend (unadjusted)	0.04	0.9	0.002
<i>P</i> for trend (adjusted) ^{a, b}	0.03	0.8	0.003
Ponderal index (kg/m ³)			
– 26	116 (51)	138 (29)	93 (22)
– 28	145 (60)	135 (32)	157 (28)
> 28	153 (39)	126 (16)	176 (23)
<i>P</i> for trend (unadjusted)	0.04	0.7	0.003
<i>P</i> for trend (adjusted) ^{a, c}	0.03	0.5	0.005
Free cortisol index			
Birth weight (g)			
– 3000	0.21 (26)	0.25 (19)	0.13 (7)
– 3500	0.23 (81)	0.23 (41)	0.22 (40)
> 3500	0.30 (44)	0.28 (18)	0.32 (26)
<i>P</i> for trend (unadjusted)	0.02	0.9	0.0001
<i>P</i> for trend (adjusted) ^{a, d}	0.02	0.9	0.0004
Ponderal index (kg/m ³)			
– 26	0.20 (51)	0.26 (29)	0.15 (22)
– 28	0.25 (60)	0.24 (32)	0.26 (28)
> 28	0.29 (39)	0.23 (16)	0.34 (23)
<i>P</i> for trend (unadjusted)	0.01	0.9	0.0002
<i>P</i> for trend (adjusted) ^{a, e}	0.01	0.6	0.0004

P values are based on regression models with birth weight, ponderal index or gestational age as continuous variables. a = adjusted for age, BMI and use of oral oestrogen treatment. *P* for interaction with gestational age: b = 0.056, c = 0.003, d = 0.03, e = 0.0004.

Figure 1 Scatterplots showing the relationship between birth weight and total cortisol after overnight 0.25 mg dexamethasone suppression in subjects born before and after 40 weeks of gestation.

the HPA axis to dexamethasone suppression. The interaction calculations showed that the higher the gestational age at birth, the stronger became the association between low birth weight and hyper-responsivity to dexamethasone.

The women we studied may not be representative of the original birth cohort since subjects with, for example, increased cardiovascular risk are more likely to have died by this age. However, our findings are based on internal comparisons within the sample. A selection bias would be expected to detect such findings only if the relationship of adult HPA axis function with birthweight and gestational age differed between the women who attended the study and those who did not, which seems unlikely. In addition, our gestational age data were based on the date of the mother's last menstrual period. While dating by the last menstrual period has been validated against dating by ultrasound measurement of fetal biparietal diameter (15), this may still introduce inaccuracy. One might also argue that the use of ACTH and dexamethasone doses not adjusted for the subjects' weight, which was done to maintain consistency with previous work (5), could constitute another source of inaccuracy. However, these inaccuracies would only weaken our ability to detect existing effects.

Dexamethasone suppression has become a standard test of the feedback responsiveness of the HPA axis by glucocorticoids. The response to this test is impaired in people with altered central control of cortisol secretion, such as Cushing's disease or depression (16). In this population-based birth cohort study, we used a smaller dexamethasone dose (5) than routinely used in

diagnosing endocrine disorders. Among adults born at a lower gestational age, there was no relationship between birth size and dexamethasone responsiveness, suggesting that low birthweight babies in this group who have relative hypercortisolaemia (9, 10) are normally responsive to dexamethasone suppression. This finding is in accordance with a previous study in Hertfordshire, UK, which showed no association between birthweight and the response to dexamethasone (5). However, in the Hertfordshire study gestational age data were not available.

In contrast, in the present study women who were born with low birthweight at a more advanced gestational age were more responsive to dexamethasone. Together with the low fasting cortisol levels we have previously described in this group (10), this suggests that their HPA axis is down-regulated. Although the health consequences of low cortisol concentrations remain poorly understood, interestingly recent research has proposed this to be a key element in various pathologies. For example, relative hypocortisolaemia together with enhanced dexamethasone suppression is a feature of certain psychosomatic disorders, such as atypical depression, fibromyalgia or post-traumatic stress disorder (17–19). Whether such a low HPA axis activity could also be beneficial for some individuals, for example by lowering their cardiovascular risk, is not known. There are findings suggesting that in some cases the situation may in fact be the reverse (19). It is also of note that a subgroup of individuals with metabolic syndrome paradoxically exhibit low morning cortisol concentrations, probably as a sign of blunted diurnal variation (20).

Our studies of adrenal suppression and stimulation in relation to glucose tolerance parallel findings in the previous study in men born in Hertfordshire, UK (5). There was no association between baseline cortisol concentration following dexamethasone suppression and either glucose or insulin measurements during an oral glucose tolerance test. However, there were associations between the peak cortisol concentration following an ACTH test and fasting or post-load glucose concentrations, in accordance with a wide body of evidence linking increased glucocorticoid exposure with various health problems including impaired glucose tolerance, hypertension and depression (1–5, 10, 19). These associations were observed only in subjects whose gestational age at birth was 40 weeks or less. We have previously shown that low birthweight is associated with high fasting cortisol concentrations in this group (10), and although we were unable to show increased ACTH responsiveness, the relatively small numbers may have limited the power of our study. Taken together, these findings are however consistent with the hypothesis that there are different patterns of HPA function in the different gestational age subgroups we have described.

Most studies linking different adult cardiovascular risk factors with birth data have found no association with gestational age at birth, at least within the narrow variation of gestational ages in a general adult population. Our findings show that glucocorticoid metabolism seems to be an exception. This may, in part, be explained by the action of glucocorticoids in the initiation of labour. A key regulator of human parturition is corticotrophin releasing hormone (CRH), secreted in abundance by the placenta (21). Glucocorticoids increase placental CRH synthesis (22). In turn, CRH by stimulating fetal and/or maternal cortisol synthesis, creates a positive feedback loop that again raises CRH concentrations and subsequently leads to delivery (21, 23). It is therefore possible that gestational age at birth actually serves as an indicator of existing individual differences in fetal or maternal glucocorticoid metabolism. Possible reasons for such differences include, apart from frank pregnancy disorders such as pre-eclampsia (24), genetic polymorphisms regulating glucocorticoid metabolism (25, 26) and fetal programming earlier during pregnancy. Another explanation for the effect of gestational age could be dissimilarities in the types of prenatal stress characteristic of different gestational ages. Animal experiments show that the nature of programming effects on glucocorticoid metabolism is strongly dependent on the type and timing of the programming stimulus (1).

In conclusion, the findings in the present study reinforce our previous observations (10) suggesting that there are different patterns of adulthood HPA function in the different gestational age subgroups. Of low birthweight babies, those born early at term are in adulthood characterised by high cortisol

concentrations, while low cortisol concentrations are more typical for those born late at term.

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