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HIF-1A gene polymorphism (rs11549465) as a possible general genetic predictor of anemia in pregnant women and fetal intrauterine growth retardation in women living in the conditions of the high anthropogenic load

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ABSTRACT

Introduction. Intrauterine growth retardation of the fetus, especially in combination with anemia in pregnant women, is becoming an increasingly urgent global problem. The impaired adaptation of the mother's and the embryo's bodies to physiological hypoxia during pregnancy may have common genetically determined bases that manifest themselves at both the maternal and fetoplacental levels. Adaptation to endogenous hypoxia is particularly relevant in environments with high levels of anthropogenic stress.

Materials and methods. Two independent pilot studies were conducted on a cohort of pregnant women living in a large industrial region. The first group consisted of thirty seven pregnant women with anemia and 53 pregnant women without this pathology. The second group included 23 women who gave birth to newborns with intrauterine growth retardation, 33 women who gave birth to healthy newborns; 19 babies diagnosed with intrauterine growth retardation, and 40 healthy babies. All participants were tested for HIF-1A gene variants using polymerase chain reaction.

Results. The CC genotype of the HIF-1A gene has been shown to increase the likelihood of developing anemia during pregnancy ($\chi^2 = 4.73$; OR – 3.57). The CC genotype of the HIF-1A gene in newborns is reliably associated with intrauterine growth retardation ($\chi^2 = 4.59$; OR – 7.71). Polymorphic CT variant rises the resistance to the development of these pathologies. The combination of CC/CC genotypes in the mother and the fetus leads to a synergistic effect and a high probability of intrauterine growth retardation ($\chi^2 = 5.76$; OR – 6.26).

Limitations. The study was of a pilot nature, so it is advisable to increase the sample.

Conclusion. The obtained data allow us considering the HIF-1A (rs11549465) polymorphism as a candidate marker for stratifying the risk of developing pregnancy adaptation disorder syndrome, which includes maternal anemia and fetoplacental insufficiency.

Keywords: hypoxia-inducible factor-1 α ; intrauterine growth retardation of the fetus; anemia of pregnant women; HIF-1A gene; hypoxia; industrial region; benz(a)pyrene, formaldehyde

Compliance with ethical standards. The study was approved by the local Ethics Committee of the Research Institute for Complex Problems of Hygiene and Occupational Diseases" (Protocol of the Meeting No. 4, § 1 dated 11/18/2021), it was conducted in accordance with the commonly accepted scientific principles of the Declaration of Helsinki of the World Medical Association "Ethical Principles for Medical Research Involving Human Subjects" as amended 2013.

For citation: Gulyaeva O.N., Kazitskaya A.S., Yadykina T.K., Tereshkin I.E., Zagorodnikova O.A., Matoshin S.V. HIF-1A gene polymorphism (rs11549465) as a possible general genetic predictor of anemia in pregnant women and fetal intrauterine growth retardation in women living in the conditions of the high anthropogenic load. *Gigiena i Sanitariya / Hygiene and Sanitation, Russian journal.* 2026; 105(4): 438–444. <https://doi.org/10.47470/0016-9900-2026-105-4-438-444> <https://elibrary.ru/jirhkp> (In Russ.)

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Contribution: Gulyaeva O.N. – concept and design of the study, literature review, collection and processing of material, writing the text; Kazitskaya A.S. – material processing; Yadykina T.K. – material processing; Tereshkin I.E. – material processing; Zagorodnikova O.A. – collection of material; Matoshin S.V. – collection of material. All authors are responsible for the integrity of all parts of the manuscript and approval of the manuscript final version.

Conflict of interest. The authors declare no conflict of interest.

Funding. The study had no sponsorship.

Received: February 17, 2026 / Accepted: March 24, 2026 / Published: May 18, 2026

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Полиморфизм гена *HIF-1A* (rs11549465) как возможный общий генетический предиктор анемии беременных и задержки внутриутробного развития плода у женщин, проживающих в условиях высокой антропогенной нагрузки

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РЕЗЮМЕ

Введение. Задержка внутриутробного развития плода, особенно в сочетании с анемией беременных, становится всё более распространённой мировой проблемой. Нарушение адаптации организма матери и эмбриона к физиологической гипоксии беременности может иметь единые генетически детерминированные основы, проявляющиеся как на материнском, так и на фетоплацентарном уровнях. Адаптация к эндогенной гипоксии особенно актуальна в условиях высокой антропогенной нагрузки.

