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Diagnostic significance of autoantibody combination in fetal growth restriction with early and late manifestation

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ABSTRACT

BACKGROUND: Fetal growth restriction (FGR) is one of the current problems in modern obstetrics and perinatology, which is associated with a large number of adverse perinatal outcomes.

AIM: This study aimed to assess the diagnostic significance of the combination of autoantibodies (AAB) in the early and late FGR manifestation.

MATERIALS AND METHODS: The study involved 117 pregnant women, classified into Group 1 (90 women with FGR) and Group 2 (27 women with a physiological course of pregnancy). Pregnant women with FGR were divided into two subgroups depending on the time of manifestation, i.e. FGR subgroups with early and late manifestation (45 patients each), respectively. Upon hospital admission, all patients of the study groups had blood sampling to determine autoimmune AABs using the ELI-P-test.

RESULTS: An isolated increase in AABs to human chorionic gonadotropin (hCG) antigen, TrM (AAB markers of changes in vascular and hemostasis system), S100 protein, antineutrophil cytoplasm antibodies (ANCA), and KiMS (AABs to the cytoplasmic antigen of glomerular kidney cells) were observed in the early FGR manifestation when comparing the abnormal AAB spectrum in the early and late FGR manifestation, while a statistically significant isolated increase in the level of AABs to DNA and insulin was found in the late FGR manifestation.

CONCLUSIONS: The study revealed the diagnostic significance of AAB combinations, as well as the combinations of increased AAB levels to hCG, S100, ANCA, and KiMS and an increase in AABs to DNA, collagen, and S100 protein in the early and late FGR manifestation, respectively.

Keywords: fetal growth restriction with early manifestation; fetal growth restriction with late manifestation; autoimmune autoantibodies; ELI-P-test.

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Диагностическая значимость комбинации аутоантител при задержке роста плода с ранней и поздней манифестацией

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АННОТАЦИЯ

Введение. Задержка роста плода (ЗРП) — одна из актуальных проблем в современном акушерстве и перинатологии, связанная с большим числом неблагоприятных перинатальных исходов.

Цель исследования — оценить диагностическую значимость комбинации аутоантител в возникновении задержки роста плода с ранней и поздней манифестацией.

Материалы и методы. В исследование включили 117 беременных: в 1-ю группу вошли 90 женщин с ЗРП, во 2-ю группу — 27 женщин с физиологическим течением беременности (контроль). Беременных с ЗРП в зависимости от срока манифестации разделили на две подгруппы: ЗРП с ранней манифестацией — 45 пациенток, ЗРП с поздней манифестацией — 45 пациенток. При поступлении в стационар у всех пациенток исследуемых групп производили забор крови с целью определения аутоиммунных аутоантител при помощи панели ЭЛИ-П-Тест.

Результаты. При сравнении аномального спектра аутоантител (АТ) при ЗРП с ранней и поздней манифестацией следует отметить, что концентрации АТ к антигену ХГЧ (хорионический гонадотропин человека), АТ к TrM (АТ-маркеры изменений в сосудах и системе гемостаза), АТ к белку S100, АТ к ANCA (антитела к цитоплазме нейтрофилов), АТ к KiMS (АТ к цитоплазматическому антигену клеток клубочков почек) изолированно повышались при ранней манифестации ЗРП. При поздней манифестации ЗРП установлено статистически значимое изолированное повышение уровня АТ к DNA (ДНК) и АТ к инсулину.

Заключение. В результате исследования выявлена диагностическая значимость аутоантител в их комбинации: при ранней манифестации задержки роста плода — комбинация повышения уровня АТ к ХГЧ, плюс АТ к белку S100, плюс АТ к ANCA, плюс АТ к KiMS. При поздней манифестации ЗРП показала диагностическую значимость комбинация повышенных значений АТ к DNA, плюс АТ к коллагену, плюс АТ к белку S100.

