Deinichenko O.V., Krut Yu.Ya. Angiogenesis factors and placental hormones in the first trimester of pregnancy of women with arterial hypertension of stage 1 and 2 with further fetal growth retardation. Journal of Education, Health and Sport. 2019;9(9):1037-1048. eISNN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.3463041
http://ojs.ukw.edu.pl/index.php/johs/article/view/7505

The journal has had 5 points in Ministry of Science and Higher Education parametric evaluation. § 8. 2) and § 12. 1. 2) 22.02.2019.

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 25.08.2019. Revised: 31.08.2019. Accepted: 22.09.2019.

Angiogenesis factors and placental hormones in the first trimester of pregnancy of women with arterial hypertension of stage 1 and 2 with further fetal growth retardation

Deinichenko O.V. [1], Krut Yu.Ya. [1]

[1] Zaporizhzhia State Medical University, Zaporizhzhia, Ukraine

Correspondence to:

Olena Deinichenko, Postgraduate Student, Department of Obstetrics and Gynecology, ZSMU. Tel. 0979055451. Email Address: agol0309@gmail.com. ORCID ID: http://orcid.org/0000-0002-8932-230X

Kruty Yuriy Yakovlevich, MD, Professor, Head of the Department of Obstetrics and Gynecology, ZSMU. Tel. 0688775795. Email address: yuriy.krut@ukr.net. ORCID ID: http://orcid.org/0000-0002-0501-6752

Abstract

The disbalance of pro-angiogenic and anti-angiogenic factors, hormonal balance shift in fetal growth retardation (FGR) among high-risk pregnant women plays a significant role in the pathogenesis of this pathological condition and may serve as a prognostic criterion in early pregnancy. **Materials and**

methods. We conducted a prospective study of 88 pregnant women at 12-13 weeks of pregnancy. The pro-angiogenic placental growth factor (PIGF) and anti-angiogenic – placental soluble fms-like tyrosine kinase (sFlt-1) and their ratio (sFlt-1/PIGF coefficient) were determined. Estradiol (E), progesterone (PG), and chorionic gonadotropin (CG) were determined among the placental hormones. **Results.** PIGF was statistically significantly reduced in pregnant women with FGR (6,7 pg/ml) comparing to the results of group 2 (18,7 pg/ml; $p<0,05$) and it was reduced comparing to group 3 (15,5 pg/ml; $0,05< p<0,1$). The levels of sFlt-1, by contrast, were highest among the women in group 1: (1972,3 pg/ml; $p<0,05$) compared to the control group (1384,4 pg/ml) and compared to 3 group (1595,3 pg/ml; $0,05<p<0,1$). sFlt-1/PIGF was significantly higher for patients of group 1 (596,5 units) compared to group 2 (252,2 units), $p<0,05$. **Conclusion.** In pregnant women with hypertension of 1 and 2 degrees, which in the first trimester of pregnancy (12-13 weeks of gestation) there was the decrease in levels of PIGF, increase in sFlt-1 levels and increase in the sFlt-1/PIGF ratio, the fetal growth retardation develops in future in comparison to women without hypertension. The levels of PIGF are significantly lower and the coefficient values are higher than those ones of pregnant women with hypertension of 1st degree. The levels of placental hormones of this pathology are not statistically significantly different from the data of the control group.

Key words: fetal growth retardation; growth factor; placental hormones; pregnancy; hypertension.

Introduction. FGR is an urgent medical and social problem in obstetrics today [1-4]. FGR is diagnosed if there is a decrease in the mass-growth rate below the 10-percentile according to the gestational age in the presence of placental insufficiency. Chronic hypoxia of the mother's body and placental hypofunction due to impaired uterine-placental circulation and impaired

transportation of oxygen and essential nutrients to the fetus as a result play the main role among the various pathogenetic mechanisms of FGR [2, 4]. FGR is the second cause of infant death after prematurity. The frequency of FGR is about 10%, at antenatal fetal death it reaches 20%, and at preterm pregnancy - from 15% to 22% [5].

Arterial hypertension contributes to the development of vascular and metabolic disorders for pregnant women, which leads to impaired uterine-placental circulation and forwards the development of further FGR [6, 7].

