УДК 618.33-07
https://doi.org/10.20538/1682-0363-2025-3-34-41

Evaluation of the role of biochemical and biophysical parameters of combined prenatal screening of the first trimester in the development of fetal growth restriction

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ABSTRACT

Aim. To evaluate the role of biochemical and biophysical parameters in the combined first-trimester prenatal screening for the development of clinical forms of fetal growth restriction.

Materials and methods. Group I (main) included 73 patients, whose pregnancies were complicated by the fetal growth restriction. The main group was divided into two subgroups: Ia with 30 patients whose pregnancies were complicated by fetal growth restriction (FGR) and Ib with 43 patients whose pregnancies were complicated by small for gestational age fetuses (SGA). Group II (control) included 118 patients whose pregnancies resulted in the birth of a live, full-term infant with normal height and weight. All patients underwent combined first-trimester prenatal screening with calculation of biochemical (pregnancy-associated plasma protein A (PAPP-A), free β-subunit of human chorionic gonadotropin (β-hCG) and biophysical (mean arterial pressure (MAP), uterine artery pulsatility index (PI) parameters, the values of which were subsequently analyzed.

Results. The level of PAPP-A was statistically significantly lower in the FGR group (0.793 MoM) compared to the control group (1.048 MoM), $p = 0.005$. The level of PAPP-A in the blood below 0.793 MoM increases the risk of fetal growth restriction by 3.244 times (odds ratio (OR) = 3.244; 95% confidence interval (95% CI) 1.394–7.554, $p = 0.005$). An increase in the pulsation index was found in Doppler ultrasound of the uterine arteries in patients with FGR compared to the SGA group (OR = 2.254; 95% CI 0.990–5.129, $p = 0.017$). Statistically significant differences were not found in the studied parameters of the combined first-trimester prenatal screening in relation to SGA.

Conclusion. Differences in the biochemical and biophysical parameters of combined prenatal screening for the clinical forms of FGR were identified. Further research is needed to identify new prognostic markers of FGR, which will help reduce perinatal losses. Additional research is required to expand the sample size of the Russian population to clarify the role of the prenatal screening components.

Keywords: fetal growth restriction, small for gestational age fetus

Conflict of interest. The authors declare the absence of obvious or potential conflicts of interest related to the publication of this article.

Source of financing. The authors declare no funding.

Conformity with the principles of ethics. All patients signed an informed consent to participate in the study. The study was approved by the local Ethics Committee at Siberian State Medical University (Minutes No. 9330 dated January 30, 2023).

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For citation: Izhoykina E.V., Trifonova E.A., Gavrilenko M.M., Kutsenko I.G., Stepanov V.A. Evaluation of the role of biochemical and biophysical parameters of combined prenatal screening of the first trimester in the of insufficient fetal growth development. *Bulletin of Siberian Medicine.* 2025;24(3):34–41. https://doi.org/10.20538/1682-0363-2025-3-34-41.

Оценка роли биохимических и биофизических параметров комбинированного пренатального скрининга первого триместра в развитии недостаточного роста плода

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РЕЗЮМЕ

Цель: оценить роль биохимических и биофизических параметров комбинированного пренатального скрининга первого триместра в развитии клинических форм недостаточного роста плода.

Материалы и методы. Группа I (основная) – 73 пациентки, чьи беременности были осложнены развитием недостаточного роста плода. Основная группа была разделена на две подгруппы: Ia – 30 пациенток, чьи беременности были осложнены развитием задержки роста плода (ЗРП), Ib – 43 пациентки, чьи беременности были осложнены развитием маловесного для гестационного возраста плода (МГВ). Группа II (контрольная) – 118 пациенток, чьи беременности закончились рождением живого доношенного ребенка с нормальными росто-весовыми показателями. Всем пациенткам проведен комбинированный пренатальный скрининг первого триместра с расчетом значений биохимических (ассоциированный с беременностью плазменный белок А – PAPP-A, свободная β-субъединица хорионического гонадотропина человека – β-hCG) и биофизических (среднее значение артериального давления – САД, пульсационный индекс в маточных артериях – PI MA) параметров, значения которых в дальнейшем были подвергнуты анализу.