Ключевые слова: задержка роста плода с ранней манифестацией; задержка роста плода с поздней манифестацией; аутоиммунные аутоантитела; ЭЛИ-П-Тест.

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BACKGROUND

Fetal growth restriction (FGR) is a common placenta-associated complication of pregnancy that increases the risk of preterm delivery and premature birth, antepartum and intrapartum death of the fetus and newborn, and other adverse outcomes [1]. FGR is characterized by impaired fetoplacental blood flow, fetal weight 5th percentile, frequent oligohydramnios, and signs of hypoxia according to cardiotocography (CTG).

Pregnancy complications caused by placental dysfunction negatively affect the growth and functional status of the fetus and further development of the individual throughout postnatal life, which enabled us to describe "adverse fetal programming". Thus, prediction and early diagnostics of FGR, which involves the optimization of the obstetric approach, are significant in improving long-term pediatric and therapeutic outcomes.

A population-based study (*n*=480,448) conducted in France in 2017 has demonstrated that the costs of antenatal and postnatal healthcare for mothers and newborns with FGR were much higher than those for children corresponding to a gestational age. It is estimated that maternal and neonatal hospital care costs associated with FGR account for 23% of total maternal healthcare costs in France [2].

The etiology of FGR remains unclear. However, FGR is believed to be caused by an interaction between environmental and genetic factors of embryonal, placental, or maternal origin [3]. Understanding the etiopathogenesis of FGR is crucial for timely diagnosis and optimization of the obstetric approach. FGR usually occurs because of disturbances in the formation and development of the placental complex. Impairment of wave 2 of trophoblast invasion and vascular remodeling leads to the development of ischemic placental disease, which underlies obstetric syndromes such as preeclampsia (PE), placental abruption, and FGR [4]. The more pronounced the disturbance in the remodeling of spiral arteries, damage to the chorionic villi, and decrease in oxygen supply to the intervillous space, the earlier the FGR manifests, reaching a critical condition of the fetus, and the higher the risk of developing adverse perinatal outcomes and long-term consequences.

There are two phenotypes of fetal growth restriction: FGR with early manifestation until week 32 of pregnancy and FGR with late manifestation after week 32 of pregnancy. In clinical practice, to distinguish between early and late phenotypes of FGR, the criteria proposed by the international Delphi consensus are used [6].

Currently, despite a wide variety of studies on the search for informative diagnostic and prognostic markers, FGR is considered a complex obstetric and perinatal problem.

Natural autoantibodies (AAB) are an integral part of the immune system of healthy people. Scientists continue to study the frequency of deviations in the level of AAB in the blood serum of pregnant women to predict various somatic diseases, reproductive disorders, and pregnancy complications [6].

This study aimed to evaluate the diagnostic significance of isolated and combined changes in the level of autoantibodies in the prognosis and diagnostics of FGR with early and late manifestation.

MATERIALS AND METHODS

The main study group consisted of pregnant women with FGR (*n* = 90) hospitalized at the Maternity Hospital of the S.S. Yudin City Clinical Hospital, and the control group included women with a normal pregnancy (*n*=27) registered in the Consultative and Diagnostic Department of the same hospital. The study was conducted from September 2020 to September 2021. This study was approved by the Local Ethics Committee of the I.M. Sechenov First Moscow State Medical University (dated February 19, 2020; extracted from protocol No. 03-20). All pregnant women provided informed voluntary consent to participate in the study. The study groups included patients aged >18 years with a gestation period of ≥28 weeks. The study did not include patients aged <18 years or those with multifetal pregnancies. The exclusion criteria in all groups were diabetes mellitus (gestational, types I and II), intake of immunosuppressants, antiphospholipid syndrome, and acute infectious process.

The diagnosis of FGR was made based on clinical recommendations [5], and then in the hospital, venous blood was collected from pregnant women in the study group to determine the serum AAB level. Pregnant women from the control group underwent a standard blood sampling procedure for a clinical study at weeks 28–38.

