

## Androgen Levels in the Third Trimester of Pregnancy in Patients with Preeclampsia

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### ABSTRACT

**Background:** Although the aetiology of pre-eclampsia is not entirely known, numerous theories have been put in relation to its causes. Finding its risk factors is crucial because to its morbid course. However, because to a lack of information regarding its origin, numerous studies have been conducted on a variety of materials in an effort to identify its causes. One of these ideas focuses on the underlying endocrine changes and quantification of different androgens.

**Objective:** This study aimed to compare between androgens level (serum total and free testosterone) in women with preeclampsia and normal ones in the 3<sup>rd</sup> trimester of pregnancy (28-40 weeks).

**Patients and methods:** During this study, 80 pregnant women were enrolled in this study. They were divided into two groups: Group A comprised 40 pregnant women in their 3<sup>rd</sup> trimester with preeclampsia at the time of admission, whereas group B consisted of 40 healthy normotensive women in their 3<sup>rd</sup> trimester who served as control group A with matched maternal age, gestational age, and BMI.

**Results:** Our study revealed that free and total testosterone levels were significantly higher among pre-eclamptic cases compared to healthy women with no differences regarding maternal age, gestational age and fetal sex.

**Conclusion:** Pre-eclamptic women had greater serum androgen levels (free and total testosterone) throughout the 3<sup>rd</sup> trimester of pregnancy, this may suggest that androgens have a role in the development of pre-eclampsia.

**Keywords:** Androgen, Third trimester of pregnancy, Preeclampsia.

### INTRODUCTION

One of the most significant pregnancy problems is hypertension, which along with bleeding and infections constitute a lethal trifecta and is the leading cause of maternal morbidity and death in 3.7 to 5% of all pregnancies <sup>(1)</sup>. The aetiology of preeclampsia is not completely known, but numerous theories have been put up in combination with its causes. Finding its risk factors is crucial because of its morbid course. However, because of lack of information regarding its origin, numerous studies have been conducted on a variety of materials to identify its causes <sup>(2)</sup>.

One of these ideas focuses on the various androgens' measurements and the underlying endocrine alterations. Animal investigations have shown that testosterone enhances the vascular response to vasoconstrictor drugs such as arachidonic acid and norepinephrine <sup>(3)</sup>. Contrarily, oestrogen boosts vascular nitric oxide and inhibits platelet aggregation, whilst testosterone increases platelet thromboxane A<sub>2</sub> (TXA<sub>2</sub>) receptors and enhances platelet aggregation in response to TXA<sub>2</sub> <sup>(4)</sup>.

Other fundamental research have revealed that testosterone improves the body's microvascular response to TXA<sub>2</sub>, this is why castrated rats had lower mean arterial pressure. According to earlier research, androgen receptor blocking should be looked into as a potential treatment for hypertensive endotheliopathy. In light of these discoveries, investigations on androgens and their potential significance in the development of pre-eclampsia have expanded, and pregnant pre-eclamptic women's serum androgen levels have been tested <sup>(5)</sup>.

In one study, the researchers observed that pre-eclamptic women have lower serum oestrogen levels than normotensive women and proposed that this might

be attributable to reduced aromatase activity. Because this reduction in aromatase activity prevents blood androgens from being converted to oestrogens, preeclamptic women have higher serum androgen concentrations. Androgens may have a role in the aetiology of pre-eclampsia, according to certain ideas <sup>(6)</sup>.

Some studies have shown that pre-eclamptic women had greater levels of androgen, while another study was unable to find a higher level of androgen in pre-eclamptic women <sup>(7, 8)</sup>. Pre-eclamptic women exhibited higher free testosterone levels, which **Ghorashi et al.** <sup>(8)</sup> identified as a risk factor for pre-eclampsia.

More study is needed to establish the possible use of anti-androgens in the treatment of pre-eclampsia. Previous studies discovered that testosterone and androgens have a role in the aetiology of the illness <sup>(7-9)</sup>. Further research on the function of androgens in the pathophysiology of pre-eclampsia appears to be necessary in light of the aforementioned investigations.

### PATIENTS AND METHODS

This prospective case control study was conducted at the Obstetrics and Gynaecology Department, Faculty of Medicine, Menoufia University Hospitals and Shebin Al-Kom Teaching Hospital through the period from February 2022 until February 2023.

