

CLINICAL STUDY

Maternal testosterone levels during pregnancy are associated with offspring size at birth

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Abstract

Objective: Animal studies have indicated that maternal androgen levels influence the intrauterine environment and development of the offspring. Human data are missing. We therefore investigated the possible association between maternal androgens and offspring size at birth in humans.

Design: A random sample of parous Caucasian women ($n=147$) was followed prospectively through pregnancy.

Methods: Maternal serum levels of dehydroepiandrosterone sulfate (DHEAS), androstenedione, testosterone and sex hormone-binding globulin (SHBG) were measured at gestational weeks 17 and 33. The main outcome measures were weight and length at birth. Associations between maternal androgen levels and offspring birth weight and length were investigated using multiple linear regression modeling adjusted for potential confounding by maternal height, pre-pregnancy body mass index, smoking, parity, offspring gender and gestational age at birth.

Results: Elevated maternal testosterone levels at week 17 and 33 were both associated with lower birth weights and lengths. Accordingly, at week 17, an increase in maternal testosterone levels from the 25th to the 75th percentile was associated with a decrease in birth weight by 160 g (95% confidence interval (CI); 29–290 g), while at week 33 that estimate was 115 g (95% CI; 21–207 g). No similar associations were observed for DHEAS, androstenedione or SHBG.

Conclusions: Elevated maternal testosterone levels during human pregnancy are associated with growth restriction *in utero*. Our results support animal studies, which have indicated that maternal androgen levels influence intrauterine offspring environment and development.

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Introduction

Low birth weight (LBW) has been associated with increased risk of cardiovascular and metabolic diseases in adult life. Epidemiologic studies have reported inverse associations between birth weight and systolic blood pressure (1–3), blood lipids (4), adiposity (5), stroke (6) and cardiovascular disease and mortality (1, 7, 8). Moreover, it has been repeatedly documented that birth weight is inversely related to insulin resistance (9, 10), subsequent risk of type 2 diabetes (9, 11) and other characteristics of the metabolic or insulin resistance syndrome (3, 9, 12).

Although these findings support the 'fetal origins hypothesis' – that susceptibility to these chronic adult conditions may be programmed *in utero* – the understanding of the underlying mechanism(s) is still meager (9,13). One possible mechanism involves the capacity of insulin secretion later in life (14–16). Another one is that lasting fetal metabolic changes lead to insulin resistance in adult life. In humans, reduced birth weight

is associated with later-increased insulin resistance rather than with reduced β -cell function (9).

In the prenatally androgenised rhesus monkeys, female fetuses exposed to testosterone in early gestational life showed impaired insulin secretion in adult life, while those which were exposed later showed decrements in insulin sensitivity, preserved insulin secretory function and increased adiposity (16). Further, prenatally androgenised male rhesus monkeys also developed insulin resistance and impaired insulin secretion (17). In ewes, prenatal testosterone exposure caused intrauterine growth retardation (18). A recent review of animal data indicates that excess fetal androgen exposure can induce metabolic and endocrine deficits in females, possibly by an adverse, permanent programming of the metabolic pathways (19).

Reduced insulin sensitivity, decreased insulin secretion and adiposity during gestation are associated with reduced birth size (5, 9, 10). Hence, we tested the hypothesis that in humans, endogenous maternal circulating androgen levels are negatively associated

with birth size of the offspring. We used data from a prospective multicenter study that were originally designed to investigate causes and consequences of being born small for gestational age (SGA) in Scandinavia.

Subjects and methods

Subjects

The study was based on the Scandinavian part of an international multicenter study initiated and financed by the US National Institute of Child Health and Human Development (NIHCD). This was a prospective study with an aim to identify causes and consequences of being born SGA. The design of the study has been published in detail elsewhere (20). Briefly, Scandinavian participants were recruited between 1 January 1986 and 31 March 1988 at the university hospitals in Trondheim and Bergen (Norway) and Uppsala (Sweden). Para 1 and para 2 women of Caucasian origin who spoke one of the Scandinavian languages were included. A total of 6354 pregnant women were invited to participate and 5722 women with singleton pregnancies responded and were included at one of the study sites before gestational week 20. Among these women, two groups were followed up in detail at weeks 17, 25, 33 and 37 of pregnancy and at birth. The first group consisted of a random sample of 10% of women included in the study ($n=561$), while the other ($n=1384$) consisted of women with one or more defined risk factors for giving birth to SGA child. All the 147 participants of the present subset were selected at random from the 10% random sample of pregnant women.