Autoimmune antibodies were determined using an enzyme-linked immunosorbent assay using the ELI-P-Test panel, which includes 12 immunoreagents to autoantibodies: AAB markers of anti-hCG syndrome (AAB to hCG, human chorionic gonadotropin); AAB markers of infectious-inflammatory, scar-adhesive, and autoimmune processes (AAB to DNA, AAB to β_2-GP, AT to collagen, AAB to Fc-IgC); AAB markers of changes in the Langerhans islets (AAB to insulin); AAB markers of changes in thyroid tissue (AAB to thyroglobulin); AAB markers of changes in the central and/or peripheral nervous system (AAB to S100); AAB markers of changes in the pelvic organs (AAB to Spr); AAB markers of changes in the vessels and hemostatic system (AAB-TrM, AAB-ANCA); and AAB markers of changes in kidney tissue (AAB-KiMS).

Statistical methods

Statistical analysis was performed using the StatTech v. 2.8.5 program (developer Stattekh, Russia). Quantitative indicators were assessed for compliance with normal distribution using the Shapiro–Wilk test (for <50 participants) or the Kolmogorov–Smirnov test (for >50 participants). Quantitative indicators with a normal distribution were described using arithmetic means (M) and standard deviations (SD) and

limits of the 95% confidence interval (95% CI). In the absence of a normal distribution, quantitative data were described using the median (*Me*) and lower and upper quartiles (Q1–Q3). Categorical data were described using absolute values and percentages. Comparison of three or more groups according to a quantitative indicator, whose distribution differed from normal, was performed using the Kruskal–Wallis test, and post hoc comparisons were performed using Dunn's test with Holm's correction.

Comparison of percentages in the analysis of four-field contingency tables was performed using Pearson's chi-square test (for values of the expected phenomenon >10) and Fisher's exact test (for values of the expected phenomenon <10).

A prognostic model of the probability of a certain outcome was constructed using the logistic regression method. Nigelkirk's R^2 coefficient served as a measure of certainty, indicating that part of the variance can be explained using logistic regression. To assess the diagnostic significance of quantitative characteristics in predicting a certain outcome, the ROC curve analysis method was used. The separating value of a quantitative characteristic at the cut-off point was determined by the highest value of the Youden index.

Differences in indicators were considered statistically significant at p <0.05.

RESULTS

The examined pregnant women of the main group, depending on the period of FGR manifestation, were divided into two subgroups in accordance with the Delphi consensus criteria [6], where subgroup 1 (1A) included 45 patients with early FGR manifestation, and subgroup 2 (1B) included 45 patients with late FGR manifestation. The age of pregnant women in subgroup 1A was 34 (29; 37) years and in subgroup 1B was 33 (25; 35) years. The age of pregnant women in group 2 (control group) ranged from 22 to 28 years and averaged 23 years. When assessing age, statistically significant differences were revealed depending on the groups (p <0.001).

Furthermore, 26 (59.1%) primigravidas among 45 patients (subgroup 1A) had early manifestation of FGR; 22 (48.9%) primigravidas among 45 patients of subgroup 1B had late manifestation of FGR; and 8 (29.6%) primigravidas among 27patients of group 2 (control) had normal pregnancy. No statistical differences by parity was noted (p=0.054).

Current pregnancy occurred spontaneously in all patients with early manifestation of FGR and in 42/45 (93.3%) patients with late manifestation of FGR, and in 3/45 (6.7%) patients of this subgroup, pregnancy occurred because of in vitro fertilization (IVF). In all patients with normal gestation, pregnancy occurred spontaneously.