**Inclusion criteria:** Pregnant women attended antenatal care clinic aged 20 – 35 years old, primigravida with gestational age between 28 and 40 weeks, singleton pregnancy, living fetus and didn't receive anti-hypertensive drugs or steroid hormones. Women with preeclampsia and healthy pregnant normotensive women in the third trimester as a control group with matched maternal age, gestational age and BMI.

**Exclusion criteria:** First- and second-trimester expectant mothers, those under 20 and over 35 who have experienced intrauterine foetal death or intrauterine growth restriction, those with known structural or chromosomal abnormalities, those who have smoked, those with polycystic ovarian syndrome, those with a history of pregestational hypertension, those with thyroid gland disorders and hyperprolactinemia, those with diabetes mellitus, and those who take medications expecting regular supplementation (iron or folic acid were excluded).

**Study procedures:**

A total of 80 pregnant women were enrolled and were divided into two equal groups: Group A consisted of 40 women in the third trimester of pregnancy with preeclampsia and group B that consisted of 40 healthy normotensive women in the third trimester who served as a control with matched maternal age, gestational age, and BMI. The quantitative assessment of serum total and free testosterone for patients in both groups was also estimated.

**Ethical approval:** Menoufia Faculty of Medicine Ethics Committee approved this study. After obtaining the necessary information, all participants provided signed consents. The Helsinki Declaration was observed throughout the study's duration.

**Statistical analysis:** SPSS version 23.0 was employed to evaluate the gathered information. The range and mean ± SD, were used to portray quantitative data. To compare two or more sets of qualitative variables,  $\chi^2$  test was used. To compare two independent groups of regularly distributed variables (parametric data), an independent samples t-test was employed. Figures and percentages were also used to illustrate qualitative variables. Utilising the Kolmogorov-Smirnov and Shapiro-Wilk tests, the normality of the data was examined. A p-value was considered significant if it was equal to or less than 0.05.

**RESULTS**

There was no significant difference in maternal age between normotensive and preeclamptic group (Table 1).

**Table (1):** Comparison between normotensive group and pre-eclamptic group according to maternal age “years”

Maternal age (years)	Normotensive patients(n=40)	Preeclamptic patients(n=40)	t-test	p-value
Mean ± SD	22.53±1.97	22.38±1.72	0.131	0.718
Range	20-28	20-26		

There was no significant difference in gestational age between normotensive and pre-eclamptic groups (Table 2).

**Table (2):** Comparison between normotensive group and pre-eclamptic group according to gestational age “weeks”

Gestational age (wks)	Normotensive patients(n=40)	Preeclamptic patients(n=40)	t-test	p-value
Mean ± SD	38.55±1.11	37.60±1.48	10.546	0.002*
Range	37-40	35-40		

There was no significant difference in neonatal sex between normotensive and pre-eclamptic groups (Table 3).

**Table (3):** Comparison between normotensive group and preeclamptic group according to neonatal sex

Neonatal Sex	Normotensive patients(n=40)		Preeclamptic patients(n=40)		Total		$\chi^2$	p-value
	No.	%	No.	%	No.	%		
Female	16	40.0%	19	47.5%	35	43.8%	0.457	0.499
Male	24	60.0%	21	52.5%	45	56.3%		
<b>Total</b>	40	100.0%	40	100.0%	80	100.0%		

Free testosterone and total testosterone levels were significantly higher in pre-eclamptic group than normotensive group (Table 4).

**Table (4):** Comparison between normotensive group and pre-eclamptic group according to free testosterone and total testosterone

	Normotensive patients(n=40)	Preeclamptic patients(n=40)	t-test	p-value
<b>Free testosterone [pg/ml]</b> Mean ± SD	2.75±0.66	8.51±2.08	245.353	<0.001**
<b>Total testosterone [nmol/l]</b> Mean ± SD	0.38±0.08	2.03±0.49	160.608	<0.001**

## DISCUSSION

Our study revealed that free and total testosterone levels were significantly higher among pre-eclamptic cases compared to healthy women with no differences between groups regarding maternal age, gestational age and fetal sex.

The majority of studies have looked into the favorable effects of sex steroid hormones on cardiovascular health in pregnant women, particularly estradiol and progesterone. However, research on the connection between testosterone and maternal cardiovascular health is still in its infancy. Following a thorough review of 40 publications found by a PubMed search using the keywords "testosterone, preeclampsia, and women," 14 full-length papers reporting testosterone levels in both preeclampsia and control groups were found. Similar result to our study. Similar results were found in several studies as *Al-Maiah et al.*<sup>(9)</sup> and *Sharifzadeh et al.*<sup>(10)</sup>.