Результаты. Уровень PAPP-A был статистически значимо ниже в группе ЗРП (0,793 MoM) по сравнению с контрольной группой (1,048 MoM), $p = 0{,}005$. Содержание PAPP-A в крови менее 0,793 MoM увеличивает риск развития задержки роста плода в 3,244 раза (отношение шансов (OR) 3,244; 95%-й доверительный интервал (95% ДИ) 1,394–7,554, $p = 0{,}005$). Выявлено повышение пульсационного индекса при допплерометрии маточных артерий у пациенток с ЗРП по сравнению с группой МГВ (OR = 2,254; 95% ДИ 0,990–5,129, $p = 0{,}017$). Статистически значимые различия изученных параметров комбинированного пренатального скрининга первого триместра с развитием МГВ не были выявлены.

Заключение. Выявлены различия по биохимическим и биофизическим параметрам комбинированного пренатального скрининга для клинических форм недостаточного роста плода. Необходим дальнейший поиск новых прогностических маркеров недостаточного роста плода, что приведет к снижению перинатальных потерь. Требуется дополнительное проведение исследований для увеличения объема выборки российской популяции с целью уточнения роли составляющих компонентов пренатального скрининга.

Ключевые слова: задержка роста плода, маловесный для гестационного возраста плод

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

Соответствие принципам этики. Все пациенты подписали информированное согласие на участие в исследовании. Исследование одобрено этическим комитетом ФГБОУ ВО СибГМУ (протокол № 9330 от 30.01.2023).

Для цитирования: Ижойкина Е.В., Трифонова Е.А., Гавриленко М.М., Куценко И.Г., Степанов В.А. Оценка роли биохимических и биофизических параметров комбинированного пренатального скрининга первого триместра в развитии недостаточного роста плода. *Бюллетень сибирской медицины.* 2025;24(3):34–41. https://doi.org/10.20538/1682-0363-2025-3-34-41.

INTRODUCTION

Reducing perinatal losses is one of the priority areas in obstetrics. Fetal growth restriction (FGR) is a pregnancy complication in which the fetus does not achieve its optimal physical development for the gestational age and is a probable risk factor for complications such as neonatal respiratory distress syndrome, hypothermia, hypoglycemia, pulmonary hemorrhage, intraventricular hemorrhage, necrotizing enterocolitis, and sepsis [1–3]. The development of screening programs for early detection of pregnant women with a high risk of FGR remains relevant. The obstetric community continues to actively search FGR predictors to create mathematical models and algorithms that would have high prognostic significance in stratifying the pathological gestation risk.

In 2020, with the support of the Fetal Medicine Foundation (FMF, UK), a large-scale study was conducted involving 60,875 pregnant women to assess the predicting effectiveness of a birth of a child weighing less than the 10th percentile based on biochemical and biophysical parameters of prenatal screening. According to the results of this study, the best biophysical predictor was the uterine artery pulsatility index (PI), and the best biochemical marker was the placental growth factor (PIGF) [4]. The evaluation of the parameters was conducted in many countries around the world with their subsequent implementation in wide clinical practice [5–8].

In the Russian Federation, the calculation of biochemical (free β-subunit of human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein A (PAPP-A)) and biophysical (uterine artery pulsatility index (PI) and mean arterial pressure (MAP)) marker values is performed as part of prenatal screening for fetal developmental disorders in the first trimester. In 2017, a group of Russian researchers assessed the use of first-trimester biochemical screening parameters and the uterine artery PT to form a risk group for FGR. It was shown that the probability of developing FGR is 68% with an increase in the PI value > 2.5 MoM in combination with a decrease in PAPP-A < 0.7 MoM. However, in our country at the time of the study, a different clinical classification of FGR was in effect, based on the fetometry parameter lag from the norm by two or more weeks, which in turn determined the inclusion criteria in this work [9].

In 2019, T.A. Yarygina et al. published the findings of a study devoted to assessing the effectiveness of biophysical and biochemical parameters of prenatal screening in predicting the birth of a SGA child. The analysis conducted in this work established an acceptable quality of the model for predicting the birth of a preterm low birth weight baby only for the PAPP-A biomarker (area under the curve (AUC) 0.74). However, the inclusion criterion in the main group was the value of the estimated fetal weight less than the 10th percentile [10]. Given the small number of studies assessing the effectiveness of biochemical and biophysical parameters of prenatal screening in the development of FGR, further research in this area is required.