According to prenatal screening 1, a high risk of FGR was identified in 27/45 (61.4%) pregnant women with early manifestation of FGR and in 14/45 (31.1%) pregnant women with late manifestation of FGR (p=0.004). In 21 of 45 (47.7%) pregnant women with early manifestation of FGR and in 14/45 (31.1%) pregnant women with late manifestation of FGR, a high risk of preeclampsia (PE) was registered according to prenatal screening 1. However, according to prenatal screening 1, patients in the main group with a high risk of FGR and PE did not take acetylsalicylic acid for prophylactic purposes. Five of 27 (26.3%) pregnant women from the control group had a high risk of FGR and PE according to trimester 1 screening conducted using the Astraia program. All patients with a high risk of FGR and PE from the control group took acetylsalicylic acid (150 mg orally) [5, 7].

The complications of current pregnancy and somatic diseases in the examined patients are presented in Table 1. Table 1 shows statistically significant differences in the characteristics of the course of pregnancy between the groups.

Moderate preeclampsia and chronic arterial hypertension were significantly more common in the subgroup with early manifestation of FGR than in the subgroup with late manifestation and in the control group; the study results [8] confirm this conclusion.

Acute respiratory viral infection (ARVI) during pregnancy occurred in subgroups 1A and 1B with the same incidence, but statistically significantly more often in the main group than in the control group (p=0.004).

The threat of miscarriage with the formation of retrochorial hematoma in trimester I in patients in the subgroup with early manifestations of FGR was significantly more frequent (8/45; 17.8%). A study conducted in 2016 [9] revealed a correlation between an increased concentration of autoantibodies to hCG and the formation of retrochorial hematomas in trimester I of pregnancy.

Anemia in pregnant women was diagnosed statistically significantly more often in the main group; when comparing the incidence in the subgroup with early and late manifestations of FGR, no statistically significant differences were revealed. Pregnant women with anemia have a high risk of obstetric complications, such as preterm delivery, FGR, and maternal postpartum infections, which indicates the need to pay attention to the diagnosis and treatment of anemia for its prevention [10]. Statistically significant differences were revealed when assessing myopia of varying degrees and varicose veins of the lower extremities; their incidence in the main group was significantly higher than that in the group with normal pregnancy, which may indicate connective tissue dysplasia.

Based on the abnormal levels of autoimmune antibodies in the blood serum in pregnant women of the main and control groups, statistically significant differences were obtained, namely, AABs to the hCG antigen (p <0.001), AABs to DNA (p <0.001), AABs to β_2-GP (p=0.035), AABs to collagen (p <0.001), AABs to Fc-IgG (p=0.001), AABs to insulin (p <0.001), AABs to S100 (p <0.001), AABs to Spr (p <0.001), AABs to TrM (p <0.001), AABs to ANCA (p <0.001), and AABs to KiMS (p <0.001) (Fig. 1).

Table 1. Features of the course of the present pregnancy and somatic diseases in the examined patients, abs. (%)

Indicator	Subgroup 1A (FGR with early manifestation, *n*=45)	Subgroup 1B (FGR with late manifestation, *n*=45)	Group 2, control (*n* = 27)	*p*
Somatic anamnesis				
Chronic arterial hypertension	18 (40,0%)	8 (17,8%)	1 (3,7%)	$p_{1A-1B-2}$=0,001* p_{1A-1B} =0,04* p_{1A-2} =0,02*
Mitral valve prolapse stage I	4 (8,9%)	4 (8,9%)	1 (3,7%)	$p_{1A-1B-2}$=0,395
Chronic pyelonephritis	9 (20,0%)	5 (11,1%)	–	$p_{1A-1B-2}$ =0,040* p_{1A-2}=0,039*
Myopia of varying degrees	31 (70,5%)	33 (73,3%)	4 (14,8%)	$p_{1A-1B-2}$ <0,001* p_{1A-2} <0,001* p_{1B-2} <0,001*
Varicose veins of the lower extremities	9 (20%)	13 (28,9%)	1 (3,7%)	$p_{1A-1B-2}$ =0,034* p_{1B-2} =0,027*
Complications of pregnancy				
Moderate preeclampsia	23 (51,1)	14 (31,1)	2 (7,4)	$p_{1A-1B-2}$ <0,001* p_{1A-2} <0,001* p_{1B-2} =0,038*
ARVI with fever	18 (40,9)	19 (42,2)	2 (7,4)	$p_{1A-1B-2}$ =0,004* p_{1A-2} =0,005* p_{1B-2}=0,005*
Chronic cystitis and exacerbation	9 (20,5%)	6 (13,3%)	2 (7,4%)	$p_{1A-1B-2}$ =0,304
Anemia during pregnancy	24 (54,5)	27 (60,0)	3 (15,8)	$p_{1A-1B-2}$ =0,004* p_{1A-2}=0,009* p_{1B-2} =0,004*
Threatened miscarriage with the formation of a retrochorial hematoma in trimester I	8 (17,8%)	1 (2,2%)	–	$p_{1A-1B-2}$ =0,005* p_{1A-1B} =0,042* p_{1A-2} =0,042*
Preterm placental abruption	–	2 (4,4%)	–	$p_{1A-1B-2}$ =0,196