Материалы и методы. Проведены два независимых пилотных исследования на когорте беременных женщин, проживающих в крупном промышленном регионе. Первая группа: 37 беременных женщин с анемией и 53 беременные без данной патологии. Вторая группа: 23 женщины, родившие детей с задержкой внутриутробного развития, и 33 женщины, родившие здоровых детей; 19 детей с диагнозом задержки внутриутробного развития, 40 здоровых детей. Методом полимеразной цепной реакции у всех обследованных определены варианты гена *HIF-1A*.

Результаты. Показано, что генотип *CC* гена *HIF-1A* повышает вероятность развития анемии во время беременности ($\chi^2 = 4,73$; $OR = 3,57$). Генотип *CC* гена *HIF-1A* у новорождённых достоверно связан с задержкой внутриутробного развития ($\chi^2 = 4,59$; $OR = 7,71$). Полиморфный вариант *CT* повышает устойчивость к развитию данных патологий. Сочетание генотипов *CC/CC* у матери и плода приводит к синергическому эффекту и высокой вероятности задержки внутриутробного развития ($\chi^2 = 5,76$; $OR = 6,26$).

Ограничения исследования. Исследование носило пилотный характер, поэтому целесообразно увеличение выборки.

Заключение. Полученные данные позволяют рассматривать полиморфизм *HIF-1A* (rs11549465) в качестве кандидатного маркера для стратификации риска развития синдрома нарушения адаптации к беременности, включающего материнскую анемию и фетоплацентарную недостаточность.

Ключевые слова: гипоксией индуцируемый фактор-1 α ; задержка внутриутробного развития плода; анемия беременных; ген *HIF-1A*; гипоксия; промышленный регион; бенз(а)пирен; формальдегид

Соблюдение этических стандартов. Исследование одобрено локальным этическим комитетом ФГБНУ «Научно-исследовательский институт комплексных проблем гигиены и профессиональных заболеваний» (протокол заседания № 4, § 1 от 18.11.2021 г.), проведено согласно общепринятым научным принципам Хельсинкской декларации Всемирной медицинской ассоциации «Этические принципы проведения медицинских исследований с участием человека в качестве субъекта» с поправками 2013 г.

Для цитирования: Гуляева О.Н., Казизкая А.С., Ядыкина Т.К., Терешкин И.Е., Загородникова О.А., Матошин С.В. Полиморфизм гена *HIF-1A* (rs11549465) как возможный общий генетический предиктор анемии беременных и задержки внутриутробного развития плода у женщин, проживающих в условиях высокой антропогенной нагрузки. *Гигиена и санитария*. 2026; 105(4): 438–444. <https://doi.org/10.47470/0016-9900-2026-105-4-438-444> <https://elibrary.ru/jirhkp>

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Вклад авторов: Гуляева О.Н. – концепция и дизайн исследования, обзор литературы, сбор и обработка материала, написание текста; Казизкая А.С. – обработка материала; Ядыкина Т.К. – обработка материала; Терешкин И.Е. – обработка материала; Загородникова О.А. – сбор материала; Матошин С.В. – сбор материала. Все соавторы – утверждение окончательного варианта статьи, ответственность за целостность всех её частей.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов в связи с публикацией данной статьи.

Финансирование. Исследование не имело спонсорской поддержки.

Поступила: 17.02.2026 / Принята к печати: 24.03.2026 / Опубликовано: 18.05.2026

Introduction

Fetal growth restriction (FGR) is becoming an increasingly common problem not only in Russia but also worldwide. According to aggregated epidemiological data, around 30 million babies are born with this condition each year worldwide [1, 2]. Fetal growth restriction accounts for around 30% of stillbirths, contributes to high perinatal morbidity and mortality, and is a common cause of preterm delivery, as well as adverse psychoneurological consequences [3–5]. A wide range of fetal, maternal and placental factors have been identified among the causes [6]. Impaired placentation and uteroplacental blood flow, oxidative stress and inflammation associated with various pregnancy complications lead to chronic fetal hypoxia. One of the most common extragenital complications of pregnancy is anemia, which contributes significantly to the development of hypoxic conditions in both the mother and the fetus [7]. Alongside classical etiological factors (iron and folic acid deficiencies), the role of genetic predisposition has been actively investigated in recent years [8]. Of particular interest are the genes involved in adaptation to the physiological hypoxia of pregnancy.

