

Association between Fetal Sex and Maternal Serum Testosterone Levels in Normotensive and Preeclamptic Pregnancies

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ABSTRACT

Objective: To determine the association between fetal gender and serum testosterone levels in normotensive and preeclamptic pregnancies matched for height, weight, age and gestational age.

Methods: This comparative cross sectional study, conducted in the Department of Physiology B.M.S.I. J.P.M.C. Karachi, in collaboration with Department of Gynaecology and Obstetrics from November 2005 to July 2006, consisted of 100 women with singleton pregnancies. Fifty pregnancies were uncomplicated; with 25 carrying male fetus and 25 carrying female fetus. Fifty pregnancies were complicated by preeclampsia; out of which 25 were carrying male and 25 carrying female fetuses. Serum testosterone was measured in maternal peripheral blood.

Result: The maternal serum levels of total testosterone are significantly higher in preeclamptics than in normotensive pregnancies with male ($P < 0.05$) as well as with female fetuses ($P < 0.05$). Male bearing preeclamptic pregnancies have significantly higher maternal serum testosterone levels than female bearing pregnancies complicated by preeclampsia ($P < 0.001$). In uncomplicated pregnancies no significant gender differences are found in the maternal serum testosterone values.

Conclusion: It is thus concluded from our study that there exist an association between a particular fetal gender and maternal serum testosterone levels. So if a mother is carrying male fetus frequent antenatals could be instructed in these preeclamptic women. This strategy may reduce a higher perinatal and maternal loss associated with preeclampsia.

Keywords: Maternal serum testosterone levels, preeclamptic pregnancies

INTRODUCTION

Preeclampsia is a pregnancy specific, heterogeneous, multisystem disorders, which has the classical features of pregnancy induced hypertension and new onset proteinuria during the second half of pregnancy and may lead to eclampsia^{1,2}.

It is recognized that abnormal placentation and placental vascular insufficiency are core features of preeclampsia, but why these and associated systemic abnormalities occur remains uncertain. Among the many proposed causes are immunologic derangements, genetic factors, increased insulin resistance, dietary calcium deficiency and hormonal imbalance³.

Women with preeclampsia may have inherent endocrine or metabolic abnormalities expressed during preeclampsia⁴. The incidence of eclampsia increases with the strength of invading hormones; hence eclampsia is very rare when the concentration of fetal hormones is weak, i.e. in the first half of pregnancy but it becomes progressively commoner as the growing baby produces more hormones, and it is commoner still with double amount of hormones

produced by twins⁵.

Although it is likely that the cause of preeclampsia is multifactorial⁶, the most recent theory is that preeclampsia is due to vascular endothelial dysfunction⁷ elevated plasma levels of testosterone could contribute the endothelial dysfunction involved in the pathogenesis of preeclampsia⁸.

Several independent investigators have demonstrated, through human and animal studies, the association of testosterone and hypertension. Interestingly, accumulating evidence indicates that testosterone has important effects on vascular reactivity, the renin-angiotensin system, eicosanoids, and platelets in ways that are strikingly similar to those reported for preeclampsia⁹.

Testosterone is probably produced by maternal steroid forming glands, the ovarian theca interstitial cells and the adrenal cortex as well as by the fetoplacental unit¹⁰. Unlike the fetal adrenal and ovary the fetal testis acquire the capability to synthesize the various androgens at different stages of development¹¹.

Several investigators^{12,13,14,15,16} found increased serum testosterone levels in pregnancies destined to become hypertensive but in these studies there was no comment on the sex of the fetus.

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Since the fetus and placenta are highly integrated, it has been assumed that the maternal hormones concentrations reflect those in fetal circulation, so our aim is to find out whether fetal gender influence the maternal serum testosterone levels and finally to the development of preeclampsia.

MATERIALS AND METHODS

This study included nulliparous pregnant females divided in two groups matched for age, gestational age, height and weight. The convenience sampling was done for the selection of participants.

Group A consisted of fifty obstetric patients diagnosed as having preeclampsia according to American college of Obstetricians and Gynecologists (ACOG) criteria when they presented with a sustained blood pressure increased to levels of 140mmHg systolic or 90mmHg diastolic and proteinuria of $\geq+1$ on a urine dipstick after 20 weeks of gestation. Out of 50 preeclamptics 25 were carrying male fetus and 25 were carrying female fetus.

Group B consisted of 50 healthy pregnant subjects having blood pressure $\leq 120/85$ and no significant proteinuria. Out of fifty, 25 women were carrying male fetus and 25 women were carrying female fetus.

Women with chronic hypertension, renal disease, hyperandrogenism, polycystic ovary syndrome, multiple pregnancies, subjects with known vascular disease and diabetes were excluded from this study. Women were also excluded if using exogenous hormones.

A proforma was completed for each participant. After taking informed consents from all pregnant women who entered the study, they were examined physically. Blood pressure was measured by mercury

sphygmomanometer after 5 minutes of quiet rest. Urinary proteins were measured by Ames Multistix dipstick method. Maternal serum specimens were centrifuged, labeled and stored at -30°C until processed. Serum total testosterone was analysed by Elisa method using kit supplied from Equipar, Italy. Fetal sex was determined at the time of delivery. Statistical analysis was performed using the SPSS version 11. Values were reported as mean \pm S.E.M. The statistical significance of difference between the mean values of the two groups was evaluated by the "t" test. A P value < 0.05 was considered statistically significant.