* The differences are statistically significant (p <0.05); $p_{1A-1B-2}$ — comparison of three groups: 1A, 1B and the 2nd group (control); p_{1A-1B} — comparison of subgroups 1A and 1B; p_{1A-2} — comparison of subgroup 1A and control group 2; p_{1B-2} — comparison of subgroup 1B and control group 2.

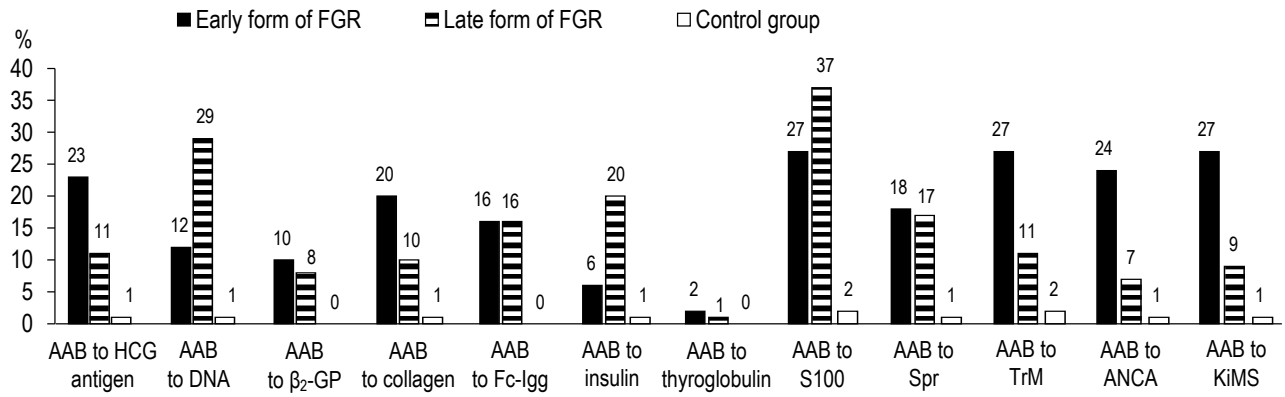

Fig. 1. The frequency of detection of deviations in the level of autoantibodies depending on the groups of subjects and forms of fetal growth retardation, %.

However, when comparing the incidence of abnormalities in the level of autoantibodies in early and late manifestation of FGR, an isolated increase in AABs to the hCG antigen, AABs to TrM, AABs to ANCA, and AABs to KiMS was noted with early manifestation of FGR.

With the late manifestation of FGR, the isolated increase in the level of antibodies to DNA and insulin is statistically significantly higher. Abnormal levels of AABs in the S100 protein occur with the same frequency in both early and late manifestations of FGR.

