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DIAGNOSTIC VALUE OF ANGIOGENIC GROWTH FACTORS IN FETAL GROWTH RESTRICTION SYNDROME

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ABSTRACT

Objective: To assess the diagnostic value of angiogenic growth factors in fetal growth restriction (FGR) syndrome during pregnancy.

Materials and Methods: A total of 70 pregnant women hospitalized at the Republican Perinatal Center in 2024–2025 were examined. Of these, 20 patients were diagnosed with early-onset FGR at 22–31^6 weeks of gestation, and 30 with late-onset FGR at 32–38 weeks. The control group consisted of 20 conditionally healthy pregnant women at ≥22 weeks of gestation. Serum levels of PLGF, VEGF-A, and IGF-1 were measured using enzyme-linked immunosorbent assay (ELISA).

Results: In early-onset FGR, PLGF levels were reduced by 33.9% compared to the control group ($p<0.01$), and by 19.8% in late-onset FGR ($p<0.05$). VEGF-A expression decreased 2.5-fold in early-onset FGR ($p<0.01$) and 1.8-fold in late-onset FGR ($p<0.05$). A similar trend was observed for IGF-1: in early-onset FGR, its level was 41.0 pg/mL, which was 44.4% lower than in the control group ($p<0.001$) and 29.7% lower than in late-onset FGR ($p<0.001$).

Conclusion: Decreased levels of VEGF-A (<60 pg/L), IGF-1 (<50 pg/mL), and their ratio (≤1.1) at 22–27 weeks of gestation may serve as prognostic markers for the development of FGR.

Keywords: *pregnancy, fetal growth restriction, angiogenic growth factors.*

ДИАГНОСТИЧЕСКАЯ ЦЕННОСТЬ АНГИОГЕННЫХ ФАКТОРОВ РОСТА ПРИ СИНДРОМЕ ЗАДЕРЖКИ РОСТА ПЛОДА

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АННОТАЦИЯ

Цель: оценить диагностическую ценность ангиогенных факторов роста при синдроме задержки роста плода (СЗРП) у беременных.

Материал и методы: проведено обследование 70 беременных женщин, госпитализированных в Республиканский перинатальный центр в 2024–2025 гг. Из них 20 пациенток имели раннюю форму СЗРП на сроках гестации 22–31^6 недель, 30 — позднюю манифестацию СЗРП на сроках 32–38 недель. Контрольную группу составили 20 условно здоровых беременных женщин на сроке гестации от 22 недель. Уровни PLGF, VEGF-A и IGF-1 в сыворотке крови определяли методом иммуноферментного анализа (ИФА).

Результаты: при раннем СЗРП уровень PLGF был снижен на 33,9% по сравнению с контрольной группой ($p<0,01$), при позднем — на 19,8% ($p<0,05$). Экспрессия VEGF-A при раннем СЗРП снижалась в 2,5 раза ($p<0,01$), при позднем — в 1,8 раза ($p<0,05$). Аналогичная тенденция выявлена для IGF-1: при раннем СЗРП его уровень составлял 41,0 пг/мл, что на 44,4% ниже, чем в контрольной группе ($p<0,001$), и на 29,7% ниже, чем при позднем СЗРП ($p<0,001$).

Выводы: снижение уровня VEGF-A (<60 пг/л), IGF-1 (<50 пг/мл) и их соотношения (≤1,1) на сроках гестации 22–27 недель может быть рекомендовано для прогнозирования развития СЗРП.

Ключевые слова: *беременность, синдром задержки роста плода, ангиогенные факторы роста.*

HOMILA O'SISHINI ORQADA QOLISHI **SINDROMIDA ANGIOGEN O'SISH OMILLARINING DIAGNOSTIK QIMMATI**

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ANNOTATSIYA

Maqsad: homiladorlikda homila o‘sishining orqada qolishi sindromida (HO‘OQS) angiogen o‘sish omillarining diagnostik ahamiyatini baholash.

