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Original Article

# Evaluation of serum testosterone levels in pre-eclampsia

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## ABSTRACT

**Background:** Pre-eclampsia (PE) is a multi-system disorder that affects 3%–6% of human pregnancies and causes substantial maternal and foetal mortality and morbidity. Various studies have implicated testosterone as a causative factor in the pathogenesis of PE. The present study evaluated the association of serum testosterone levels with PE and maternal and foetal outcomes.

**Aim:** The objectives of the study were to assess serum testosterone levels in PE compared to normotensive pregnant mothers, to look for its association with PE and to identify its utility as a biomarker for PE.

**Materials and Methods:** A prospective cohort study was conducted in the 2nd trimester pregnant mothers ($n = 110$) attending the outpatient department at Vinayaka Mission's Kirupananda Variyar Medical College Hospital, Salem. Serum testosterone, uric acid, high-sensitivity C-reactive protein (hsCRP) and creatinine were evaluated and compared amongst the pre-eclamptic and normal pregnant women.

**Results:** The mean serum testosterone level was higher in PE women (2.625 ± 1.40 ng/dL) when compared to normal pregnant women (1.217 ± 0.258 ng/dL) ($P < 0.001$). Serum testosterone was found to be positively correlated with uric acid ($r = 0.517$, $P < 0.001$), hsCRP ($r = 0.307$, $P < 0.001$), systolic blood pressure (BP) ($r = 0.480$, $P < 0.000$) and diastolic BP ($r = 0.544$ $P < 0.001$). Receiver operating characteristic curve analysis for serum testosterone levels was done (area under the curve = 0.815), with sensitivity and specificity of 78.18% and 78.18%, respectively.

**Conclusion:** This study attempted to identify the association between serum testosterone levels, PE and pregnancy outcomes in a small South Indian population. Serum testosterone levels were found to be significantly elevated in pre-eclamptic women compared to normal pregnancies and could be used as a predictive biomarker. Serum uric acid and hsCRP also showed a significant positive association with PE.

**Keywords:** High-sensitivity C-reactive protein, pre-eclampsia, pregnancy, testosterone

## INTRODUCTION

Pre-eclampsia (PE) is a pregnancy-related severe complication accounting for 4%–8% of all pregnancies and is linked with maternal and foetal mortality.[1] PE is described by hypertension and proteinuria after 20 weeks of gestation, which, if developed before 34 weeks of gestation, is called early-onset PE, and when developed after 34 weeks of gestation, is called late-onset PE.[1] Maternal PE predisposes pregnant women to future metabolic and cardiovascular disorders due to PE-induced endothelial dysfunction and inflammatory changes.[2] It is recognised that abnormal placentation and placental vascular insufficiency are core

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features of PE, but why these and associated systemic abnormalities occur remains uncertain.[3]

The risk factors for PE are varied and unique. Genetic factors are at least partially responsible because both a maternal and a paternal family history of the disease predisposes to PE.[4] Although the cause of PE is likely multifactorial, the most recent theory is that PE is due to vascular endothelial dysfunction, and elevated plasma levels of testosterone could contribute to the endothelial dysfunction involved in the pathogenesis of PE.[5-8] Testosterone is a steroidogenic hormone that plays an essential role in the modulation of vascular reactivity and endothelial functions through the activation of platelet aggregations and the renin–angiotensin system. Maternal steroid-forming glands probably produce testosterone, the ovarian theca interstitial cells, the adrenal cortex and the foetoplacental unit.[9]

Various studies have implicated testosterone as a causative factor in the pathogenesis of PE.[3-6] Similarly, high testosterone levels in women with PCOS augment the risk and incidence of PE in future pregnancies. Hence, the present study is undertaken to identify the association of serum testosterone levels with PE and determine whether serum testosterone analysis will help in the earlier diagnosis of PE, thereby providing better foetal and maternal outcomes.