We conducted binary logistic regression to study the probability of developing FGR with early and late manifestation depending on the level of autoimmune AABs determined by the ELI-P test.

We developed a prognostic model to determine the probability of early FGR manifestation depending on the level of AABs to hCG, S100 protein, ANCA, and KiMS using binary logistic regression.

The dependence observed is described by the following equation:

$$P = 1/(1+e^{-z}) \times 100\%$$

$$z = 0.605 - 0.092X_{\text{AABs to hCG antigen}} + 0.147X_{\text{AABs to S100}} + 0.113X_{\text{AABs to ANCA}} + 0.192X_{\text{AABs to KiMS}},$$

where P is the probability of FGR with early manifestation, e is the base of natural logarithms and has a value of 2.71828182845904, and z is the standard regression equation.

The resulting regression model is statistically significant (p <0.001). Based on the value of the Nigelkirk coefficient of determination, the model explains 59.4% of the observed group variance (Table 2).

The area under the ROC curve was 0.924±0.044 (95% CI, 0.838–1.000). The resulting model was statistically significant (p <0.001).

The threshold value of the logistic function P at the cut-off point, which corresponded to the highest value of the Youden index, was 0.405. FGR with early manifestation was predicted when the value of the logistic function P was higher than or equal to this value. The sensitivity and specificity of the model were 94.7 and 87.8%, respectively (Fig. 2).

A prognostic model was developed to determine the probability of developing FGR with late manifestation depending on autoantibodies to DNA, collagen, and S100 protein using binary logistic regression.

The noted dependence is described by the following equation:

$$P = 1/(1+e^{-z}) \times 100\%$$

$$z = 0.290 + 0.077X_{\text{AAB to DNA}} + 0.102X_{\text{AAB to collagen}} + 0.072X_{\text{AAB to S100}},$$

where P is the probability of FGR with late manifestation, e is the base of natural logarithms and has a value of 2.71828182845904, and z is the standard regression equation.

The resulting regression model is statistically significant (p <0.001). Based on the value of the Nigelkirk coefficient of determination, the model explains 42.6% of the observed group variance (Table 3).

The area under the ROC curve was 0.866±0.057 (95% CI, 0.754–0.978). The resulting model was statistically significant (p <0.001).

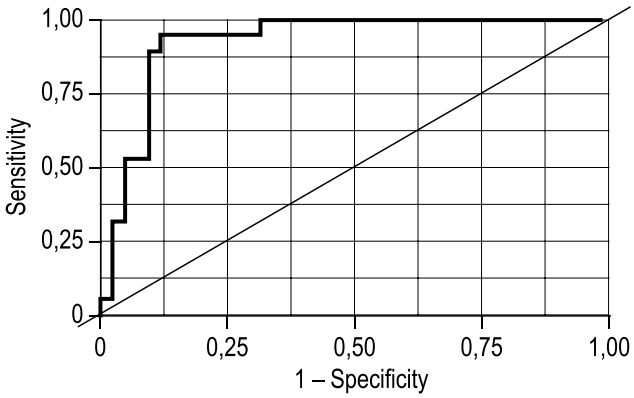

Fig. 2. ROC curve characterizing the dependence of the probability of fetal growth retardation with early manifestation on a combination of autoantibodies.

Table 2. Characteristics of the association between autoantibodies and the probability of detecting fetal growth retardation with early manifestation

Autoantibodies	COR (95% CI)	*p*	AOR (95% CI)	*p*
AAB to HCG antigen	0,957 (0,913–1,002)	0,060	0,912 (0,837–0,995)	0,037*
AAB to S100 protein	1,049 (0,994–1,107)	0,082	1,158 (1,035–1,296)	0,011*
AAB to ANCA	1,078 (1,016–1,145)	0,012*	1,119 (1,010–1,240)	0,032*
AAB to KiMS	1,107 (1,038–1,182)	0,002*	1,212 (1,075–1,366)	0,002*

*Differences between subgroup 1A with delayed fetal development with early manifestation and the control group are statistically significant (p <0.05); COR (crude odds ratio) unadjusted odds ratio; AOR (adjusted odds ratio) — adjusted odds ratio; AT to ANCA — cytoplasmic antigen of vascular endothelial cells; AT to KiMS — membrane antigen of kidney glomerular cells.