The activity of placental angiogenesis is controlled by a spectrum of growth factors with pro-angiogenic and anti-angiogenic properties. The source of pro-angiogenic growth factors is PIGF. PIGF stimulates the synthesis of trophoblastic DNA, increases the number of trophoblast cells and improves the conditions for its invasion during the first trimester of pregnancy [8, 9]. Anti-angiogenic factors include sFlt-1. It counteracts the action of PIGF on specific receptors [10]. The imbalance between the pro- and anti-angiogenic factors contributes to the development of FGR in pregnant women. The decrease in the levels of PIGF in the blood of pregnant women is a very important prognostic factor of FGR during the first trimester of pregnancy. PIGF levels may be 5-fold less compared to the control [8, 11]. Other scholars have discovered an increase in anti-angiogenic growth factors against the decrease in pro-angiogenic factors for pregnant women with placental insufficiency, which would have FGR in future [12]. Angiogenesis in pregnant women with arterial hypertension was investigated. It was determined that pregnant women have the increased serum level of sFlt-1 in response to a decrease in PIGF concentration. In pregnant women with arterial hypertension of stage 1 who have FGR later, the scientists point out the high prognostic significance of the sFlt-1/PIGF ratio. It grew in cases of FGR development [13]. The authors explain this by the presence of latent preclinical dysfunction of the endothelium that leads to disorders of the

circulation of the internal organs, their ischemia and the progressive lesion of target organs in this group of the patients.

Placental hormones such as E, PG, and CG contribute to the formation and function of the feto-placental complex. The group of researchers [14] discovered a decrease in E levels and an increase in CG in women with FGR, but the differences were not statistically significant. The similar results have been reported by other researchers [15], who found a decrease in E levels for pregnant women with hypertension during 16-20, 28-34, and especially 35-40 weeks of pregnancy compared with rates of pregnant women without hypertension.

Thus, the imbalance of pro-angiogenic and anti-angiogenic factors, hormonal balance shift of FGR high-risk pregnant women plays a significant role in the pathogenesis of this pathological condition and may serve as a prognostic criterion in early pregnancy. However, nowadays this problem has not been studied well yet.

Purpose. To determine the indicators in the system of pro-/anti-angiogenic factors and placental hormones during the first trimester of pregnancy of women with AG of 1 and 2 grades who have FGR developed later compared to those ones of pregnant women who have not the detected FGR.

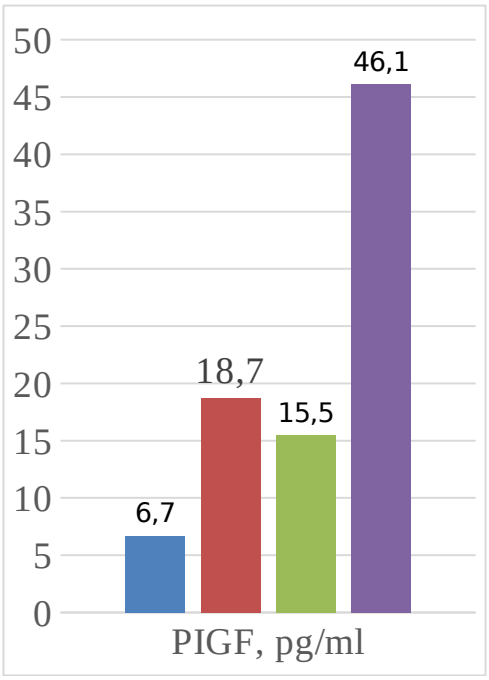
Materials and methods. We conducted a prospective study of 88 pregnant women at 12-13 weeks of pregnancy. The patients were divided into 4 groups. Group 1 (main group) included 10 women with AG1 and AG2, who have children with FGR. Group 2 (comparison group 1) included 25 pregnant women with AG1 who did not have FGR. Group 3 (comparison group 2) included 26 patients with AG2 who did not have FGR. Group 4 (control group) included 27 pregnant women with physiological pregnancy and who did not have AG and FGR in children. The average age of patients in group 1 was 30,2 ± 1,2 years, in group 2 it was 26,5 ± 0,9 years., in group 3 it was 34,3 ± 0,7