Materiallar va usullar: 2024–2025 yillarda Respublika Perinatal markaziga yotqizilgan jami 70 nafar homilador ayol tekshiruvdan o‘tkazildi. Ulardan 20 nafari homiladorlikning 22–31[6] haftalarida erta boshlanuvchi FGR bilan, 30 nafari esa 32–38 haftalarda kech boshlanuvchi HO‘OQS bilan tashxis qo‘yilgan. Nazorat guruhiga homiladorlik muddati 22 haftadan ortiq bo‘lgan 20 nafar shartli sog‘lom homilador ayollar kiritildi. Qon zardobida PLGF, VEGF-A va IGF-1 darajalari fermentativ immunotahlil (ELISA) usuli bilan o‘lchandi.

Natijalar: erta HO‘OQSda PLGF darajasi nazorat guruhiga nisbatan 33,9% ga kamaygan (p<0,01), kech HO‘OQSda esa 19,8% ga kamaygan (p<0,05). VEGF-A ekspressiyasi erta HO‘OQSda 2,5 barobar (p<0,01), kech HO‘OQSda esa 1,8 barobar kamaygan (p<0,05). IGF-1 uchun ham xuddi shunday tendensiya kuzatildi: erta HO‘OQSda darajasi 41,0 pg/ml bo‘lib, bu nazorat guruhiga nisbatan 44,4% (p<0,001) va kech HO‘OQSga nisbatan 29,7% (p<0,001) past edi.

Xulosa: VEGF-A (<60 pg/L), IGF-1 (<50 pg/ml) darajalari va ularning nisbati (≤1,1) 22–27 haftalik homiladorlikda HO‘OQS rivojlanishini oldindan bashorat qilishda muhim belgi bo‘lishi mumkin.

Kalit so‘zlar: *homiladorlik, homila o‘sishining orqada qolishi sindromi, angiogen o‘sish omillari.*

Fetal Growth Restriction Syndrome (FGRS), or intrauterine growth restriction (IUGR), remains a significant issue in modern obstetrics and perinatology [7]. This pathology is interdisciplinary and attracts the attention of obstetricians, gynecologists, perinatologists, neonatologists, neurologists, and endocrinologists. In clinical obstetrics, FGRS remains an important medical and social problem due to its high prevalence and the wide range of consequences in the postnatal period.

According to literature, among full-term newborns, children with FGRS make up to 15.4%, while in preterm infants, the incidence reaches 39%. The highest number of cases of IUGR is recorded in Asian countries—about 75% of all newborns. In Africa and Latin America, this figure is 20% and 5%, respectively [6]. In the Russian Federation, the frequency of IUGR remains high: from 3% to 24% among full-term newborns and from 18% to 40% among preterm newborns [3,16].

IUGR increases the risk of stillbirth by four times. The neonatal mortality rate for IUGR is 8% [15], in the antenatal period it reaches 12%, and in 40% of cases, fetal growth restriction recurs in subsequent pregnancies [14]. Currently, IUGR is considered one of the so-called “great obstetric syndromes” [11].

Many researchers note that the issues of etiology, pathogenesis, prediction, diagnosis, treatment, and prevention of this pregnancy complication remain insufficiently studied [5,8]. According to our data [1], the manifestation of IUGR most often occurs at early gestational periods—before 32 weeks (57.1%). The main factors for the early development of the pathology include age 20–24 years, previous abortions, chronic arterial hypertension, and inflammatory diseases of the urinary tract. On the other hand, factors for late IUGR more often include age 35 years and older, third and subsequent pregnancies, a history of pregnancy loss, and severe preeclampsia.

According to the literature, there is a need to continue searching for the most informative criteria for diagnosing and predicting IUGR [4,13].

It is known that IUGR is a pathology caused by placentation disorders. Among the many causes, the most significant role is played by disturbances in angiogenesis and the transformation of the vessels of the uteroplacental complex, regulated by growth factors. In the available literature, there are no studies on angiogenic growth factors in pregnant women with IUGR, taking into account the gestational period, in the Uzbek population.

Research goal: To determine the diagnostic significance of angiogenic growth factors in pregnant women for detecting fetal growth restriction.

