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THE ROLE OF HYPOXIA-INDUCIBLE FACTOR HIF-1α IN THE PATHOGENESIS OF INTRAPARTUM FETAL DEATH IN PREECLAMPSIA

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Abstract
The purpose of this study was to investigate the role of hypoxia-inducible factor HIF-1α in the formation of fetoplacental insufficiency and the development of intrapartum fetal death in preeclampsia. The study included analysis of molecular genetic data in conjunction with Doppler measurements of fetoplacental blood flow. The findings established that HIF-1α hyperexpression is associated with endothelial cell apoptosis, reduced angiogenesis, and critical abnormalities in Doppler indices that precede acute intrapartum fetal hypoxia in preeclampsia.

Keywords: HIF-1α, placental dysfunction, preeclampsia, hypoxia-inducible factor, fetoplacental insufficiency, intrapartum fetal death, genetic polymorphism, endothelial dysfunction.

Introduction

Preeclampsia represents one of the most prevalent and clinically significant complications of pregnancy. The condition is characterized by the development of arterial hypertension after 20 weeks of gestation, frequently accompanied by proteinuria, elevated serum creatinine levels, hepatic transaminase elevation, thrombocytopenia, central nervous system involvement, and pulmonary edema. Contemporary understanding of preeclampsia pathogenesis indicates its multifactorial nature, involving complex interactions between genetic, epigenetic, and environmental factors. According to the timing of disease manifestation, preeclampsia is classified into early-onset preeclampsia, developing before 33 weeks of pregnancy, and late-onset preeclampsia, occurring at 34 weeks of gestation or later. Although late-onset preeclampsia accounts for more than half of all preeclampsia cases, the early-onset form contributes most significantly to maternal and perinatal mortality rates. It should be noted that currently the only definitive treatment for preeclampsia remains early delivery, which underscores the urgent need for new pathogenetically justified prognostic and therapeutic approaches. The key pathogenic mechanism in preeclampsia involves impaired remodeling of uterine spiral arteries, leading to chronic placental ischemia and episodes of hypoxic-reperfusion injury to the trophoblast. These processes are accompanied by increased production of syncytiotrophoblast microparticles, dysregulation of the cytokine profile, and pronounced imbalance between angiogenic and antiangiogenic factors in the maternal circulation, ultimately resulting in generalized endothelial dysfunction and clinical manifestation of preeclampsia.

In early-onset preeclampsia, decreased partial oxygen pressure and impaired oxygen-sensing mechanisms in the placenta are associated with pronounced activation of hypoxia-inducible factor-1α (HIF-1α) in placental tissues. Persistent HIF-1α hyperexpression in the placenta and maternal circulation promotes superficial trophoblast invasion into spiral arteries and formation of placental

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insufficiency during preeclampsia pathogenesis. Furthermore, hypoxia and oxidative stress in placental tissues of patients with preeclampsia can induce abnormal expression of growth factors and regulatory molecules, including transforming growth factor beta (TGF-β) and several other functionally significant genes. Specifically, alterations in expression and polymorphisms of vascular endothelial growth factor (VEGF) genes, which play a crucial role in angiogenesis regulation, have been repeatedly identified in these patients. Additionally, the association of matrix metalloproteinases (MMP) with the development and progression of preeclampsia has been established, emphasizing the significance of extracellular matrix remodeling disturbances in disease pathogenesis. Intrapartum fetal death caused by acute decompensation of fetoplacental circulation represents a particularly clinically significant outcome. Under conditions of chronic placental hypoxia, hypoxia-inducible factor HIF-1α plays a crucial role, regulating angiogenesis, cell survival, and apoptosis. Hypoxia-inducible factor 1α (HIF-1α) is regarded as a key regulator of cellular response to hypoxia and a potential mediator of placental microvascular endothelial damage. Despite the substantial body of accumulated data, the molecular mechanisms underlying preeclampsia development, particularly the role of HIF-1α in placental dysfunction formation and adverse obstetric outcomes, remain insufficiently studied and require further in-depth investigation.

To investigate the role of hypoxia-inducible factor HIF-1α in the development of intrapartum fetal death in preeclampsia.

Methodology

This prospective case-control study included pregnant women hospitalized in the pregnancy pathology department of the Fergana branch of the Republican Specialized Scientific-Practical Medical Center for Maternal and Child Health Protection. Sample formation was conducted from September 2023 to July 2025. The study included 65 patients, of whom 35 women had physiological pregnancy course and constituted the control group, while 30 pregnant women were assigned to the late-onset preeclampsia group. Among patients with preeclampsia, 12 women were diagnosed with mild disease, whereas 18 demonstrated severe course. Intrapartum fetal death was diagnosed in all patients with preeclampsia complications. Preeclampsia diagnostic criteria were applied in accordance with international clinical guidelines and normative documents of the Ministry of Health of the Republic of Uzbekistan. Mild preeclampsia criteria included blood pressure of at least 140/90 mm Hg persisting for at least 6 hours, combined with proteinuria ≥300 mg/day after the 20th week of gestation. Severe preeclampsia was diagnosed at blood pressure levels ≥160/110 mm Hg persisting for at least 6 hours and daily proteinuria ≥2 g after 20 weeks of pregnancy. Additionally, severe disease was confirmed by the presence of at least one of the following clinical features: intense headache, visual disturbances, epigastric pain syndrome, or nausea.Patients with chronic arterial hypertension, type 1 and type 2 diabetes mellitus, gestational diabetes, renal diseases, and autoimmune pathology were excluded from the study.

