Maternal Testosterone Levels During Pregnancy Are Not associated with Birth Weights of Offspring: A Prospective Cohort Study

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Abstract

Background Testosterone is an important sex hormone which participates in many physiological processes. However, there is conflicting evidence on effect of testosterone on fetal development. We aim to investigate the associations between maternal testosterone levels and pregnancy outcomes.

Design and Methods We conducted a prospective cohort in a university-affiliated hospital. A total of 1,087 singleton pregnant women were included in the study. They were followed-up until delivery. The primary outcome was birth weight. The second outcomes were the prevalence of preterm birth, low birth weight, small for gestational age, preeclampsia, gestational diabetes mellitus, intrahepatic cholestasis of pregnancy, premature rupture of membranes, and low APGAR score (<7).

Results We did not observe any significant association between maternal testosterone level and birth weight after adjustment. Prevalence of medical complications was also not associated with maternal testosterone levels.

Conclusions Maternal testosterone levels during pregnancy is not associated with birth weights as well as the prevalence of medical complications.

Introduction

The effects of prenatal exposure on developing neural, endocrine and metabolic systems of the fetus have drawn wide attention. Among these factors, the maternal endocrine factor is prominent. Throughout the gestational period, supraphysiological hormonal changes may lead to short- and long-term health problems of the offspring. Previous studies reported that prenatal high estradiol exposure negatively correlated with birth weight, cardiovascular function, and neurodevelopment of the offspring.^[1–3]

Testosterone is an important sex hormone which participates in many physiological processes, mainly pro-growth, especially in skeletal muscle^[4]. There is conflicting evidence on the effect of testosterone in fetal development. A U.S. cohort of 147 women reported no associations between maternal testosterone levels and birth weights.^[5] According to other cohorts and animal studies, increased prenatal testosterone exposure was associated with lower birth weight.^[6–8] However, these cohorts had limitations such as small sample size or failed to rule out polycystic ovary syndrome (PCOS).

We hypothesize that maternal testosterone levels during pregnancy is associated with birth weight. To address this hypothesis, we conducted a university hospital-based cohort to examine the 2nd-trimester maternal serum testosterone levels in human pregnancy in relation to pregnancy outcomes. Our study may fill the knowledge gap of understanding the relationship between testosterone and pregnancy outcomes.

Methods

Study design

Women were recruited in the prospective cohort study during their antenatal visits at 24–26 weeks at Women's Hospital, Zhejiang University School of Medicine. The recruitment time was from Jan 2016 to July 2016. Inclusion criteria were: Singleton pregnant women, age 18–42 year-old. Exclusion criteria were: BMI > 40, twin pregnancy, polycystic ovary syndrome, maternal hypertension, diabetes mellitus, chronic diseases (severe heart, liver and kidney diseases) or mental disorders. Polycystic ovary syndrome was diagnosed according to the Rotterdam criteria [9]. At baseline recruitment, demographic and pregnancy information was obtained by interview. Blood samples were collected in the morning of recruitment day for routine prenatal lab test. The residual blood samples after routine blood test were used for testosterone test. Delivery characteristics were collected through review of medical records after delivery. Cases with missing data were excluded from the analysis. After the loss of cases due to the failed blood sample check (n = 24), lost to follow up (n = 99) and missing data (n = 52), 1087 women were included in the final analysis (Figure 1).

Figure 1. Flowchart of participant recruitment and exclusion

The Ethics Committee of Women Hospital, Zhejiang University School of Medicine approved the study in 2015 (Ref. No.20150043). Written informed consents were obtained from the participants. The investigation was registered in the Chinese Clinical Trial Registry (ChiCTR1800016310).

Measurements of serum testosterone

Blood samples were collected in the early morning of recruitment day for routine prenatal examinations, the residual blood was stored at -20°C . All samples were measured at one time after the estimated sample size was achieved. Serum total testosterone (TT) levels were measured by an auto-analyzer (Abbott Architect I2000, IL, USA) using chemiluminescent microparticle immunoassay (CMIA) with its dedicated kits.

The sensitivity of the test is 0.48 nmol/L, the intra-essay coefficient of variation is 3.40%, the inter-essay coefficient of variation is 5.60%.

The testosterone levels during pregnancy were inconsistent among various studies[5–8]. The manufacturer did not provide pregnancy-specific reference ranges for testosterone. Therefore, we used the quartile value of our own data as cut-off value.

Only one technician performed all testosterone measurement who was blind to medical records of subjects to minimize selection bias.