Hypoxia-inducible factor-1 α (HIF-1 α), encoded by the *HIF-1A* gene, is a key regulator of the cellular response to hypoxia. It controls the expression of hundreds of genes, including erythropoietin (EPO), the primary stimulator of erythropoiesis [9]. The rs11549465 polymorphism (C>T, Pro582Ser) is functionally significant: the T allele is associated with increased transcriptional activity of the protein and improved adaptation to hypoxia [10]. Previously, its role has primarily been studied in the context of placental dysfunction, pre-eclampsia and fetal growth restriction; however, evidence has emerged suggesting that *HIF-1A* variants that impair the hypoxic response may disrupt the physiological stimulation of erythropoiesis during pregnancy, predisposing women to anemia [11].

Novokuznetsk is a major industrial centre in the Kemerovo Region (Kuzbass), where enterprises in the metallurgical, coal-processing and chemical industries are concentrated. Just under half of the region's territory is classified as an environmental crisis zone, and, according to Roshydromet, Novokuznetsk has very high levels of atmospheric pollution. The greatest potential threat to the population of towns in southern Kuzbass is posed by benzo(a)pyrene, formaldehyde, particulate matter, nitrogen

Таблица 1 / Table 1

Average annual concentrations of carcinogenic pollutants in the atmospheric air of the Novokuznetsk, expressed in mg/m³/share of MPC

Среднегодовые концентрации канцерогенных загрязняющих веществ в атмосферном воздухе Новокузнецка, выраженные в мг/м³/доли ПДК

Год Year	Загрязняющее вещество / Pollutant		
	Бенз(а)пирен Benzo(a)pyrene	Формальдегид Formaldehyde	Углерод (сажа) Carbon (soot)
2021	0.0000071/7.1	0.0051/1.7	0.0175/0.7
2022	0.0000112/11.2	0.0102/3.4	—
2023	0.0000062/6.2	0.0117/3.9	—
2024	0.0000063/6.3	0.01185/3.95	—

dioxide (NO₂), hydrogen fluoride, nitrogen monoxide (NO), carbon monoxide (CO), and sulphur dioxide (SO₂) [12]. Chronic exposure to air pollutants, typical of industrial centres, disrupts maternal oxygen homeostasis and exerts direct embryotoxic and foetotoxic effects, leading to intrauterine growth restriction. Numerous epidemiological studies and laboratory animal studies confirm that the main mechanisms of this effect are the induction of oxidative stress, direct damage to the DNA of the placenta and fetus, and endocrine disorders [13].

The aim of this study is to identify the association between the *HIF-1A* gene polymorphism, anemia during pregnancy and fetal growth restriction in women living in a region with high anthropogenic pressure.

Materials and methods

An assessment of total atmospheric emissions and average annual concentrations of pollutants in Novokuznetsk was carried out for the period from 2021 to 2024. Data were obtained from the Kemerovo Centre for Hydrometeorology and Environmental Monitoring, a branch of the Federal State Budgetary Institution 'West Siberian Directorate for Hydrometeorology and Environmental Monitoring'. Two independent pilot case-control studies were conducted on a cohort of pregnant women living in Kuzbass (Novokuznetsk), a major industrial centre in the Kemerovo Region.

The first group comprised of 37 pregnant women (mean age 28.3 ± 4.1 years) diagnosed with anaemia complicating pregnancy, childbirth and the puerperium (ICD-10 code O99.0) and 53 pregnant women without this condition (mean age 27.8 ± 3.9 years). Venous blood samples for clinical and genetic analysis were collected upon booking at the antenatal clinic. The diagnosis of anemia was made according to WHO criteria (Hb < 110 g/L).