Information on maternal demographic characteristics, reproductive and family history was collected from all study participants through structured individual interviews. Ethical considerations and informed consent were ensured according to local institutional requirements. Genomic DNA extraction was performed from the leukocyte fraction of peripheral venous blood using standard established methods. For amplification of the 178 base pair segment corresponding to exon 12 of the

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human HIF1A gene, the polymerase chain reaction (PCR) method was used according to previously described protocols. PCR amplification was conducted using specific oligonucleotide primers: forward primer 5′-CAT GTA TTT GCT GTT TTA AAG-3′ and reverse primer 5′-GAG TCT GCT GGA ATA CTG TAA CTG-3′.

A comparative study of clinical and laboratory parameters was performed in patients with preeclampsia and control group women. Quantitative data are presented as mean values with standard error of the mean (M ± m). Student's t-test was applied for comparing two independent samples. Statistical evaluation of differences in genotype distribution frequencies between compared groups was conducted using contingency tables followed by Fisher's exact test. Odds ratios (OR) with 95% confidence intervals (CI) were calculated for quantitative characterization of associations.

Results

This case-control study was performed to assess the association of two single nucleotide polymorphisms of the HIF1A gene with intrapartum fetal mortality in preeclampsia among pregnant women of Uzbek nationality.

Table 1. Main demographic and clinical parameters of examined patients according to preeclampsia presence

Parameters	**Control Group**	**PE**	**P-value**
n	35	30	
Maternal age (years)	25.4 ± 0.6	29.1 ± 0.4	
Primiparous (%)	33.9	39.6	
BMI (kg/m²)	27.6 ± 0.3	29.8 ± 0.8	0.001
Newborn weight (g)	3074.3 ± 54.2	2889.7 ± 68.7	< 0.001
Gestational age at delivery (weeks)	40.2 ± 0.2	38.1 ± 0.3	< 0.001

		Mild PE	**Severe PE**	
Systolic blood pressure (mm Hg)	118.2 ± 0.5	139.8 ± 1.7	165.4 ± 1.5	< 0.001*
Diastolic blood pressure (mm Hg)	69.3 ± 0.4	88.9 ± 1.2	102.8 ± 1.4	< 0.001**
Proteinuria (mg/24 h)	Absent	443.6 ± 63.5	2482.0 ± 377.4	< 0.001**

Values are presented as mean ± standard error of the mean. PE, preeclampsia; BMI, body mass index; compared with control group; compared with mild PE. Comparative genetic analysis of HIF1A gene polymorphisms in women with preeclampsia and those with physiological pregnancy course revealed statistically significant differences in genotype and allele distribution of the C1772T variant (Table 2). The frequency characteristics of this polymorphism in the studied sample generally corresponded to data previously published for other ethnic groups and populations. At the same time, this study documented a higher prevalence of the C1772T allelic variant compared to several previously studied populations, which may reflect population-specific features or the influence of regional genetic factors.

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Table 2. Distribution of genotypes and alleles of the C1772T polymorphism of the HIF1A gene in pregnant women with preeclampsia and in the control group

Genotypes	PE (%)	Control Group (%)	P-value	OR (95% CI)
CC	0.0	90.1		
CT	10.3	9.9		
TT	89.7	0.0		
Alleles				
C	6.6	93.4	0.831	0.807 (0.375-1.102)
T	96.6	3.4		

Additional analysis of C1772T polymorphism genotype distribution of the HIF1A gene according to clinical form of preeclampsia demonstrated that T allele carriage is associated with more severe disease course. In patients with severe preeclampsia, the frequency of heterozygous and homozygous variants (CT and TT) was higher compared to both women with mild preeclampsia and the control group with physiological pregnancy course. The identified trend was accompanied by more pronounced clinical and obstetric disturbances, including shortened gestational period, decreased newborn body weight, increased frequency of intrauterine growth restriction, and development of complicated forms of preeclampsia, including intrapartum fetal death. These data indicate the potential role of the C1772T polymorphism of the HIF1A gene in forming the hypoxic placental phenotype and progression of endothelial dysfunction in severe forms of preeclampsia. From a pathophysiological perspective, T allele carriage may be associated with increased HIF1A transcriptional activity, leading to sustained activation of hypoxia-induced signaling pathways, impaired trophoblast invasion, and progression of placental ischemia. Under conditions of chronic and acute hypoxia, such molecular changes can intensify vascular disturbances and worsen fetoplacental perfusion, which clinically manifests as more severe preeclampsia course and adverse perinatal outcomes.

The obtained results indicate that the C1772T polymorphism of the HIF1A gene is associated not only with preeclampsia development risk but also with its clinical severity. T allele carriage and corresponding genotypes (CT and TT) are associated with more severe disease forms and increased frequency of obstetric and perinatal complications. Thus, the C1772T polymorphism of the HIF1A gene can be considered as a promising molecular genetic marker of unfavorable preeclampsia course and a potential factor for early risk stratification of intrapartum complications in pregnant women.

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