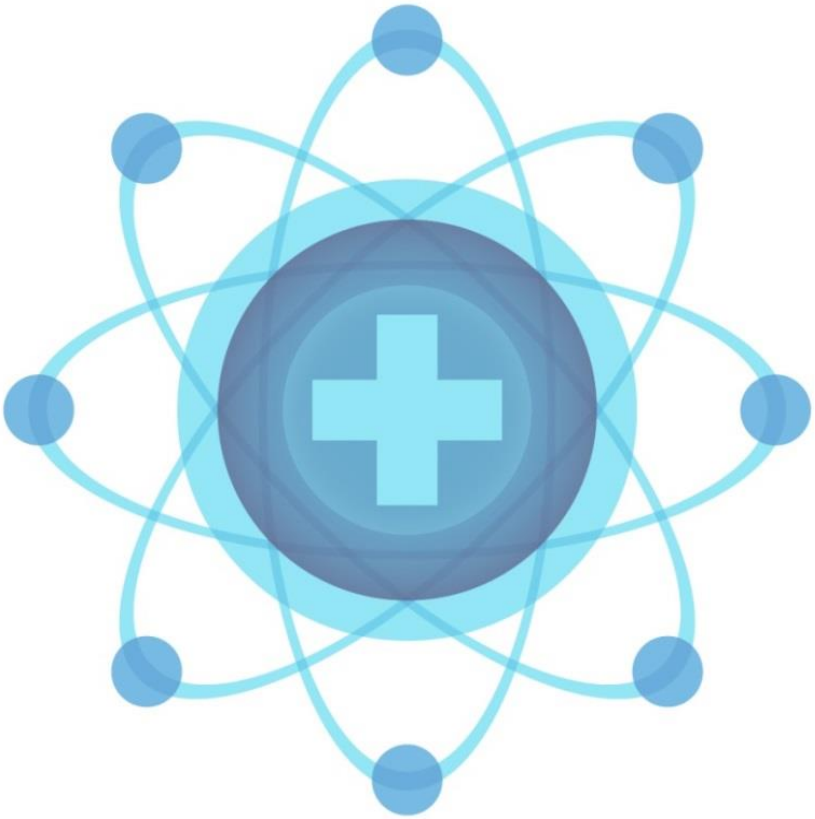

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Biochemical markers of preeclampsia development and criteria for early diagnosis

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Abstract It has been proved that the amount of sFlt-1 in the blood serum of pregnant women with the risk of developing early and late preeclampsia increases rapidly, the amount of PlGF decreases, and the ratio of sFlt-1/PlGF increases progressively. If the sFlt-1/PlGF ratio is higher than 28 in the 1st trimester of pregnancy, there is a high risk of developing early PE, if it is higher than 57-60 in the 2nd trimester, PE may develop, and if it is higher than 80-100, it can predict the development of severe preeclampsia.

Keywords: preeclampsia, sFlt-1, PlGF, pregnancy

Approximately 10-15% of pregnant women worldwide still suffer from complications of hypertensive diseases, among which complications from preeclampsia occupy a special place [1,2].

Preeclampsia is a condition that occurs as a result of dysfunction of several systems of the body, which develops only in pregnant women; usually manifests with arterial hypertension and proteinuria; in rare cases, it occurs before the 20th week and has a negative effect on the course of pregnancy [3,5].

According to researchers, hypertensive disorders in pregnant women, including preeclampsia and eclampsia, cause 50,000-60,000 maternal deaths worldwide each year[4,6]. According to the WHO, hypertensive disorders in pregnancy are the cause of maternal death in 14% of cases, second only to bleeding.

The National Committee analyzed 86 cases of maternal deaths between 2013 and 2015, and the results of the analysis showed that preeclampsia was one of the leading causes of maternal deaths. This was 22.8 percent of all maternal deaths within 3 years. Hypertensive cases take 4th place in the list of causes of maternal death in Russia, accounting for 15.7 percent.

It is known that PE, which is a form of thrombotic microangiopathy, despite its various clinical manifestations, first damages 1-2 systems, and when it progresses, it leads to polyorgan failure. It should be said that the pathogenetic basis of early developed PE is the opening of the spiral arteries to the chorionic invasion at the expense of the trophoblast. As a result, uterine-chorionic blood flow is formed.

