# ANDROGEN LEVELS IN PREECLAMPSIA

**M. Valadan*, N. Qadrdoost-Nakhchee and F. Davari-Tanha**

Department of Obstetric and Gynecology, Mirza Koochack Khan Hospital, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

**Abstract-** Preeclampsia is a major cause of morbidity and mortality during pregnancy. Several independent investigators have demonstrated the association of androgens with hypertension. The main purpose of this study was to determine whether maternal levels of sex hormones, especially testosterone, are higher in patients with preeclampsia than in matched normotensive control subjects. Serum levels of testosterone, free testosterone, dehydroepiandrosterone sulfate (DHEA-S) and estradiol were measured in 60 subjects in the 3rd trimester of pregnancy with documented preeclampsia (including 30 cases of mild and 30 cases of severe preeclampsia) and 60 healthy normotensive women with similar maternal and gestational ages and body mass index (BMI) and neonatal sex. All subjects were primigravid with singleton pregnancies. Cases of polycystic ovary (PCO), diabetes, chronic hypertension and chronic systemic diseases such as lupus and patients using steroid hormones and anti-hypertensive drugs were excluded. Levels of testosterone, DHEA-S and estradiol were not higher in primigravid women with preeclampsia than in normotensive women with similar gestational and maternal ages, BMI and neonatal sex. There were no significant differences in sex hormones measured between groups of mild and severe preeclampsia and normotensive women. There were also no significant differences in sex hormone levels according to neonatal sex. These findings are against the hypothesis of mediating or amplifying role of high androgen levels in pathophysiology of preeclampsia.
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**Key words:** Androgen, sex hormone, preeclampsia, testosterone, estradiol, dehydroepiandrosterone sulfate

## INTRODUCTION

Preeclampsia is a major cause of morbidity and mortality during pregnancy. Although the pathophysiology of preeclampsia has not yet been fully elucidated, vascular and homeostatic hyperactivity involving the renin-angiotensin system, eicosanoids and platelets have all been implicated (1).

Several independent investigators have demonstrated, through human and animal studies, the association of androgens, especially testosterone, with hypertension (2-8). Interestingly accumulating evidence indicates that androgens have important effects on vascular reactivity, the renin-angiotensin system, eicosanoids, and platelets, in ways that are strikingly similar to those reported for preeclampsia (1). Some studies have shown that women with polycystic ovary (PCO), a disease associated with hyperandrogenemia, are at risk for pregnancy-induced hypertension independent of body mass index (BMI) (1). It has been suggested that overproduction of steroid hormones, especially androgens, is the main factor for appearance of preeclampsia in PCO patients (9). Recently it has also been found that serum concentrations of inhibin A were higher in patients with preeclampsia than in control subjects with matched pregnancies and this finding was interpreted as further evidence for

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*** Corresponding Author:**
M. Valadan, Department of Obstetric and Gynecology, Mirza Koochak-Khan Hospital, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 912 1832177, +98 21 -8897762-4
Fax: +98 21 88904172
E mail: mehrnaz_valadan@yahoo.com

trophoblastic dysfunction in preeclampsia (10). Additionally, inhibin was recently shown to increase androgen production by ovarian theca cells, in turn increasing circulating androgen levels in women. It is thus possible that effects of increased serum inhibin in preeclampsia may be manifested through increased circulating androgen levels (1).

We therefore hypothesized that levels of sex androgens, and more specially that of testosterone, may be increased in pregnancies complicated by preeclampsia. We suspected that such an increase might be implicated in pathogenesis of preeclampsia. Of course, there have been some studies that have not demonstrated this correlation between androgens and preeclampsia (11, 12). To determine whether elevated androgen concentrations were associated with preeclampsia, we studied primigravid women and compared sex steroid concentrations between those with preeclampsia and those with normotensive pregnancies after controlling for BMI, maternal age, gestational age and neonatal sex. We have also compared the sex steroids between severe and mild preeclampsia to see whether levels of sex hormones correlate with severity of preeclampsia.

## MATERIALS AND METHODS

We studied 120 primigravid women with singleton pregnancies at Mirza Koochak Khan Hospital who consented to participate. All women included in the study were taking a multivitamin supplement with iron, and none were receiving or had received antihypertensive drugs or steroid hormones. None of the subjects had any history of hypertension, hyperandrogenism, PCO disease or other systemic diseases such as lupus erythematosus.

Studied women were divided into two groups. Group A consisted of 60 women in the 3$^{rd}$ trimester of pregnancy, in labor, with preeclampsia at the time of admission, including 30 cases of mild preeclampsia and 30 cases of severe preeclampsia. Group B consisted of 60 healthy, normotensive women in 3$^{rd}$ trimester, in labor; 30 cases of which were controls for group of mild preeclampsia and 30 other cases controls for group of severe preeclampsia with respect to maternal age, gestational age, neonatal sex and BMI.

