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THE IMPORTANCE OF PRENATAL SCREENING OF SERUM BIOMARKERS OF QUADRIPLE TEST AND FETOPLACENTAL UNIT IN THE PREDICTION OF PERINATAL RISK AND PREGNANCY OUTCOME

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Abstract

Fetal compromise of uteroplacental blood flow leads to utero-placental insufficiency. This study aimed to find a correlation between serum biomarkers from Quadriple test and fetoplacental unit, in the second trimester of pregnancy, as possible predictors for the adverse perinatal outcome.
Material and method: This cohort study was conducted in a SHOG "Mother Theresa", Skopje, from November 2019 to June 2021. It includes 673 second trimester pregnant women, followed up and monitored till delivery.
Results: From 673 respondents, 523 that is 77.7% made up the control group, while 150 that is 22.3% of pregnant women made up the examined group. From the examined group, 48 (7.13%) had preeclampsia, 32 (4.75%) had pregnancy-induced hypertension, 20 (2.97%) had a small fetus for gestational age, and 50 (7.43%) had intrauterine growth retardation.
Discussion: high values of Inhibin A in pregnant women with adverse outcome, statistically was confirmed as significant, while HCG values were significantly higher in group with preeclampsia. Pregnant women with preeclampsia significantly more often than pregnant women from control group had higher values of serum AFP, and it wasn't found significantly statistical difference in medial values of unconjugated Estriol in four examined groups compared to control group. It was confirmed the hypothesis that the placental volume by screening in second trimester is important for pregnancy outcome, as well as the flows in uterine and umbilical arteries.
Conclusion: Inhibin A value as a single marker for adverse pregnancy outcome was the best predictor, while the combination of biomarkers from Quadriple test and the uterine arteries flow in the second trimester of pregnancy, represents the best differentiating ability test for pregnant women for adverse and favorable pregnancy outcome.

Keywords: screening in the second trimester, perinatal growth, biomarkers, utero-placental insufficiency.

1. Introduction

Placenta and fetoplacental circulation have a crucial role in the perinatal growth of the fetus and the pregnancy outcome. Proteomic studies that research certain proteins that are released from the fetus to the maternal circulation offer a new ability to the identification of one or more protein markers in noninvasive prenatal diagnosing and will be useful for screening during pregnancy. Kolialexi (2011).

The fetal compromise and the utero-placental blood flow changes can result in uteroplacental insufficiency. Placenta produces several specific proteins that flow in the maternal serum, in different quantities, and they have important role in the normal development of the fetus, Boss (2018). According to the literature data, there is a correlation between the maternal serum protein values and the pregnancy outcome, thus the prediction of potential placental insufficiency is very important. Adverse pregnancy outcome includes pregnancy-induced hypertension, preeclampsia, intrauterine growth retardation, preterm birth, etc.

Pregnancy-induced hypertension is high blood pressure during the pregnancy, (140/90mmHg or higher), measured at least twice, four hours apart, or 160/110 mmHg once measured, without proteins in urine or other signs or symptoms of preeclampsia. The incidence is 5-10% of all pregnancies, worldwide. The risk of

pregnancy-induced hypertension is due to placental ischemia, pathological values of the fetoplacental unit, restrictive changes in intrauterine fetal growth, and indications for preterm delivery. (Aplin, 2020).

Criteria for diagnosing preeclampsia are systolic blood pressure of 140 mmHg or more, or diastolic blood pressure of 90 mmHg or more, on two occasions at least 4 hours apart after 20 weeks of gestation, in a woman with previously normal blood pressure or systolic blood pressure of 160 mmHg or more, or diastolic blood pressure of 110 mm Hg or more. (Severe hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy). Usually, it is found after 20 gestational weeks, in previously normotensive women, but it can be found also during delivery and after it, (ACOG, 2020). A certain etiology isn't known, but it is met usually in women who have previous preeclampsia, hypertensive disease, gestational and familiar hypertension. It happens more often at first pregnancy, in the oldest pregnant women (up 40 years), in black women, obese pregnant women, multiple pregnancies, etc. than between pregnancies with the wide period, in vitro fertilization, placental insufficiency, disturbed lipidemic metabolism, diabetes, and other endocrinal diseases, alcohol and drug consumption, diets, etc. Pathophysiology is due to immunological and genetic factors, placental ischemia, oxidative stress, and other factors that result in spiral arteries abnormality, disfunction or inadequate trophoblastic invasion, and shallow implantation. The result is placental hypoperfusion and ischemia, producing different substances that enter the maternal blood circulation. Except for high blood pressure, as the first sign of preeclampsia, the appearance of proteins in urine, more than 0.3 g./24h, and joint and face swelling are the other accompanying signs. Other signs and symptoms in preeclampsia are headaches, frontal or occipital, pulsatile, or continuous, or simultaneous with visual symptoms. When it is intensive, is a sign of convulsions. Visual symptoms are in patients that will develop eclampsia, and it includes scotoms and transitory perception of black and light points. Epigastric or right abdominal upper part pain is often in patients with the severe stage of the disease, but it can appear also as previously classical signs. If not diagnosed on time, it can lead to eclampsia, a state of high risk for both mother and baby, and may end lately, (Hannah et al 2020).

Intrauterine growth retardation is a complex complication that appears in the fetus and the incidence is 10-15% of all pregnancies, worldwide. It is a fetal growth restriction under the 10th percentile, accompanied by other pathological restrictions and perinatal risk, due to shallow placentation. The etiology can be placental, maternal, or fetal, whereby can be caused by a disturbed metabolism or lowering of oxygen supply in fetal circulation. Except for the biometrical small fetus, it is a progressive decrease of diastolic flow in the umbilical artery, thus increasing the resistant index of the fetoplacental unit, and in very progressive stadium appearance of reverse flow. In the case of IUGR, an induction of preterm delivery is indicated very often, Chawanpaiboon (2019).

Preterm birth is pregnancy termination before the 37th gestational age. The incidence is different in different countries, but it is about 9-12% worldwide. It is the cause of 75% of all neonatal mortality and about 50% of lifetime neurological consequences (cerebral paralysis, deafness, blindness, etc.) and other damages such as chronic lung disease, premature retinopathy, etc. The cause of preterm delivery is uteroplacental ischemia, preeclampsia, preexisting hypertension in pregnant women, gestational diabetes, obesity or malnutrition, cervical insufficiency, infections, etc., Osuchukwu (2021). Early detection of preterm delivery has a crucial role in pregnancy outcome, its prevention, or close to-term pregnancy ending.

The quadruple test is a prenatal serum screening test for Down Syndrome, and it's been in use since 1996th. It is based on follow-up and evaluation of four biomarkers: Alpha-fetoprotein (AFP), Human chorionic gonadotropin (hCG), unconjugated Estriol (uE3) и Inhibin A. The same biomarkers are used as indicators and predictors that refer to risk, not just for the above-mentioned numeric chromosomic aberration but also to correlation with other pathophysiological fetal changes, pregnancy outcome, preeclampsia, pregnancy induced hypertension, preterm birth, intrauterine growth retardation, etc.