Pregnancy outcomes

The participants were followed up till delivery. The primary outcome was birth weight. Second outcomes were prevalence of medical complications during pregnancy and at delivery, including the prevalence of preterm birth, low birth weight (< 2500g), small for gestational age, preeclampsia, gestational diabetes mellitus, intrahepatic cholestasis of pregnancy, premature rupture of membranes and low 1 min APGAR score (<7). Small for gestational was defined as birth weight below the 10th percentile for the gestational age. Preeclampsia was diagnosed according to ACOG'S 2013 guideline[10]. Gestational diabetes mellitus was diagnosed according to the new IADPSG criteria [11]. Intrahepatic cholestasis of pregnancy was diagnosed according to guideline from American College of Gastroenterology [12].

All the above information was obtained from the medical record database of Women's Hospital, Zhejiang University School of Medicine.

Statistical Analysis

Power calculation was performed before the study on the basis of database of our hospital and previously reported offspring birth weights of women with different testosterone levels.[7] Considering difference of 100g in birth weight between high and low testosterone group (Mean birth weight of high testosterone group = 3300g, mean birth weight of low testosterone group = 3400g, SD = 350g; power = 0.9; α = 0.05; sampling ratio = 1), 257 cases were required for each group.

Data were analyzed by R (Version 3.5.2). For analysis of birth weight, multivariate linear regression controlled for maternal age, body mass index, age of husband, parity, gravidity and gestational age at birth were used. For analysis of prevalence of medical complications, multivariate logistic regression controlled for maternal age, body mass index, age of husband, parity and gravidity at birth were used.

Results

In the final analysis, 1087 singleton pregnant women were included. Baseline characteristics of the participants are listed in Table 1.

The description of pregnancy outcomes was listed in Table 2. The mean birth weight was 3,333 g. The prevalence of medical complications were: preeclampsia 1.4%, gestational diabetes mellitus 12.9%, intrahepatic cholestasis of pregnancy 3.0%, preterm birth 4.1%, low birth weight 1.8%, small for gestational age 2.7%, premature rupture of membranes 21.9% and 1 min APGAR <7 0.7%.

We did not observe a significant association between maternal testosterone levels and birth weights of the newborn using the multivariate linear regression model. An increase in testosterone of 1 mmol/l is associated with an increase of in birth weight of 9.93 g after adjustment. However, the association is not significant as the 95% confidential interval of the coefficient was -3.55 – 23.40, with a *p* value of 0.15 (Table 3).

We also did not observe a significant association between maternal testosterone levels and birth weights of the prevalence of any medical complication using the multivariate logistic regression model (Table 3).

Discussion

We conducted a Chinese cohort study to examine the associations of maternal serum testosterone levels during the 2nd trimester of gestation and pregnancy outcomes mainly birth weight. Contrary to our hypothesis, we found that birth weights and medical complications during pregnancy and at delivery were not associated with maternal testosterone levels. The large case number enabled us to draw a relatively solid conclusion on the topic.

The association between testosterone and pregnancy outcomes was not clear. Prenatal administration of testosterone in sheep resulted in reduced body weights and heights of newborns.[8] A cohort including 49 women reported elevated maternal morning testosterone levels were associated with lower birth weights and greater infant weight gains in 6 months after birth.[13] Similar negative correlation was observed in a cohort including 147 women reporting that elevated maternal testosterone levels at week 17 and 33 were both associated with lower birth weights and lengths.[7] However, another cohort including 101 infants with low birth weight reported that maternal testosterone levels have no association with pregnancy complications, labor complications, or infant health.[5] All the above studies were either animal study or limited in sample size. So far, no human study with a large sample size was reported.

What is the role of testosterone in fetal growth? Testosterone exerts its stimulatory effect on pulsatile GH secretion, body weight, and longitudinal bone growth in a rat model.[14] Testosterone can also increase neonatal weights by enhancing the growth of bone, which accounts for about 10% of body weight. However, testosterone may modify placental function to decrease nutrient transportation to fetus or exert a direct effect on fetal growth, it may activate the maternal or fetal stress axis and produce extra cortisol which reduces offspring birthweight[8, 15]. The neutralization of both stimulative and inhibitive effect of testosterone may explain the absence of significant association between testosterone and fetal growth.

There are several limitations and considerations with regard to the study. First, relying on endogenous testosterone sampling at a single point in mid-term gestation not persistent variation may limit the results of the study. Thus, we are unable to evaluate whether maternal testosterone levels in other pregnancy stages are related to birth weight. Since the late pregnancy is the main period pregnant women experiencing endocrine and metabolic changes, and a critical period for fetal development[16], study of the effect of maternal testosterone levels on birth weight and pregnancy complications during this period may give us different results. Unfortunately, due to the difficulty of collecting clinical cases and financial constraints, we have not been able to carry out this study at the same time, which is also the direction of our follow-up research. Second, the outcome included in the study was only pregnancy outcomes. However, we plan to continue the follow-up and include the health information of the infants at 12 months old. Third, the sex hormone binding globulin (SHBG) were not measured due to fund limitation.