Preeclampsia was defined as new onset hypertension after 20 week's gestation such that systolic blood pressure of $\geq$ 140 mmHg or diastolic blood pressures of $\geq$ 90 mmHg were seen repeatedly, accompanied by significant proteinuria ($\geq$ 300 mg/24h or $\geq$ +1 in random urine analysis) (13, 14, 15). Venous blood samples were collected, labeled, and centrifuged promptly. Serum samples were stored frozen in laboratory until determination.

Levels of total and free testosterone, dehydroepiandrosterone sulfate (DHEA-S) and estradiol (E2) was determined by means of commercially available radioimmunoassays. The sensitivity and the intra- and inter-assay coefficients of variation of the assays used were respectively as follows: for testosterone, 0.017 ng/ml, 1.5 to 6.1%, 7.8 to 9.3%, for DHEA-S, 20 ng/ml, 4.9 to 9.6%, 7.2 to 9.7%, for free testosterone, 0.1 pg/ml, 3.2 to 9.5%, 7.4 to 24.6%, and for E2, 10 pg/ml, 2 to 3.3%, 2.6 to 3.5%. No significant cross reactivity was observed between the hormones measured.

Serum levels were reported as mean ± SD for each group. Means of hormonal concentrations between groups were compared with the ANOVA (analysis of variance) and Tukey multiple comparison tests. The frequencies of high androgen levels (including free testosterone and DHEA-S above upper limits of assays) were compared between groups with the Fisher's exact test.

## RESULTS

Mean maternal age, mean gestational age and BMI were not significantly different between groups ($P > 0.05$, Table 1).

There was no significant difference between normal and preeclampsia groups in terms of described hormones (*P*: 0.35, 0.28, 0.42 and 0.41, respectively for total Te, free Te, DHEA-S and E2, Table 2). There was also no significant difference between groups of mild and severe preeclampsia in means of hormone levels (*P*: 0.35, 0.28, 0.42 and 0.41, respectively for total Te, free Te, DHEA-S and E2, Table 2). These two groups were not different in terms of maternal age, neonatal sex and BMI ($P > 0.05$), but there was significant difference in gestational age (37.9 ± 2.3 wk and 35.3 ± 2.95 wk,

**Table 1.** Demographic characteristics of study groups

| | | Mild pre.(n=30) | Control mild(n=30) | Severe pre.(n=30) | Control severe (n=30) |
|---|---|---|---|---|---|
| Sex | Female | 18 (60%) | 18 (60%) | 14 (47%) | 14 (47%) |
| | Male | 12 (40%) | 12 (40%) | 16 (53%) | 16 (53%) |
| Age (y) | | 23.6 ± 4.7 | 22.2 ± 2.8 | 24.6 ± 4.6 | 23.2 ± 3.8 |
| Gest. age (wk) | | 37.3 ± 1.9 | 37.9 ± 2.3 | 35.3 ± 2.95 | 35.3 ± 3.9 |
| BMI (kg/m2) | | 31.9 ± 4.3 | 30.6 ± 4.7 | 29.9 ± 5.1 | 30.8 ± 5.4 |

**Table 2.** Hormones levels in different study groups

| | Mild pre. (n=30) | Control mild (n=30) | Severe pre.(n=30) | Control severe (n=30) |
|---|---|---|---|---|
| Total Te (ng/mL) | 0.98 ± .71 | 1.04 ± 0.85 | 1.14 ± 1.4 | 0.54 ± .44 |
| Free Te (pg/mL) | 2.2 ± 1.8 | 2.5 ± 2.5 | 2.4 ± 2.6 | 1.45 ± 1.01 |
| DHEA-S (ng/mL) | 696 ± 451 | 664 ± 383 | 1003 ± 1163 | 654 ± 586 |
| Estradiol (pg/mL) | 5050 ± 3932 | 6707 ± 5538 | 7355 ± 8258 | 7940 ± 6596 |

**Table 3.** Demographic characteristics in normal and preeclampsia groups by fetal sex

| | Preeclampsia | | Normal | |
|---|---|---|---|---|
| | Female | Male | Female | Male |
| Age(y) | 24.53 ± 5.17 | 23.54 ±3.94 | 23.13 ± 3.43 | 22.21 ± 3.18 |
| Gest. age (wk) | 36.16 ± 2.48 | 36.43 ± 3.94 | 36.97 ± 3.51 | 36.25 ± 3.41 |
| BMI (kg/m2) | 31.32 ± 4.39 | 30.35 ± 5.21 | 31.23 ± 5.11 | 30.04 ± 4.85 |