The placenta is a high specific organ in pregnancy that carries out the physiological growth and

development of the fetus. The development and function of the placenta is very precisely regulated and coordinated for the maximal effective exchange of nutrients and end products between the maternal and fetal circulatory system. In normal pregnancy, fetoplacental circulation is increased proportionally with the pregnancy, thus enabling the physiological intrauterine growth of the fetus. (Habek, 2017). Feto-placental insufficiency leads to decreased oxygen and nutrition transport to the fetus, and it suffers, from stagnating intrauterine growth, thus increasing the possibility of some other complications during pregnancy and delivery. It is a possibility of measuring the blood circulation in certain organs, using high frequent ultrasound waves by ultrasound doppler. (Gomez, 2006) In pregnancies with high blood pressure, preeclampsia, intrauterine growth retardation, etc., the circulatory impedance of a. uterine is increased, that is highly resistant index or appearance of early diastole notch. Also, it can appear a high impedance of a. umbilicalis, if the obliteration of placental circulation is up to 60%, (Cnossen et al. 2008).

Aim: This study aims to do a prenatal screening in pregnant women during the second trimester and to evaluate the correlation between biomarkers of the Quadruple test, and fetoplacental unit placental volume as possible indicators and predictors for early diagnosis of eventual adverse pregnancy outcome.

Material and method: This cohort study was realized in a Special Hospital for Gynecology and Obstetrics "Mother Theresa", Skopje, from November 2019 to June 2021. It includes 673 second-trimester pregnant women, followed up and monitored till delivery. All participants have been assigned a statement voluntarily agreeing to participate in the study. Also, it was respected the law on personal data protection. Firstly, were taken the bodily measures and blood pressure after that was taken 2 ml of venous blood was for the Quadruple test and ultrasound for fetal biometry, amount of amniotic fluid, placental maturation and volume, pulsatility index resistant index umbilical and both uterine arteries. All participants were monitored till the end of pregnancy by regular (weekly) measuring blood pressure and biochemical analysis also, as by indication of proteinuria. Inclusion criteria were: singleton pregnancy, age at least 18 years old of pregnant women, gestational age 18-23.6 weeks, excluded anomalies by ultrasound. Exclusion criteria were: twin or multiple pregnancies, fetus mortus in utero, findings of fetal anomalies, pre-hypertension, other diseases in pregnant women (diabetes, autoimmune diseases, etc.), and pregnant women that used Aspirin.

Statistical processing was conducted by a statistical analysis of maternal characteristics in examined and control groups, there were determined the variables significantly associated with poor pregnancy outcomes, the validity of diagnostic tests for adverse pregnancy outcomes, and in the end were followed performances of the test.

Results: From 673 respondents, 523 that is 77.7% had favorable pregnancy outcomes and made up the control group, while in 150 that is 22.3% of pregnant women the pregnancy outcome was unfavorable, and they made up the examined group. From the examined group, 48 (7.13%) had preeclampsia, 32 (4.75%) had pregnancy-induced hypertension, 20 (2.97%) had a small fetus for gestational age, and 50 (7.43%) had intrauterine growth retardation.

Table 1. Mother's characteristics in research and control group

Mother's characteristics	Statistical parameters	**Research group**	**Control group**	**p-level**
Age Years	mean ±SD	27.3 ± 3.8	27.8 ± 4.5	t=1.22 p=0.22 ns
	min – max	22 – 37	18 – 48	
BMI kg/m^2	mean ±SD	28.10 ± 2.8	27.02 ± 3.8	t=3.22 **p=0.0014 sig
	min – max	23 – 34.5	18 – 45.1	
TA systolic (mmHg)	mean ±SD	132.50 ± 10.8	124.72 ± 9.4	t=8.61 ***p=0.000000 sig
	min – max	105 – 155	102 – 145	
TA diastolic (mmHg)	mean ±SD	85.67 ± 7.5	78.77 ± 6.2	t=11.47 ***p=0.000000 sig
	min – max	70 – 105	64 – 95	

Gestational week /Admission	mean ±SD	21.1 ± 1.0	20.9 ± 1.3	t=2.05 *p=0.041 sig
	min – max	18.6 – 24	17.1 – 24.6	
Gestational week /Delivery	mean ±SD	37.5 ± 1.1	39.7 ± 1.05	t=21.9 ***p=0.000000 sig

t(Student t-test) **p<0.05; **p<0.01; ***p<0.0001*

Table 1 depicted pregnant women with adverse and favorable pregnancies were a similar age, the mean age was 27.3 ± 3.8 и 27.8 ± 4.5 years, in the research and control groups respectively, without statistical significance (p=0.22).

The body mass index has a significantly higher value in research than in the control group (the difference value was 28.10 ± 2.8 vs 27.02 ± 3.8, p=0.0014).

The systolic and diastolic pressure were measured significantly higher in the research group compared with the control group (p<0.0001); 132.50 ± 10.8 и 124.72 ± 9.4 mean values for systolic pressure, respectively in the research and control group; 85.67 ± 7.5 и 78.77 ± 6.2 mean values of diastolic pressure, respectively in research and control group.

The gestational week in admission and at delivery was significantly different in the research and control group (21.1 ± 1.0 vs 20.9 ± 1.3, p=0.041, и 37.5 ± 1.1 vs 39.7 ± 1.05, p<0.0001, consequently).