According to these researches, plasma testosterone levels in late pregnancy vary between 1.5 to 2.4 times greater in preeclamptic pregnant women than in normotensive pregnant women. In addition, preeclamptic women have reported mean unbound or "free" testosterone levels that are 1.4 to 3.4 times greater than those in normotensive pregnancies. On the other hand other studies found no significant difference in the level of total serum testosterone when comparing preeclamptic patients and normotensive ones as *Ghorashi et al.*<sup>(8)</sup> and *Taghavi et al.*<sup>(11)</sup>. Most of studies that disagree with our results were due to several causes as different study methodology, sample size, different medical conditions and gestational age of studied cases at time of enrollment.

Although this is not a general conclusion, some research suggest that the amount of testosterone in the blood correlates with the severity of preeclampsia<sup>(2, 8)</sup>. Only testosterone levels in the blood are high during preeclampsia, despite the fact that other androgens, including the relatively inefficient testosterone precursors dehydroepiandrosterone (DHEA) and androstenedione (A4), are not elevated. Preeclamptic hyperandrogenic measures include elevated levels of total testosterone, free testosterone, free androgen index (FAI) (total testosterone 100/sex hormone binding globulin), and testosterone-to-estradiol ratio<sup>(2, 11)</sup>.

Preeclampsia risk is increased in hyperandrogenic pregnant women with polycystic ovary syndrome (PCOS), and it has been suggested that overproduction of testosterone by the polycystic ovary is the primary reason activating preeclampsia in PCOS women<sup>(12)</sup>. Preeclampsia is predicted by obesity and the compensatory hyperinsulinemia it causes due to insulin resistance<sup>(2)</sup>. Insulin induces theca cells in normal ovaries to produce androgens, including testosterone<sup>(13)</sup>. Thus, the enhanced hyperinsulinemia of obesity during preeclamptic gestation probably leads to elevated maternal testosterone levels<sup>(14)</sup>. Given that pregnant hyperandrogenic women with PCOS had increased incidence of obesity, hyperinsulinemia, and preeclampsia than pregnant women without PCOS do, obesity-related

increases in maternal testosterone may be a factor in PCOS-related preeclampsia<sup>(6)</sup>.

Additionally linked to hyperandrogenism-related preeclampsia is ethnicity. African-American women who are pregnant have high amounts of testosterone in their bodies (120–130%), which increases the risk of preeclampsia in the fetus's blood at term<sup>(2)</sup>. Additionally, in a number of conditions during pregnancy, such as classic congenital adrenal hyperplasia, plasma testosterone levels rise<sup>(19)</sup>. Those are all recognized preeclampsia risk factors. Additionally, environmental toxins and anabolic steroids (endocrine disruptors) expose pregnant women unintentionally to high testosterone levels.

In current study, there was no significant difference in neonatal sex between normotensive and preeclamptic groups. Preeclamptic women showed variable degrees of hyperandrogenism regarding the gender of their foetus. According to *Kumar et al.*<sup>(2)</sup>, preeclamptic women who are carrying sons had greater testosterone levels than preeclamptic women who are carrying daughters, such pregnant mothers who have male fetuses are more likely to develop preeclampsia and placental malfunction<sup>(16)</sup>.

Furthermore, preeclamptic gestational girls have higher amounts of circulating testosterone when they reach adolescence<sup>(7)</sup>. In women who have a history of preeclampsia, elevated testosterone levels persist for at least 17 years<sup>(2)</sup>. Thus, these studies offer convincing circumstantial evidence that links higher testosterone levels to preeclampsia. However, the 17-hydroxylase and 17, 20-desmolase, which are essential for the biosynthesis of androgens, are absent from the human placenta<sup>(2)</sup>. Nevertheless, it expresses the estrogen-preferring 3-hydroxysteroid dehydrogenase type 1 (HSD3B1) that gives it the ready ability to convert DHEA into A4 as well as the weak 17-hydroxysteroid dehydrogenase type 1 (HSD17B1) that gives it the ability to synthesize testosterone from A4. After mid-gestation, the primary sources of C19 steroids for placental androgen production are the maternal and fetal adrenals<sup>(2)</sup>.

