EVALUATION OF ANDROGEN AND PROGESTERONE LEVELS OF WOMEN WITH PREECLAMPSIA IN THIRD TRIMESTER

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SUMMARY : The purpose of the study was to determine whether maternal serum levels of androgen and progesterone, are higher in patient with preeclampsia than in matched control subjects.

Serum progesterone, total testosterone, free testosterone and dehydroepiandrosterone levels were measured in 19 subjects in third trimester of pregnancy with documented preeclampsia and 17 healthy normotensive women with similar maternal and gestational ages. All subjects were primigravida women with singleton pregnancy who were visited in Kosar Medical center in Uromiyeh.

There were no significant differences between two groups in maternal age, gestational age and body mass index. Progesterone and free testosterone levels were significantly lower (p=0.01) in patients with preeclampsia (75.1 ± 8.6 ng/dL and 2.27 ± 1.71 pg/dL, respectively) than in control group (111.6±9.71 ng/dL and 3.73±1.31 pg/dL, respectively). There were no significant differences in total testosterone and dehydroepiandrosterone levels between cases (1.02 ± 0.10 ng/dL and 0.99 ± 0.13 µg/dL, respectively) and controls (1.37 ± .019 ng/dL and 0.98 ± 5.15 µg/dL, respectively).

Accentuated sex hormone binding globulin increase in preeclampsia is the cause of significant decreased free testosterone of preeclamptic cases. Levels of progesterone were pathologically and significantly lower in preeclamptic cases than control women with similar age, gestational age and body mass index. This difference raises the possibility for a role of progesterone in the pathogenesis of preeclampsia.

Key Words : Preeclampsia, androgen, progesterone.

INTRODUCTION

Preeclampsia is a transient but potentially dangerous complication of pregnancy that affects 3 to 5 percent of pregnant women (1). An estimated number of 50,000 women per year worldwide die from preeclampsia (2). In spite of so many researches, the pathology of preeclampsia has not yet been fully elucidated. Hormonal features of this condition have lead to speculation about hormonal causes.

Many studies conclude that higher blood androgen levels measured in preeclamptic patients may be implicated in the pathogenesis of preeclampsia (3,4). Some studies found no difference in concentration of unconjugated estrogen and androgen in the cord sera of preeclamptic and uncomplicated pregnancies (5). Subcu-

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Table 1: Identification of patients in case and control groups.

Data of study	Case	Control	Significant
Number of patients	19	17	NS
Age (year)	25.7 ± 1.2	22.7 ± 1.5	-
Body mass index (kg/m^2)	12.58 ± 5.22	12.38 ± 5.13	NS
Estimated gestational age (week)	35.2 ± 0.8	36.7±1.1	NS

NS: Non Significant

taneous injection of progesterone to pregnant mouse with preeclampsia resulted in reduction of blood pressure (6). Recently published studies highlight the role of progesterone changes in animal as the cause of preeclampsia. Attention was then attracted to the role of progesterone in human preeclampsia. Omental vascular relaxant effect of progesterone in pregnant women was demonstrated by a study (7). In regard to above-mentioned causes we therefore hypothesized that there may be a difference between the level of progesterone in pregnant women complicated with preeclampsia and matched ones without preeclampsia? To determine whether the changes in serum progesterone, were associated with preeclampsia, we studied total testosterone, free testosterone and dehydroepiandrosterone concentration along with progesterone levels in primigravida preeclamptic women. We cannot find any previous publication that searches these four hormones in the same patients simultaneously.

MATERIALS AND METHODS

Research Council of Uromieh University approved the protocol of this study. We secruited 36 primigravida women in third trimester with singleton pregnancies at Kosar Obstetrics Hospital who admitted to participate in this study after informed consent. The patients were enrolled from September 2002 to December 2003. Study had 80% power to detect a 30% difference in mean progesterone concentration between case and control groups using a two-tailed test and alpha level of 0.05. All women included in the study neither had received antihypertensive medications nor were administered hormones. None of subjects had any history of hypertension or other disease that results in hormone disorders. The cases diagnosed as preeclampsia for the first time in our center after routine pregnancy examinations. Nineteen subjects with peeclampsia diagnosis included in the case group and 17 subjects with normotensive noncomplicated pregnancy accepted to the control group. Maternal chronological age, body mass index and gestational age considered in matching of groups.

Preeclampsia was defined as new onset hypertension after 20 weeks' gestation such that systolic blood pressure of ≥140 mm Hg, diastolic pressure of ≥ 90 mm Hg or both were measured on two occasions ≥ 6 hours apart, with significant proteinuria (300 mg/24 h). Venous blood samples were collected, labeled and centrifuged promptly. Serum samples were stored at -70°C until determination. Levels of progesterone, total testosterone, free testosterone and dehydroepiandrosterone were determined by means of RIA.