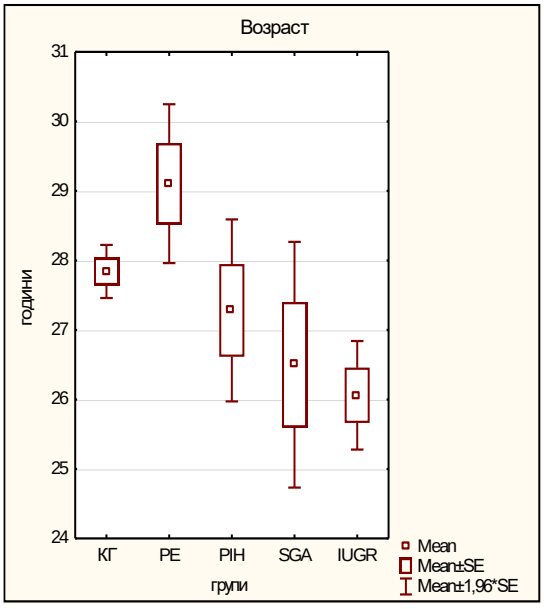

Figure 1. Age of pregnant women

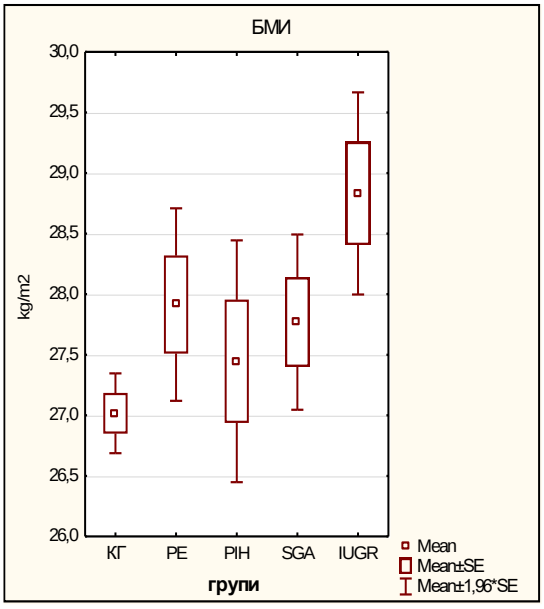

Figure 2. BMI of pregnant women

Figure 1. depict the age of pregnant women included in the study, thus pregnant women with preeclampsia have the highest average age (29.1 ± 4.0), followed by pregnant women from control group (27.8 ± 4.5), pregnant women with PIH (27.3 ± 3.8), Pregnant women with SGA (27.3 ± 3.8), pregnant women with IUGR (26.1 ± 2.8). It was confirmed the statistically significant difference in age between the group with IUGR and control group (p=0.006) and borderline significance between the group with preeclampsia and control group (p=0.059)

Figure 2. depict BMI of pregnant women included in the study, thus pregnant women with IUGR have significantly the biggest body mass index that pregnant women from control group (28.83 ± 3.0 vs 27.02 ± 3.8; p=0.013). Pregnant women with PE, PIH and SGA has similar mean values of BMI comparing to

control group (p>0.05).

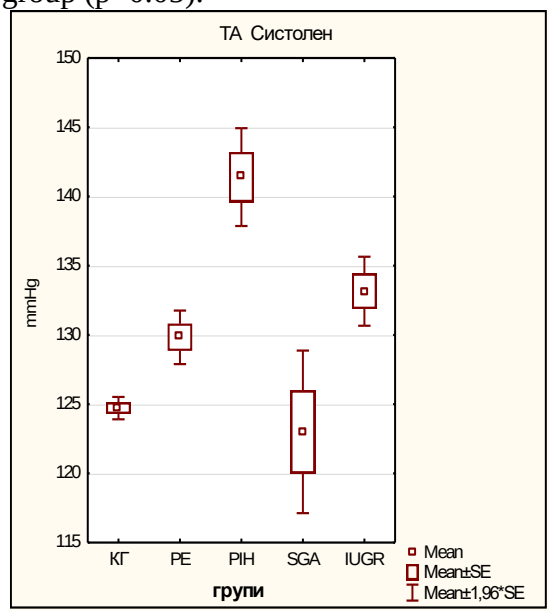

Figure 3. Systolic blood pressure

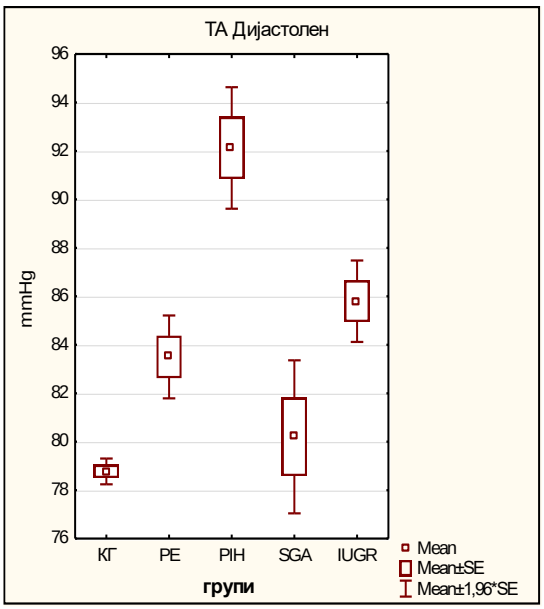

Figure 4. Diastolic blood pressure

Figure 3. depicts the systolic blood pressure in all pregnant women included in the study, thus the mean systolic blood pressure was 129.83±6.8, 141.41±10.2, 123.0±13.4, 133.16±8.9 и 124.72±9.4 mmHg, respectively in groups with PE, PIH, SGA, IUGR, and CG. Compared to CG, the mean systolic pressure was significantly higher in a group with PE (p=0.0003), in a group with PIH (p,0.0001), and in a group with IUGR (p<0.0001). Figure 4. depicts diastolic blood pressure in all pregnant women included in the study, thus the mean diastolic pressure was significantly higher in the group with PE versus CG (83.50 ± 6.1 vs 78.77 ± 6.2, p<0.0001), than in the group with PIH versus CG (92.12 ± 7.2 vs 78.77 ± 6.2, p<0.0001), and in a group with IUGR versus CG (85.80 ± 6.1 vs 78.77 ± 6.2, p<0.0001). In groups with SGA and CG the difference wasn't statistically significant (80.20 ± 7.2 vs 78.77 ± 6.2, p=0.31).

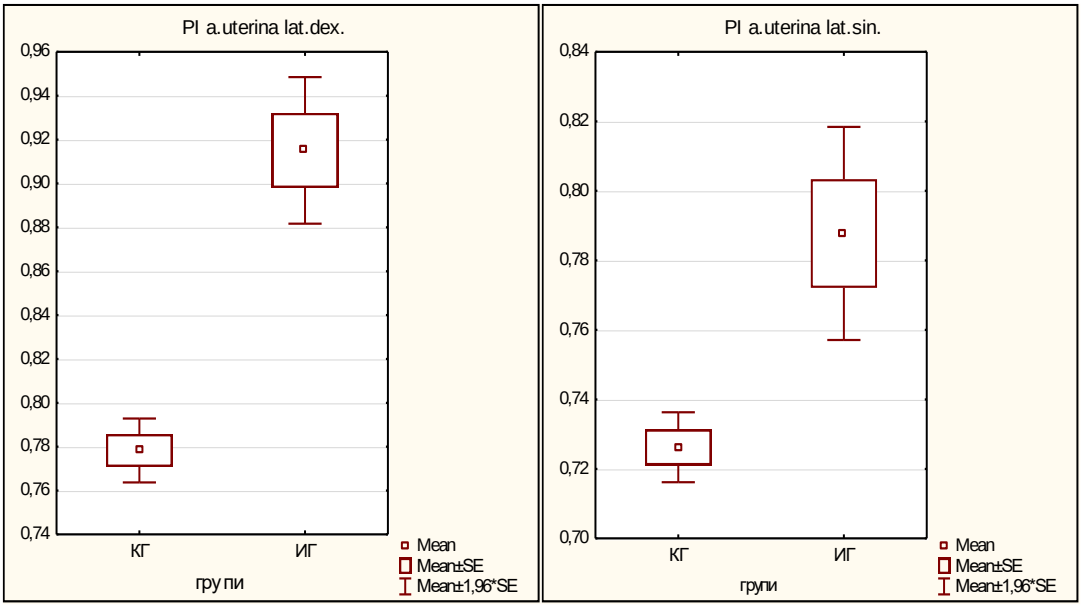

Figure 5. PI a. uterine lat. dex. et a. uterine lat. sin.

