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Epigenetic mechanisms of preeclampsia: Role of plasma microRNAs

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ABSTRACT

BACKGROUND: Despite the retentive relevance of preeclampsia (PE) among the main causes of maternal morbidity and mortality, its etiology remains unclear. Despite gaps in its pathophysiology, highly effective methods of prognosis, prevention, and treatment are still not devised yet. In recent years, the use of microRNA molecules that epigenetically control the expression of target genes at the post-transcriptional level received great interest as are they of key importance in the proliferation, differentiation, invasion, migration, and apoptosis of trophoblast cells and regulation of angiogenesis, immune response, and other processes during pregnancy

AIM: This study aimed to investigate the epigenetic mechanisms of PE development based on the evaluation of the expression of pathogenetically significant microRNAs in women's blood plasma.

MATERIALS AND METHODS: The study included 62 female patients divided into the main study group (*n*=42 with PE) and the control group (*n* = 20 healthy women with uncomplicated pregnancy, childbirth, and post-natal period). All patients have undergone general clinical, laboratory, and instrumental examinations. The expression levels of 15 microRNAs in the blood plasma were evaluated using a quantitative real-time polymerase chain reaction. DIANA miRPath v. 3.0 was used to evaluate the effect of differentially expressed microRNAs on the functioning of signaling pathways. Statistical data analyses were performed using Statistica 6.0.

RESULTS: Multidirectional changes in the expression levels of 13 of 15 plasma microRNAs were found in the PE group compared with the control group; however, the expression levels of the following eight microRNAs decreased significantly: hsa-miR-146a-5p (*p*=0.011), hsa-miR-181a-5p (*p*=0.015), hsa-miR-210-3p (*p*=0.031), hsa-miR-517a-3p (*p*=0.004), hsa-miR-517c-3p (*p*=0.007), hsa-miR-574-3p (*p*=0.048), hsa-miR-574-5p (*p*=0.003), and hsa-miR-1304-5p (*p*=0.001). The expression levels of hsa-miR-20a-5p (FC=0.39; *p*=0.049) and hsa-miR-143-3p (FC=0.71, *p*=0.05) significantly decreased in pregnant women with PE and symptoms of fetal growth retardation (FGR) compared with the subgroup without FGR. No significant differences in the expression level of the analyzed microRNAs were found between the subgroups with moderate and severe PE and early and late PE. The functional evaluation of differentially expressed microRNAs among women with PE, considering the identification of their potential target genes, revealed the dysregulation of >40 signaling pathways and biological processes in which these molecules are involved.

CONCLUSION: PE progresses alongside significant epigenetic changes accompanied by changes in the microRNA expression profile, which are associated with cardiovascular and cerebrovascular diseases and placental disorders. The detected differentially expressed microRNAs may be potential diagnostic markers of PE.

Keywords: preeclampsia; microRNA; transcriptome; epigenetics.

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Эпигенетические механизмы развития преэклампсии: роль плазменных микроРНК

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АННОТАЦИЯ

Введение. Несмотря на сохранение значимости преэклампсии (ПЭ) в структуре основных причин материнской заболеваемости и смертности, остается неясной этиология данного осложнения беременности, много пробелов в вопросах патофизиологии, соответственно по-прежнему не разработаны высокоэффективные методы прогнозирования, профилактики и лечения. В последние годы большой интерес вызывают перспективы использования молекул микроРНК, которые эпигенетически контролируют экспрессию генов-мишеней на посттранскрипционном уровне и имеют ключевое значение в пролиферации, дифференцировке, инвазии, миграции, апоптозе клеток трофобласта, регуляции ангиогенеза, иммунного ответа и других процессов во время беременности.

Цель. Изучение эпигенетических механизмов развития ПЭ на основании оценки экспрессии патогенетически значимых микроРНК в плазме крови женщин.