Clinical protocol

The detailed follow-up during pregnancy included questionnaires and clinical evaluation of the mother with blood pressure and ultrasound measurements and urinary and blood samples. The expected date of delivery was based on menstrual history. In cases where the last menstrual period (LMP) was unknown or if LMP and ultrasound dates differed by more than ± 14 days, the term was based on routine ultrasonography at week 17. Information about maternal age, smoking habits and pre pregnancy weight was collected at the beginning of the study. At birth, the infants were weighed to the nearest 10 g on a standard scale and birth length to the nearest centimeter (cm). The regional committee for medical research ethics in each of the study sites approved the study and a signed informed consent was obtained from all the participants.

Analytical methods

Non-fasting serum samples were drawn during working hours (mainly during the morning) and centrifuged at

room temperature within 60 min. Before the assays were performed, serum was stored in screw-capped vials at -80°C for a mean of 12 years (11–13 years). Dehydroepiandrosterone sulfate (DHEAS) and sex hormone-binding globulin (SHBG) were measured using competitive immunoassay on the Immulite 2000 analyzer using the reagents and calibrators delivered by the supplier (Diagnostic Products Corporation, Los Angeles, CA, USA). The lower detection limits for DHEAS and SHBG were $0.054\ \mu\text{mol/l}$ and $0.2\ \text{nmol/l}$ respectively. Testosterone and androstenedione were measured using RIA technique with reagents and calibrators delivered by Orion Diagnostica, Espoo, Finland (testosterone) and Diagnostic Products Corporation (androstenedione). The lower detection limits for testosterone and androstenedione were 0.1 and $0.14\ \text{nmol/l}$ respectively.

Statistical analysis

We used linear multiple regression analyses to assess the concurrent contribution to birth size for each measured factor, after adjustment for well-known predictors associated with intrauterine growth. They were maternal height, pre pregnancy body mass index (BMI), smoking, parity, offspring gender and gestational age at birth. Pearson statistics were used to correlate androgen levels measured at different time points during pregnancy. All the statistical procedures were performed by the use of SPSS for Windows, version 13.0 (SPSS Inc., Chicago, IL, USA).

Results

Maternal characteristics, distribution of androgen levels during pregnancy and birth characteristics are given in Table 1.

In multiple linear regression models, we observed significant associations between maternal levels of testosterone and birth weight (Table 2) and birth length (Table 3) corrected for maternal age, height, pre pregnancy BMI, smoking during pregnancy, parity, offspring gender and gestational age at birth. An increase in maternal testosterone of $1\ \text{nmol/l}$ at gestational week 17 was associated with a decrease in birth weight of $133\ \text{g}$ (95% confidence interval (CI); $24\text{--}242\ \text{g}$) and a decrease in birth length of $0.6\ \text{cm}$ (95% CI; $0.2\text{--}1.1\ \text{cm}$). Thus, an increase in maternal testosterone levels at week 17 from the 25th to the 75th percentile was associated with a decrease in birth weight of $160\ \text{g}$ (95% CI; $29\text{--}290\ \text{g}$) and birth length of $0.8\ \text{cm}$ (95% CI; $0.2\text{--}1.3\ \text{cm}$). At week 33, the corresponding estimates were $115\ \text{g}$ (95% CI; $21\text{--}207\ \text{g}$) and $0.5\ \text{cm}$ (95% CI; $0.1\text{--}0.8\ \text{cm}$). No similar associations were observed for DHEAS, androstenedione or SHBG. Leaving testosterone out of the multivariate models did not materially change the effect of

Table 1 Maternal characteristics, distribution of androgen levels during pregnancy and birth characteristics of the study population.