The aim of the study was to evaluate the role of biochemical and biophysical parameters of combined first-trimester prenatal screening in the development of clinical forms of FGR.

MATERIALS AND METHODS

The study group consisted of 191 women who had a singleton spontaneously conceived pregnancy that resulted in a live birth at 24 weeks or more of gestation between 2021 and 2023.

Inclusion criteria for the main group were as follows: singleton pregnancy complicated by the development of FGR. Inclusion criteria for the control group were singleton normal pregnancy resulting in the birth of a healthy newborn with a body weight corresponding to the gestational age. Exclusion criteria for both groups were the presence of severe extragenital pathology in the woman; pregnancy

resulting from assisted reproductive technologies; multiple pregnancy; hereditary diseases in the mother; acute phase or exacerbation of chronic infectious diseases; chromosomal abnormalities, and congenital malformations of the fetus.

All patients underwent combined first-trimester prenatal screening to diagnose fetal developmental disorders at the Medical Genetic Center of the Research Institute of Medical Genetics of Tomsk National Research Medical Center and the I.D. Evtushenko Regional Perinatal Center in Tomsk at a gestational age of 11–13.6 weeks. Prenatal screening included ultrasound examination (US) of the fetus and biochemical examination of the mother's blood with an assessment of the concentration of free β-subunit of human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein A (PAPP-A) [10]. Screening was supplemented by determination of the uterine artery pulsatility index (PI) and double measurement of blood pressure (BP) in both arms, followed by the mean BP (MBP) value calculation. The obtained values of PI, MBP, serum protein concentrations considering the crown-rump length of the fetus and the body weight of the pregnant woman were converted into MoM. The standard reference values of 0.5–2.0 MoM were considered. All women signed an informed consent to participate in the study, which was approved by the Ethics Committee at Siberian State Medical University.

Statistical analysis was performed in several stages. The quantitative data were tested for compliance with the normal distribution law using the Kolmogorov–Smirnov test (for a sample size of $n > 50$) and the Shapiro–Wilk test (for $n < 50$). In our study, the distribution was not normal, therefore, quantitative data are presented as the median and the interquartile range Me (Q_1; Q_3). To compare differences between groups, nonparametric statistical methods were used including the Kruskal–Wallis and Mann–Whitney tests. Differences were considered statistically significant at $p < 0.05$. To adjust for multiple comparisons, the Bonferroni correction was used ($p_{adjusted}$, the adjusted p-value, was 0.017). The analysis of four-field contingency tables was performed using the Pearson's chi-squared test, since the value of the expected phenomenon was more than 10. In order to assess the influence of biochemical and biophysical parameters on the development of FGR, the odds ratio (OR) was calculated with a 95% confidence interval (95% CI). Statistical analysis was performed using the statistical packages Excel and SPSS Statistics 26.

RESULTS

All study participants were divided into two groups. The main (I) included includes patients whose pregnancy was complicated by the development FGR. According to the clinical guidelines in force in the Russian Federation, the group was divided into two subgroups, depending on the clinical form of FGR. Group Ia included patients with antenatally diagnosed FGR ($n = 30$). FGR was defined as an ultrasound value of the estimated fetal weight (EFW) less than the 3rd percentile or an EW less than the 10th percentile in combination with abnormal blood flow according to ultrasound Doppler data. Group Ib includes patients whose pregnancy was complicated by the formation of a small-for-gestational-age (SGA) fetus ($n = 43$). SGA was defined when ultrasound values of the EFW were in the range from the 3rd to the 9th percentile in combination with normal blood flow parameters according to Doppler data.

The control (II) group consisted of patients whose pregnancy ended with the birth of a healthy full-term newborn with normal weight and height ($n = 118$). The postnatal assessment of weight and height in newborns was carried out according to the INTERGROWTH-21st centile tables to confirm the antenatal diagnosis of FGR and SGA fetus, as well as to establish normal growth and weight of newborns in the control group. Data on the course and outcomes of pregnancy were obtained from the primary medical documentation of I.D. Evtushenko Regional Perinatal Center, Tomsk.

All patients participating in the study underwent combined first-trimester prenatal screening with calculation of biochemical and biophysical parameter values, the results of which are presented in Table 1.