Similar to the maternal zona reticularis, the innermost zone of the maternal adrenal cortex, the human fetal adrenal cortex contains a fetal zone that expresses StARD1, CYP11A1, CYP17A1, and SULT2A1. These enzymes are necessary for the formation of DHEA and DHEAS sulfate (DHEA-S). Sulfonated testosterone precursors (DHEA-S), which are transported into placental syncytiotrophoblast cells by membrane uptake carriers, are desulfonated to produce DHEA by the enzyme sulfatase (STS). The conversion of DHEA to A4 (HSD3B1) and A4 to testosterone (ARK1C3) by placental steroidogenic enzymes follows. High levels of placental aromatase expression ensure the quick conversion of placental androgens, such as testosterone, into non-androgenic, estrogenic metabolites, such as estrone, estradiol, and their catechol and methoxy metabolites<sup>(2)</sup>, some of which exhibit placental bioactivity comparable to that of E2<sup>(17)</sup>.

The fact that there are no statistically significant variations in the levels of DHEA-S and A4 in the blood of

the control pregnant women and preeclamptic pregnancies suggests that adrenal steroids are not responsible for the hyperandrogenism of preeclampsia. However, the preeclamptic placenta demonstrates lower placental aromatase mRNA and protein expression, which inhibits the conversion of A4 and testosterone into estrogenic metabolites and shifts the balance of oestrogens and androgens in favour of androgens (18). During preeclamptic pregnancies, it appears that there is a decrease in hepatic conjugation and concomitant inactivation of oestrogens. But compared to pregnant women with normotension, maternal circulation levels of unconjugated estrogens are unaltered (2).

According to studies, testosterone inhibits the production of the aromatase gene in human trophoblast cells through a miR-22-mediated mechanism (19-21). Other variables that are elevated during preeclampsia downregulate aromatase, including tumor necrosis factor alpha (20), and lipid radicals (21). Additionally, hypoxia downregulates placental aromatase (which, in the context of preeclampsia, mimics the real circumstances of the placenta (22)). The occurrence of impaired aromatase expression in tissues and organs other than the placenta during preeclamptic pregnancy should be studied. The first steps of steroidogenesis are catalyzed by the enzyme known as CYP11A1, which is overexpressed in human trophoblast cells. This leads to elevated testosterone levels and preeclampsia-like placental malfunction, both of which can be treated with the androgen receptor antagonist flutamide (23). Together, these data support the hypothesis that higher levels of testosterone during preeclamptic pregnancies may have placental origins, however other possible sources cannot be ruled out.

Our results found that the gestational age of the normotensive and preeclamptic groups did not differ significantly. In healthy pregnant women with no complications, arterial pressure remains stable in the early stages of the first trimester before progressively decreasing to its lowest point in the second trimester (24). Preeclampsia is assumed to be distinguished by the absence of a pregnancy-related reduction in blood pressure, which is considered a failure in normal cardiovascular adaptation (25).

Through studies on humans and animals, a number of independent researchers have shown that androgens, particularly testosterone, are linked to hypertension (26). During and after preeclampsia, testosterone levels correlate favorably with both systolic and diastolic blood pressure (2). Systemic arterial pressure is increased when maternal testosterone levels are artificially raised in pregnant rats to levels that are similar to those found in preeclamptic pregnancies in humans (27). This shows that testosterone has a causal role in increasing blood pressure during pregnancy. Although the precise mechanism by which testosterone influences a mother's blood pressure during pregnancy is unknown, accumulating data indicates that it modifies eicosanoid metabolism, raises vascular reactivity, and activates the renin-angiotensin system. Preeclampsia-related platelet aggregation is closely resembled by these alterations, which also favour

an increase in the thromboxane A2 to prostacyclin (PGI2) ratio (2). Losartan, a selective AT1R antagonist, was used to treat the pregnant rats' hypertension, which had been brought on by testosterone (28). These results imply that at least a portion of the blood pressure elevation brought on by testosterone during rat pregnancy is due to AT1R activation.

Along with alterations in the systemic vasculature, the uteroplacental circulation frequently adjusts to maintain a low vascular tone to allow a more than 20-fold increase in uterine blood flow in the near term (29). Current study found, the preeclamptic group had considerably greater levels of free and total testosterone than the normotensive group. High maternal testosterone levels have been connected with greater uterine artery resistance index and lower blood flow in hyperandrogenic women with PCOS (31).