Variable		n	Mean	(s.d.)	Minimum	25th percentile	Median	75th percentile	Maximum
DHEAS ($\mu\text{mol/l}$)	Week 17	147	2.9	(1.4)	0.5	1.9	2.8	3.6	8.2
	Week 33	141	2.2	(1.2)	0.4	1.4	2.1	2.8	7.7
Androstenedione (nmol/l)	Week 17	147	10.6	(4.5)	2.3	7.6	9.8	12.4	27.3
	Week 33	143	16.7	(7.0)	5.8	12.1	15.2	19.0	49.0
Testosterone (nmol/l)	Week 17	147	2.0	(1.0)	0.5	1.4	1.8	2.6	7.2
	Week 33	144	2.6	(1.8)	0.9	1.6	2.2	3.0	14.5
SHBG (nmol/l)	Week 17	147	320	(77)	166	266	315	361	593
	Week 33	145	366	(81)	167	316	362	412	580
Smoking (yes/no)	Week 17	46/101	–	–	–	–	–	–	–
	Week 33	43/104	–	–	–	–	–	–	–
Number of previous births (1/2)		102/45	–	–	–	–	–	–	–
Offspring gender (male/female)		75/72	–	–	–	–	–	–	–
Maternal age (years)		147	29	(4)	18	26	28	31	39
Maternal height (cm)		147	167	(6)	152	162	166	171	182
Pre pregnancy BMI (kg/m^2)		147	21.8	(2.4)	17.6	20.1	21.3	23.2	32.7
Gestational age at birth (days)		147	280	(9)	250	274	280	286	298
Birth weight (g)		147	3660	(490)	2000	3380	3630	3940	5450

DHEAS, dehydroepiandrosterone sulfate; SHBG, sex hormone-binding globulin.

Table 2 Multivariable linear regression of birth weight (grams) according to maternal androgen levels at weeks 17 and 33 adjusted for maternal and fetal factors.

Covariate	Coefficient	Week 17 95% CI	P-value	Coefficient	Week 33 95% CI	P-value
Study center						
Trondheim*	0			0		
Bergen	112	(–48 to 272)	0.2	84	(–69 to 237)	0.3
Uppsala	79	(–89 to 247)	0.4	–20	(–180 to 140)	0.8
Number of previous births (number)†	57	(–92 to 206)	0.5	31	(–114 to 177)	0.7
Mother's age at study entry (years)†	5	(–13 to 24)	0.6	1	(–18 to 20)	0.9
Mother's height (cm)†	25	(14 to 36)	<0.001	21	(10 to 32)	<0.001
Pre pregnancy BMI (kg/m^2)†	56	(29 to 84)	<0.001	49	(22 to 76)	<0.001
Smoking						
Non-smoking*	0			0		
Smoking	–124	(–268 to 20)	0.09	–138	(–286 to 10)	0.07
Offspring gender						
Male*	0			0		
Female	–160	(–295 to –26)	0.02	–172	(–303 to –40)	0.01
Gestational age at birth (days)†	18	(12 to 25)	<0.001	20	(13 to 26)	<0.001
DHEAS ($\mu\text{mol/l}$)	–24	(–79 to 32)	0.4	–25	(–87 to 37)	0.4
Androstenedione (nmol/l)†	19	(–10 to 47)	0.2	4	(–15 to 23)	0.7
SHBG (nmol/l)†	1	(0 to 1)	0.2	0	(–1 to 1)	0.7
Testosterone (nmol/l)†	–133	(–242 to –24)	0.02	–82	(–148 to –15)	0.02

CI, confidence interval; DHEAS, dehydroepiandrosterone sulfate; SHBG, sex hormone-binding globulin.

*Baseline category.

† Per unit.

Table 3 Multivariable linear regression of birth length (cm) according to maternal androgen levels at gestational weeks 17 and 33 adjusted for maternal and fetal factors.