## MATERIALS AND METHODS

### Study design and setting

Our study was conducted at Vinayaka Mission's Kirupananda Variyar Medical College Hospital, Salem, Tamil Nadu. It was a facility-based prospective cohort study conducted from May 2020 to November 2021. One hundred and ten pregnant women in their second trimester were included as our study participants. The sample size was calculated from already reported mean testosterone levels amongst pre-eclamptic (2.136 ± 2.59 ng/mL) and healthy pregnant women (0.5 ± 0.1 ng/mL).[10] The study would require a sample size of 90 for estimating the expected proportion (i.e. 0.2 × 0.1 = 2% absolute precision) with 20% precision relative to the expected proportion and 95% confidence.[11]

PE was defined as a new onset of hypertension (systolic pressure ≥140 mmHg and diastolic pressure ≥90 mmHg), proteinuria or hypertension and significant end-organ dysfunction with or without proteinuria after 20 weeks of gestation in a previously normotensive woman.[10,12] Proteinuria was defined as ≥0.3 g in a 24-h urine specimen or dipstick ≥2+ if a quantitative measurement is unavailable. Severe PE was considered when systolic blood pressure (SBP) >160 mmHg and diastolic blood pressure (DBP) >110 mmHg with proteinuria >1 mg by dipstick. Other signs and symptoms, including headache, convulsion, oliguria and visual disturbances, were regarded as evidence of PE.

Pre-eclamptic pregnant women with blood pressure (BP) ≥140/90 mmHg without a previous history of hypertension were included. Healthy pregnant women in the second trimester were recruited as the control group. Pregnant women with chronic hypertension, gestational hypertension, cardiovascular disorders, endocrine and metabolic disorders that cause hypertension and gestational diabetes mellitus were excluded from the study.

Institutional Ethical Committee approval and informed consent were obtained from all the study participants. Tracking ID: VMKVMC and H/IEC/20/130, dated 30 December, 2020. Data were collected from all the study subjects using a detailed questionnaire. All the demographic data and detailed histories were collected, and the general examination findings were entered.

### Sample collection and laboratory analysis

Blood samples of 5–7 mL were drawn (by venipuncture) from an anterior cubital vein after 12 h of overnight fasting from normotensive and pre-eclamptic pregnant mothers in the 2nd trimester. The samples were analysed for serum high-sensitivity C-reactive protein (hsCRP) uric acid in a fully automated analyser EM 200. The serum total testosterone was estimated and measured using an enzyme-linked fluorescence assay in a Mini-VIDAS analyser using the ELFA-VIDAS kit method. The pre-eclamptic mothers are followed up to their 3rd trimester, and again, 5 mL of sample will be collected in their 3rd trimester and analysed for the same parameters.

### Statistical analysis

Statistical analysis was done using the software SPSS version 23, and the data were expressed as the mean ± standard deviation (SD). Shapiro–Wilk's test was applied to check the normality of the primary data. All the above parameters were compared between the two groups using the Student's independent *t*-test. Pearson's correlation test was applied to find the correlation between serum testosterone and other parameters. Binary logistic regression analysis was used to find the significant predictors for PE in pregnant mothers, such as hsCRP and uric acid. $P < 0.05$ was considered statistically significant. The receiver operating characteristic (ROC) curve was computed to find the cut-off value for serum testosterone level to discriminate pre-eclamptic women from normal pregnancies.

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## RESULTS

One hundred and ten pregnant women in the 2nd trimester of pregnancy (20–26 weeks) were enrolled in the study. Amongst them, 55 were healthy pregnant women, and the remaining 55 were pregnant women diagnosed with PE.

### Demographic characteristics

The mean age of the participants was 25.86, the mean age of pre-eclamptic women was 26.1 ± 3.72 and that of healthy pregnant women was 25.8 ± 3.72. All of them were in their 2nd trimester of pregnancy, between 20 and 26 weeks at the beginning of the study. The demographic details are shown in Table 1.

### Serum testosterone levels in preeclampsia women

The mean serum testosterone level in PE women was 2.625 ± 1.40 ng/dL, and that in healthy pregnant women was 1.217 ± 0.258 ng/dL, with a mean difference of 1.41. The testosterone levels were significantly elevated in the PE group when compared to normotensive pregnant women, $P < 0.001$ [Table 1].

Serum testosterone showed a moderate positive correlation with SBP ($r = 0.480$) and DBP ($r = 0.544$), $P < 0.001$. It also significantly correlated with serum uric acid and hsCRP levels, with Pearson's correlation coefficients $r = 0.517$ and 0.307, respectively, $P < 0.001$ [Table 2].