Comparison of hormonal concentration between groups was performed with Student t-test. Statistical analysis was performed with the SPSS package.

RESULTS

A total of 36 patients were accepted to this study.

The mean maternal age, mean gestational age and body mass index were not significantly different ($p > 0.5$) between the groups (Table 1).

Serum hormone concentrations are presented in Table 2. No significant differences ($p>0.05$) in total testosterone and dehydroepiandrosterone levels were observed between preeclamptic cases (1.02 ± 0.10 ng/dL and 0.99 ± 0.13 μg/dL, respectively) and controls (1.37 ± .019 ng/dL and 0.98 ± 5.15 μg/dL, respectively).

Free testosterone levels were significantly lower ($p= 0.01$, power=80%) in the preeclamptic group (2.27 ± 0.55 pg/dL) than in control group (3.73 ± 1.31 pg/dL).

Progesterone levels were significantly lower ($p=0.01$, power=80%) in the preeclamptic group (75.1±8.6 pg/dL) than in control group (111.6 ± 9.7 pg/dL).

Total testosteron in the preeclamptic and the control groups were on fellows: 1.02 ± 0.10 ng/dL and 0.99 ± 0.13 μg/dL, respectively) than in controls (1.37 ± .019 ng/dL and 0.98 ± 5.15 μg/dL, respectively), ($p>05$).

DISCUSSION

In this study levels of progesterone and free testosterone were found to be significantly lower in women with preeclampsia than in normotensive women with similar body mass index, gestational age and chronological age. No significant difference was observed at levels of total testosterone and dehydroepiandrosterone between two groups (Table 2).

In many studies increase of androgen levels were cited as the cause of preeclampsia pathogenesis (8,9). However most studies revealed that there are no changes

Table 2: Serum hormone concentration in preeclampsia and control groups.

Data of Study	Case	Control	P-value	Significant
Progesterone (ng/dL)	75.1 ± 8.6	111.6 ± 9.71	0.01	S
Total testosterone (ng/dL)	1.02 ± 0.10	1.37 ± .019	>0.05	NS
Free testosterone (pg/dL)	2.27 ± 1.74	3.73 ± 1.31	0.01	S
Dehydroapiandrosterone (µg/dL)	0.99 ± 0.13	0.98 ± 5.15	> 0.05	NS

S: Significant NS: No Significant

in the levels of androgens in preeclampsia and these hormones do not play clinically significant role in the pathogenesis of the disease (10). Our findings about androgen levels are compatible with results of these studies.

In this study significant changes were observed at levels of free testosterone between case and control groups. Sex hormone binding globulin levels increase in normal pregnancy (11). The accentuation of this phenomenon in preeclampsia which was postulated in a study (12), results in reduction of free testosterone levels without increase of total testosterone levels.

In a study progesterone was considered as main steroid hormone with major action on vascular tension during pregnancy (13). Because progesterone injection in induced preeclampsia of rats resulted in reduction of blood pressure (6). Also progesterone administration in pregnancy induced hypertension leading to significant decrease in both systolic and diastolytic blood pressures, significant increase in urinary output, amelioration of the edema, slight reduction in weight gain, but no change in the proteinuria (14).

In a study conducted by Belfort on isolated human artery from premenopausal nonpregnant women and from normotensive and preeclampsic pregnant women, it was established progesterone have direct *in vitro* activity in human omental artery from normal and hypertensive women in different hormonal states (7).

Alterations in vascular sensitivity of endogen hormones (angiotension II, catecholamin and vasopressin) and absence or decrease of nitric oxide concentration may have an important role in the increase of blood pressure, which were observed in preeclampsia (11,15). In preeclampsia the thromboxane (vasoconstrictor) A_2 / prostacyclin ratio has been found to be increased (15). Progesterone vascular relaxant effect probably is able to ameliorate these effects. Progesterone's vascular relaxant effect may depend on the release of the prostacycline or the nitrite oxide (16). Other important mechanism for progesterone antihypertensive character is direct effect on vascular muscles by blocking of calcium channels (17).

In conclusion, levels of progesterone were pathologically and significantly lower in preeclamptic cases than control women with similar age, gestational age and body mass index. This difference indicates a role of progesterone in the pathogenesis of preeclampsia. Because increase of vascular resistant has the important disorder in preeclampsia and progesterone by many ways including reduction of the sensitivity of angiotension, increasing endothelial vasodilatator like prostacycline, nitrite oxide and direct effect on vascular muscles, leading to reduction of vascular resistance.

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