Transcutaneous micro ultrasonography was utilised to assess the 40% decrease in uterine arterial blood flow produced by an intentionally created rise in maternal testosterone levels in pregnant rats (29). Additionally, increased testosterone increases resistance and pulsatile index while decreasing uterine artery diameter (29). These findings suggest that greater maternal testosterone levels disrupt the systems that control blood pressure and uterine artery hemodynamics during pregnancy. In agreement in our study, estrone, estradiol-17, and estriol, which are primary estrogens, are essential for maintaining uterine blood flow and minimising vascular responses during pregnancy (30). Also, *Jobe et al.* (32) showed that preeclampsia decreases these main oestrogens and the bulk of their catechol and methoxy metabolites, including those with placental bioactivity. Lower amounts of primary oestrogens, along with reduced expression of placental aromatase, may result in precursor steroid hormone accumulation, which would raise C19 steroids, particularly testosterone. It is unknown whether increased testosterone causes preeclampsia to proceed on its own or whether it works in concert with decreased downstream C18 estrogens. However, it has been observed that progesterone levels in preeclampsia are normal, lowered, or elevated (2,33).

## CONCLUSION

Pre-eclamptic women had greater serum androgen levels (free and total testosterone) throughout the third trimester of pregnancy, which may indicate that androgens have a role in the pathogenesis of preeclampsia.

## REFERENCES

1. Phipps E, Prasanna D, Brima W *et al.* (2016): Preeclampsia: updates in pathogenesis, definitions, and guidelines. *Clinical Journal of the American Society of Nephrology*, 11 (6): 1102-13.
2. Kumar S, Gordon G, Abbott D *et al.* (2018): Androgens in maternal vascular and placental function: implications for preeclampsia pathogenesis. *Reproduction*, 156 (5): 155-59.