Covariate	Coefficient	Week 17 95% CI	P-value	Coefficient	Week 33 95% CI	P-value
Study center						
Trondheim*	0			0		
Bergen	0.9	(0.2 to 1.5)	0.009	0.8	(0.1 to 1.4)	0.02
Uppsala	0.7	(0.0 to 1.4)	0.04	0.4	(-0.2 to 1.1)	0.2
Number of previous births (number)†	-0.2	(-0.8 to 0.4)	0.5	-0.3	(-0.9 to 0.3)	0.3
Mother's age at study entry (years)†	0.1	(0.0 to 0.2)	0.06	0.1	(0.0 to 0.1)	0.1
Mother's height (cm) †	0.1	(0.1 to 0.1)	<0.001	0.1	(0.0 to 0.1)	0.001
Pre pregnancy BMI (kg/m ²) †	0.2	(0.1 to 0.3)	0.005	0.1	(0.0 to 0.2)	0.02
Smoking						
Non-smoking*	0			0		
Smoking	-0.3	(-0.9 to 0.3)	0.3	-0.2	(-0.8 to 0.4)	0.5
Offspring gender						
Male*	0			0		
Female	-1.0	(-1.5 to -0.4)	0.001	-1.0	(-1.5 to -0.4)	<0.001
Gestational age at birth (days)†	0.1	(0.0 to 0.1)	<0.001	0.1	(0.0 to 0.1)	<0.001
DHEAS (μmol/l)	0.1	(-0.2 to 0.3)	0.6	0.1	(-0.2 to 0.3)	0.5
Androstenedione (nmol/l)†	0.1	(-0.1 to 0.2)	0.2	0.0	(-0.1 to 0.1)	1.0
SHBG (nmol/l)†	0.0	(0.0 to 0.0)	0.3	0.0	(0.0 to 0.0)	0.7
Testosterone (nmol/l)†	-0.6	(-1.1 to -0.2)	0.006	-0.3	(-0.6 to -0.1)	0.01

CI, confidence interval; DHEAS, dehydroepiandrosterone sulfate; SHBG, sex hormone-binding globulin.

*Baseline category.

†Per unit.

androstenedione or any of the other risk factors on offspring size at birth (data not shown).

Significant associations between levels at pregnancy week 17 and 33 were seen for androstenedione ($r=0.80$; $P<0.0005$), DHEAS ($r=0.69$; $P<0.0005$), testosterone ($r=0.75$; $P<0.0005$) and SHBG ($r=0.71$; $P<0.0005$).

Discussion

This study presents human data that show the associations between increasing circulating endogenous maternal testosterone levels during pregnancy and a decrease in offspring birth weight and length in a random selection of pregnant women. This inverse association remained unchanged after correction of several well-known factors associated with intrauterine growth. At gestational week 17, an increase in circulating maternal testosterone levels from the 25th to the 75th percentile corresponded to a decrease in birth weight of 160 g. This weight difference is similar to the impact that traditional factors such as fetal gender or maternal smoking have on birth weight.

Newborn size characteristics are important predictors of a multitude of disorders in adult life (1–12). Hence, our identification of elevated maternal testosterone levels as a new indicator of intrauterine growth restriction in humans is important as it opens up the possibility to better understand the mechanisms involved in intrauterine growth. This in turn, may help to elucidate the mechanism(s) behind the 'fetal origins hypothesis' (9, 13).

Our findings are supported by animal data. For instance, in sheep, testosterone treatment of the mother during early to mid pregnancy reduced birth weight and height in the offspring of either gender (21). This supports the concept that fetal growth retardation, an early marker of adult diseases, can be initiated through prenatal excess exposure to sex steroids. Studies in non-human primates and other animals have shown that prenatal exposure to testosterone led to female hyperandrogenism (19), infertility (22, 23), behavior modifications (24) abdominal adiposity (25) and insulin resistance (17) during adulthood in the offspring. In all these studies, testosterone was administered to otherwise normal pregnant female animals and hence the increase in circulating maternal testosterone was of exogenous origin and not caused by any maternal disease.