ROC curve analysis was computed for testosterone to assess its efficiency as a biomarker for PE [Figure 1]. The area under the curve (AUC) was 0.815, and at an optimum cut-off level

**Table 1: Comparison of parameters amongst normotensive pregnant women and pregnant women with pre-eclampsia in II trimester (*n*=110)**

| Parameters | Mean±SD (*n*=55) | | *P* |
|---|---|---|---|
| | Group 1 (healthy pregnancy) | Group 2 (PE) | |
| Age (years) | 25.8±3.22 | 26.1±3.72 | 0.682 |
| SBP (mmHg) | 108.50±11.45 | 149.92±10.45 | <0.001* |
| DBP (mmHg) | 71.82±6.48 | 94.46±6.43 | <0.001* |
| Testosterone (ng/mL) | 1.217±0.258 | 2.625±1.40 | <0.001* |
| hsCRP (mg/L) | 4.45±1.72 | 6.04±1.59 | <0.001* |
| Uric acid (mg/dL) | 4.01±0.6 | 6.705±1.22 | <0.001* |
| Baby birthweight (kg) | 3.32±0.36 | 2.97±0.45 | <0.001* |

*$P<0.001$ highly significant. hsCRP: High-sensitivity C-reactive protein, SD: Standard deviation, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, PE: Pre-eclampsia

**Table 2: Correlations of serum testosterone with uric acid, high-sensitivity C-reactive protein, systolic blood pressure, diastolic blood pressure and birthweight in pre-eclampsia women**

| Parameters | Correlation coefficient (*r*) | *P* |
|---|---|---|
| Uric acid | 0.517 | <0.001* |
| hsCRP | 0.307 | <0.001* |
| SBP | 0.480 | <0.001* |
| DBP | 0.544 | <0.001* |

*$P<0.05$ is considered statistically significant. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, hsCRP: High-sensitivity C-reactive protein

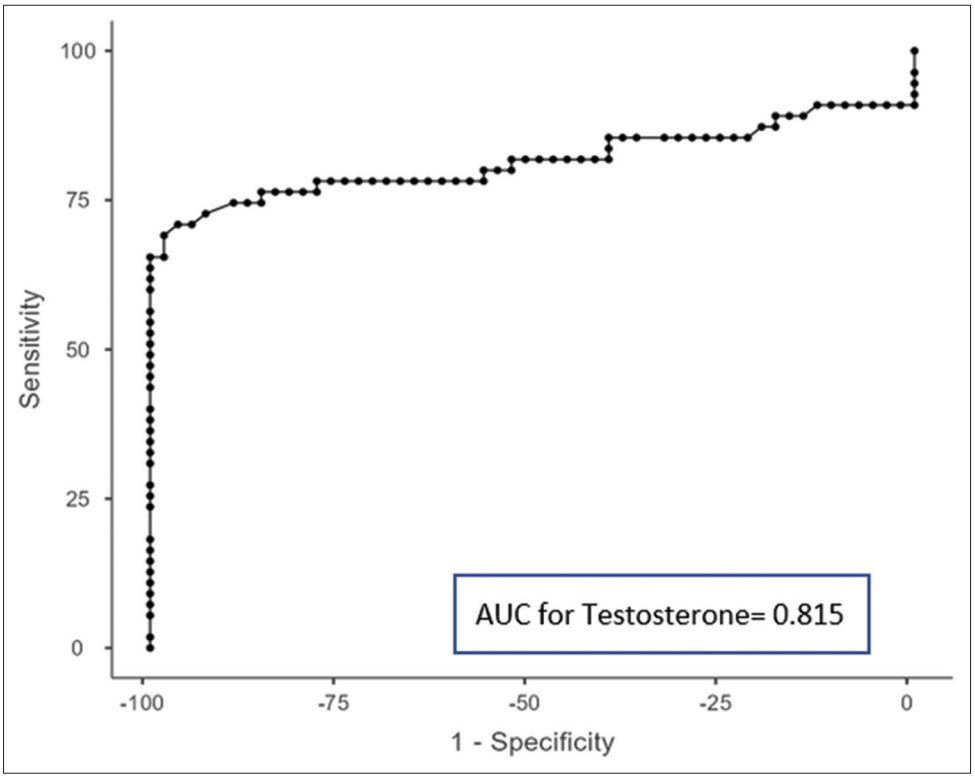


**Figure 1: Receiver operating characteristic curve: Testosterone (ng/mL). AUC: Area under the curve**

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of 1.42 ng/mL of serum testosterone could classify PE from normal pregnancy, with an optimum sensitivity and specificity of 78.18% and 78.18%, respectively.

All the participants were followed up till childbirth. The testosterone levels were measured in the 3rd trimester, but the levels were not significantly increased in the 3rd trimester compared to the 2nd trimester ($P = 0.452$).

### Comparison of serum testosterone levels in primigravidas and multigravidas

Serum testosterone levels were compared between primigravidas and multigravidas. Table 3 shows the mean and SD of serum testosterone levels in both groups. No significant association was seen between serum testosterone levels in both groups.