Abbreviations

SHBG: sex hormone binding globulin

PCOS: polycystic ovary syndrome

TT: total testosterone

Declarations

Ethics approval and consent to participate

The Ethics Committee of Women Hospital, Zhejiang University School of Medicine approved the study in 2015 (Ref. No.20150043). Written informed consents were obtained from the participants. The investigation was registered in the Chinese Clinical Trial Registry (ChiCTR1800016310).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

GFX and LJS analyzed the data and wrote this manuscript. MLY, YL, YC, MEL and YYW enrolled the participants and collected the information and blood samples of participants. GD C and QL designed the cohort study.

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References

- 1.Xu GF, Zhou CL, Xiong YM, Li JY, Yu TT, Tian S, Lin XH, Liao Y, Lv Y, Zhang FH *et al: Reduced Intellectual Ability in Offspring of Ovarian Hyperstimulation Syndrome: A Cohort Study. EBioMedicine* 2017, 20:263–267.
- 2.Xu GF, Zhang JY, Pan HT, Tian S, Liu ME, Yu TT, Li JY, Ying WW, Yao WM, Lin XH *et al: Cardiovascular dysfunction in offspring of ovarian-hyperstimulated women and effects of estradiol and progesterone: a retrospective cohort study and proteomics analysis. The Journal of clinical endocrinology and metabolism* 2014, 99(12):E2494–2503.
- 3.Hu XL, Feng C, Lin XH, Zhong ZX, Zhu YM, Lv PP, Lv M, Meng Y, Zhang D, Lu XE *et al: High Maternal Serum Estradiol Environment in the First Trimester Is Associated With the Increased Risk of Small-for-Gestational-Age Birth. The Journal of clinical endocrinology and metabolism* 2014, 99(6):2217–2224.
- 4.Herbst KL, Bhasin S: *Testosterone action on skeletal muscle. Current opinion in clinical nutrition and metabolic care* 2004, 7(3):271–277.
- 5.Cho J, Su X, Holditch-Davis D: *Associations of Maternal Testosterone and Cortisol Levels With Health Outcomes of Mothers and Their Very-Low-Birthweight Infants. Biological research for nursing* 2017, 19(4):409–418.
- 6.Sir-Petermann T, Hittsfield C, Maliqueo M, Codner E, Echiburu B, Gazitua R, Recabarren S, Cassorla F: *Birth weight in offspring of mothers with polycystic ovarian syndrome. Human reproduction* 2005, 20(8):2122–2126.
- 7.Carlsen SM, Jacobsen G, Romundstad P: *Maternal testosterone levels during pregnancy are associated with offspring size at birth. European journal of endocrinology* 2006, 155(2):365–370.
- 8.Manikkam M, Crespi EJ, Doop DD, Herkimer C, Lee JS, Yu S, Brown MB, Foster DL, Padmanabhan V: *Fetal programming: prenatal testosterone excess leads to fetal growth retardation and postnatal catch-up growth in sheep. Endocrinology* 2004, 145(2):790–798.
- 9.Broekmans FJ, Knauff EA, Valkenburg O, Laven JS, Eijkemans MJ, Fauser BC: *PCOS according to the Rotterdam consensus criteria: Change in prevalence among WHO-II anovulation and association with metabolic factors. BJOG: an international journal of obstetrics and gynaecology* 2006, 113(10):1210–1217.

- 10.American College of O, Gynecologists, Task Force on Hypertension in P: *Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstetrics and gynecology* 2013, 122(5):1122–1131.
- 11.International Association of D, Pregnancy Study Groups Consensus P, Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, Dyer AR, Leiva A *et al: International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care* 2010, 33(3):676–682.
- 12.Mahadevan U, Kane S: *American gastroenterological association institute medical position statement on the use of gastrointestinal medications in pregnancy. Gastroenterology* 2006, 131(1):278–282.
- 13.Voegtline KM, Costigan KA, Kivlighan KT, Henderson JL, DiPietro JA: *Sex-specific associations of maternal prenatal testosterone levels with birth weight and weight gain in infancy. Journal of developmental origins of health and disease* 2013, 4(4):280–284.
- 14.Jansson JO, Ekberg S, Isaksson O, Mode A, Gustafsson JA: *Imprinting of growth hormone secretion, body growth, and hepatic steroid metabolism by neonatal testosterone. Endocrinology* 1985, 117(5):1881–1889.
- 15.Seckl JR: *Glucocorticoid programming of the fetus; adult phenotypes and molecular mechanisms. Molecular and cellular endocrinology* 2001, 185(1–2):61–71.
- 16.Tal R, Taylor HS, Burney RO, Mooney SB, Giudice LC: *Endocrinology of Pregnancy*. In: *Endotext*. edn. Edited by Feingold KR, Anawalt B, Boyce A, Chrousos G, Dungan K, Grossman A, Hershman JM, Kaltsas G, Koch C, Kopp P *et al*. South Dartmouth (MA); 2000.