Материалы и методы. В исследование включены 62 пациентки, которых разделили на основную (42 беременные с ПЭ) и контрольную (20 здоровых женщин с неосложнённым течением беременности, родов и послеродового периода) группы. Всем пациенткам проводили общеклиническое, лабораторное и инструментальное обследование. Уровень экспрессии 15 микроРНК в плазме крови оценивали с помощью количественной полимеразной цепной реакции в режиме реального времени. Для оценки влияния дифференциально экспрессируемых микроРНК на функционирование сигнальных путей использовали программное обеспечение DIANA miRPath v.3.0. Статистическую обработку данных проводили с использованием лицензионного пакета программ Statistica 6.0.

Результаты. У женщин с ПЭ выявлены разнонаправленные изменения экспрессии 13 из 15 плазменных микроРНК по сравнению с контрольной группой, однако статистически значимо было снижение уровней экспрессии 8 микроРНК: hsa-miR-146a-5p (p=0,011), hsa-miR-181a-5p (p=0,015), hsa-miR-210-3p (p=0,031), hsa-miR-517a-3p (p=0,004), hsa-miR-517c-3p (p=0,007), hsa-miR-574-3p (p=0,048), hsa-miR-574-5p (p=0,003), hsa-miR-1304-5p (p=0,001). В подгруппе беременных, у которых ПЭ протекала с симптомами задержки роста плода, отмечено значимое снижение экспрессии молекул hsa-miR-20a-5p (FC=0,39; p=0,049) и hsa-miR-143-3p (FC=0,71, p=0,05) по сравнению с подгруппой без задержки роста плода. Не выявлено значимых различий в уровне экспрессии анализируемых микроРНК между подгруппами с умеренной и тяжёлой ПЭ, ранней и поздней ПЭ. Функциональная оценка дифференциально экспрессируемых микроРНК у женщин с ПЭ с учётом идентификации их потенциальных генов-мишеней показала наличие дисрегуляции более 40 сигнальных путей и биологических процессов, в которые вовлечены указанные молекулы.

Заключение. Развитие ПЭ сопровождается значимыми эпигенетическими изменениями, при которых изменяется профиль экспрессии микроРНК, ассоциированных с сердечно-сосудистыми и цереброваскулярными заболеваниями, а также плацентарными нарушениями. Выявленные дифференциально экспрессируемые микроРНК могут быть потенциальными диагностическими маркерами ПЭ.

Ключевые слова: преэклампсия; микроРНК; транскриптом; эпигенетика.

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子痫前期的表观遗传学机制：血浆microRNA的作用

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摘要

论证。尽管子痫前期在孕产妇发病率和死亡率的主要原因中一直占有重要地位，但这种妊娠并发症的病因仍不清楚，病理生理学方面也存在许多空白。因此，目前仍未开发出高效的预测、预防和治疗方法。近年来，人们对利用microRNA分子的前景产生了浓厚的兴趣，这些分子在转录后水平对靶基因的表达进行表观遗传学控制，在妊娠期间滋养层细胞的增殖、分化、侵袭、迁移、凋亡、血管生成调控、免疫反应和其他过程中起着关键作用。

目的。通过评估妇女血浆中具有重要病理意义的 microRNA 表达，研究子痫前期发生的表观遗传学机制。

材料与方法。研究包括62名患者，他们被分为主要组（42名子痫前期孕妇）和对照组（20名无并发症妊娠、分娩和产后健康妇女）。所有患者均接受了一般临床、实验室和仪器检查。通过实时定量聚合酶链反应评估了血浆中15种microRNA的表达水平。使用DIANA miRPath v.3.0软件评估不同表达的microRNA对信号通路功能的影响。使用Statistica 6.0软件许可包进行统计数据处理。

结果。与对照组相比，患有子痫前期的妇女血浆中15种microRNA中有13种的表达发生了多向变化。然而，有8种microRNA的表达水平出现了统计学意义上的显著下降： hsa-miR-146a-5p (p=0.011), hsa-miR-181a-5p (p=0.015), hsa-miR-210-3p (p=0.031), hsa-miR-517a-3p (p=0.004), hsa-miR-517c-3p (p=0.007), hsa-miR-574-3p (p=0.048), hsa-miR-574-5p (p=0.003), hsa-miR-1304-5p (p <0.001). 子痫前期有胎儿生长迟缓症状的孕妇亚组与无胎儿生长迟缓亚组相比，hsa-miR-20a-5p (FC=0.39; p=0.049), hsa-miR-143-3p (FC=0.71; p=0.05)的表达水平显著下降。在中度和重度子痫前期、早期和晚期子痫前期亚组之间，所分析的microRNA表达水平没有明显差异。对子痫前期妇女体内差异表达的microRNA进行功能评估，并对其潜在靶基因进行鉴定，结果表明这些分子参与的40多种信号通路和生物过程存在失调。