The second group comprised of 23 women, who had given birth to infants with intrauterine growth restriction, and 33 women with uncomplicated pregnancies resulting in the birth of healthy, full-term infants. The neonates born to these women were also examined: 19 neonates with intrauterine growth restriction and 40 healthy neonates. The diagnosis was confirmed in accordance with clinical guidelines, 'Assessment of the physical development of children and adolescents' (Ministry of Health Letter No. 15-2/10/2-8090, dated 21 November 2017), whereby the asymmetric form of FGR is diagnosed when body weight is below the 10th percentile for the given gestational age, and the symmetric form (hypoplastic type) is diagnosed when both the infant's weight and length are below the expected values. Genomic DNA was isolated using the phenol-chloroform extraction method from peripheral blood leucocytes [14]. Gene typing was performed

using real-time PCR on a DTprime 4 instrument (NPO DNA-Technology LLC, Russia). Test kits for the molecular genetic analysis of polymorphisms in the *HIF-1A* (hypoxia-inducible factor-1α) gene were developed by the Institute of Biochemistry and Physiology of Metabolism, Siberian Branch of the Russian Academy of Sciences, and synthesized by SibDNA LLC. A comparison of genotype frequencies to identify an association with the risk of developing anemia and fetal growth restriction was carried out using the χ^2 test to determine statistically significant differences between observed and expected frequencies. Odds ratios (OR) were calculated to assess the association between the risk factor and the outcome [15]. Deviation from Hardy–Weinberg equilibrium was tested using the exact test [16].

The study was approved by the local ethics committee of the Federal State Budgetary Scientific Institution 'Research Institute for Complex Problems of Hygiene and Occupational Diseases' (Minutes No. 4, Section 1, 18 November 2021), and was conducted in accordance with the principles of the World Medical Association's Declaration of Helsinki 'Ethical Principles for Medical Research Involving Human Subjects', as amended in 2013.

Results

The total volume of atmospheric emissions in Novokuznetsk from 2021 to 2024 decreased slightly, from 268,297 to 256,683 thousand tonnes. The reduction amounted to 11,614 thousand tonnes, which is attributable to Novokuznetsk's participation in the national 'Clean Air' project.

Table 1 shows the average annual concentrations of carcinogenic pollutants, expressed in mg/m³ and as a percentage of the maximum permissible concentration (MPC).

The annual average concentrations of benzo(a)pyrene were 6.2 to 11.2 times higher than the established MPC throughout the entire study period; the greatest exceedance (11.2-fold) was observed in 2022. Annual average concentrations of formaldehyde were 1.7 to 3.95 times higher than the corresponding MPC between 2021 and 2024. In 2021, annual average concentrations of carbon (soot) were below the MPC; since 2022, concentrations of this substance have not been measured in the city.

Molecular genetic studies identified polymorphic variants of the *HIF-1A* gene (rs11549465) that are significantly associated with the development of anemia complicating pregnancy and fetal growth restriction, as well as variants associated with a protective effect against these conditions.

The CC genotype of the *HIF-1A* gene (rs11549465) was significantly associated with the development of anemia ($\chi^2 = 4.73$; OR = 3.57), whilst the CT genotype was associated with a reduced risk of anemia ($\chi^2 = 4.00$; OR = 0.31) (Table 2).

Analysis of the results presented in Table 3 showed that, in the group of patients who gave birth to infants with intrauterine growth restriction, no statistically significant associations with the *HIF-1A* gene polymorphism were found.

In the group of neonates with FGR a statistically significant association was demonstrated between the homozygous CC genotype of the *HIF-1A* gene and intrauterine growth restriction ($\chi^2 = 4.59$; OR = 7.71), and between the heterozygous CT genotype and normal development ($\chi^2 = 3.93$; OR = 0.15) (Table 4).

Analysis of the combinations of *HIF-1A* gene variants in the mother and infant revealed a statistically significant association between the combination of homozygous CC/CC genotypes of the *HIF-1A* gene in both the mother and infant, and intrauterine growth restriction ($\chi^2 = 5.76$; OR = 6.26), whilst the combination of the homozygous CC genotype in the mother with the heterozygous CT genotype in the infant was associated with normal neonatal development ($\chi^2 = 4.90$; OR = 0.18) (Table 5).

Таблица 2 / Table 2

HIF-1A gene polymorphism in pregnant women with anemia**Полиморфизм гена HIF-1A у беременных женщин с анемией**

Группа Group	HIF-1A (rs11549465)		
	CC	CT	TT
Беременные женщины с анемией / Pregnant women with anemia (<i>n</i> = 37)	33	4	0
Контроль / Control (<i>n</i> = 53)	37	15	1
χ^2	4.73	4.00	0.71
OR	3.57	0.31	Ошибка / Error

Примечание. χ^2 и OR — критерии различий распределений генотипов в контроле и у беременных женщин с анемией.