The pulsatile index in both uterine arteries was different among the research and control groups. The mean PI in the right uterine artery was 0.92 ± 0.2 in women with adverse pregnancy outcomes, while 0.78 ± 0.2 in pregnant women with favorable pregnancy outcomes, and the difference of 0.14 was confirmed as a statistical pulsatile index of 0.79 ± 0.2 in pregnant women with adverse pregnancy, while 0.73 ± 0.1 in pregnant women with favorable pregnancy and the difference 0.06 was confirmed as statistically significant for p=0.000002. (Figure 5).

Table 2. Depiction of resistant index in both uterine arteries

Variable	calculated parameter	**Groups**		**p-level**
		Research group	**Control group**	
RI a.uterina lat.dex	mean ±SD	0.81 ± 1.2	0.74 ± 0.15	t=5.12
	min - max	0.57 – 1.21	0.37 – 1.19	***p=0.000000 sig
RI a.uterine lat.sin.	mean ±SD	0.79 ± 0.2	0.75 ± 0.15	t=2.76
	min - max	0.49 – 1.16	0.47 – 1.96	**p=0.0059 sig

t(Student t-test) ***p<0.01; ***p<0.0001*

Pregnant women with adverse and favorable pregnancy outcomes have a different resistant index in both uterine arteries. RI of the right uterine artery was a mean value of 0.81 ± 1.2 in the research group, and 0.74 ± 0.15 in the control group, and the difference of 0.07 was confirmed as statistically significant for p<0.0001. RI of the left uterine artery has to mean value of 0.79 ± 0.2 in the research group, 0.75 ± 0.15 in the control group, and the difference of 0.04 was confirmed as statistically significant for p=0.0059 (table 2).

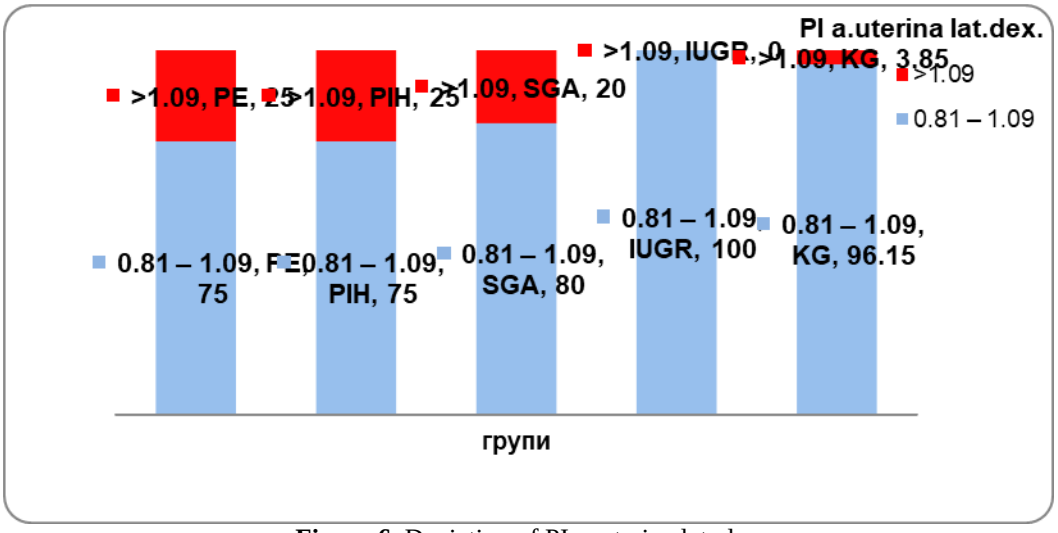

Figure 6. Depiction of PI a. uterine lat. dex.

Increased values of PI a. uterine lat. dex. were registered in 25% of pregnant women with preeclampsia, 25% with PIH, 20% with SGA, and 3.85% in pregnant women of CG. Compared to CG, increased PI of the right uterine arter`y significantly was found in pregnant women with preeclampsia (p<0.0001), in pregnant women with PIH (p<0.0001), and pregnant women with SGA (p=0.0006). (Figure 6)

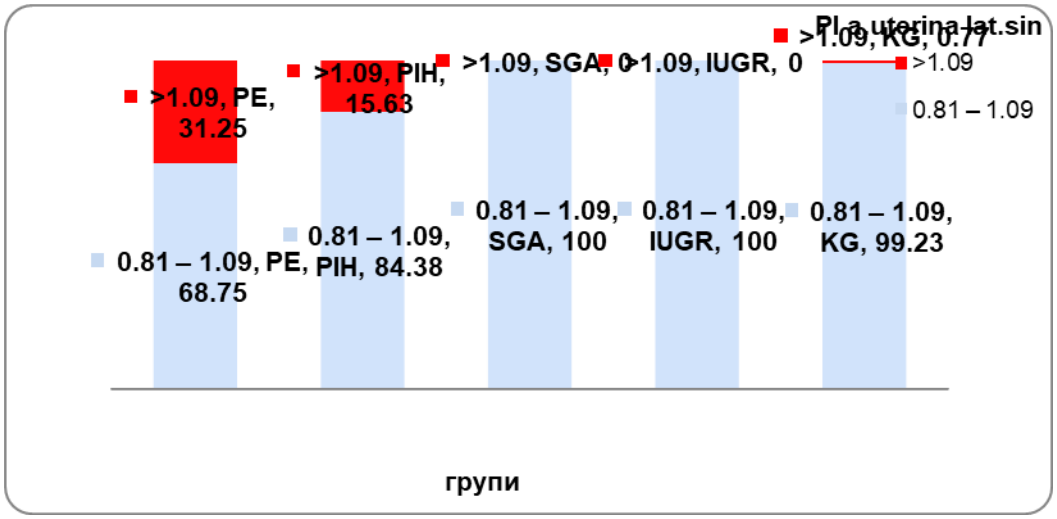

Figure 7. Depiction of a. uterine lat. sin.