$p_{Ia\text{-}II}$ is the level of statistical significance of differences between FGR and control groups; $p_{Ib\text{-}II}$ is the level of statistical significance of differences between SGA and control groups; $p_{Ia\text{-}Ib}$ is level of statistical significance of differences between FGR and SGA groups; $p_{adj} = 0.017$.

It should also be noted that the median values of all presented parameters did not exceed the reference limits. The Kruskal–Wallis test revealed statistically significant differences between the groups in such parameters as PAPP-A and PI levels ($H = 9.113$, $p = 0.010$; $H = 6.594$, $p = 0.37$, respectively). There were no significant differences between the groups in the level of MAP and β-hCG content ($H = 1.695$, $p = 0.428$; $H = 0.905$, $p = 0.636$, respectively).

Table 1

Results of Biochemical and Biophysical Parameters of Prenatal Screening in the Study Groups, MoM, *Me* (Q_1; Q_3)

Biochemical marker	Main (Ia) group, *n* = 30	Main (Ib) group, *n* = 43	Control (II) group, *n* = 118	*p*
PAPP-A	0.793 (0.548; 0.997)	0.958 (0.524; 1.346)	1.048 (0.656; 1.346)	$p_{Ia\text{-}II}$ = 0.005 $p_{Ib\text{-}II}$ = 0.062 $p_{Ia\text{-}Ib}$ = 0.583
β-hCG	1.305 (0.605; 1.476)	1.088 (0.538; 1.301)	1.124 (0.603; 1.391)	$p_{Ia\text{-}II}$ = 0.644 $p_{Ib\text{-}II}$ = 0.437 $p_{Ia\text{-}Ib}$ = 0.433
PI	1.082 (0.801; 1.234	0.886 (0.691; 1.061)	0.956 (0.818; 1.126)	$p_{Ia\text{-}II}$ = 0.06 $p_{Ib\text{-}II}$ = 0.155 $p_{Ia\text{-}Ib}$ = 0.017
MAP	1.075 (0.993; 1.099)	1.078 (0.976; 1.147)	1.042 (0.952; 1.133)	$p_{Ia\text{-}II}$ = 0.698 $p_{Ib\text{-}II}$ = 0.185 $p_{Ia\text{-}Ib}$ = 0.638

Note. PAPP-A is pregnancy associated plasma protein A; β-hCG is free β-subunit of human chorionic gonadotropin; PI is uterine artery pulsatility index; MAP is mean arterial pressure.

If statistically significant differences between groups were detected using the Kruskal–Wallis test, post-hoc comparisons were then performed using the Mann–Whitney test.

In both main groups, the median for PAPP-A was lower compared with the control group. However, statistically significant differences were obtained only between the main Ia (FGR) group and the control group (p = 0.005). Subsequent calculation of the odds ratio showed that the values of PAPP-A ≤0.793 MoM obtained during prenatal screening increased the risk of developing FGR by 3.244 times (OR = 3.244; 95% CI 1.394–7.554, p = 0.005) and increased the risk of developing a SGA fetus by 2.049 times (OR = 2.049; 95% CI 1.010–4.157, p = 0.045). The median for PI was higher in group Ia (FGR) compared with groups Ib (SGA) and the control. However, statistically significant differences were obtained only between groups Ia (FGR) and Ib (SGA) (p = 0.017). Subsequent calculation of the odds ratio showed that the values of PI MA ≥1.082 MoM obtained during prenatal screening increased the risk of developing FGR by 2.254 times (OR = 2.254; 95% CI 0.990–5.129, p = 0.017). For the remaining indicators analyzed in this work, no statistically significant differences were found using the Mann–Whitney test.

DISCUSSION

Initially, maternal serum markers were studied in the context of fetal chromosomal abnormalities screening. However, research on its role in predicting "major obstetric syndromes" is currently gaining traction [11–13]. Of the parameters making up the prenatal screening, statistically significant differences between groups were found only for PAPP-A, which is a metalloproteinase in the insulin-like growth factor (IGF) system [14, 15]. It has been shown that PAPP-A increases IGF bioavailability by adjustable splitting of IGF-binding protein 4 (IGFBP4). This process promotes activation of cell proliferation, migration, and differentiation, thereby determining normal fetal growth and development. During pregnancy, PAPP-A synthesis occurs mainly in the syncytiotrophoblast [15].

