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Do androgen levels play a role in predicting complications of preeclampsia?

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Abstract
Preeclampsia is a multisystem disorder characterized by new-onset hypertension and proteinuria after 20 weeks of gestation. The association between androgens and hypertension has been demonstrated. The purpose of this study was to determine the relationship between androgen levels and fetal and maternal complications in patients with preeclampsia. This study included 178 patients who were followed up with the diagnosis of preeclampsia and gave birth in High-Risk Pregnancy Clinic of Zekai Tahir Burak Women's Health Research and Education Hospital. Androstenedione, dehydroepiandrosterone sulfate, total testosterone and free testosterone levels were measured by the Immulite 200 chemiluminescence method on the BioDPC Isodata 100 Series Gamma Counter in venous blood samples. Maternal complications and fetal complications were recorded. The relationship between these complications and androgen levels was examined. Free testosterone levels were significantly higher in those with a 1-min Apgar score <7 than in those with a 1-min Apgar score ≥7. Total testosterone levels were significantly lower in the preterm group than in the non-preterm group. Androstenedione levels were significantly higher in the IUGR group than in the non-IUGR group. Total testosterone levels were significantly lower in the fetal distress group than in the non-fetal distress group. Total testosterone and androstenedione levels were significantly higher in patients with increased AST and ALT levels. Total testosterone levels were significantly higher in the group with maternal complications than in the group without maternal complications. While higher total testosterone levels indicated maternal complications in preeclampsia, total testosterone levels were shown to be lower in those with preterm birth and fetal distress. Androstenedione levels were shown to be higher in those with IUGR and elevated liver enzyme levels. No significant association was found between dehydroepiandrosterone sulfate levels and fetal/maternal complications.

Keywords: Preeclampsia, androgens, maternal complications, fetal complications

Introduction

Preeclampsia (PE) is a multisystem disorder characterized by new-onset hypertension and proteinuria after 20 weeks of gestation [1]. Hypertension is the most common medical problem encountered during pregnancy. The incidence of PE in nulliparous women is estimated between 3% and 14% [2]. It is estimated that nearly 50,000 women die every year from eclampsia in the world [3].

Abnormal trophoblastic invasion is responsible for preeclampsia due to maternal intolerance to allogeneic fetus and change in maternal immune response in early pregnancy. [4-6]. Abnormal placental steroidogenesis has also been reported in women with PE [7].

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Preeclampsia can result in maternal complications such as severe hypertension, eclampsia and haemolysis, elevated liver enzymes and low platelet count (HELLP syndrome), or fetal complications such as growth restriction, fetal distress and even perinatal death [1].

Treatment options for preeclampsia are very limited. There are non-effective methods such as the regulation of blood pressure with drugs [8] and the prevention of eclamptic seizures with magnesium sulfate [9]. The only definitive cure of preeclampsia is to deliver the placenta. While delivery before 37 weeks of gestation may cause fetal complications, waiting for fetal maturation may lead to maternal complications. The prediction of these complications is important in terms of planning the timing of delivery.

Several independent investigators have demonstrated through human and animal studies that androgens (especially testosterone) are associated with hypertension [10,11]. Androgens also decrease prostacyclin production in vitro and increase production of other

eicosanoids (including thromboxane), resulting in a thromboxane to prostacyclin ratio which favors vascular constriction and coagulation in a way similar to that seen in preeclampsia. It has also been shown that androgens directly increase platelet aggregation [12].

The aim of this study was to determine whether androgen levels play a role in predicting fetal and maternal complications in preeclampsia patients.

Material and Methods

This study included 178 patients who were followed up with the diagnosis of preeclampsia and gave birth in High-Risk Pregnancy Clinic of Zekai Tahir Burak Women's Health Research and Education Hospital between March 2000 and December 2002. 75 patients were excluded from the study due to various reasons (delivery, giving birth in other centers after discharge, inability to reach androgen level results and prognosis information). Finally, a total of 103 patients completed the study. It was designed prospectively and approved by the Ethics Committee of Zekai Tahir Burak Women's Health Research and Education Hospital (ECTN:02-114).

Preeclampsia was initially defined as a rise in systolic blood pressure to ≥140 mmHg or in diastolic pressure to ≥90 mmHg on two separate occasions in a patient who was previously normotensive, as well as proteinuria of ≥300 mg in a 24-hour collection, of 0.3 g/g by urine protein/creatinine ratio or +1 by urine dipstick if quantitative methods are unavailable, occurring after 20 weeks of pregnancy [11].