**Table 4.** Hormone levels in normal and preeclampsia groups by fetal sex

| | Preeclampsia | | Normal | |
|---|---|---|---|---|
| | Female | Male | Female | Male |
| Total Te ng/mL | 1.15 ± 1.35 | 0.96 ± 0.73 | 0.79 ± 0.67 | 0.79 ± 0.77 |
| Free Te pg/mL | 2.57 ± 2.51 | 2.03 ± 1.8 | 2.11 ± 1.71 | 1.82 ± 2.19 |
| DHEA-S ng/mL | 923.22 ± 1057 | 765.18 ± 653 | 611.34 ± 421 | 712.75 ± 563 |
| Estradiol pg/mL | 6595.29 ± 7446 | 5753.2 ± 5361 | 6277.39 ± 6472 | 8518.97 ± 5444 |

**Table 5.** Prevalence of high androgen levels in study groups

| High levels of: | Mild pre. (n=30) | Control mild (n=30) | Severe pre. (n=30) | Control severe (n=30) |
|---|---|---|---|---|
| Free Te | 4 (13.33%) | 7 (23.33%) | 6 (20%) | 0 (0%) |
| DHEA-S | 1 (3.33%) | 0 (0%) | 4 (13.23%) | 2 (6.67%) |

respectively for mild and severe preeclampsia, $P$ = 0.0004) as shown in Table 1. Both preeclampsia and normal groups consisted of 32 (53.33%) female and 28 (46.67%) male neonates. In both groups of normal and preeclampsia, there was no significant difference, between pregnant women with female and male fetuses, in terms of maternal age, gestational age, and BMI ($P$ > 0.05, Table 3). We found no significant relation between maternal hormone levels and neonates' gender in preeclampsia and normal groups, as shown in table 4 ($P$: 0.57, 0.27, 0.83 and 0.54, respectively for total Te, free Te, DHEA-S and E2 in both groups). The results of Fisher's exact test showed that there were no significant differences between mild preeclampsia and its control as well as mild and severe preeclampsia in prevalence of high androgen levels ($P$ > 0.05), but this statistical test revealed that, high free testosterone level was significantly more prevalent in severe preeclampsia compared with its normal control (20% and 0% respectively with $P$ = 0.02). This is shown in table 5.

## DISCUSSION

In this study, levels of the sex hormones including total and free testosterone, DHEA-S and estradiol were not significantly different between groups of preeclamptic and normotensive pregnant women with similar maternal age, gestational age, neonatal sex and BMI. There was also no significant difference in these hormone levels between severe and mild pre eclamptic women, and not between pregnancies with male fetus and female ones. There was significant difference in gestational age between severe and mild preeclamptic women ($P = 0.0004$). This difference may have an adverse effect on reliability of the result, although the effect of this difference on hormone levels is not clear and it does not seem to be clinically important. Difference between groups of severe preeclampsia and its normal control in prevalence of high free testosterone does not seem to be clinically important as well.

As said before, in several studies, higher androgen levels have been found in preeclampsia compared with normal pregnancies (1-8, 16). It has been shown that androgens have important effects on vascular reactivity, renin-angiotensin system, eicosanoids and platelets, which are strikingly similar to those of preeclampsia (1). It also has been suggested that inhibin A has a pathophysiologic effect on preeclampsia that is probably mediated by stimulation of androgen production from theca cells of ovary (1). The higher incidence of preeclampsia in PCO disease is attributed to higher androgen levels in these patients (9). In addition, testosterone treatment has been shown in animal studies to accentuate the vascular responses to the pressor agents arachidonate and norepinephrine (2).

In most studies the comparison of the hormone levels between preeclampsia and normal groups have resulted in higher levels of androgens in preeclampsia and equal levels of estrogens (1-8, 16). In one study, even several years after treatment of preeclampsia, the level of testosterone has seen to be higher than those without any history of preeclampsia. The author concluded that this higher level of testosterone may contribute to increased risk for vascular morbidity in such women (3). Of course there have been some recent studies that have not demonstrated the probable relation between androgens and preeclampsia (11, 12). In these two studies, androgen levels had not significant difference between preeclampsia and normal groups, as well as severe and mild preeclampsia.

One of previous studies has shown that in preeclamptic women with female fetus maternal serum testosterone level is higher than with male fetus, but this difference did not exist in normal pregnancies (17). Our study shows that there is no difference in sex hormone levels according to neonatal sex, in both pre eclamptic and normal groups. The absence of significant difference in sex hormone levels between normal and preeclamptic pregnancies, as well as mild and severe preeclampsia, in our study, is compatible with results of two recent studies (11, 12). Our study refuses the hypothesis of mediating or amplifying role of high androgen levels in pathophysiology of preeclampsia. Although, androgens have different effects on vascular and homeostatic systems and can produce changes similar to that of preeclampsia, *in vivo* and *in vitro*, but clinically they seem not to have significant role in pathogenesis of preeclampsia.

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### Conflict of interests

We have no conflict of interests.

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