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The relationship between serum concentration of free testosterone and pre-eclampsia

Zależność między stężeniem wolnego testosteronu w surowicy a występowaniem stanu przedrzucawkowego

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Abstract

Introduction: Hyperandrogenism may be implicated in the pathogenesis of pre-eclampsia. We hypothesised that there may be a difference between the levels of testosterone in pregnant women complicated with pre-eclampsia and those of matched women without this complication.

Material and methods: A case-control study conducted in Tehran, Iran between January and June 2006 included 20 women with moderate to severe pre-eclampsia and 20 normotensive pregnant women without complications who were matched for age, body mass index and gravity. Maternal levels of free testosterone was measured in the two groups and compared.

Results: Free testosterone levels were significantly higher in the pre-eclamptic group (mean = 1.97, SD = 0.58, median = 1.90 ng/dL) than in the control group (mean = 0.58, SD = 0.29, median=0.50 ng/dL) ($P < 0.001$).

Conclusions: An increase in serum free testosterone concentration may be considered an important risk factor for pre-eclampsia and might be implicated in the pathogenesis of pre-eclampsia. **(Pol J Endocrinol 2008; 59 (5): 390–392)**

Key words: *testosterone, pre-eclampsia, pathogenesis, pregnancy*

Streszczenie

Wstęp: Hiperandrogenizm może mieć wpływ na patogenezę stanu przedrzucawkowego. Autorzy założyli, że istnieją różnice w zakresie stężeń testosteronu u kobiet w ciąży powikłanej stanem przedrzucawkowym i dobranych odpowiednio ciężarnych kobiet z grupy kontrolnej bez tego powikłania.

Materiał i metody: W badaniu kliniczno-kontrolnym przeprowadzonym w Teheranie w okresie od stycznia do czerwca 2006 roku uczestniczyło 20 kobiet z umiarkowanym lub ciężkim stanem przedrzucawkowym i 20 ciężarnych kobiet z prawidłowym ciśnieniem tętniczym bez powikłań, dobranych pod względem wieku, wskaźnika masy ciała i parametrów ciążowych. Stężenie wolnego testosteronu w surowicy ciężarnych kobiet zmierzono i porównano między grupami.

Wyniki: Stężenie wolnego testosteronu w surowicy było istotnie wyższe u kobiet, u których ciąża była powikłana stanem przedrzucawkowym (średnia = 1,97, SD = 0,58, mediana = 1,90 ng/dl) niż w grupie kontrolnej (średnia = 0,58, SD = 0,29, mediana = 0,50 ng/dl) ($P < 0,001$).

Wnioski: Zwiększenie stężenia wolnego testosteronu w surowicy kobiet ciężarnych może być ważnym czynnikiem ryzyka stanu przedrzucawkowego i odgrywać znaczącą rolę w patogenezie tego powikłania ciąży. **(Endokrynol Pol 2008; 59 (5): 390–392)**

Słowa kluczowe: *testosteron, stan przedrzucawkowy, patogeneza, ciąża*

Introduction

Pre-eclampsia and its complications, such as prematurity, intrauterine growth retardation, perinatal asphyxia and placental abruption, can lead to high maternal and fetal morbidity and mortality, so that an estimated 50 000 women per year worldwide die from pre-eclampsia [1]. Owing to its morbid course, it is necessary to identify those at risk of the illness and take precautions [2]. The role of androgens in the pathogenesis of pre-eclampsia has been studied in many human and animal samples and hyperandrogenism has been considered one of the important risk factors of pre-eclampsia [3]. Some studies conclude that hyperandrogenism in pre-eclamptic patients may be implicated in the pathogenesis of pre-eclampsia [4, 5], while others have found no difference in concentrations of androgens in the cord sera of pre-eclamptic and uncomplicated pregnan-

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cies [6, 7]. In addition, some experimental studies have been published on the association between testosterone concentration and enzymes which are activated in pre-eclampsia. Steegers et al. considered the effects of testosterone on the enzyme epoxide hydrolase, which is associated with pre-eclampsia. They concluded that a polymorphism in the gene for microsomal epoxide hydrolase is associated with pre-eclampsia, and that women with the high activity genotype in exon 3, which could reflect differences in the metabolic activation of endogenous or exogenous toxic compounds, may have an enhanced susceptibility to pre-eclampsia [8]. In the light of the results of these studies, therefore, we hypothesised that there may be a difference between the levels of testosterone in pregnant women complicated with pre-eclampsia and those of matched women without this complication. To determine whether the changes in serum testosterone were associated with pre-eclampsia, we studied the concentrations of free testosterone in pre-eclamptic women with the aim of demonstrating the role of this factor in the pathogenesis of pre-eclampsia.

Material and methods

A case-control study was made of 20 primigravidae who were in the third trimester, carrying singleton pregnancies and suffering from moderate to severe pre-eclampsia, and who had been referred to Mofatteh Hospital in Tehran between January and June 2006. The women participated after giving their informed consent and the protocol of the study had been approved by the Research Council of Shahid Beheshti University. A further 20 normotensive pregnant women without complications and matched for age, body mass index and gravity were randomly selected. None of the women included in the study had received either antihypertensive medications or hormone treatment. None of the subjects had any history of hypertension or other conditions resulting in hormone disorders such as hirsutism or polycystic ovarian syndrome. Pre-eclampsia 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, labelled and centrifuged promptly. Serum samples were stored at –70°C until determination [9]. The level of free testosterone was determined by means of RIA.