In pregnant women with preeclampsia and PIH, PI of the left uterine artery was significantly higher compared to CG ($p<0.0001$). (Figure 7)

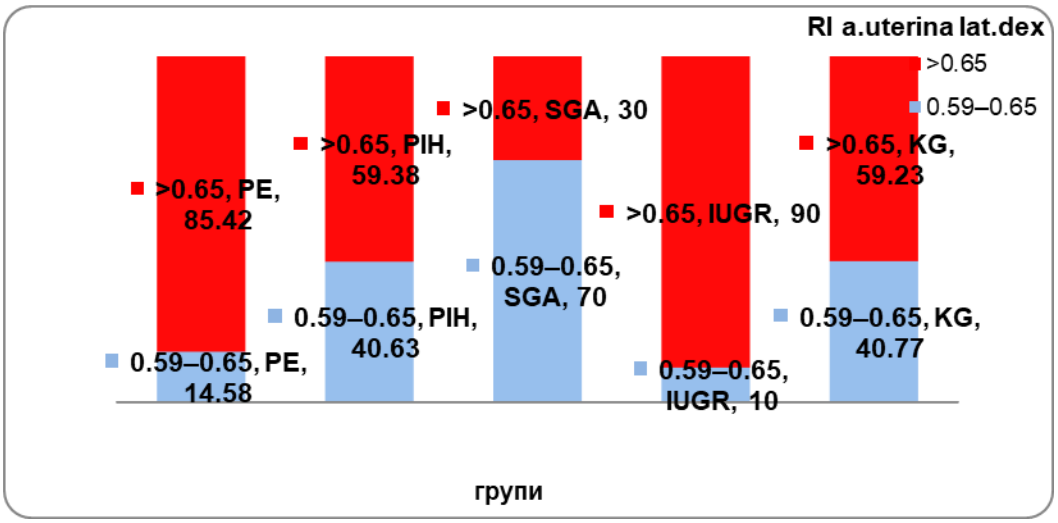

Figure 8. Depiction of RI a. uterine lat. dex.

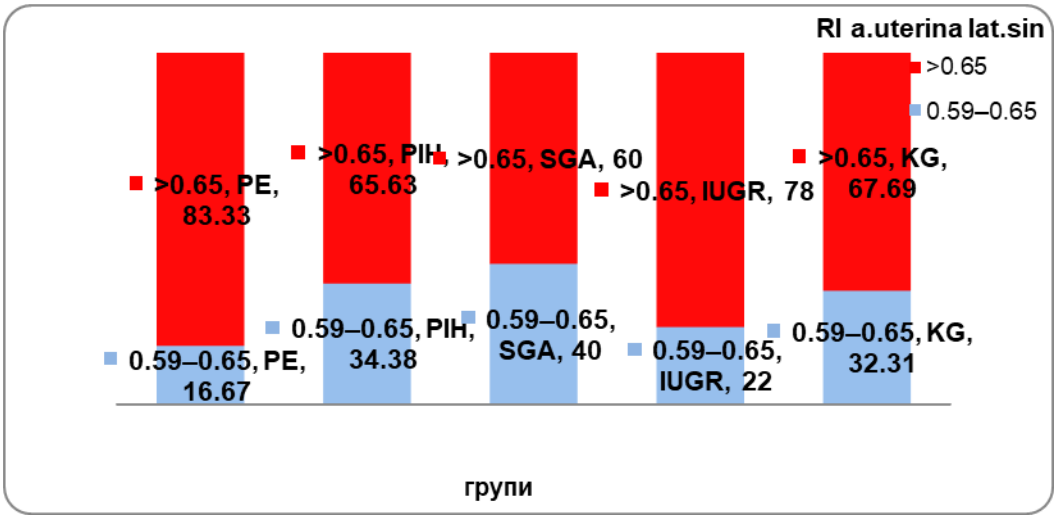

Figure 9. Depiction of RI a. uterine lat. sin.

Pregnant women with PE more frequently have increased right and left RI a. uterine, comparing to referent values (p=0.0004, p=0.025, respectively). Pregnant women with SGA and IUGR have increased values of RI a. uterine lat dex. comparing to CG (p=0.009, p<0.0001, respectively). (Figure 9)

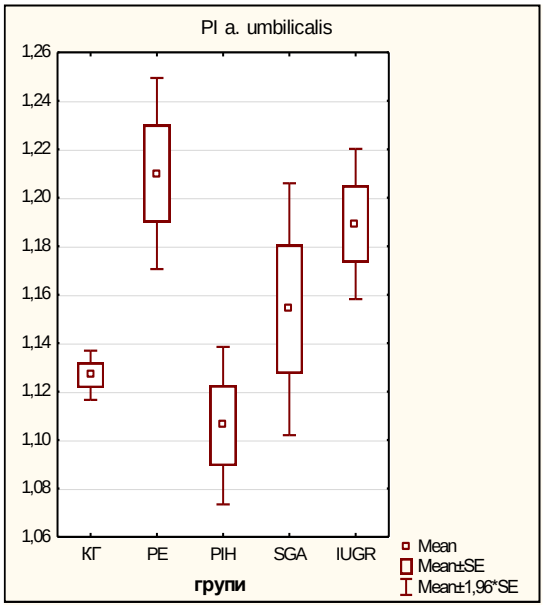

Figure 10. PI a. umbilicalis

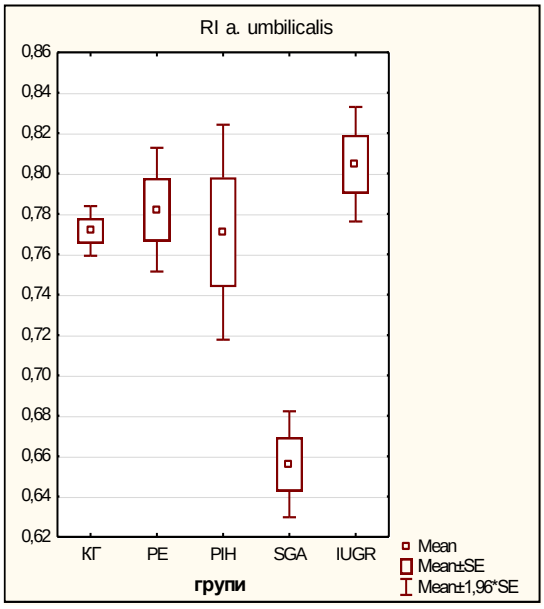

Figure 11. RI a. umbilicalis

The mean PI of the umbilical artery was significantly higher in a group with preeclampsia, compared to the control group CG (1.21 ±0.1 vs 1.13±0.1, p<0.0001) and in a group with IUGR compared to CG (1.19±0.11 vs 1.13±0.1, p=0.0004). The difference between groups with PIH and SGA compared to CG were statistically nonsignificant (p=0.33 и p=0.31, respectively). (Figure10)

The mean RI of the umbilical artery was significantly lower in a group with SGA compared to CG (0.66±0.06 vs 0.77±0.14, p=0.0004). In groups with PE, PIH and IUGR were measured with higher mean values of RI compared to CG, but statistically nonsignificant (p=0.62, p=0.98 и p=0.11, respectively). (Figure 11).