Demographic characteristics such as gravidity, parity, and body mass index (BMI) were recorded. Systolic and diastolic blood pressure values were recorded. CBC analysis was performed on the Beckman Coulter AcT Diff II Hematology Analyzer. Biochemical analysis (sodium, potassium, calcium, urea, creatinine, total protein, albumin, SGOT, SGPT, total bilirubin, alkaline phosphatase) was performed on the Roche Hitachi 912 Chemistry Analyzer. Androstenodion (A), dehydroepiandrosterone sulfate (DHEAS), total testosterone (TT), free testosterone (FT) levels were measured by the Immulite 200 chemiluminescence method on the BioDPC Isodata 100 Series Gamma Counter. The quantity of protein in a 24-hour urine was analyzed by the Purdy method.

HELLP syndrome, eclampsia, pulmonary edema, placental abruption, cardiac or respiratory arrest, pulmonary embolism, disseminated intravascular coagulation, hypertensive encephalopathy, and hepatic dysfunction (AST>40 IU/L and ALT>40 IU/L) were considered as maternal complications. Intrauterine and intrapartum fetal deaths, preterm birth, intrauterine growth retardation (IUGR), and low 1-min Apgar scores were considered as fetal complications. The relationship between these complications and androgen levels was examined. The 1-min Apgar score in cases of intrauterine and intrapartum fetal deaths was accepted as 0.

Statistical analysis

Statistical analysis was performed with SPSS version 20.0 software (SPSS Inc., Chicago, IL). The mean, median, minimum and maximum values of demographic characteristics were calculated. The mean levels of androgens (A, DHEAS, TT and FT) were calculated according to 1-min Apgar score (<7 and ≥7), preterm birth (yes/no), IUGR (yes/no), fetal distress (yes/no), ALT and AST levels (>40 IU/L and <40 IU/L), and maternal complications (yes/no). They were evaluated in terms of maternal prognosis.

While the median, minimum and maximum were employed for nonparametric statistics, the mean and standard deviation were employed for parametric statistics. The Mann Whitney-U test was applied when the data were not normally distributed . The median (minimum and maximum) was used when the standard deviation was very high. Student t test was used when the data were normally distributed. A p-value of < 0.05 was considered statistically significant.

Results

The mean age was 27.49±5.32 years. The mean number of pregnancies was 2.55±1.63. The mean number of prior live births was 1.9±1.37. The rate of nulliparity was 41%. The mean gestational ages at first attendance and at birth were respectively 33.58±3.6 and 34.72±3.46 weeks. The mean body mass index was 25.29±3.04. The mean values of systolic and diastolic blood pressure were respectively 153.6 and 96.7 mmHg. The mean 24-hour urine protein level was 4.15±2.46 gr/24h. The mean values of hemoglobin, hematocrit, platelet, total protein, albumin, ALT and AST were respectively 12.61±1.82 gr/dl, 37.92±5.04%, 226,252±91,311/mm³, 5.42±0.79 gr/dl, 2.66±0.46 gr/dl, 69.59±155 U/L and 60.95±147 U/L (Table 1). The mean levels of A (n:61), DHEAS (n:97), TT (n:75) and FT (n:30) measured by RIA were respectively 6.27±5 ng/ml, 1.11±0.73 µg/dl, 222.87±206.32 ng/dl and 1.01±0.65 pg/ml. (Table1)

Table 1. Sociodemographic, clinical and laboratory data of patients

	N	Mean ±SD
Age(years)	103	27.49 ±5.32
Mean number of pregnancies	103	2.55 ±1.63
Mean gestational age at first attendance weeks)	103	33.58 ±3.6
Mean gestational age at birth (weeks)	103	34.72 ±3.46
BMI (kg/m²)	103	25.29±3.04
Hemoglobin mg/dl	103	12.61 ±1.82
Hematocrit %	103	37.92 ±5.04
Platelet count /mm³	103	226252 ±91311
Protein gr/dl	103	5.42 ±0.79
Albumin gr/dl	103	2.66 ±0.46
ALT IU/L	103	69.59 ±155
AST IU/L	103	60.95 ±147
Urine protein gr/24 h	103	4.15 ±2.46
DHEA-S µg/dl	97	1.11 ±0.73
Total testosterone ng/dl	78	222.87 ±206.32
Free testosterone pg/ml	30	1.01 ±0.65
Androstenedione ng/ml	61	6.27 ±5