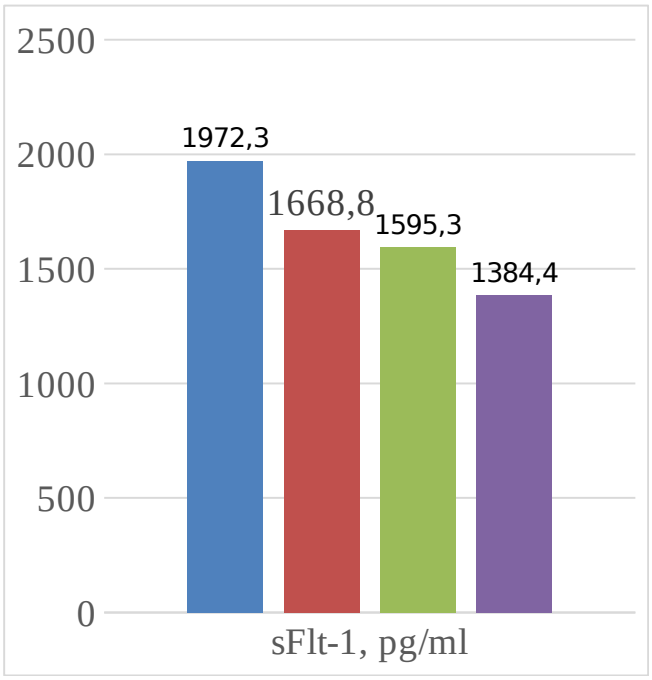
years, control group`s age was 32,0 ± 1,0 years. Patients in group 2 were definitely the youngest, p<0,05, and women in group 3 were significantly older, p<0,05 in terms of age (except compared with the control group, p>0,05). According to the obstetric and gynecological anamnesis the patients were compatible.

The degree of hypertension and FGR were diagnosed according to the clinical protocols in Ukraine. The pro-angiogenic PIGF factor and anti-angiogenic –sFlt-1 and their ratio (sFlt-1/PIGF coefficient) were determined. E, PG, CG were determined among the placental hormones. These parameters were determined by enzyme-linked immunosorbent assay according to the instructions using the enzyme analyzer Sirio-S (Italy) at the Medical Laboratory Center of Zaporizhzhya State Medical University. Placental hormones were determined using kits from Monobind Inc, USA; angiogenesis factors were determined using kits from R&D systems, Inc., USA&Canada.

Statistical analysis was made using Statistica for Windows 6.0. The data results are presented as M ± m, where M is the average of the parameter, and m is the error of mean. The normality of distribution in patient groups was determined using the Shapiro-Wilk method. In the case of normal distribution, the Student's method was used to compare results; in the absence of normality, the Mann-Whitney method was used.

Results and their discussion. PIGF levels were significantly lower in all patients with hypertension (groups 1, 2, 3) compared with those ones in the control group (46,1 pg/ml; p<0,001). However, this pro-angiogenic factor was statistically significantly reduced for pregnant women of group 1 (FGR; 6,7 pg/ml) compared to the results of group 2 (18,7 pg/ml; p<0,05) and it was reduced compared to group 3 (15,5 pg/ml; 0,05< p<0,1). It has been determined that pregnant women with hypertension have the reduced level of PIGF. If its levels reach the values of 6,7 ± 1,9 pg/ml, then FGR develops (Fig. 1).


50
45
40
35
30
25
20
15
10
5
0
46,1
18,7
15,5
6,7
PIGF, pg/ml


2500
2000
1500
1000
500
0
1972,3
1668,8
1595,3
1384,4
sFlt-1, pg/ml

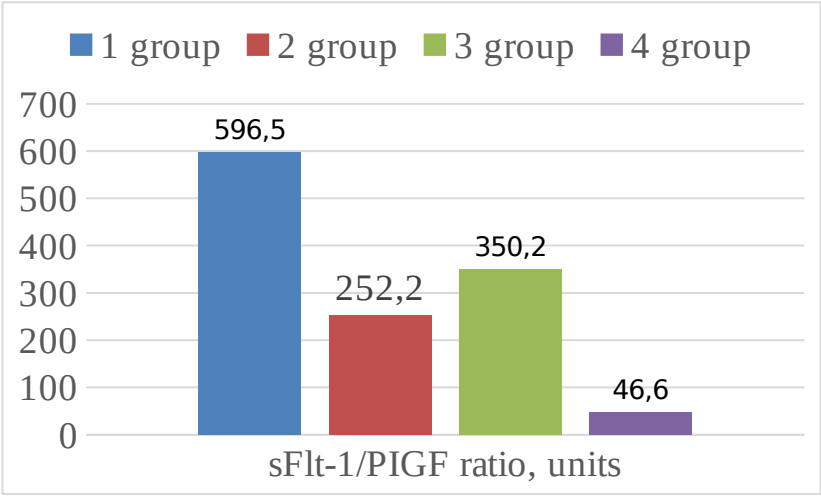


Figure 1. **Indicators of angiogenesis in serum in patient groups**

The levels of sFlt-1, by contrast, were highest among women in group 1: (1972,3 pg/ml; $p<0,05$) compared to the control group (1384,4 pg/ml) and compared to group 3 (1595,3 pg/ml; $0,05<p<0,1$). This indicator was significantly increased for patients of group 2 (1668,8 pg/ml) in relation to the control one ($p<0,05$). The levels of sFlt-1 for pregnant women with AG2 did not differ from the data of group 4 ($p>0,05$).