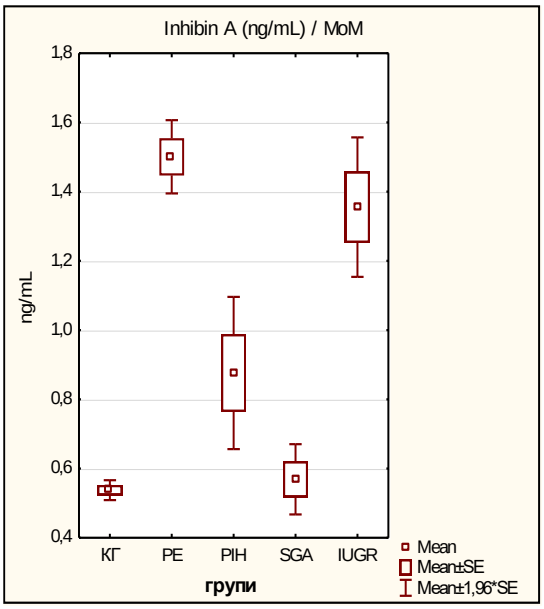

Figure 12. Inhibin A in all groups

Serum Inhibin A has the highest medial values in the group with preeclampsia (1.37 MoM), followed by the group with IUGR (1.16 MoM), PIH (0.81 MoM), SGA (0.55MoM) and the lower values were measured in the control group (0.45 MoM). There were confirmed statistically significant higher values of Inhibin A in a group with preeclampsia compared to CG, PIH versus CG, and IUGR versus CG. (Figure 12,13). 13)

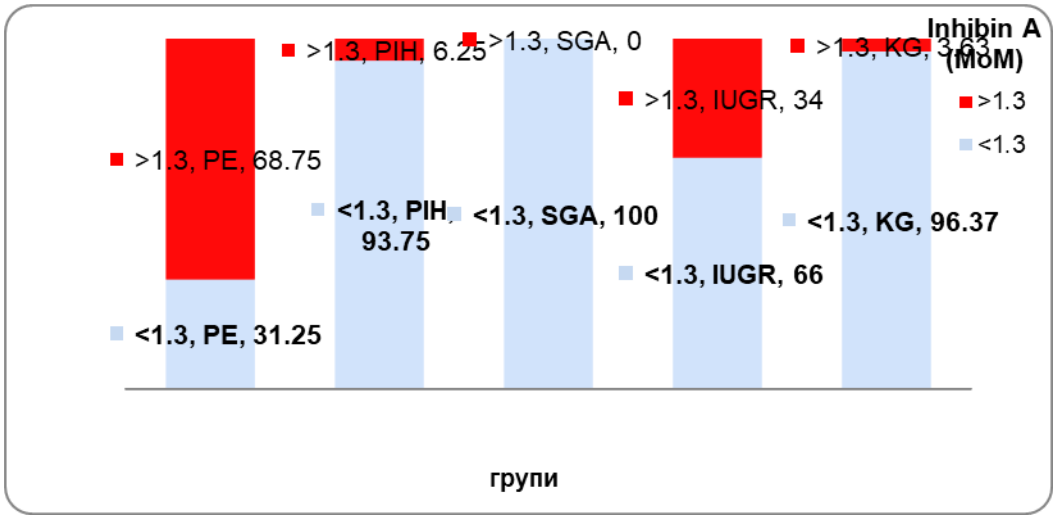

Figure 13. Depiction of Inhibin A in all groups

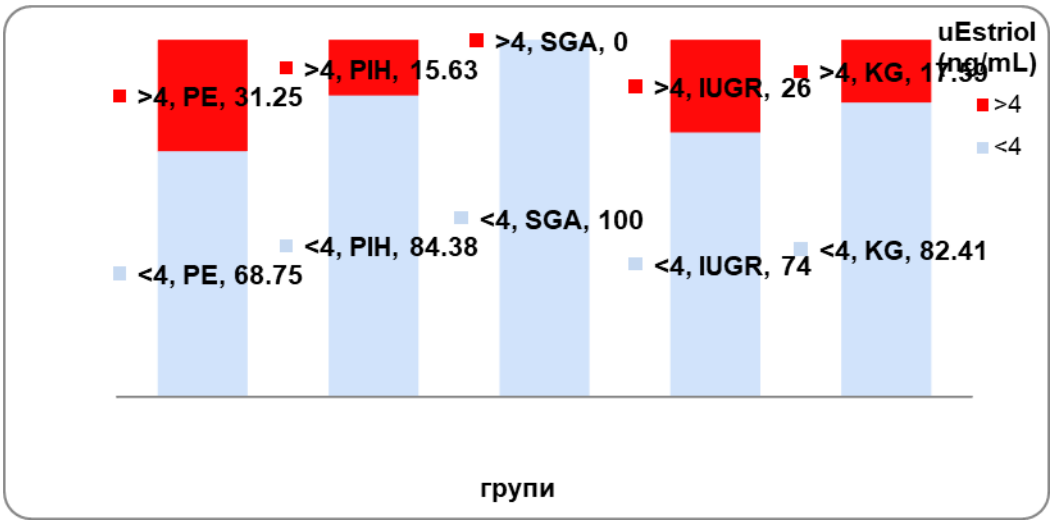

Figure 14. Depiction of uEstriol in all groups

Pregnant women with PE, significantly less frequently than women from CG have decreased values of uEstriol (68.75% vs 82.41%), while pregnant women with SGA more frequently than pregnant women from CG have decreased values of uEstriol. (Figure14).

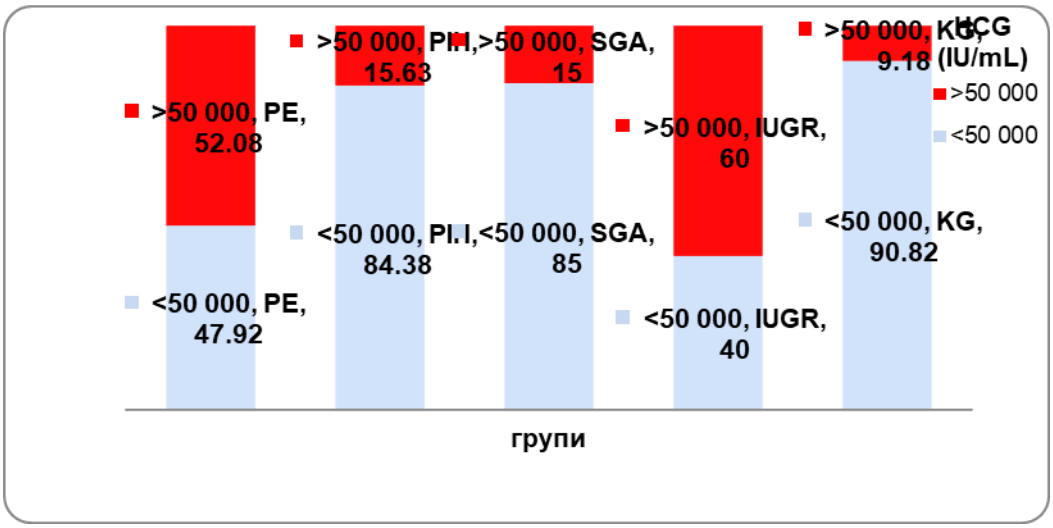

Figure 15. Depiction of HCG in all groups

Medial values of serum HCG were 50 780, 20 844, 33 172, 50 780, and 24 113 IU/mL, respectively in groups with PE, PIH< SGA, IUGR, and CG. Concerning to CG, the values were significantly higher in pregnant women with PE ($p<0.0001$), pregnant women with SGA ($p=0.0019$), and pregnant women with IUGR ($p<0.0001$) (Figure 15).