MATERIALS AND METHODS. A prospective study was conducted on 70 pregnant women hospitalized at the Republican Perinatal Center in 2024–2025. The participants included 20 patients with early-onset Fetal Growth Restriction Syndrome (FGRS) (gestational age 22–31 weeks), 30 with late-onset FGRS (32–38 weeks), and a control group consisting of 20 women with a physiologically progressing pregnancy at 22 weeks of gestation or more.

The levels of Placental Growth Factor (PlGF), Vascular Endothelial Growth Factor (VEGF-A), and Insulin-like Growth Factor (IGF-1) in the blood serum were determined by enzyme-linked immunosorbent assay (ELISA) using test systems from AO "Vector-Best" (Russia) at the Institute of Immunology and Human Genomics of the Academy of Sciences of Uzbekistan (Director — Academician T.U. Aripova), in the Laboratory of Reproductive Immunology (Head — D.Sc. D.A. Musakhodzhayeva).

All participants underwent standard clinical, obstetric, and laboratory examinations. The localization of the placenta, fetal biometric parameters, and signs of FGRS, as well as the parameters of the uteroplacental-fetal blood flow (UPFB), were assessed using color Doppler mapping on a VOLUSON P8 ultrasound machine.

The obtained data were analyzed using methods of variance statistics: mean values (M±m) were calculated, and the Student's t-test was applied. Statistical significance was accepted at $p<0.05$.

RESULTS AND DISCUSSION

The majority of the pregnant participants were aged 20 to 30 years: 72.0% (n=36) in the control group and 62.9% (n=44) in the main group. The groups were comparable in terms of age, social status, parity, and obstetric-gynecological history, ensuring the correctness of the comparative analysis.

The main causes of FGRS were chronic arterial hypertension (58.6%), iron-deficiency anemia (52.9±6.0%), early severe preeclampsia (85.7%), and early-stage severe placental insufficiency (90.0%) [1]. According to ultrasound data, most of the patients were diagnosed with stage II FGRS.

The summary results of the immunological studies are presented in Table 1.

Table 1

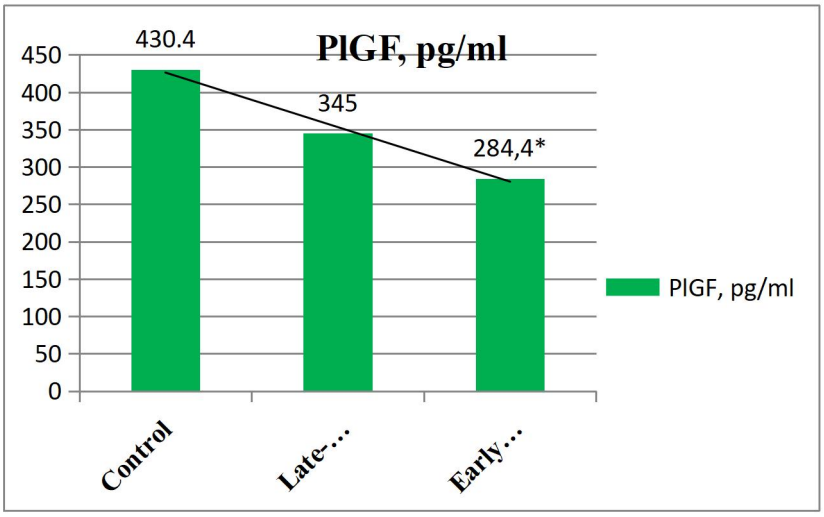
Levels of angiogenic growth factors in FGRS depending on gestational age

Growth Factor, pg/ml	**Control (n=20)**	**Early FGRS (n=20)**	**Late FGRS (n=30)**
PlGF	430.36 ± 24.03	284.41 ± 44.47*	344.95 ± 34.89
VEGF-A	117.74 ± 17.86	46.48 ± 1.35*^	63.99 ± 2.10*
IGF-1	73.79 ± 5.19	40.99 ± 3.59*^	58.28 ± 3.58*

Note: *-$p<0.05$ compared to the control group;

^- $p < 0.05$ compared to the late FGRS group

In the comparative analysis, the level of placental growth factor (PlGF) in the blood of pregnant women with FGRS differed depending on gestational age. As shown in Figure 1, patients with early-onset FGRS had a significantly lower PlGF level compared to the control group ($p < 0.05$).