Table 3. Characteristics of the association of autoantibodies with the probability of detecting delayed fetal development with late manifestation

Autoantibodies	COR (95% CI)	*p*	AOR (95% CI)	*p*
AAB to DNA	1,079 (1,022–1,138)	0,006*	1,080 (1,013–1,153)	0,019*
AAB to collagen	1,114 (1,022–1,214)	0,013*	1,108 (1,003–1,224)	0,044*
AAB to S100	0,911 (0,856–0,970)	0,004*	0,931 (0,868–0,998)	0,045*

*Statistically significant differences between subgroup 1B and the control group (p <0.05); COR (crude odds ratio) — unadjusted odds ratio; AOR (adjusted odds ratio) — adjusted odds ratio; AT to DNA — autoantibodies to DNA.

The threshold value of the logistic function *P* at the cut-off point, which corresponded to the highest value of the Youden index, was 0.338. The late FGR was predicted when the logistic function *P* value was higher than or equal to this value. The model sensitivity and specificity were 100.0% and 81.6%, respectively (Fig. 3).

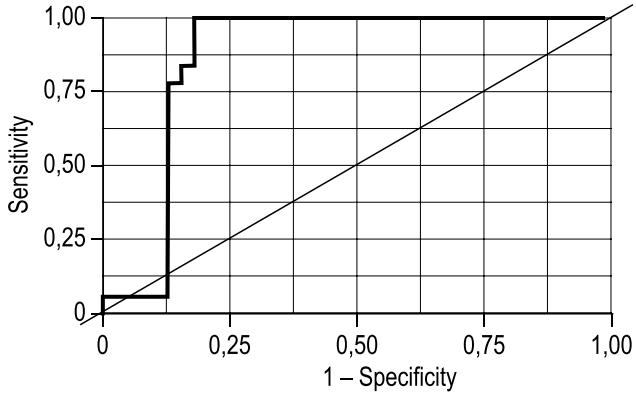

Fig. 3. ROC curve characterizing the dependence of the probability of fetal growth retardation with late manifestation on a combination of autoantibodies.

CONCLUSION

Thus, when studying the probability of identifying FGR with early and late manifestation based on the determination of autoimmune autoantibodies using an enzyme-linked immunosorbent assay using the ELI-P-Test panel, diagnostically significant combinations were identified. For early manifestation of FGR, the combination was AABs to hCG + AABs to S100 + AABs to ANCA + AABs to KiMS. For late manifestation of FGR, the combination AABs to DNA + AABs to collagen + AABs to protein S100 showed diagnostic significance.

The results obtained have practical significance; the implementation of these results in practical activities will allow for preventive measures, which will help reduce the incidence of adverse perinatal outcomes.

ADDITIONAL INFO

Authors' contribution. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work. The concept of the study — I.V. Ignatko, D.I. Yakubova; data collection and processing of the material — D.I. Yakubova, A.D. Megrabyan, T.M. Silaeva, I.M. Bogomazova; statistical processing of the material — D.I. Yakubova; writing text — D.I. Yakubova, I.V. Ignatko; editing — D.I. Yakubova, I.M. Bogomazova.

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Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией. Концепция исследования — И.В. Игнатко, Д.И. Якубова; сбор и обработка материала — Д.И. Якубова, А.Д. Меграбян, Т.М. Силаева, И.М. Богомазова; статистическая обработка материала — Д.И. Якубова; написание текста — Д.И. Якубова, И.В. Игнатко; редактирование — Д.И. Якубова, И.М. Богомазова.

Финансирование. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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

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