During follow-up, one patient died due to disseminated intravascular coagulation (DIC), one patient died due to intracranial hemorrhage related to hypertensive encephalopathy, and one patient died due to cardiopulmonary insufficiency. 20 (19.4%) began to receive magnesium treatment. 8 (7.8%) had cardiopulmonary problems, 18 (17.5%) had transient liver failure, and 15 (14.6%) had kidney problems. 4 (3.9%) had hypertensive encephalopathy, 6 (5.8%) had visual impairment (retinal detachment and exudation), 4 (3.9%) had DIC, and 4 (3.9%) had eclampsia.

After the patients were divided into two groups according to ALT and AST levels (>40 IU/L and <40 IU/L), androgen levels were compared between two groups. TT (p=0.01) and A (P=0.008) levels were significantly higher in those with AST levels greater than 40 U/L than in those with AST levels less than 40 U/L. Similarly, TT (p=0.018) and A (p=0.039) levels were significantly higher in those with ALT levels greater than 40 U/L than in those with ALT levels less than 40 U/L. No significant difference was found in the levels of other androgens between two groups (Tables 2and 3).

After the patients were divided into two groups according to the presence of maternal complications, androgen levels were compared between two groups. TT levels were significantly higher in the group with maternal complications than in the group without maternal complications (p=0.028). No significant difference was found in the levels of other androgens between two groups (Table 4).

The mean birth weight for infants was 2089 grams. 63 (61.2%) had a 1-min Apgar score <7. Of them, 6 (5.8%) died in utero and 10 (9.7%) died intrapartum. 60 (58.3%) were born prematurely. 45 (43.7%) had IUGR, 40 (38.8%) had oligohydramnios, and 33 (32%) developed fetal distress during delivery. While no infants died in the early neonatal period, 56 (54.4%) were treated in a newborn service due to various reasons (especially respiratory distress).

After the infants were divided into two groups according to 1-min Apgar score (<7 and ≥7), androgen levels were compared between two groups. FT levels were significantly higher in those with a 1-min Apgar score <7 than in those with a 1-min Apgar score ≥7 (p=0.042). No significant difference was found in the levels of other androgens between two groups (Table 5).

After the infants were divided into two groups according to the presence of preterm birth (<37 weeks and ≥37 weeks), androgen levels were compared between two groups. TT levels were significantly lower in the preterm group than in the non-preterm group (p=0.026). No significant difference was found in the levels of other androgens between two groups (Table 6).

Table 2. Relationship between ALT and androgen levels

	ALT>40 U/L	ALT<40 U/L	P
DHEA-S µg/dl	0.96(0.06-2.51)(n:33)	1.17(0.20-3.35)(n:64)	0.226
Total testosterone ng/dl	185(20-828)(n:23)	113(20-575)(n:55)	0.018
Free testosterone pg/ml	1.05(0.16-2.37)(n:10)	0.80(0.06-1.62)(n:20)	0.597
Androstenedione ng/ml	4.9(1.43-25.87)(n:26)	4.43(1.33-7.30)(n:35)	0.039

Table 3. Relationship between AST and androgen levels

	AST>40U/L	AST<40U/L	P
DHEA-S µg/dl	1.055(0.06-3.35)(n:66)	0.83(20-2.80)(n:31)	0.951
Total testosterone ng/dl	207(20-828)(n:85)	48(20-575) (n:23)	0.001
Free testosterone pg/ml	1.04(0.16-2.37)(n:22)	1.07(0.06-1.62)(n:8)	0.851
Androstenedione ng/ml	5.69(1.43-25.87)(n:41)	3.89(1.31-7.30)(n:20)	0.008

Table 4. Relationship between maternal complication and androgen levels

	Maternal Complication (Yes)	Maternal Complication (No)	P
DHEA-S µg/dl	1.12 (0.06-2.51)(n:50)	0.83(0.15-3.35)(n:47)	0.778
Total testosterone ng/dl	207 (20-828) (n:36)	140 (20-575)(n:42)	0.028
Free testosterone pg/ml	1.145(0.06-2.37)(n:20)	0.800(0.20-1.14)(n:10)	0.217
Androstenedione ng/ml	3.95(1.33-25.87)(n:30)	4.85 (2.79-9.30)(n:31)	0.977