Most of these markers indicate a violation of the placentation process, insufficient development of spiral arteries in the uterus leads to trophoblast invasion and decreased placental perfusion, resulting in ischemia in the placenta, which leads to the release of anti-inflammatory factors, thrombocyte activation, the development of endothelial dysfunction and renal failure in the mother.

By the second period of invasion (16-18 weeks of pregnancy), clinical signs tending to the development of arterial hypertension, microalbuminuria, and thrombocytopenia are gradually observed. At the beginning of the 3rd trimester, polyorgan failure accelerates and the condition of the fetus worsens, which leads to

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the need for urgent delivery. Therefore, the development of PE begins at 11–14 weeks of pregnancy, and screening is necessary during these periods [7,8,9].

According to the data of the last 10 years, placental insufficiency is observed to decrease the release of factors controlling angiogenesis (placental growth factor (PlGF) and placental protein 13 (PP-13)) into the maternal blood stream, and increase the amount of antiangiogenic factors (fms-like tyrosine kinase 1 (sFlt-1 , or sVEGFR-1) [4,6,10].

The purpose of the study: It consists of studying biochemical signs of preeclampsia development and early diagnosis criteria

Materials and methods:

This research work was carried out in 2019-2022 at the Department of Obstetrics and Gynecology No. 2 of the Bukhara Medical Institute, the maternity complex of the Zhondar District Medical Association and the Perinatal Center of the Bukhara Region.

Pregnant women at risk of PE were studied according to the level of risk in the I and II trimesters, when analyzed by trimesters, 100 (66.6%) pregnant women in the main group were women at risk of preeclampsia, of which 50 (33.3%) were in the I trimester. , 50 (33.3%) pregnant women in the II trimester and 50 (33.3%) pregnant women complicated by preeclampsia according to severity were studied.

In all cases, there is a risk of preeclampsia, and pregnant women complicated by preeclampsia developed PE against the background of various somatic and gynecological diseases.

The control group consisted of 50 women whose pregnancy was physiological.

The age of all the women under observation was around 19-42 years. Average age in group 1^A is 26.2±0.8 (19-42) years; 27.2±0.9 (19-48) years in group 1^B, 28.8±0.8 (42-19) in group 2, and 25.7±0.7 (20-37) in the control group .

The sVEGF-R1 FMS-associated tyrosine kinase-1 (sFLT-1)-human sVEGF-R1 ELISA kit is an enzyme-linked immunosorbent assay method used to quantify VEGFR1. Catalog number: BMS268-3 and BMS268-3TEN. Developed in 2019 by Thermo Fisher Scientific Inc. Soluble VEGF-R1 (sFLT-1) is a naturally occurring endogenous form of VEGF-R1 that was originally discovered in human vascular endothelial cell supernatant. It is formed as a result of differential proteinization of the flt-1 gene. In vitro, VEGF-R1 indirectly inhibits VEGF-A-mediated signaling in endothelial cells and can be used to block physiological angiogenesis in several organs in vivo.

Results

In physiological pregnancy, the amount of PlGF is 365 pg/ml [237–582 pg/ml], sFlt-1 is 1193 pg/ml [844–1630 pg/ml], and sEng is 5.1 ng/ml [4.3–6, 2 ng/ml], PlGF to sEng ratio – 71 [44–114], sFlt-1 to PlGF ratio – 3.1 [1.8–5.8] [Valerie A et al., 2019]. Based on the above information, we determined the amount of antiangiogenic and proangiogenic factors in the blood serum of pregnant women (Table 1). In our studies, the amount of sFlt-1 - 1312.69±20.72 pg/ml [960-1520 pg/ml], the amount of PlGF - 370.86±43.32 pg/ml [110.2-1108 pg/ml] in physiological transient

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pregnancies. ml] and the ratio of sFlt-1 to PlGF - 5.72±0.41 [1.22–12.88]. The obtained results differed from the indicators of the above-mentioned scientists and, in our opinion, may be related to the specificity of some biochemical indicators in races and nationalities.

Table 1

Amount of antiangiogenic and proangiogenic factors in blood serum of pregnant women complicated by physiological and preeclampsia, M±m

Groups	sFlt-1, пг/мл	PLGF, пг/мл	sFlt-1/PlGF
Control group, n=50	1312,69±20,72	370,86±43,32	5,72±0,41
Group 1^{A}	2335,55±346,57[а]	83,39±6,61[а]	33,62±4,04[а]
Group 1^{B}	3955,72±290,86[а,б]	84,36±6,77[а]	57,21±5,82[а,б]
2nd group	12235,38±160,87[а,б]	71,12±4,48[а]	216,32±17,49[а,б]

Note: the differences compared to the indicators of the 1st (control) group are reliable (R<0.05), the differences compared to the indicators of the 2nd group are reliable (R<0.05).