Note: χ^2 and OR — criteria for the differences in the genotype distributions in the control and in pregnant women with anemia.

Таблица 3 / Table 3

HIF-1A (rs11549465) gene polymorphism in the women who gave birth to babies with intrauterine growth retardation**Полиморфизм гена HIF-1A (rs11549465) у женщин, родивших детей с задержкой внутриутробного развития**

Группа Group	HIF-1A (rs11549465)		
	CC	CT	TT
Женщины с задержкой внутриутробного развития плода Women with intrauterine growth retardation of the fetus <i>n</i> = 23	21	2	0
Контроль / Control (<i>n</i> = 33)	25	7	1
χ^2	2.63	1.89	0.77
OR	3.68	0.32	Ошибка / Error

Примечание. χ^2 и OR — критерии различий распределений генотипов в контроле и у женщин с задержкой внутриутробного развития плода.

Note: χ^2 and OR — criteria for the differences in the genotype distributions in the control and in women with intrauterine growth retardation of the fetus.

Таблица 4 / Table 4

HIF-1A (rs11549465) gene polymorphism in newborns with intrauterine growth retardation**Полиморфизм гена HIF-1A (rs11549465) у новорождённых с задержкой внутриутробного развития**

Группа Group	HIF-1A (rs11549465)		
	CC	CT	TT
Дети с задержкой внутриутробного развития / Babies with intrauterine growth retardation <i>n</i> = 19	18	1	0
Контроль / Control (<i>n</i> = 40)	28	11	1
χ^2	4.59	3.93	0.48
OR	7.71	0.15	Ошибка / Error

Примечание. χ^2 и OR — критерии различий распределений генотипов в контроле и у новорождённых с задержкой внутриутробного развития.

Note: χ^2 and OR — criteria for the differences in the distributions of genotypes in the control and in newborns with intrauterine growth retardation.

Таблица 5 / Table 5

Combination of polymorphism of the HIF-1A (rs11549465) gene in women who gave birth to babies with intrauterine growth retardation and in their babies**Сочетание полиморфизма гена HIF-1A (rs11549465) у женщин, родивших детей с задержкой внутриутробного развития, и у их детей**

Группа Group	HIF-1A (rs11549465)		
	CC/CC	CC/CT	CT/CT
Женщины, родившие детей с задержкой внутриутробного развития / их дети Women who gave birth to babies with intrauterine growth retardation / their babies <i>n</i> = 19	17	2	0
Контроль / Control (<i>n</i> = 33)	19	13	1
χ^2	5.76	4.90	0.59
OR	6.26	0.18	Ошибка / Error

Примечание. χ^2 и OR — критерии различий распределений генотипов в контроле, у женщин, родивших детей с задержкой внутриутробного развития, и у их детей.

Note: χ^2 and OR — criteria for the differences in the distributions of genotypes in the control and in women who gave birth to babies with intrauterine growth retardation and in their babies.

Thus, a statistically significant association was identified between the CC genotype of the *HIF-1A* gene and the development of anemia in pregnant women and fetal growth restriction, particularly when these genotypes are combined in the mother and infant, whilst the CT genotype is associated with an increased likelihood of a normal pregnancy and the birth of a healthy child.

Discussion

Pathological endogenous hypoxia develops in virtually all diseases, whether infectious or non-infectious, under conditions of stress, as well as in cases of impaired uteroplacental blood flow, smoking, alcoholism and other adverse factors [17, 18]. A reduction in the efficiency of oxygen delivery to tissues leads to disturbances in the regulation of the microcirculatory bed, extravasation, and the activation of leucocytes and other immune and pro-inflammatory resident cells, which produce reactive oxygen species, leading to oxidative stress and mitochondrial dysfunction [19–22]. The oxygen-sensitive subunit HIF-1 α , whose activity is genetically determined, plays a leading role in the body's adaptation to hypoxia. To date, 16 single-nucleotide polymorphisms (SNPs) in the *HIF-1A* gene have been identified that influence the subunit's activity and are associated with various pathologies. One of the most extensively studied is rs11549465 C>T, which results in the substitution of serine for proline (Pro582Ser; C1772T) and affects HIF-1 α stability and transcriptional activity, leading to increased expression of the HIF-1 α protein [23–28].