Table 5. 1. Relationship between 1-min Apgar score and androgen levels

	Maternal Complication (Yes)	Maternal Complication (No)	P
	1-min Apgar score <7	1-min Apgar score ≥7	P
DHEA-S µg/dl	0.965 (0.06-3.35) (n:60)	1.12 (0.13-2.8) (n:35)	0.513
Total testosterone ng/dl	152 (23.5-589) (n:54)	261.5 (20-828) (n:24)	0.053
Free testosterone pg/ml	1.345 (0.06-2.37)(n:12)	0.80 (0.16-1.48) (n:18)	0.042
Androstenedione ng/ml	5.21 (1.33-25.87) (n:36)	4.01 (1.43-9.03)(n:25)	0.340

After the infants were divided into two groups according to the presence of IUGR, androgen levels were compared between two groups. A levels were significantly higher in the IUGR group than in the non-IUGR group (p=0.034). No significant difference was found in the levels of other androgens between two groups (Table 7).

Table 6. Relationship between preterm birth and androgen levels

	Preterm Birth (Yes)	Preterm Birth (No)	P
DHEA-S µg/dl	1.17(0.06-2.80) (n:58)	0.73(0.13-3.35)(n39)	0.126
Total testosterone ng/dl	121(20-589)(n:42)	187(20-828) (n:36)	0.026
Free testosterone pg/ml	1.105(0.06-2.37) (n:24)	0.80(0.16-0.92)(n:6)	0.062
Androstenedione ng/ml	3.98(1.33-25.87)(n:33)	5.21(1.43-21.1)(n:28)	0.148

Table 7. RRelationship between IUGR and androgen levels

	IUGR (Yes)	IUGR (No)	P
DHEA-S µg/dl	0.99(0.06-2.51)(n:43)	1.005(0.13-3.35)(n:54)	0.561
Total testosterone ng/dl	167(23.5-575)(n:41)	153 ((20-828)(n:37)	0.861
Free testosterone pg/ml	1.48(0.66-2.03)(n:6)	0.98(0.06-2.37)(n:24)	0.146
Androstenedione ng/ml	6.03(2.73-25.87)(n:28)	4.01(1.33-9.03)(n:33)	0.034

Discussion

In this study, the complications of preeclamptic pregnant women and their infants were examined according to androgen levels.

The disruption of uteroplacental circulation due to abnormal trophoblastic invasion during early pregnancy in patients with genetic or immune susceptibility plays a role in the development of preeclampsia. Intrauterine growth retardation and fetal complications may occur due to placental hypoxia and increased local oxidative stress after apoptosis and necrosis in trophoblasts [13].

Early prediction of preeclampsia is very important in preventing complications. This prevents unnecessary application of antenatal care to a low-risk group and finally allows early treatment and reduces fetal and maternal morbidity/mortality. Aspirin use and calcium supplementation for patients with dietary calcium deficiency have been shown to be effective preventive interventions in preeclampsia [13].

The production of steroid hormones by the placenta becomes abnormal in preeclampsia [7,14,15]. Estradiol levels decline due to reduction in placental aromatization [7]. This background suggests that aromatase deficiency, leading to low estrogen levels, might modify both the angiogenic/anti-angiogenic balance and the uterine vasculature properties, thereby promoting the clinical features of PE.

Clinicians are aware of the increased risk of fetal death among pregnancies diagnosed with preeclampsia in the preterm period. The rate of stillbirth in preeclampsia has been reported to be 0.52% in Norway [16]. It is possible to observe the vulnerability of the neonates of women with eclampsia, being close to 27%, higher than all other groups of mothers with preeclampsia [17]. Our study found that the rates of intrauterine and intrapartum fetal deaths were respectively 5.8% and 9.7%. There was a big difference between the our results and the literature. The diagnosis of preeclampsia is delayed because the majority of patients do not receive adequate antenatal care in their environment. They are referred late to our center, and sometimes intrauterine deaths occur when they present. Induction of delivery in a non-viable period in order to reduce maternal morbidity and mortality occasionally increases the rate of intrapartum or postpartum fetal death higher than expected.