### Binomial logistic regression

Serum testosterone, uric acid and hsCRP showed a significant positive association with PE. The regression model was statistically significant, $\chi^2 = 135$, $P < 0.001$, and it explained 94.1% (Nagelkerke $R^2 = 0.941$) of PE occurrence in pregnant women [Table 2]. Increased serum testosterone was associated with an increased likelihood of PE by a factor of 34.96, which was significant ($P = 0.006$) after adjusting for uric acid and hsCRP levels [Table 4].

### High-sensitivity C-reactive protein and uric acid levels in preeclampsia

Serum hsCRP (inflammatory marker) and uric acid levels were also increased in PE with $P < 0.001$ [Table 1].

### Association of serum testosterone with birthweight and gender

The pregnant mothers were followed up until delivery, and the birthweight and gender of the babies were assessed. The birthweight of the babies born to them was found to have a significant negative correlation with serum testosterone levels [Figure 2].

The mean birthweight of babies born to mothers with serum testosterone levels >1.42 ng/dL was significantly

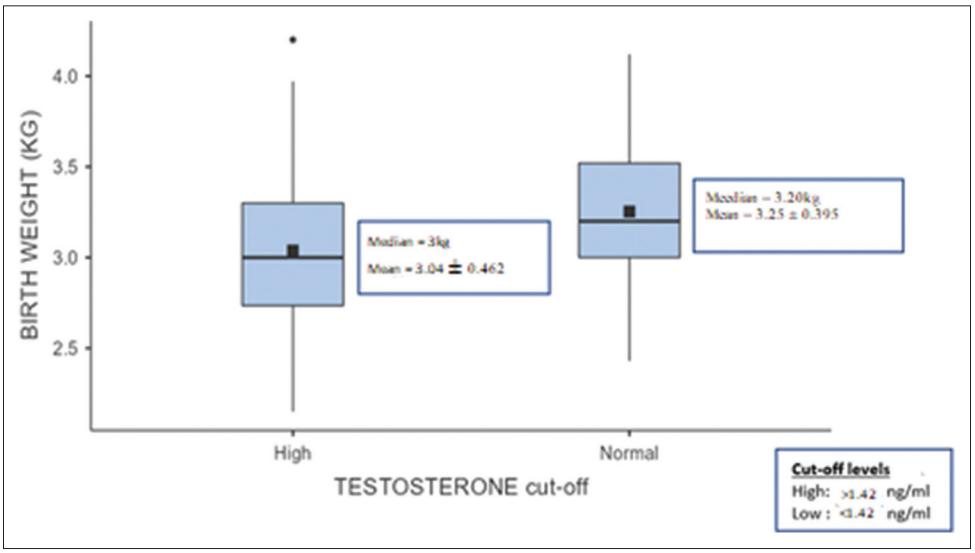


**Figure 2: Birthweight of babies born to mothers with testosterone levels above and below the cut-off levels**

**Table 3: Serum testosterone levels (ng/mL) in primigravida and multiparous healthy pregnancies and pre-eclampsia**

| | Mean±SD | | Mean difference and SE | *P* |
|---|---|---|---|---|
| | Primigravida (*n*=26) | Multigravida (para 2 and 3) (*n*=29) | | |
| Group 1 (healthy pregnancy) | 1.18±0.28 | 1.24±0.25 | 0.064±0.072 | 0.382 |
| Group 2 (PE) | 2.92±1.48 | 2.36±1.28 | −0.561±0.373 | 0.139 |

SD: Standard deviation, PE: Pre-eclampsia

**Table 4: Binary logistic regression model for serum testosterone and other parameters in pre-eclampsia**

| Variable | Crude OR with 95% CI | *P* | AOR with 95% CI | *P* |
|---|---|---|---|---|
| Testosterone (ng/mL) | 6.90 (2.83–16.81) | <0.001 | 34.96 (2.71–450.7) | 0.006 |
| Uric acid (mg/dL) | 9.08 (4.06–20.3) | <0.001 | 92.53 (3.57–2395.2) | 0.006 |
| hsCRP (mg/L) | 1.89 (1.43–2.49) | <0.001 | 5.36 (1.06–27.0) | 0.042 |

OR: Odds ratio, AOR: Adjusted OR, CI: Confidence interval, hsCRP: High-sensitivity C-reactive protein

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low, $P < 0.010$ [Figure 2]. We could not find any significant association between the gender of babies born to PE mothers and their serum testosterone levels.