Against the backdrop of a slight reduction in overall atmospheric emissions in Novokuznetsk between 2021 and 2024, there has been a persistent exceedance of the maximum permissible concentrations (MPCs) for the annual average concentrations of benzo(a)pyrene and formaldehyde, which are classified as hazard classes 1 and 2. The combined effect of these pollutants is capable not only of causing direct damage to the respiratory system, but also of inducing chronic tissue hypoxia, which is particularly critical during gestation.

One of the key compounds disrupting oxygen homeostasis is formaldehyde. Traditionally, its toxicity has been linked to the formation of DNA–protein cross-links and local inflammation; however, recent studies have revealed its direct destructive effect on the central regulator of adaptation to hypoxia. Formaldehyde is classified as a phototoxic stressor – an agent that causes structural damage to proteins. It has been established that the *HIF-1 α* and *HIF-2 α* subunits contain extensive intrinsically disordered regions, which make them extremely vulnerable to damage by aldehydes. Formaldehyde induces rapid and selective degradation of *HIF-1 α* ; in the absence of proteasome degradation, the damaged protein becomes insoluble and denatured. Consequently, rather than activating a protective response to hypoxia, *HIF-1 α* is inactivated, which deprives cells of their ability to respond adequately to oxygen deprivation [29].

Formaldehyde is also capable of switching metabolism to anaerobic glycolysis even in the presence of oxygen, stimulating this process via the induction of *HIF-1 α* . This results in a paradoxical situation of oxygen deprivation amidst an excess of

oxygen, which exacerbates mitochondrial stress [30]. Chronic exposure to formaldehyde can lead to the depletion of the normal physiological response to hypoxia.

Benzo(a)pyrene, a typical representative of PAHs and a priority carcinogen in industrial cities, is a potent pro-oxidant. It has been shown that benzo(a)pyrene influences cell proliferation by modulating metabolic genes and the *ROS/HIF-1 α /HO-1* signaling pathway, which is accompanied by the induction of reactive oxygen species. Furthermore, benzo(a)pyrene simultaneously activates the aryl hydrocarbon receptor (AhR), triggering a signaling cascade that potentiates mitochondria-mediated apoptosis [31].

Thus, living in conditions of chronic exposure to formaldehyde and benzo(a)pyrene creates a synergistic background of mitochondrial dysfunction and oxidative stress. This leads to the depletion of the normal physiological response to hypoxia, mediated by *HIF-1A*, which is critically important for the realization of the genetic risk associated with the rs11549465 polymorphism, particularly in pregnant women.

In our study, we demonstrated a single, genetically determined basis for impaired adaptation to pregnancy-related hypoxia, which manifests as anemia in the mother and as fetal growth restriction in the fetoplacental unit. In mothers who are carriers of the CC polymorphic variant of the *HIF-1A* gene, insufficient stimulation of erythropoiesis is observed in response to hemodilution and an increasing demand for oxygen [32]. In the fetus, a weak HIF-1 α response in the placenta leads to suboptimal vascularization and impaired trophoblast invasion, which is a known mechanism underlying placental insufficiency and FGR [33–35].

A woman with the CC genotype initially has reduced compensatory reserves for adapting to pregnancy. She is at higher risk of developing anemia, and her body may be less able to support the formation of a fully functional placenta. If the fetus also inherits the low-activity C allele, its own ability to stimulate angiogenesis and growth, even in the context of mild placental insufficiency, is reduced. This leads to a synergistic effect and a high probability of developing FGR (OR = 6.26). In an industrial region, this genetic predisposition may be exacerbated by exogenous hypoxia and other environmental factors.

Limitations. As this was a pilot study, it was limited by a small sample size.

Conclusion

The data obtained suggest that the *HIF-1A* (rs11549465) polymorphism can be considered a candidate marker for stratifying the risk of developing pregnancy-related adaptation disorders, comprising maternal anemia and placental insufficiency, in environments with high anthropogenic stress. Identifying women with the CC genotype, particularly in cases where the fetus is likely to inherit the C allele, identifies them as being at high risk of developing associated complications (anemia and placental insufficiency). These women require enhanced preventive measures: pre-pregnancy preparation, early monitoring of hemoglobin levels and fetoplacental parameters, and adjustments to working and living conditions.

Prospective studies involving larger cohorts are required to confirm these findings.

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