Results were reported as mean ± standard deviation (SD), median for the quantitative variables and percentages for the categorical variables. The groups were compared using Student's *t*-test or the Mann-Whitney U test for the continuous variables. This study was done with the power of 90%. P values of 0.05 or less were considered statistically significant. All the statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA) for Windows.

Table I. *Identification of patients in case and control groups*

Tabela I. *Charakterystyka ciężarnych z grupy „przypadków" i grupy kontrolnej*

Characteristics	Age (year)	BMI [kg/m²]	SBP [mm Hg]	DBP [mm Hg]
Pre-eclamptic group: (n = 20)				
Mean	23.55	12.61	16.15	9.90
Median	22.00	12.00	16.00	9.00
Standard Deviation	3.30	5.60	1.78	1.65
Healthy group: (n = 20)				
Mean	23.85	12.41	11.25	6.95
Median	22.00	12.00	11.00	6.00
Standard Deviation	5.26	5.20	0.55	0.39
P value	0.830	0.907	< 0.001	< 0.001

BMI — body mass index; SBP — systolic blood pressure; DBP — diastolic blood -pressure

Table II. *Serum total testosterone concentration in pre-eclampsia and control groups*

Tabela II. *Całkowite stężenie testosteronu w grupie ciężarnych ze stanem przedrzucawkowym i w grupie kontrolnej*

Groups studied	Pre-eclamptic (n = 20)	Healthy (n = 20)	P value
Mean	1.97	0.58	
Median	1.90	0.50	
Standard Deviation	0.58	0.29	< 0.001
Maximum	3.60	1.00	
Minimum	1.20	0.20	

Data are presented as ng/dL

Results

There were no significant differences in maternal age and body mass index between the two groups. However, both systolic and diastolic blood pressure readings in the pre-eclamptic group were higher than in the control group (Table I). In the group with pre-eclampsia, 30% of patients had proteinuria 2+, 45% of them had proteinuria 3+ and others had proteinuria 4+. Free testosterone levels were significantly higher in the pre-eclamptic group than in the control group (Table II).

Discussion

The results of previous studies concerning the role of androgens in the pathogenesis of pre-eclampsia have varied. Some studies cited the increase in androgen levels as one of the causes of pre-eclampsia, whereas this relationship was not revealed in others. In a study by Acromite et al. total testosterone and free testosterone levels were significantly higher in patients with pre-eclampsia than in the control group [4]. This result was also obtained in studies by Gerulewicz-Vannini et al. and Salamalekis et al. [9, 10]. Zhorzholadze et al. also found that testosterone levels increased by 51% in comparison with those of women with a physiological pregnancy [11]. However, Fiçicioðlu et al. obtained no statistically significant difference in total and free testosterone content between pre-eclamptic and healthy pregnant groups, in their study no difference was found in testosterone levels in a severely pre-eclamptic group and in a mildly pre-eclamptic group [2]. Furthermore, in the study conducted by Valadan et al. the testosterone levels were not higher in primigravidae with pre-eclampsia than in normotensive women of similar gestational and maternal ages, body mass index and neonatal sex [12].

It seems that different predictors may influence the relationship between serum testosterone level and the incidence and severity of pre-eclampsia. Geographical and social differences may be one of these effective factors. In a similar study in Iran, but in a different population, the results obtained were not comparable to those of the present study [13]. Gestational age may be another effective factor. In the study performed by Carlsen et al. it was found that testosterone was elevated in gestational weeks 17 and 33 in women who eventually developed pre-eclampsia. However, at week 33 elevated levels of testosterone were seen only in women with male foetuses [3]. Furthermore, in the study by Troisi et al. androgen levels were, after adjustments for age and race, significantly associated with a higher average second trimester systolic blood pressure, although this rise was not observed for second trimester diastolic pressure or for third trimester blood pressure [14].

However, several mechanisms in the pre-eclampsia pathogenesis have been studied in relation to the increase in serum testosterone levels. It has been indicated that alterations in the vascular sensitivity of some endogen hormones, such as angiotensin II, catecholamine and vasopressin, and also a decrease in nitric oxide concentration or its absence may have an important role in the increase in blood pressure observed in pre-eclampsia [15, 16]. It has also been suggested that inhibin A has a pathophysiological effect on pre-eclampsia that is probably mediated by stimulation of androgen production from theca cells of the ovary [4]. The role of some gene repeats was also investigated. Tanja et al. found no significant differences in the mean androgen receptor gene CAG repeat lengths between unrelated pre-eclamptic women and controls. However, the shortest CAG repeat lengths were found only in the pre-eclamptic women. According to their study result, an association is possible between the shortest CAG repeats and pre-eclampsia [17].

In view, therefore, of the probable role of androgen concentration changes in the occurrence of pre-eclampsia as a serious complication of pregnancy, it seems that anti-androgens may have a potential role in the management of pre-eclampsia [10]. However, this subject should be investigated further in future studies.

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