结论。子痫前期的发生伴随着显著的表观遗传学变化，其中与心脑血管疾病和胎盘疾病相关的microRNA的表达谱发生了改变。已检测到的差异表达的microRNA可能是子痫前期的潜在诊断标志物。

关键词：子痫前期；microRNA；转录组；表观遗传学。

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INTRODUCTION

Preeclampsia (PE) is a complication that occurs in the second half of pregnancy. Its pathophysiology is determined by various molecular and biological processes, which collectively result in the activation of endothelial cells, intravascular inflammation, and placental syncytiotrophoblast stress [1].

PE occurs in 2–8% of pregnancies. It is one of the top five causes of maternal and perinatal morbidity and mortality [2–4]. Despite advances in modern medical science, there have been no significant advances in the prediction, prevention, and treatment of PE [5].

Placental and/or maternal factors are responsible for the clinical heterogeneity of PE and play a fundamental role in its development. According to the two-stage concept of PE development, clinical manifestations result from early placentation and adaptation disorders of the spiral arteries [6]. At stage I (placental), insufficient invasive ability of extravillous trophoblast cells leads to inadequate remodeling of the spiral uterine arteries [7]. Abnormal uterine artery restructuring results in increased resistance, mechanical damage to placental villi due to increased blood pressure entering the intervillous space, and ischemic changes in placental villi caused by abnormal uteroplacental blood flow [8–11]. The development of stage II (maternal) is attributed to the release of biologically active substances from the ischemic placenta into the bloodstream of the mother and fetus, which results in generalized endothelial dysfunction and multi-organ failure in the mother [12].

The clinical heterogeneity of PE, including early and late presentations, moderate and severe cases, those with or without fetal growth retardation, proteinuria, and hypertension, has recently been actively discussed. This is significant for an individualized approach to the management of such patients. The search for noninvasive techniques and informative biomarkers for the early diagnosis and minimization of the risk of complications of obstetric pathology continues.

Recently, the focus of several scientists has shifted toward the potential use of microRNAs as both diagnostic molecules and therapeutic targets. It is established that microRNAs exert epigenetic control over the expression of target genes, primarily at the post-transcriptional level, through mRNA destabilization and protein translation inhibition [14]. Large-scale studies on microRNA profiling in women with both physiological and complicated pregnancies have identified more than a dozen microRNAs that are differentially expressed and play a key role in various processes, including proliferation, differentiation, invasion, migration, apoptosis of trophoblast cells, regulation of angiogenesis, and immune response in pregnancy [15–17]. Initially, it was postulated that nucleic acids of placental origin enter the maternal bloodstream as apoptotic cells. However, subsequent studies have demonstrated that microRNAs are exported from trophoblast cells into the maternal bloodstream through special extracellular vesicles called exosomes. Owing to their retained functional activity, these exosomes are able to modify the functions of "target cells" [18]. Long-term studies have revealed that microRNAs are present in a multitude of body fluids and tissues and remain stable in the extracellular environment, indicating the potential value of their profiling in various pathological conditions [19].

This study aimed to examine the epigenetic mechanisms underlying the development of PE and evaluate the expression of pathogenetically significant microRNAs in the blood plasma of women with this pregnancy complication.

MATERIALS AND METHODS

Study design

A one-stage study was conducted in parallel groups from 2022 to 2023. The study included 62 patients who were divided into two groups: main group (n=42), pregnant women with PE diagnosed according to the criteria specified in the clinical guidelines [20], and control group (n=20), healthy women with uncomplicated pregnancy, labor, and postpartum period.