There are also some human data that support both our findings and animal data. Women with polycystic ovary syndrome (PCOS) have ovaries with multiple cysts, menstrual disturbances and hyperandrogenism. Sir-Peterman reported that in PCOS women, maternal androgen levels are increased even in the pregnant state (26). Recently, the same authors published a study that showed a marked increase in the prevalence of SGA births in PCOS mothers compared with control pregnancies (12.8% vs 2.8%). In contrast, the prevalence of large for gestational age births (LGA) were the same in both groups (27). On the other hand, others did or did not find a gender-specific decrease of birth weight in offspring of PCOS women (28, 29).

Maternal testosterone levels can affect newborn growth and size through several potential mechanisms. Maternal testosterone may modify her energy

homeostasis and thus decrease nutrient supplies to the placenta and fetus. Alternatively, testosterone may modify placental function and reduce the capacity for transport of nutrients to the fetus. Maternal testosterone may also cross the placenta and exert a direct effect on fetal growth and/or energy homeostasis. A combination of all these mechanisms is also conceivable.

We investigated the effect of circulating endogenous androgens in a random sample of pregnant para 1 and para 2 women. The observed inverse association between circulating maternal testosterone levels and fetal growth may arise from any mechanism affecting fetal growth. Accordingly, maternal testosterone may only be a biomarker for fetal growth. However, assisted by the available animal data on the effect of the exertion of exogenously administered testosterone on otherwise normal pregnancies (19), we hypothesize that the association between maternal testosterone levels and reduced birth size is a direct effect of increased maternal androgen levels. Probably, it is mediated by one or more of the above possible mechanisms and is not just a chance-coincidental phenomenon. Testosterone is a liposoluble steroid and one may expect it to cross the placenta readily. This view is supported by a human study, which showed a second trimester association between maternal and fetal circulating testosterone levels. However, these were not normal pregnancies (30).

According to the 'fetal origin hypothesis', intrauterine programming is an adaptive response to fetal malnutrition *in utero*. In the developing world, this is mostly due to maternal malnutrition. In contrast, in the industrialized world, it is mainly considered to result from placental dysfunction, which in turn results in a reduced supply of nutrients to the fetus in an otherwise well-nourished mother (13). However, the molecular mechanism(s) involved in that process has not been clearly identified.

We observed that the effect on birth size of maternal testosterone levels tended to be more pronounced in the second than in the third trimester. In animals, it is well established that the hormonal status of the fetus during certain stages of gestation is crucial for its growth and development (24). Also, in non-human primates, testosterone exposure in early and late pregnancy tends to affect the offspring differently (16).

It has been shown in the rat that maternal treatment with androstenedione affected offspring health in a similar way to that of testosterone (31). Still, we found that testosterone, but not androstenedione, was associated with size at birth. This was also the case when testosterone was omitted from the multivariable models. A possible explanation for this is that androstenedione is a weaker androgen, which may also be converted to testosterone before it exerted its adverse effect in the rat model.

In the present study, blood samples were drawn in the non-fasting state during different times of the day and stored at a mean of 12 years before the analyses. This might have increased the variability of testosterone

levels and could be considered a weakness of the present study. However, the high association of steroid levels at pregnancy weeks 17 and 33 is not compatible with this being a major objection to the study. On the contrary, it can be argued that since we were able to show a statistical association, the biological association between testosterone levels and birth measures may be even stronger than the statistical relations we found. It further adds to the strengths of the present study that testosterone levels were related to size at birth both in the early second and mid third trimester. Also, we adjusted four maternal factors with strong and well-known prognostic properties for birth size. Still the possibility that our results are a consequence of unidentified confounding effects remains. With these limitations, we propose that maternal testosterone level emerges as a novel, independent predictor of prenatal growth deviations.

In conclusion, this study relates human maternal testosterone levels during pregnancy with offspring size at birth after control of traditional factors known to be related to birth size. The present data support animal studies that have indicated that maternal androgen exposure may influence the intrauterine environment and thereby offspring development. Further studies should aim to confirm or negate our findings and try to elucidate whether or not androgens are part of a causal pathway.

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