Women with preeclampsia may develop HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet), which occurs in 0.5% to 0.9% of all pregnancies and in 10% to 20% of women with severe preeclampsia [18]. We found that this rate was 7%. HELLP syndrome is associated with a high frequency of disseminated intravascular coagulation (DIC) ranging from 2.2% to 39% according to various reports [19,20] Our study found that 4 (3.9%) patients were diagnosed with DIC. Two substantive conclusions have been reached from these: 1) DIC is not a common complication as it is thought when considering all preeclamptic patients and 2) Many patients with subclinical DIC cannot be diagnosed based on only platelet counts and fibrinogen levels. It is very important to diagnose DIC because 1 of our 4 patients with DIC died despite close follow-up.

Eclampsia is the most severe form of preeclampsia. Our study found that the rates of eclampsia and placental abruption were respectively 3.7% and 0%. We can explain that the reason for the absence of placental abruption is that placental abruption is not specified in surgical operation notes of pregnant women who are taken into a caesarean section due to fetal distress.

When the literature has been examined, we have observed that androgen levels are higher in preeclamptic patients than in normotensive patients. The mean (±SD) levels of TT and FT were significantly higher ($p<0.01$) in the preeclamptic group compared to the control group. The mean values of DHEA-S, A and sex hormone binding globulin (SHBG) were lower in the preeclamptic group, but this difference did not reach statistical significance [21]. Acromite et al. found that TT and FT levels were higher in the

preeclamptic group. Similarly, our study found that TT, FT and A levels were higher than normal. DHEA-S levels remained within the normal range [22]. In our study, we evaluated these levels according to only previous study results because we had no a control group. Androgen levels obtained from our study are also consistent with the literature. However, the fact that DHEA-S levels are not different between the two groups in the literature shows that ovarian androgens can play a role in the pathophysiology of preeclampsia, but adrenal androgens may not play a role.

Since ALT and AST levels >40 IU/L indicate HELLP syndrome, they are important parameters for maternal prognosis.Total testosterone and androstenedione levels were significantly higher in patients with increased AST and ALT levels.This can be attributed to the fact that the production of SHBG decreases due to liver damage. We can say that a recent increase in A and TT levels may be an indicator of liver damage and possible HELLP syndrome.

Our study found that TT levels were significantly higher in the group with maternal complications than in the group without maternal complications. Although the physiopathology is not clearly defined, this occurs because TT further activates the effect of preeclampsia on the renin-angiotensin system, eicosanoids, platelets and increases vascular reactivity. [23].

The Apgar score was considered to be the first indicator of fetal well-being. Our study found that FT levels were significantly higher in those with a 1-min Apgar score <7 than in those with a 1-min Apgar score ≥7. No significant difference was found in the levels of other androgens between two groups. We have to worry about the fact that the 1-min Apgar score can be low when FT levels reach over 1 pg/ml. Care should be taken with respect to fetal complications in patients with higher levels of FT. The need for neonatal intensive care should be considered at time of delivery.

Our study found that A levels were significantly higher in the IUGR group than in the non-IUGR group. Previous studies have shown that patients with high androgen levels develop IUGR. The basic mechanism is attributed to placental cell destruction [24].

The most important factor affecting the prognosis is the week of birth. It is useful to predict delivery time to reduce fetal morbidity. Our study found that TT levels were significantly lower in the preterm group than in the non-preterm group. This can be related to fetal maturation. In other words, the greater the week of birth, the higher TT levels.

Our study found that TT levels were significantly lower in the fetal distress group than in the non-fetal distress group. Thus, we can say that infants of pregnant women with high levels of TT are less likely to develop fetal distress. This can be related to fetal maturation. No significant difference was found in the levels of other androgens between two groups.

Conclusion

Consequently, androgen levels except for the adrenal androgen (DHEA-S) increase in preeclampsia. It was determined that while the 1-min Apgar score is likely to fall below 7 in infants of patients with higher levels of FT, IUGR can occur in infants of patients with higher levels of A. Increased total testosterone levels show us that fetal maturation would be complete and that fetal distress would be lower than expected. Higher levels of testosterone and androstenedione suggest us that maternal complications can increase. The adrenal androgen (DHEA-S) had no benefit in predicting prognosis. While measurement of androstenedione, total and free testosterone levels may be useful in predicting prognosis in preeclamptic patients, extensive studies are needed to support this.

Conflict of interest
The authors declare that there are no conflicts of interest.

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All authors declare no financial support.

Ethical approval
It was approved by the Ethics Committee of Zekai Tahir Burak Women's Health Research and Education Hospital

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