The sFlt-1/PIGF ratio was higher among all women with hypertension than in the control group (46,6 units; for 1, 2, 3 groups, $p<0,001$. However, it was significantly higher among patients of group 1 (596,5 units) compared to group 2 (252,2 units), $p<0,05$.

Thus, among pregnant patients with hypertension at decrease in the levels of PIGF and increase in sFlt-1 levels and the value of the coefficient of 596,5 ± 161,5 units FGR is developing.

There were no significant differences in the levels of angiogenesis indicators among women of groups 2 and 3 (fig.2).

There were no statistically significant differences in the levels of placental hormones in the groups of women (Fig. 2).

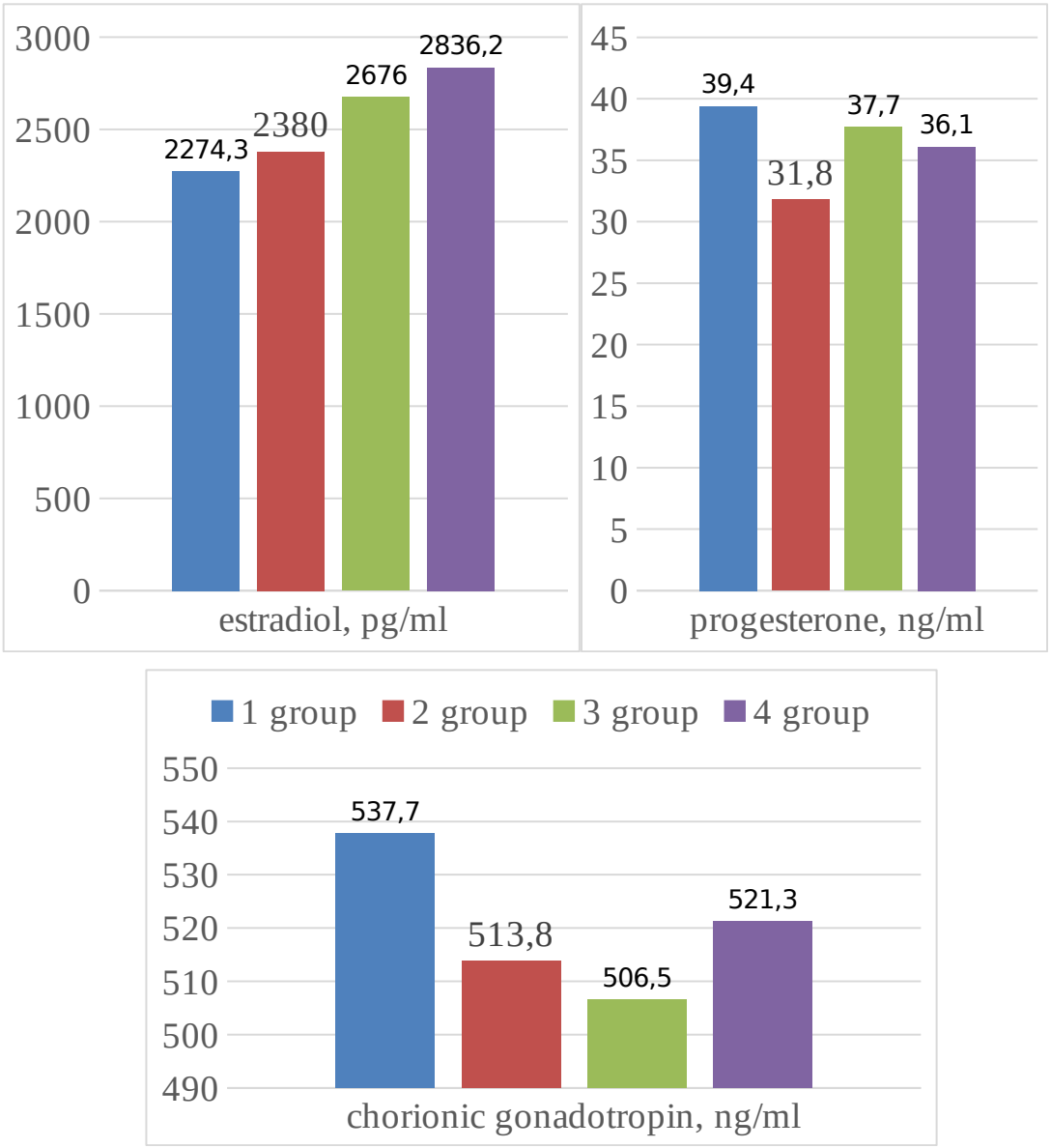


Figure 2. **Indicators of placental hormones in serum in patient groups**

However, we can see a relative decrease in E levels, an increase in PG and CG levels among patients with hypertension who have the developed FGR in the future.