In the 1st trimester of pregnancy, the amount of sFlt-1 in blood serum increased by 1.78 (P<0.01) times and was 2335.55±346.57 pg/ml [512–14511 pg/ml] in women at risk of developing PE. In this group, the amount of PlGF in the blood serum of pregnant women decreased by 4.45 (P<0.001) times and was 83.39±6.61 pg/ml [25.2–190.5 pg/ml]. The ratio of sFlt-1 to PlGF in this group was 33.62±4.04 [4.24–126.22], which was 5.88 (P<0.001) times higher than that of the control group.

In the 2nd trimester of pregnancy, the amount of sFlt-1 in blood serum increased by 3.01 (P<0.001) times and was 3955.72±290.86 pg/ml [1013–9611 pg/ml]. Its amount was 1.69 (P<0.01) times higher than that of group 1^{A}. The amount of PlGF in the blood serum of the fetuses of this group did not differ from the indicators of the 1B group, and compared to the standard indicators, it decreased by 4.4 (P<0.001) times and amounted to 84.36±6.77 pg/ml [22.8–228 pg/ml] . The ratio of sFlt-1 to PlGF in this group was 57.21±5.82 [20.07–199.73], 10 (P<0.001) than the control group and was 1.7 (P<0.01) times higher than that of group 1^{A}.

We observed even stronger changes in the group of pregnant women who developed PE. In particular, the amount of sFlt-1 in the blood serum of pregnant women increased by 9.33 (P<0.001) times and was 12235.38±160.87 pg/ml [1105–1570 pg/ml]. These indicators were 5.24 (P<0.001) and 3.09 (P<0.001) times higher than those of 1A and 1B pregnant women. At the same time, the amount of PlGF in the serum of pregnant women in this group was 71.12±4.48 pg/ml [21–130 pg/ml] and decreased by 5.21 (P<0.001) times compared to the control group, but 1^{A} and 1^{B} a tendency to decrease compared to the indicators of the groups was determined. The ratio of sFlt-1 to PlGF in this group was 216.32±17.49 [89.94–604.33], which was 37.82 (P<0.001) times higher than that of the control group. statistically reliable 6.43 (P<0.001) and 3.78 (P<0.001) times higher.

Therefore, a decrease in proangiogenic factors, an increase in antiangiogenic factors in the blood serum of pregnant women and their mutual ratio indicate the risk of PE. According to scientists, determining the amount of angiogenic and

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antiangiogenic factors in the 2nd trimester of pregnancy can be used as a criterion for predicting the risk of developing PE [Valerie A., Yang S., 2019].

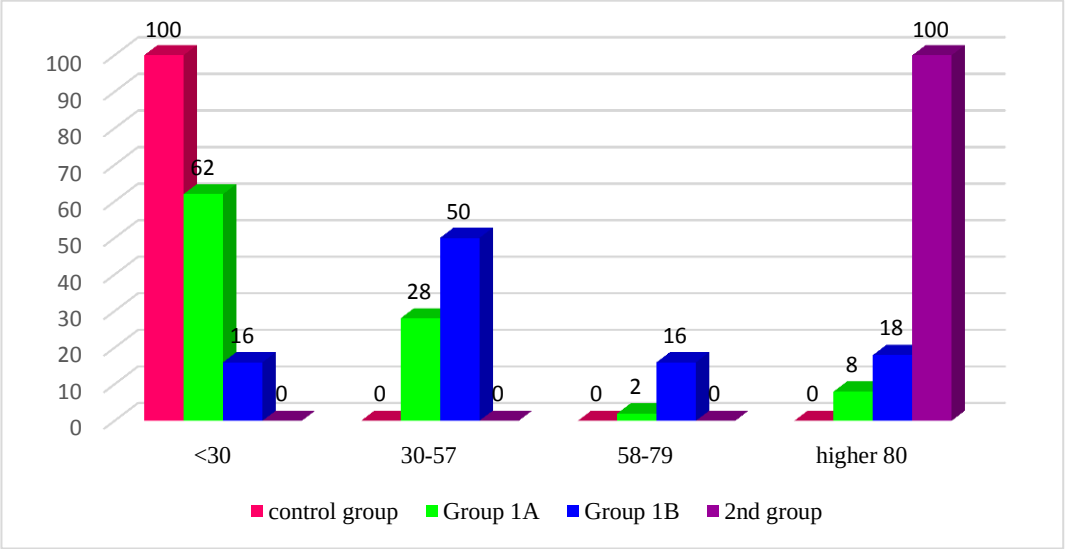
According to the authors, the ratio of sFlt-1 to the amount of PlGF can be used as a criterion for early diagnosis. The results obtained in our research show that detection in blood serum of women in the 1st trimester of pregnancy is also of prognostic value, especially the amount of sFlt-1 increased by 1.78 ($P<0.001$) times and the amount of PlGF decreased by 4.45 ($P<0.001$) times in the group with risk of PE, and these indicators increased later. The strongest changes were observed in pregnant women who developed PE. Such changes are a process aimed at ensuring that the pressure in the space between the villi changes according to the demand in order to provide the developing fetus with oxygen and nutrients. But if the adaptation processes in the female body are slow, the high pressure created starts to damage the space between the villi and there is a risk of developing PE.