The most recognized causes of FGR development are inadequate trophoblast invasion into the uterine wall, explaining low PAPP-A levels, which, in turn reduce the IGF bioavailability, which, as noted above, is an important determinant of fetal growth [15–17]. In our study, the median PAPP-A in the FGR group was 0.793 MoM, which is significantly lower compared to the control group.

It is known that abnormal placentation is the main cause of FGR. In this regard, there is a justified interest in studying the level of β-hCG synthesized by syncytiotrophoblast in the blood, which may indicate placental dysfunction and thereby predict the development of complicated pregnancy [14, 15]. Despite a large number of studies devoted to the study of β-hCG levels in FGR, there is still no consensus on this issue. Some studies have noted a decrease in this biomarker level at 11–14 weeks in pregnancies that were subsequently complicated by FGR. For example, P. Sirikunalai et al. showed that the risk of the pathology under consideration increased

significantly at a β-hCG level <0.5 MoM [18]. On the contrary, other authors note an increased level of the biomarker in FGR [11, 19]. These results confirm the necessity of a more in-depth study of the β-hCG level in various forms of FGR. The β-hCG values in our study were slightly higher in the FGR group compared to the control, but the differences were not statistically significant.

Ultrasound diagnostics is the mainstay in assessing the fetus condition in modern obstetrics [1, 5, 6]. The use of ultrasound equipment in antenatal diagnostics, whose operation is based on the Doppler effect, allows us to study the state of the uteroplacental, fetoplacental and fetal blood flow. Since FGR is characterized by a disruption of normal trophoblastic invasion and a lack of uterine spiral arteries remodeling, leading to highly resistant uteroplacental circulation, studying blood flow in the uterine arteries at the end of the first trimester of pregnancy is one of the methods for predicting this pathology [20]. Most researchers agree that PI in the first trimester above the 95th percentile indicates a high risk of developing FGR, rather than a SGA fetus, which is characterized by the absence of increased resistance in the uterine arteries [21–23].

The results of our study showed that the PI value in the FGR group, although not exceeding the reference values, is significantly higher compared to the SGA group, which confirms the idea of the formation of a highly resistant type of blood flow. The absence of significant differences with the control group may be due to the small sample size in our work.

With the widespread implementation of combined first-trimester screening, a significant amount of data has accumulated on the MAP role in predicting the preeclampsia development, which formed the basis for studying the possibility of its use in FGR screening [12, 24]. It should be noted that to date, the role of MAP in terms of isolated FGR prediction has been poorly studied. The median MAP values obtained in our study do not allow us to identify risk groups for the FGR and SGA development in the first trimester.

CONCLUSION

Fetal gowth restriction as a significant risk factor for perinatal losses still requires a search for prognostic criteria, since intrauterine development is determined by a complex of factors. Researchers are trying to find new prognostic parameters for the early prediction of FGR, hoping that this will lead to a decrease in perinatal losses. However, at present in the Russian Federation, there is a limited number of studies focusing on the use of biochemical and biophysical parameters of prenatal screening to assess the birth of children with insufficient body weight.

Our study showed that the values of biochemical (PAPP-A and β-hCG) and biophysical (MAP and PI) parameters of prenatal screening in the main and control groups did not exceed the reference limits. No significant differences in the values of PAPP-A, β-hCG, MAP, and PI were found between the SGA and control groups. It was shown that the PAPP-A level was significantly lower in the FGR group (0.793 MoM) compared to the control group (1.048 MoM) (p = 0.005), which is consistent with the findings of extensive studies [4, 9, 16]. The median PI was higher in the FGR group (1.082 MoM) and there were statistically significant differences with the SGA group (p = 0.018). The values of β-hCG and MAP between the FGR and control groups had no significant differences.

Thus, further research is required to increase the sample size of the Russian population in order to clarify the data we obtained. It is necessary to study the role of soluble fms-like tyrosine kinase-1 (sFlt-1) and PIGF in the FGR development, the prognostic effectiveness of which has been shown in foreign literature [21, 25]. It seems relevant to continue research to clarify the role of combined prenatal screening parameters in FGR development.

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Received on January 19, 2025;
approved after peer review on February 14, 2025;
accepted on February 27, 2025