Discussion. We found decreased levels of PIGF, increased levels of sFlt-1 and sFlt-1/PIGF ration as a result for all patients with arterial hypertension. The similar results were detected by other authors [9, 13]. But they checked pregnant

women during 2d and 3d trimesters of pregnancy contrary to our examination during 12-13 weeks. Some researchers used these indices for prognosis of preeclampsia during 1 trimester [17]. The most expressed disbalance was observed among women with further FGR. It means, arterial hypertension when severe disbalance between pro- and anti-angiogenic factors presented cause placental hypofunction due to impaired uterine-placental circulation and impaired transport of oxygen and essential nutrients to the fetus as a result lead to FGR.

Previous researchers discovered the decreased levels of E for women with FGR [15, 16, 18]. We also detected a little reduction of E among such patients, but differences was not statistical. There were no statistically significant differences in the levels of other placental hormones in the groups of women.

Conclusions. Among pregnant women with 1st and 2nd degree hypertension during the first trimester of pregnancy (12-13 weeks of gestation) there is the decrease in levels of PIGF, increase in sFlt-1 levels and increase in the sFlt-1/PIGF ratio, the fetal growth retardation develops in future compared to women without hypertension. The levels of PIGF are significantly lower and the coefficient values are higher than those ones of pregnant women with 1st degree hypertension. The levels of placental hormones for this pathology are not statistically significantly different from the data of the control group.

References

1. Egorova YaA, Zabolotnov VA, Rybalka AN. Zaderzhka vnutriutrobnogo razvitiya ploda v perinatalnoj medicine (obzor) [Fetal growth retardation in perinatal medicine (review)]. Zdorove zhenshchiny 2015; 4(100): 48-51. Russian.
2. Kolokot NH. Udoskonalennia diahnostyky zatrymky rostu ploda u vahitnykh shliakhom vykorystannia biokhimichnykh markeriv, shcho kharakteryzuiut

porushennia stres adaptatsii [Improvement of fetus growth restriction diagnostics in pregnant women by means of biochemical markers that characterize the disorder of stress-adaptation]. Zaporozhskij medicinskij zhurnal. 2018; 2(107): 231-235. Doi 10.14739/2310-1210. 2018.2.125275. Ukrainian.

3. Korostil MO, Chorna OO. Zatrymka rostu ploda pry donoshenii i nedonoshenii vahitnosti [Fetal growth retardation in term and premature pregnancy]. Akusherstvo. Hinekolohiia. Henetyka. 2016; 1: 20-23. Ukrainian.
4. Jacqueline EAK. Bamfo Anthony O. Odibo. Diagnosis and management of fetal growths restriction. Journal of pregnancy. 2011; Article ID 640715, doi: 10.1155/2011/640715.
5. Kosilova SYe. Akusherski ta perynatalni uskladnennia, yak faktory ryzyku zatrymky rostu ploda [Obstetrical and perinatal complications as risk factors of fetal growth retardation]. Bukovynskyi medychnyi visnyk. 2016; 20, 2(78): 48-50. Ukrainian.
6. Korol TM. Fetoplatsentarna nedostatnist (FPN) – aktualna problema medytsyny. Kliniko-etiopatohenetychni kryterii diahnostyky, likuvannia ta profilaktyky [Fetoplacental insufficiency (FPN) – actual problem of medicine. Clinical-etiopathogenetical diagnostic criteria, tretment and prevention]. Visnyk problem biolohii i medytsyny, 2013; 1(2): 49-54. Ukrainian.
7. Alekseeva LL, Borgolov AV, Mangataeva MR, Afanaseva OM, Radnaeva SA. Mehanizm formirovaniya HFPN pri arterialnoy gipertenzii u beremennyih zhenschin [The mechanism of chronicle fetoplacental deficiency forming due to arterial hypertension of the pregnant women]. Vestnik buryatskogo gosudarstvennogo universiteta. 2008;. 12: 82-86. Russian.