In the development of PE, sFlt-1 is a receptor for VEGF-A and is produced in placental syncytiotrophoblasts. VEGF-A is a growth factor of the vascular endothelium and ensures the formation of placental blood vessels, their proliferation, viability and permeability [Ignacio Erraiz., Elisa Simon., 2019]. Therefore, the decrease in its production in podocyte cells causes proteinuria. According to Shibuya M., PlGF is also a proangiogenic factor belonging to the VEGF family and is synthesized in the placenta and binds to Flt-1 and enhances the effect of VEGF-A. According to the authors, in response to hypoxia, alternative splicing of the Flt-1 gene leads to the formation of sFlt-1 mRNA, increased production of sFlt-1 protein, secretion from the placenta into maternal blood, and reduction of proangiogenic factors by binding to VEGF and PLGF. This is the main factor in the development of hypertension and proteinuria in pregnant women [Sircar M., Tadhani R., 2018].

Currently, most scientists and most European countries use the sFlt-1/PlGF ratio to predict the risk of developing PE [Verlohren S., Galindo A., 2019]. According to them, if the ratio of sFlt-1/PlGF is 38 or less in the first weeks, PE does not develop (negative prognostic efficiency >99%), if it is higher than 38, 40% can be a positive result, if it is higher than 85 - early development of pulmonary encephalopathy and PE (sensitivity 89% and specificity 97%).

Based on the above, we also attempted to gradate the sFlt-1/PlGF ratio. In our opinion, in the 1st trimester of pregnancy, this indicator is 5 times higher than the standard indicators (25-28, if there is no risk of developing early PE, if it is higher, the development of PE is observed. If in the 2nd trimester of pregnancy, this indicator is 10-12 times higher (57-60) PE can develop if 15-20 times (80-100) higher can predict the development of severe PE. Based on this, we graded all

indicators in groups.



Picture 1. The risk of preeclampsia in the first and second trimesters of pregnancy, and the frequency (%) of sFlt-1/PlGF ratio in pregnant women with preeclampsia.

All of the sFlt-1/PlGF ratios in physiological transition pregnancies were within the normal range and ranged from 1.22 to 12.88 (see Figure 1). In the 1st trimester of pregnancy, 62% (31 women) of pregnant women at risk of PE had a ratio of sFlt-1/PlGF less than 30, 28% (14 cases) - 30-57, 2% (1 case) - 58-79 and 8% (4 in case) – 80 and above.

That is, 19 (38%) pregnant women could develop PE in the 1st trimester of pregnancy if pre-pregnancy preparation was not carried out. In the 2nd trimester of pregnancy, 16% (8 women) of pregnant women with a risk of PE had a ratio of sFlt-1/PlGF less than 30, 50% (25 cases) - 30-57, 16% (8 cases) - 58-79 and 18% (9 in case) – 80 and above. That is, 42 (84%) pregnant women could develop PE in the 2nd trimester of pregnancy if pre-pregnancy preparation was not carried out. All of the 2nd group (100%, 50 cases) with PE developed in the 1st trimester of pregnancy had a ratio of sFlt-1/PlGF of 80 or higher, and the variation ranged from 89.94 to 604.33. This indicates that PE has developed in all pregnant women.

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