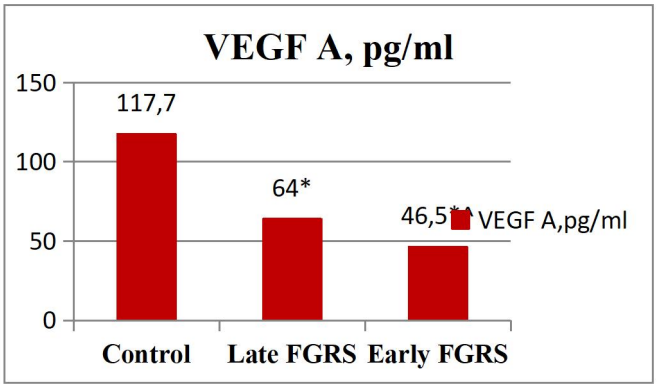


(* — p < 0.05 compared to the control) **Figure 1. PlGF level in pregnant women depending on the gestational age of FGRS development**

The analysis of the obtained data showed that in pregnant women with FGRS, the PlGF level in serum was significantly lower. Furthermore, the lower the PlGF level, the earlier the pathology developed. Specifically, in early FGRS, PlGF was decreased by 33.9% ($p < 0.01$), and in late-onset FGRS, by 19.8% compared to the control group ($p < 0.05$) (Figure 1).

According to the literature, PlGF contributes to the proliferation of extravillous trophoblasts, may enhance VEGF-induced angiogenesis, and increase vascular permeability. Research by V. Giorgione et al. (2024) [12] indicated that PlGF levels are reduced in pregnancies with placental growth restriction. Our findings confirm that insufficient expression of PlGF is associated with the development of FGRS: a reduction of 20% indicates the formation of a subcompensated form, while a reduction of 30% or more indicates a decompensated form of placental insufficiency.

From the presented data (Table 1 and Figure 2), it can be seen that in early FGRS, VEGF-A levels were significantly decreased by 2.5 times compared to the control ($p < 0.01$), and in late FGRS, by 1.8 times ($p < 0.05$).



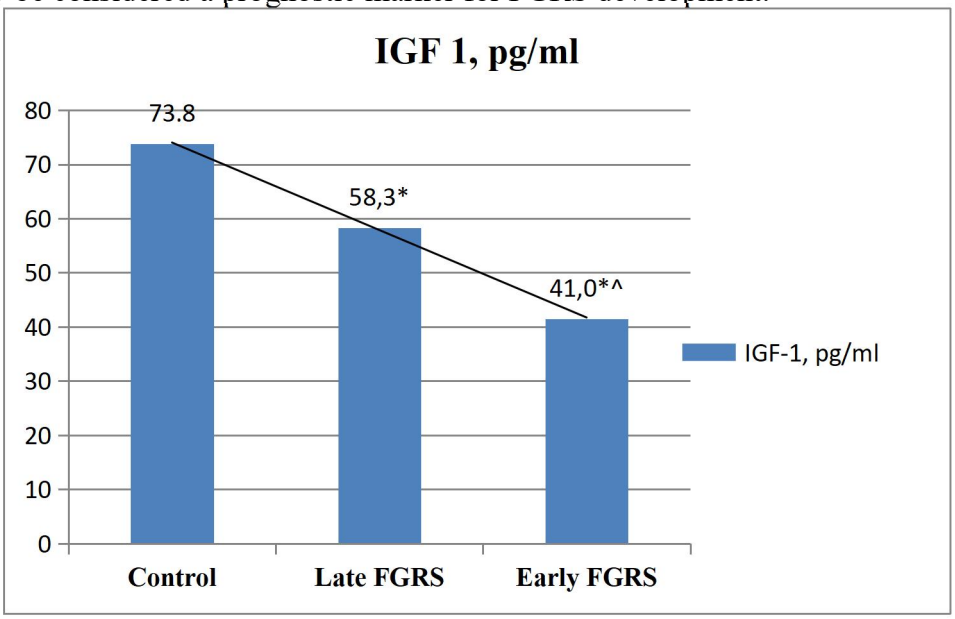
(* — p < 0.05 compared to the control; ^ — p < 0.05 compared to late FGRS)