3. **Hoffman D, Powell T, Barrett E et al. (2021):** Developmental origins of metabolic diseases. *Physiological Reviews*, 101 (3): 739-95.
4. **Shao X, Wang Y, Liu Y et al. (2019):** Association of imbalanced sex hormone production with excessive procoagulation factor Serpin F2 in preeclampsia. *Journal of Hypertension*, 37 (1): 197-205.
5. **Kautzky-Willer A, Harreiter J, Pacini G (2016):** Sex and gender differences in risk, pathophysiology and complications of type 2 diabetes mellitus. *Endocrine Reviews*, 37 (3): 278-316.
6. **Lonnebotn M, Natvig G, Benediktsdottir B et al. (2018):** Polycystic ovary syndrome, body mass index and hypertensive disorders in pregnancy. *Pregnancy Hypertension*, 11: 32–37.
7. **Alsnes I, Janszky I, Asvold B et al. (2016):** Maternal preeclampsia and androgens in the offspring around puberty: a follow-up study. *PLoS One*, 11: e0167714. 10.1371/journal.pone.0167714
8. **Ghorashi V, Sheikhvatan M (2008):** The relationship between serum concentration of free testosterone and preeclampsia. *Endokrynologia Polska*, 59: 390–392.
9. **Al-maiahy T, Al-Ghareeb A, Al-Kuraishy H (2020):** Testosterone is surrogate and proxy biomarker for severity of late onset preeclampsia; Across sectional study. *Asian Pacific Journal of Reproduction*, 9 (1): 1-8.
10. **Sharifzadeh F, Kashanian M, Fatemi F (2012):** A comparison of serum androgens in pre-eclamptic and normotensive pregnant women during the third trimester of pregnancy. *Gynecological Endocrinology*, 28: 834–836.
11. **Taghavi S (2007):** Serum Androgen in preeclamptic women. *Research Journal of Biological Science*, 2: 773- 76.
12. **Filippou P, Homburg R (2017):** Is fetal hyperexposure to androgens a cause for PCO?. *Human Reproduction Update*, 23 (4): 421-432.
13. **Cadagen D, Khan R, Amer S (2016):** Thecal cell sensitivity to luteinizing hormone and insulin in polycystic ovarians syndrome. *Reproductive Biology*, 16 (1): 53-60.
14. **Bedell S, Hutson J, Eastabrook G et al. (2021):** Effects of maternal obesity and gestational diabetes mellitus on the placental current knowledge and targets for therapeutics intervention. *Current Vascular Pharmacology*, 19 (2): 176-192.
15. **Reisch N (2019):** Pregnancy in congenital adrenal hyperplasia. *Endocrinology and Metabolism Clinics*, 48: 255-264.
16. **Li X, Zhang W, Lin J et al. (2018):** Risk factors for adverse maternal and perinatal outcomes in women with preeclampsia: analysis of 1396 cases. *Journal of Clinical Hypertension*, 20: 1049–1057.
17. **Landeros R, Pastore M, Magness R (2019):** Effects of the catechol and methoxy metabolites of 17beta-estradiol on nitric oxide production by ovine uterine artery endothelial cells. *Reproductive Sciences*, 26 (4): 459-468.
18. **Perez-Sepulveda A, Monteiro L, Dobierzewska A et al. (2015):** Placental aromatase is deficient in placental ischemia and preeclampsia. *PLoS ONE*, 10: e0139682. Doi: 10.1371/journal.pone.0139682.
19. **Shao X, Liu Y, Liu M et al. (2017):** Testosterone represses estrogen signaling by upregulating miR-22: a mechanism for imbalanced steroid hormone production in preeclampsia. *Hypertension*, 69: 721–730.
20. **Lau S, Guild S, Barrett C et al. (2013):** Tumor necrosis factor-alpha, interleukin-6, and interleukin-10 levels are altered in preeclampsia: a systematic review and meta-analysis. *American Journal of Reproductive Immunology*, 70: 412–427.
21. **Mori T, Watanabe K, Iwasaki A et al. (2014):** Differences in vascular reactivity between pregnant women with chronic hypertension and preeclampsia. *Hypertension Research*, 37: 145–150.
22. **Yu R, Chaturvedi G, Tong S et al. (2015):** Evidence for microRNA-mediated regulation of steroidogenesis by hypoxia. *Environmental Science and Technology*, 49: 1138–1147.
23. **Pan T, He G, Chen M et al. (2017):** Abnormal CYP11A1 gene expression induces excessive autophagy, contributing to the pathogenesis of preeclampsia. *Oncotarget*, 8: 89824–89836.
24. **Teng H, Wang Y, Han B et al. (2021):** Gestational systolic blood pressure trajectories and risk of adverse maternal and perinatal outcomes in Chinese women. *BMC Pregnancy and Childbirth*, 21 (1): 155. DOI:10.1186/s12884-021-03599-7
25. **Perier M, Torrado J, Sosa C et al. (2021):** Role of arterial impairment in preeclamptic should be paradigm shift?. *American Journal of Physiology Heart and Circulatory Physiology*, 320 (5): 2011-2030.
26. **Moretti C, Lanzolla G, Moretti M et al. (2017):** Androgens and hypertension in men and women: a unifying view. *Current Hypertension Reports*, 19 (5): 44. doi: 10.1007/s11906-017-0740-3.
27. **Fornes R, Hu M, Maliqueo M et al. (2016):** Maternal testosterone and placental function: effect of electroacupuncture on placental expression of angiogenic markers and fetal growth. *Molecular and Cellular Endocrinology*, 433: 1–11.
28. **Chinnathambi V, Balakrishnan M, Ramadoss J et al. (2014):** Testosterone alters maternal vascular adaptations: role of the endothelial NO system. *Hypertension*, 61: 647–654.
29. **Gopalakrishnan K, Mishra J, Chinnathambi V et al. (2016):** Elevated testosterone reduces uterine blood flow, spiral artery elongation, and placental oxygenation in pregnant rats. *Hypertension*, 67: 630–639.
30. **Mandalà M (2020):** Influence of Estrogens on Uterine Vascular Adaptation in Normal and Preeclamptic Pregnancies. *Int J Mol Sci*, 21 (7): 2592. doi: 10.3390/ijms21072592
31. **Valdimarsdottir R, Wikström A, Kallak T et al. (2021):** Pregnancy outcome in women with polycystic ovary syndrome in relation to second-trimester testosterone levels. *Reprod Biomed Online*, 42 (1): 217-225.
32. **Jobe S, Tyler C, Magness R (2013):** Aberrant synthesis, metabolism, and plasma accumulation of circulating estrogens and estrogen metabolites in preeclampsia implications for vascular dysfunction. *Hypertension*, 61: 480–487.
33. **Wan J, Hu Z, Zeng K et al. (2018):** The reduction in circulating levels of estrogen and progesterone in women with preeclampsia. *Pregnancy Hypertension*, 11: 18–25.