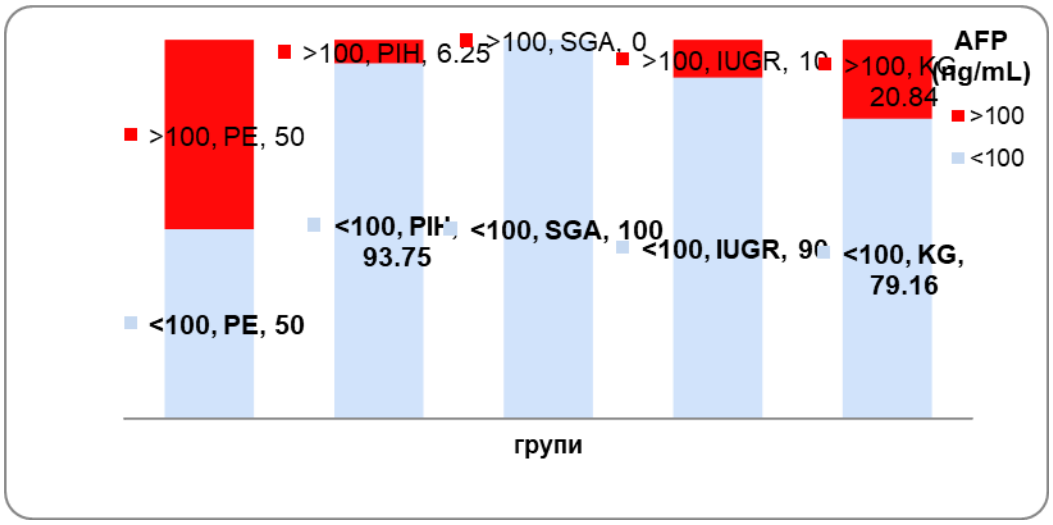

Figure 16. Depiction of AFP in all groups

Alpha-fetoprotein has significantly higher mean serum concentration in group with PE comparing to CG (94.32± 47.5 vs 78.09±38.1,p=0.0059), non-significantly higher in group with IUGR comparing to CG (81.68±23.1 vs 78.09±38.1,p=0.51), non-significantly lower in group with PIH comparing to CG (74.83± 41.2 vs 78.09±38.1,p=0.64) and non-significantly lower in group with SGA comparing to CG (75.04± 16.7 vs 78.09±38.1,p=0.51) (Figure 16).

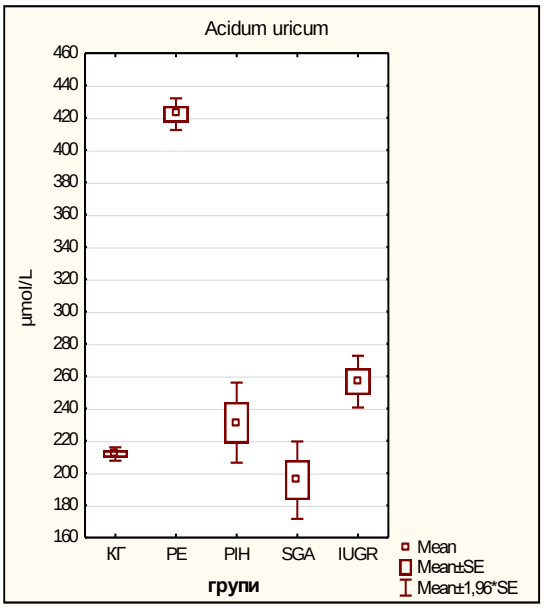

Figure 17. Depiction of Acidum uricum in all groups

Acidum uricum has significantly higher serum concentration mean values in the group with preeclampsia compared to the control group (422.25 ± 34.6 vs 211.81± 48.5,p<0.0001), significantly higher in a group with PIH compared to CG (231.21 ± 71.5 vs 211.81± 48.5,p=0.034) and significantly higher in a group with IUGR comparing to CG (256.63± 57.8 vs 211.81± 48.5,p<0.0001), while the difference between the group with SGA comparing to CG was statistically non-significant 195.60±54.7 vs 211.81± 48.5,p=0.145). (Figure17)

Table 3. Depiction of proteinuria in research and control group

Variable	Sizes	Groups			p-level
		N	RG б/n(%)	CG б/n(%)	
Proteins in urine (g/L)	Positive	46	46 (30.67)	0	X^2=172.1
	Negative	627	104 (69.33)	523 (100)	***p=0.000000 sig

X^2 (Pearson Chi-square) ***p<0.0001

From the group of pregnant women with adverse outcomes, 104 (69.3%) of them has proteinuria.