Figure 2.VEGF-A level in the blood of pregnant women depending on gestational age in FGRS

VEGF-A is known to be a potential mitogen for endothelial cells of blood vessels. It has a significant impact on vascular wall permeability, is a potent angiogenic protein, and participates in neovascularization processes. Given VEGF-A's ability to modulate angiogenesis and vascular permeability, it can be assumed that

the reduction of VEGF-A levels is involved in the pathogenesis of disturbances in uteroplacental-fetal blood flow, which, in turn, contributes to the formation of intrauterine fetal growth restriction.

According to N.R. Akhmadeyev (2019) [2], when studying the VEGF level in the blood serum of pregnant women with small gestational age (SGA), it was determined that a VEGF value below 95.5 pg/ml can be used for the differential diagnosis between SGA and FGRS when identifying a low-birth-weight fetus by ultrasound. Our findings suggest that VEGF may serve as an early marker of fetal hypoxia: levels below 60 pg/ml between 22 and 27 weeks of gestation indicate a high risk of developing decompensated placental insufficiency and may be considered a prognostic marker for FGRS development.



(* — p < 0.05 compared to the control; ^ — p < 0.05 compared to late FGRS)

Figure 3.Concentration of Insulin-like Growth Factor (IGF-1) in the serum of pregnant women depending on the gestational development of FGRS

The IGF-1 level was significantly lower than in the control group. A direct proportional decrease in IGF-1 levels was observed with the decreasing gestational age of FGRS development. The lowest level of IGF-1 was found at 22–31 weeks (41.0 pg/ml), which was 44.4% lower than the corresponding level in the control group ($p < 0.001$) and 29.7% lower than at later stages of the pathology ($p < 0.001$). The IGF-1 level in pregnant women with FGRS at gestational ages over 32 weeks was also significantly reduced by 21.0% compared to the control group ($p < 0.001$).

IGF-1 positively regulates glucose supply to the fetus. It has mitogenic properties, stimulating the growth and proliferation of somatic cells, and influences glucose and amino acid transport across the placenta. The decrease in IGF-1 expression leads to a slowdown in fetal growth [10] and is a prognostic indicator of severe FGRS [9]. Our results suggest that IGF-1 deficiency (less than 50 pg/ml) between 22 and 27 weeks can serve as a marker for FGRS development in pregnant women.

CONCLUSIONS

Thus, we have established a significant decrease in the levels of angiogenic growth factors in pregnant women with fetal growth restriction syndrome, with the most pronounced changes occurring in early-onset FGRS. Disruption of PlGF, VEGF-A, and IGF-1 production contributes to pathological changes in the placenta, including placental insufficiency, leading to the formation of fetal growth restriction syndrome. A reduction in the levels of VEGF-A (below 60 pg/ml) and IGF-1 (below 50 pg/ml), as well as their ratio (1.1 or lower) in the blood of pregnant women at gestational ages of 22–27 weeks, may be used to predict the development of fetal growth restriction syndrome.