The exclusion criteria were age below 18 years, decompensated forms of extragenital pathology, infectious and inflammatory diseases in the exacerbation phase, multiple pregnancies, pregnancies resulting from assisted reproductive technologies, and refusal to participate in the study.

The study was approved by the local ethical committee of the Sechenov First Moscow State Medical University (excerpt from the minutes of meeting no. 22–21 dated December 9, 2021).

All the study participants provided informed voluntary consent.

Research methods

All patients underwent a conventional examination, involving the collection and assessment of somatic and obstetric-gynecological anamnesis, and laboratory and instrumental examination, and the 15 microRNAs expression levels in blood plasma were determined (Table 1). The choice of microRNAs for analysis was based on published literature data on the involvement of these molecules in the pathogenesis of obstetric pathology.

RNA isolation

Venous blood was collected from the patients on an empty stomach into special VACUETTE® tubes with EDTA. Centrifugation was performed to obtain plasma. RNA isolation was conducted using the miRNEasy Serum/Plasma kit (Qiagen) with preliminary addition of 5.6×10^8 copies of synthetic microRNA cel-miR-39 (Qiagen) according to manufacturer instructions. Synthetic microRNA cel-miR-39 was used as an internal control to assess the efficiency of RNA isolation and cDNA synthesis.

Table 1. MicroRNAs and their role in obstetric pathologies

MicroRNA	Source	Expression	Targets	Functions	Study
miR-20a-5p	Maternal plasma	↑	FOXA1	Trophoblast proliferation, migration, and invasion	[21]
miR-143-3p	Maternal plasma	↑	NRG1, S100A11	Trophoblast proliferation, migration, and invasion; apoptosis; and epithelial–mesenchymal transition	[22]
miR-146a-5p	Placenta	↑	E-cadherin, vimentin, N-cadherin, and Wnt2	Trophoblast proliferation, migration, and invasion; apoptosis; and epithelial–mesenchymal transition	[22, 23]
miR-181a-5p	Placenta	↑	EFNB2, MMP-2, and MMP-9	Angiogenesis, proliferation, trophoblast migration and invasion, mitochondrial respiration, and oxidative stress	[24, 25]
miR-210-3p	Maternal plasma	↑	EFNA3, HOXA9, ISCU, KCMF1, and THSD7A	Angiogenesis, proliferation, trophoblast migration and invasion, mitochondrial respiration, and oxidative stress	[26–29]
miR-320a-3p	Maternal plasma	↑	IGF-1R	Trophoblast proliferation, invasion, and migration	[30, 31]
miR-375-3p	Maternal plasma	↑	VEGF, SHH signaling pathway	Trophoblast invasion and migration and angiogenesis	[32, 33]
miR-517a-3p	Placental tissues	↓	PRKG1	Immune response and oxidative stress	[34]
miR-517c-3p	Maternal plasma	↑	TNFSF15, FLT1 (VEGFR-1), VEGF, and PLGF	Trophoblast proliferation, migration, and invasion; apoptosis; immune response; and oxidative stress	[35]
miR-574-3p	Maternal plasma	↓	RXRA	Angiogenesis and regulation of vascular tone	[36, 37]
miR-574-5p	Maternal plasma	↑	TGF-β, VEGF, MMP2, and MMP9	Proliferation, invasion, and migration of trophoblast and maintenance of vascular tone	[38]
miR-1304-5p	Maternal plasma	↑	TGF-β-, MAPK-signaling pathway	Trophoblast invasion and migration	[39]
miR-210-5p	Maternal plasma	↑	VEGF, FLT1 (VEGFR-1), and VEGFR2	Angiogenesis	[40]
miR-4498	Maternal plasma	↓	TGF-β-, MAPK-signaling pathway	Immune response	[39]
miR-1972	Maternal plasma	↑	TGF-β, VEGF, MMP2, and MMP9	Proliferation, invasion, and migration of trophoblast and maintenance of vascular tone	[37]