## DISCUSSION

In the present study, serum testosterone levels have been assessed in the 2nd trimester of PE and normal pregnancies amongst South Indian women, and all the participants were followed up until childbirth.

The pathogenesis of PE can be considered to involve two stages: abnormal placentation and the development of the maternal syndrome.[12] Studies have shown that during normal placentation, cytotrophoblasts differentiate from an epithelial to an endothelial phenotype – a process referred to as 'pseudo-vasculogenesis' or 'vascular mimicry' – and this transformation fails to occur in PE.[13] This may lead to vascular endothelial damage that aggravates vasospasm and systemic hypertension.[14,15] The leading cause of PE is not well explained. Still, different previous studies showed testosterone hormone as a causative factor in the pathogenesis of PE, as the placentas of women with PE expressed a high density of testosterone receptors. Many human and animal studies have shown the association of androgens, especially testosterone, with hypertension.[14-16]

Some studies have proposed that testosterone could have a causal role in raising BP during gestation.[17,18] Even though the exact mechanism by which testosterone mediates an increase in maternal BP during pregnancy is not precise, the accumulating evidence indicates that testosterone increases vascular reactivity, activating the renin–angiotensin system and altering eicosanoid metabolism, thus favouring an increase in the thromboxane A2-to-prostacyclin (PGI2) ratio and causing platelet aggregation in ways that are strikingly similar to those reported in PE.[19] Elevated testosterone inhibits acetylcholine-induced relaxation of the mesenteric and uterine arteries, suggesting that elevated testosterone impairs endothelium-dependent relaxation. Specifically, nitric oxide-mediated vasodilation was significantly decreased in the mesenteric and uterine arteries in a pregnant rat model of elevated maternal testosterone.[16,19] Testosterone is also known to downregulate the expression of genes related to vascular development and angiogenesis (Ccr3, Stra6, Dhcr7, Arid1a, Ptprj, Col1a2, Lef1, Col1a1 and Mmp2) in the rat placenta.[20,21] Elevated testosterone decreases placental amino acid transport and oxygenation, leading to decreases in amino acid and oxygen availability to the foetus.[22-24] Verdonk *et al*. concluded that testosterone could contribute to the endothelial dysfunction involved in the pathogenesis of PE.[7]

In concordance with the other studies, the mean serum testosterone levels were elevated in the PE pregnancies, compared to the normal pregnant women, in the 2nd trimester ($P < 0.001$). The testosterone levels were further increased in the 3rd trimester of PE women, although it was not significant ($P = 0.452$). PE is quite prevalent in India, and this finding could have an important implication in the diagnosis and progression of PE. Besides the elevation, serum testosterone levels correlated well with SBP and DBP. Similarly, testosterone levels were found to correlate positively with SBP and DBP during and after PE, in other studies.[25-27] Although we could not find any difference amongst the testosterone levels in primigravida women and those of multigravida pregnancies, Chinnathambi *et al*. have reported testosterone levels to be significantly higher in primigravida women with PE than in normotensive women.[18] In this study, maternal serum testosterone levels above the cut-off value (>1.42 ng/dL) were associated with a lower mean birthweight in babies. Other studies have shown elevated maternal testosterone levels to be associated with reduced birthweights in specific human populations.[27,28]

Serum testosterone is associated with the occurrence of PE ($P = 0.006$), which is identical to the results of Sharifzadeh *et al*., who have proposed an association between high testosterone and the risk of PE.[14] Serum testosterone was found to have an excellent AUC (0.815, $P = 0.000$), proving it to be an excellent predictive biomarker for PE. Another study with an AUC of 0.717 has reported similar findings.[29]

This study showed a significant increase in serum levels of hsCRP and uric acid in PE women compared to normotensive women. Both markers correlate positively with serum testosterone levels ($P < 0.001$). Bansal *et al*. and Corominas *et al*. have also shown elevated levels of hsCRP and uric acid in PE women compared to normotensive women.[30,31]

### Limitations of the study

The relationship of serum testosterone levels with specific maternal and foetal outcomes was not studied in detail. Serum testosterone levels were not analysed in early pregnancy (1st trimester), and the sample size was smaller.

## CONCLUSION

As per our study results, serum testosterone levels were elevated in PE, which may have a significant role in its causation. It could be used as a predictive biomarker for PE, measuring its levels in early gestation (1st trimester). It could help monitor pregnant women with higher testosterone levels for the development of PE and related maternal and

foetal outcomes. Further studies must be conducted in the 1st trimester of pregnancies and in larger populations to confirm the findings.

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## Conflicts of interest

There are no conflicts of interest.

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