8. Fomina MP, Divakova TS, Rzheusskaya LD. Endotelialnaya disfunktsiya i balans angiogennyih faktorov u beremennyih s platsentarnyimi narusheniyami [Endothelial dysfunction and balance of angiogenic factors in pregnant women with placental disorders]. Meditsinskie novosti. 2014; 3: 63-67. Russian.
9. Volkova EV, Lysyuk EYu, Dzhokhadze LS, Makarov OV. Osobennosti izmeneniy pro- i antiangiogennyih faktorov u beremennyih s hronicheskoy arterialnoy gipertenziey [Specific features of changes in pro- and antiangiogenic factors in pregnant women with chronic arterial hypertension]. Rossiyskiy vestnik akushera-ginekologa. 2013; 3: 9-13. Russian.
10. Goryunova AG, Simonova MS, Murashko AV. Sindrom zaderzhki rosta ploda i adaptatsiya platsentyi [Fetal growth retardation syndrome and adaptation of placenta]. Arhiv akusherstva i ginekologii im. V.F. Snegireva. 2016; 3(2): 76-80. Doi 10.18821/2313-8726-2016-3-2-76-80 Russian.
11. Orlov AV, Kudinova EI. Etiopatogeneticheskie aspektyi razvitiya platsentarnoy nedostatochnosti i zaderzhki rosta ploda [Aspects etiopatogenesis of the development to insufficiency of placenta and fetal growth retardation]. Zhurnal fundamentalnoy meditsinyi i biologii. 2016; 4: 4-10. Russian.
12. Osmanova AP. Angiogennyj disbalans v patofiziologii preeklampsii i sindroma zaderzhki rosta ploda [Angiogenic imbalance in the pathophysiology of preeclampsia and fetal growth retardation]. Vestnik RGMU. 2014; 2:16-17. Russian.
13. Youssef A, Righetti F, Morano D, Rizzo N, Farina A. Uterine artery Doppler and biochemical markers (PAPP-A, PlGF, sFlt-1, P-selectin, NGAL) at 11 + 0 to 13 + 6 weeks in the prediction of late (>34 weeks) pre-eclampsia. Prenatal diagnosis. 2011;. 3: 1141–1146. Doi 10.1002/pd.2848.

14. Trishkin AG, Novikova ON, Artymuk NV, Ushakova GA, Kiprina ES, Bikmetova ES. Gormonalno-metabolicheskie osobennosti fetoplatsentarnogo kompleksa pri zaderzhke rosta ploda [Hormonal and metabolic characteristics of fetoplacental complex in women with fetal growth restriction]. Mat i ditya v Kuzbasse, spetsvyipusk 1. 2012; URL: https://cyberleninka.ru/article/n/gormonalno-metabolicheskie-osobennosti-fetoplatsentarnogo-kompleksa-pri-zaderzhke-rosta-ploda. Russian.
15. Alekseeva LL, Protopopova NV. Sostoyanie platsentarnoy sistemyi i gormonalьnaya funktsiya platsentyi u beremennyih s arterialnoy gipertenziey v raznyih etnicheskih gruppah [The state of placental system and hormonal function of placenta at pregnant women with arterial hypertensia in different ethnic groups]. Journal of Siberian Medical Sciences. 2012; 52. URL: https://cyberleninka.ru/article/n/sostoyanie-platsentarnoy-sistemy-i-gormonalnaya-funktsiya-platsenty-u-beremennyh-s-arterialnoy-gipertenziey-v-raznyh-etnicheskih. Russian.
16. Zeisler H, Lurba E, Chantraine F, Vatish M, Cathrine A, Sennström M, et al. Predictive value of the sFlt-1:PlGF ratio in women with suspected preeclampsia. The New England journal of medicine. 2016; 374:13-22. Doi 10.1056/NEJMoa1414838.
17. Youssef A, Righetti F, Morano D, Rizzo N, Farina A. Uterine artery Doppler and biochemical markers (PAPP-A, PlGF, sFlt-1, P-selectin, NGAL) at 11 + 0 to 13 + 6 weeks in the prediction of late (>34 weeks) pre-eclampsia. Prenatal diagnosis. 2011; 3: 1141–1146. Doi 10.1002/pd.2848
18. Sanghavi M, Rutherford JD. Cardiovascular physiology of pregnancy. Circulation. 2014; 130(12): 1003-1008. URL: https://doi.org/10.1161/CIRCULATIONAHA.114.009029.