RESULT

Table 1 shows clinical presentations of the normal pregnant women and preeclamptics with male and female fetuses. Mean age, gestational age, weight and height of both groups are comparable on the average, as the samples were collected from matched subjects. Also shown in the table, the distribution of normotensive and preeclamptic groups with male and female fetuses according to the values of both systolic and diastolic blood pressure and level of proteinuria and no difference was found between male and female bearing pregnancies.

The hormonal values of the two groups are presented in Table 2. In uncomplicated pregnancies no significant gender differences are found in the maternal serum testosterone values. The maternal serum levels of total testosterone are significantly higher in preeclamptics than in normotensive pregnancies with male ($P<0.05$) as well as with female fetuses ($P<0.05$). Male bearing preeclamptic pregnancies have significantly higher maternal serum testosterone levels than female bearing pregnancies complicated by preeclampsia ($P<0.001$).

Table 1: Clinical characteristics in preeclamptics and normotensive pregnant women according to the sex distribution of the new born babies (All the values are expressed in Mean \pm SEM)

| Variables | Group A (n=50) Preeclamptics | | Group B (n=50) Normotensives | | P-value |
|-------------------------|---------------------------------|------------------------|---------------------------------|------------------------|---------|
| | Male fetus (n=25) | Female fetus (n=25) | Male fetus (n=25) | Female fetus (n=25) | |
| | Mean \pm SEM | Mean \pm SEM | Mean \pm SEM | Mean \pm SEM | |
| Age (years) | 24.32 \pm 0.63 | 24.80 \pm 0.68 | 23.08 \pm 0.80 | 23.68 \pm 0.69 | N.S. |
| Gestational age (weeks) | 37.32 \pm 0.60 | 36.52 \pm 0.59 | 38.32 \pm 0.43 | 37.48 \pm 0.56 | N.S |
| Height (meter) | 1.54 \pm 0.01 | 1.55 \pm 0.01 | 1.59 \pm 0.02 | 1.54 \pm 0.02 | N.S. |
| Weight (Kg) | 59.60 \pm 1.44 | 58.36 \pm 1.37 | 57.44 \pm 1.46 | 57.68 \pm 1.36 | N.S. |
| Systolic BP(mmHg) | 149.60 \pm 3.58 | 151.60 \pm 3.64 | 112.40 \pm 1.66 | 112.80 \pm 1.69 | N.S. |
| Diastolic BP (mmHg) | 100.20 \pm 1.97 | 101.60 \pm 1.77 | 72.80 \pm 1.58 | 73.20 \pm 1.60 | N.S. |
| Proteinuria | +ve | +ve | -ve | -ve | |

n= Number of subjects

N.S. =Non- significant, $p>0.05$

Table 2: Values of serum testosterone in preeclamptics and normotensives according to the sex distribution of the new born babies (All the values are expressed in Mean±SEM)

| Fetal Sex | Group A (n=50) Preeclamptics | | Group B (n=50) Normotensives | | P-value |
|--------------|------------------------------|----------------------------------|------------------------------|----------------------------------|---------|
| | n= | Testosterone (ng/ml) Mean±SEM | n= | Testosterone (ng/ml) Mean±SEM | |
| Male fetus | 25 | 4.7±0.35 | 25 | 1.4±0.14 | <0.05 |
| Female fetus | 25 | 2.8±0.28 | 25 | 1.5±0.14 | <0.05 |
| P value | <0.001 | | 0.615 | | |

n = Number of subjects

DISCUSSION

Transport of steroid hormones from the fetus to the mother is believed to be important for the maintenance of normal pregnancy and there is an important endocrine interplay between fetus, placenta and mother that involves sex steroid hormones. Hence, the fetus may have a potential for inducing gender specific endocrine changes in the mother. These changes may be observed as a difference in maternal testosterone levels, while their origin in reality stems from a difference between fetal genders¹⁵.

Several previous studies by Naghamani¹⁷ and Bamman¹⁸ as well as our own have shown no significant gender differences in the maternal serum testosterone values in normotensive females although the fetal testis but not ovaries contain testosterone and are able to synthesize this androgen from exogenous or endogenous precursors.¹⁹ The reason why testosterone production by the fetal testes is not reflected as a sex difference in maternal serum testosterone in normal pregnancy is unclear even though it can cross the placenta. Perhaps there is rapid placental clearance of androgens which originate from the fetal testes before such androgens can enter the maternal circulation²⁰.

Contrary to this, in the present study we found that the male-bearing preeclamptic pregnancies had significantly higher maternal serum testosterone levels than female-bearing pregnancies complicated by preeclampsia. This finding was consistent with the study conducted by Lorzadeh and Kazemirad²¹ and Steier et al;²² in which serum testosterone level was found to be significantly higher in male bearing pregnancies complicated with preeclampsia than normal ones. Pregnancies complicated by hypertension have a deficiency in placental aromatization enzymes, which may lead to higher levels of androgens including testosterone²³.

Moreover it does seem that there is an increased preponderance of boys born to women who develop eclampsia^{24,25,26} indicating that a common factor is associated with both preeclampsia and fetal gender.

CONCLUSION

It is thus concluded from our study that there exist an association between a particular fetal gender and maternal serum testosterone levels in preeclamptic women, this information could help to characterize a specific subgroup of women particularly at risk of preeclampsia by implementing systemic antenatal ultrasonography, to determine if the fetus is of the incriminated sex; then a specific follow-up could be given. This strategy may reduce a higher perinatal and maternal loss associated with preeclampsia.

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