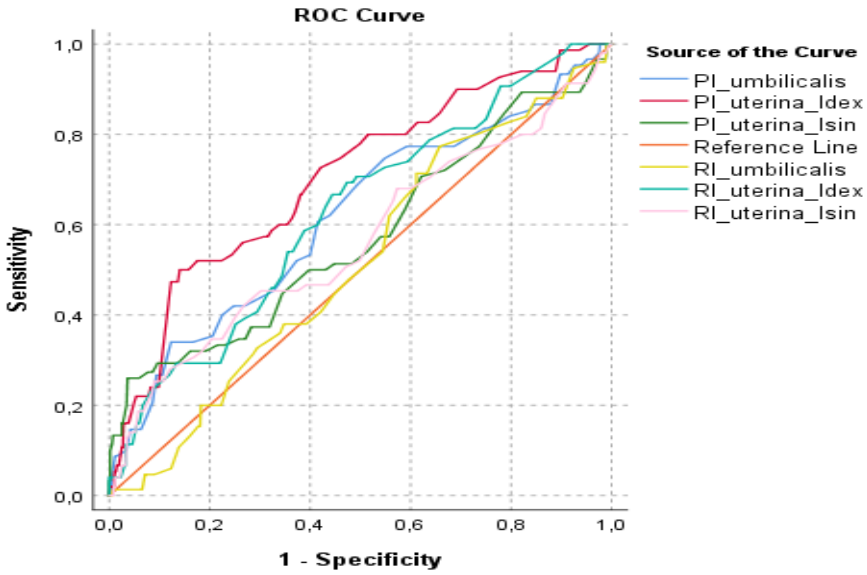

Figure 18. ROC curve of performances for doppler values

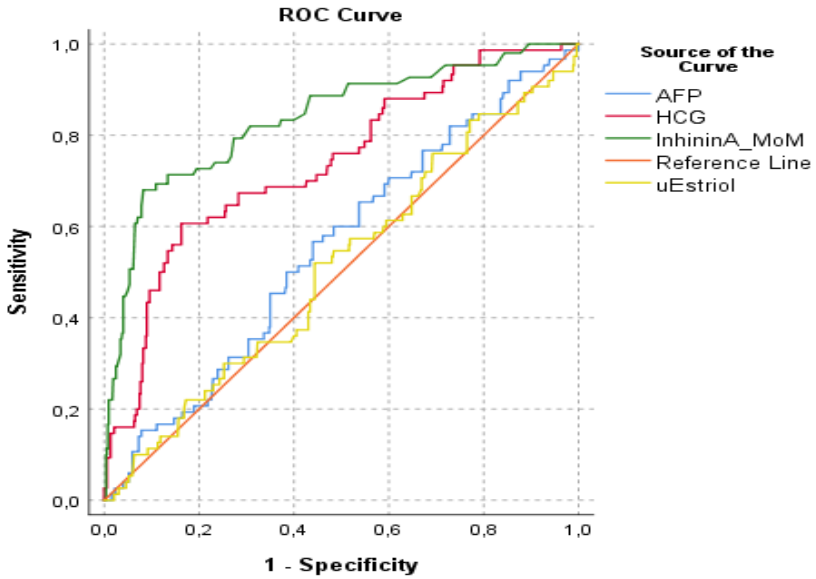

Figure 19. ROC curve for performances of serum biomarkers of Quadruple test

Results showed that according to the size of area under the ROC curve, Inhibin A as a single biomarker has the best differential ability in diagnosing pregnant women with adverse pregnancy, AUC=0.701.

The combination of Inhibin A, uEstriol, HCG and AFP has the biggest area under the ROC curve is (AUC=0.792), this combined model represents the test with the best differentiation ability for pregnant women with adverse and favorable pregnancy outcome.

2. Discussion and conclusions

This study evaluated four biomarkers that consist of Quadriple test (Inhibin A, HCG, AFP and uEstriol) and ultrasound parameters (fetal biometry, fetoplacental unit) in second trimester of pregnancy, finding it's correlation to pregnancy outcome. According to some studies, the use of Inhibin A as a predictor for IUGR have a great importance and some other studies are controversial. Increased value of maternal serum Inhibin A in second trimester of pregnancy is in an important correlation with abnormal placentation. Chowdhary et al. (2017). Our study found that the level of Inhibin A in serum of pregnant woman has the highest values in group with preeclampsia, followed by the group with IUGR, PIH and SGA. More frequently the increased serum Inhibin A values in pregnant women with adverse outcome versus those with favorable outcome, statistically was confirmed as significant, $p<0.0001$, while the performances of the test showed a good differentiation ability.

It is confirmed by Mazhari (2018) and Sanayukta (2019), that the serum level of HCG in the second trimester of pregnancy is a good predictor for PIH. In our study, median values of HCG in serum were significantly higher in a group with preeclampsia, followed by the group with SGA, and IUGR versus the control group. More than half of respondents with preeclampsia and IUGR (52.1% and 60% respectively), has increased levels of serum HCG, while in other groups, that was much lower, 15.6% in PIH, 15% SGA, and 9.2% in the control group.

According to Hu et al. (2020), an increased level of AFP in maternal serum is associated with a big risk for adverse pregnancy outcomes. This was confirmed partially in our study, because just women with preeclampsia have significantly higher values of AFP, compared to pregnant women with PIH, IUGR, and the control group. Also, our study didn't find any statistically significant difference between the median values of uEstriol, as a single biomarker in all four research groups and the control group. The area under the ROC curve showed that uEstriol has a weak discriminatory ability, thus this biomarker independently does not allow a prediction of pregnancy outcome.

In conclusion, pregnant women with adverse pregnancy outcome have a significantly higher pulsatile and resistant index in both uterine arteries (mean 0.92 ± 0.2 и 0.78 ± 0.2, respectively for the research and control group)

The results of the Quadruple test represented significantly higher values of Inhibin A, in the group with adverse pregnancy outcome (median 1.12 vs 0.45 MoM), and significantly higher values of HCG in the same group (median 45684.5 vs 24113), while uEstriol and AFP values were non significantly higher in a group with adverse pregnancy outcome.

Pregnant women with preeclampsia, PIH, SGA, and IUGR has significantly higher mean values of PI of the right uterine artery than the control group (mean 0.98 ± 0.2, 0.88 ± 0.2, 0.86 ± 0.2, 0.90 ± 0.15 and 0.78 ± 0.2, in a group with PE, PIH, SGA, IUGR, and CG, respectively). The left uterine artery has higher values of PI in a group with preeclampsia compared to CG (0.86 ± 0.25 vs 0.73 ± 0.1) and in a group with PIH compared to CG (0.84 ± 0.16 vs 0.73 ± 0.1).

Higher values of the pulsatile index of the umbilical artery were found in the group with preeclampsia (29.2%), SGA (20%), IUGR (26%), and in the control group (7.9%). The resistant index of the umbilical artery was higher in the group with preeclampsia (54.2%), in PIH 37.5%, in SGA 10%, IUGR 66%, and in CG 48%.

Inhibin A has increased serum level in the group with preeclampsia (659.2 pg./mL), followed by the group with IUGR (524.65pg/mL), PIH (376.2 pg/mL) and SGA (237. pg/mL), while the lowest serum level of Inhibin A has CG (203.7pg/mL). It was found a statistical significance between groups with PE versus CG, PIH versus CG, and IUGR versus CG.

uEstriol has no statistically significant difference in median values of uEstriol in four research groups compared to the control group 3.64, 2.92, 2,71, 3.04 vs 2.85, respectively for PE, PIH, SGA, IUGR, and CG).

The results for the validity of using serum biomarkers in our study, for diagnosing adverse pregnancy outcomes, showed that Inhibin A as a single marker has the best diagnostic performances (AUC=0.701, sensitivity 65%,

specificity 76%).
The combination of Inhibin A, u Estriol, HCG, and AFP has the biggest area under the ROC curve (AUC=0.792), so this combination of the test represents the test with the best ability for differentiation between pregnant women with adverse and favourable pregnancy outcomes.

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