References

1. Abduganieva D. F., Urinbaeva N. A., Mukhamedova U. Y. Risk factors for the development of fetal growth restriction syndrome. *International Scientific Journal Science And Innovation,* Special Issue "Innovative Approaches To Modern Pharmacotherapy", February 26, 2025. Pp. 10-18.
2. Ahmadiev N. R., Teregulova L. E., Ulyanina E. V., Ahmadiev D. G. Early and late fetal growth restriction. Differential diagnosis, criteria of adverse perinatal outcomes. *Journal of Kazan Medical School*, 2019. No. 1 (23). Pp. 158-163.
3. Ganichkina M. B., Mantrova D. A., Kan N. E., et al. Management of pregnancy with fetal growth restriction. *Obstetrics and Gynecology*, 2017. No. 10. Pp. 5-11. DOI: https://dx.doi.org/10.18565/aig.2017.10.5-11
4. Degtyareva E. A., Zakharova O. A., Kufa M. A., Kantemirova M. G., Radzinsky V. E. Effectiveness of prediction and early diagnosis of fetal growth restriction. *Russian Journal of Perinatology and Pediatrics,* 2018; 63(6): 37-45. DOI: 10.21508/1027-4065-2018-63-5-37-45
5. Ignatko I. V. Fetal growth restriction syndrome / I. V. Ignatko, M. M. Miryushchenko. *Journal of Scientific Articles "Health and Education*", 2016. Vol. 18, No. 1. Pp. 1-4, 2020.
6. Mantrova D. A. Fetal growth restriction syndrome: Clinical-immunological and morphological parallels. Abstract of the dissertation for the degree of candidate of medical sciences. Moscow, 2020. 23 p.
7. Podzolkov A. M., Denisova Y. V., Skvortsova M. Y., Denisova T. V., Shovgenova D. S. Fetal growth restriction syndrome: Unresolved issues of risk stratification, early diagnosis, and obstetric tactics. *Issues of Gynecology, Obstetrics, and Perinatology,* 2021; 20(5): 76-86. DOI: 10.20953/1726-1678-2021-5-76-86
8. Strizhakov A. N., Ignatko I. V., Timokhina E. V., Kardanova M. A. Critical condition of the fetus. Diagnostic criteria, obstetric tactics, perinatal outcomes. Moscow: GEOTAR-Media, 2018.
9. Tarabrina T. V. Clinical significance of studying angiogenic growth factors in predicting fetal growth restriction syndrome. Moscow, 2010. Abstract of the dissertation for the degree of candidate of medical sciences. 26 p.
10. Albu A. R., Horhoianu I. A., Dumitrascu M. C., Horhoianu V. Growth assessment in diagnosis of Fetal Growth Restriction. *J Med Life*. 2014 Jun 15;7(2):150-4. Epub 2014 Jun 25. PMID: 25408718; PMCID: PMC4197499.
11. Brosens I., Pijnenborg R., Vercruysse L., Romero R. The "Great Obstetrical Syndromes" are associated with disorders of deep placentation. *American Journal of Obstetrics and Gynecology*, 2011. Vol. 204, № 3. P. 193-201.
12. **Giorgione V**, Ramnarine S, Malik A, Bhide A The value of angiogenetic biomarkers in the detection of early onset fetal growth restriction. *Eur J Obstet Gynecol Reprod Biol,*2024,Aug;299:91-95. doi: 10.1016/j.ejogrb.2024.05.036. Epub 2024 May 29.PMID: 38850897
13. Morris R. K., Johnstone E., Lees C., Morton V., Smith G. Investigation and care of a small-for-gestational-age fetus and a growth restricted fetus. *BJOG: An International Journal of Obstetrics & Gynaecology*, 2024. Vol. 131, Issue 9. P. i-vi, 1165-1328, e31-e80. DOI: https://doi.org/10.1111/1471-0528.17814
14. Malacova E., Regan A., Nassar N., et al. Risk of stillbirth, preterm delivery, and fetal growth restriction following exposure in a previous birth: systematic review and meta-analysis. *BJOG*, 2018; 125(2): 183–192. DOI: https://doi.org/10.1111/1471-0528.14906
15. Pels A., Beune I. M., van Wassenaer-Leemhuis A. G. Early-onset fetal growth restriction: A systematic review on mortality and morbidity. *Acta Obstet Gynecol Scand*, 2020. Vol. 99, № 2. P. 153-166.
16. Priante E., Verlato G., Giordano G., et al. Intrauterine Growth Restriction: New Insight from the Metabolomic Approach. *Metabolites*, 2019. Vol. 9, № 11. P. 267-280.