Note. ↓ decreased expression; ↑ increased expression; IGF-1R, insulin-like growth factor 1 receptor; EFNB2, ephrin B2 gene; EFNA3, ephrin A3 gene; FOXA1, gene encoding the transcription activator of the same name; FLT1 (VEGFR-1), fms-like tyrosine kinase 1 gene (vascular endothelial growth factor receptor 2; HOXA9, homeobox protein A9 gene; ISCU, gene for a protein that assembles an iron-sulfur cluster in mitochondria; KCMF1 gene, modulating potassium channel activity factor 1; MAPK, mitogen-activated protein kinase; MMP 2, metalloproteinase 2; MMP 9, metalloproteinase 9; NRG1, neuregulin-1; PLGF, placental growth factor; PRKG1, cGMP-dependent protein kinase 1 gene; RXRA, retinoid X receptor A gene; S100A1, calcium-binding protein gene S100A1; SHH, sonic hedgehog signaling pathway; TGF-β, transforming growth factor β; THSD7A, gene encoding domain 7A of thrombospondin type 1; TNFSF15, TNF-like ligand 1A gene; VEGF, vascular endothelial growth factor; VEGFR2, receptor 2 vascular endothelial growth factors; Wnt2, a combination of the words Wingless and Integration.

Reverse transcription and quantitative real-time polymerase chain reaction

The cDNA was synthesized on the RNA matrix in a 20 µl reaction mixture at 37°C for 60 minutes, followed by incubation at 85°C for 5 minutes. The resulting cDNA (1 µl) was used as a matrix for real-time polymerase chain reaction (PCR) with a specific primer pair for each microRNA under study and a ready PCR mix 5x SYBR Green PCR Kit (Qiagen). The PCR reaction conditions were as follows: 15 minutes at 95°C, followed by 40 cycles of 20 seconds at 95°C, 10 seconds at 60°C, and 15 seconds at 72°C, in a DT-Prime amplifier (DNA Technology). The microRNA expression level in the samples was compared by 2-ΔΔCT using cel-miR-39 as reference.

Statistical processing

Statistical analysis was conducted using the licensed software package Statistica 6.0 (StatSoft Inc., USA). The normality of the quantitative data distribution was assessed using the Shapiro–Wilk criterion.

The mean and standard deviation (M±σ) represented data that exhibited a normal distribution. Data that deviated from a normal distribution were described using the median and interquartile range. The differences between unrelated samples for data that exhibited a normal distribution were assessed using the parametric Student's t-test and nonparametric Man–Whitney test for data that did not show a normal distribution. P <0.05 indicated significant differences.

Significant differences in the microRNA expression levels in both groups was assessed using a two-tailed Wilcoxon–Mann-Whitney test. Differential expression of microRNAs was determined under two conditions: the fold change (FC) in expression levels between the compared groups was >2 (or –1 <log2FC> 1) and the threshold for statistical significance was p <0.05.

The DIANA miRPath v.3.0 software (DIANA-Lab, Department of Electrical & Computer Engineering, University of Thessaly, Greece) was used to evaluate the influence of differentially expressed microRNAs on pathway function [41].

RESULTS

Table 2 shows the clinical and anamnestic characteristics of the patients in the analyzed groups and perinatal outcomes.

Analysis of microRNA expression in blood plasma samples from patients with PE and women with uncomplicated pregnancies revealed several molecular features at the transcriptome level (Table 3).

A multidirectional change in the expression of 13 plasma microRNAs was observed in the main group compared to the control group. A significant decrease in the expression level of eight microRNAs was observed in women with PE, namely, hsa-miR-146a-5p (p=0.011), hsa-miR-181a-5p (p=0.015), hsa-miR-210-3p (p=0.031), and hsa-miR-517a-3p. The results indicated a significant decrease in the expression level of the following microRNAs: hsa-miR-517c-3p (p=0.007), hsa-miR-574-3p (p=0.048), hsa-miR-574-5p (p=0.003), and hsa-miR-1304-5p (p <0.001). The most pronounced decrease in expression was observed for hsa-miR-517a-3p (14.3-fold), hsa-miR-574-5p (20-fold), and hsa-miR-1304-5p (33.3-fold).

Table 4 presents a comparative analysis of microRNA expression levels in the main group, stratified according to the clinical phenotype of PE.