Tables

Table 1 Baseline characteristics of participants

Variable	N (%)	Mean (SD)		Minimum	25th percentile	Median	75th percentile	Maximum
Maternal age, years	1087 (100)	30.6	3.7	20.0	28.0	30.0	33.0	42.0
Maternal BMI, kg/m ²	1087 (100)	20.6	2.8	14.7	18.7	20.3	22.0	38.5
Paternal age, years	1087 (100)	31.9	4.7	23.0	28.0	31.0	35.0	60.0
Paternal BMI, kg/m ²	1087 (100)	23.4	3.5	11.0	21.1	23.0	25.3	35.7
Gestational age at birth, weeks	1087 (100)	39.1	1.3	30.3	38.3	39.1	40.0	41.9
Testosterone, nmol/L	1087 (100)	2.79	1.60	0.61	1.85	2.40	3.28	16.90
Nulliparity	733 (67.4)	-	-	-	-	-	-	-
Primigravida	425 (39.1)	-	-	-	-	-	-	-
Caesarean section	680 (62.5)	-	-	-	-	-	-	-
Male sex of newborn	574 (52.8)	-	-	-	-	-	-	-

BMI, body mass index.

Table 2 Description of pregnancy outcomes

Variable	N (%)	Mean (SD)		Minimum	25th percentile	Median	75th percentile	Maximum
Birth weight, grams	1087 (100)	3333	409	1315	3060	3320	3600	4790
Medical complications during pregnancy								
Preeclampsia	15 (1.4)	-	-	-	-	-	-	-
Gestational diabetes mellitus	141 (12.9)	-	-	-	-	-	-	-
Intrahepatic cholestasis of pregnancy	33 (3.0)	-	-	-	-	-	-	-
Medical complications at delivery								
Preterm birth	45 (4.1)	-	-	-	-	-	-	-
Low birth weight	20 (1.8)	-	-	-	-	-	-	-
Small for gestational age	30 (2.7)	-	-	-	-	-	-	-
Premature rupture of membranes	238 (21.9)	-	-	-	-	-	-	-
1 min APGAR <7	8 (0.7)	-	-	-	-	-	-	-

Table 3 Association of pregnancy outcomes and testosterone levels in women

Variables	Without Adjustment for Covariates			With Adjustment for Covariates		
	Coefficient	95% CI	Pvalue	Coefficient	95% CI	Pvalue
Birth weight	12.06	-3.11 – 27.23	0.12	9.93	-3.55 – 23.40	0.15
Medical complications during pregnancy						
Preeclampsia	-0.09	-0.48 – 0.29	0.63	-0.11	-0.51 – 0.27	0.55
Gestational diabetes mellitus	-0.01	-0.12 – 0.10	0.89	0.00	-0.12 – 0.11	0.97
Intrahepatic cholestasis of pregnancy	-0.18	-0.48 – 0.11	0.22	-0.21	-0.52 – 0.09	0.17
Medical complications at delivery						
Preterm birth	0.04	-0.13 – 0.20	0.68	0.03	-0.14 – 0.20	0.72
Low birth weight	0.06	-0.16 – 0.29	0.59	0.04	-0.19 – 0.28	0.70
Small for gestational age	-0.01	-0.24 – 0.22	0.93	-0.03	-0.27 – 0.20	0.77
Premature rupture of membranes	0.01	-0.07 – 0.10	0.79	0.02	-0.06 – 0.11	0.62
1 min APGAR <7	-0.05	-0.53 – 0.43	0.85	-0.10	-0.62 – 0.42	0.71

Birth weight were analyzed in multivariate linear model, adjusted for maternal age, maternal body mass index, parity, gravidity, neonatal gender and gestational age. Medical complications were analyzed in multivariate logistic model, adjusted for maternal age, maternal body mass index, parity, gravidity and neonatal gender.

Figures

Figure 1

Flowchart of participant recruitment and exclusion