A comparative analysis of microRNA expression levels in the subgroup of pregnant women with PE and symptoms of fetal growth retardation revealed a significant decrease in the hsa-miR-20a-5p (FC=0.39; p=0.049) and hsa-miR-143-3p (FC=0.71; p=0.05) expressions compared to the subgroup without growth retardation.

No significant differences were found in the microRNA expression profile between the subgroups of patients with early and late PE and between the subgroups of moderate and severe PE.

The online platform DIANA miRPath v.3.0 [41] was employed to analyze the influence of eight microRNAs differentially expressed in PE on the functioning of signaling pathways and biological processes involved in the pathogenesis of PE.

A functional assessment of aberrantly expressed microRNAs in women with PE (i.e., hsa-miR-146a-5p, hsa-miR-181a-5p, hsa-miR-210-3p, hsa-miR-517a-3p, hsa-miR-517c-3p, hsa-miR-574-3p, hsa-miR-574-5p, and hsa-miR-1304-5p), considering the identification of their potential target genes, revealed the presence of dysregulation of over 40 signaling pathways and biological processes wherein these molecules are involved. The most significant of these processes include carcinogenesis, infectious processes of various localizations, cell proliferation and differentiation, embryogenesis processes, oxidative stress, immune response reactions, and HIF-1-, TGF-b-, and p53-signaling pathways. These indicate the intricate molecular mechanisms underlying the development of this complication of pregnancy and may determine the clinical manifestations observed.

DISCUSSION

Currently available scientific data does not provide a clear understanding of the underlying cause of PE development. The available treatments are limited to symptomatic approaches and are focused on timely delivery [5]. Early diagnosis and prediction of PE progression remain challenging, resulting in significant complications for the mother and fetus. However, the diagnostic criteria for PE are not specific, and the criteria for assessing PE severity do not correlate well with the pathophysiological changes.

Thus, identifying clinically relevant biomarkers and tools for prognosis, early diagnosis, and personalized approach to each patient with PE is warranted.

In recent years, several studies have demonstrated the potential role of microRNAs in the pathogenesis of PE, indicating their potential as noninvasive diagnostic and prognostic markers [42]. During pregnancy, placental trophoblast cells at the maternal–fetal interface produce a large number of microRNAs, with their expression levels changing according to the progression of pregnancy and placental development. This highlights their involvement in placental regulation [43].

Aberrant expression of microRNAs in early pregnancy was shown to potentially play a pivotal role in the development of placental abnormalities. Recent studies have indicated a correlation between the placental microRNA expression profile and levels of these molecules in maternal and fetal blood flow, which may influence the progression of various disorders in both [7].

Our study results demonstrated the statistical significance of eight plasma microRNAs in the pathogenesis of PE. The microRNAs included hsa-miR-146a-5p, hsa-miR-181a-5p, hsa-miR-210-3p, and hsa-miR-517a-3p. Additionally, the expression levels of hsa-miR-517c-3p, hsa-miR-574-3p, hsa-miR-574-5p, and hsa-miR-1304-5p were found to be significantly reduced in patients with uncomplicated pregnancies.

Previous studies by Russian and foreign colleagues have determined the involvement of these microRNAs in the regulation of such key pregnancy events as trophoblast invasion,

Table 2. Clinical and anamnestic characteristics of patients and perinatal outcomes

Indices	Study group (*n*=42)	Control group (*n*=20)	*p*
Age*, years	29,76 (27,85–31,67)	28,80 (25,62–31,98)	0,594
BMI*, kg/m^2	31,17 (28,73–33,62)	28,17 (26,43–29,90)	0,045
Pregnant women, abs. (%)	32 (76,19)	13 (65,00)	0,012
PE history, *n* (%)	3 (7,1)	0 (0,0)	0,231
Chronic arterial hypertension, *n* (%)	7 (16,7)	0 (0,0)	0,005
Prenatal screening, *n* (%), high risk of PE	28 (66,7)	0 (0,0)	<0,001
Early PE, *n* (%)	6 (14,3)	—	—
Late PE, *n* (%)	36 (85,7)	—	—
Moderate PE, *n* (%)	38 (90,5)	—	—
Severe PE, *n* (%)	4 (9,5)	—	—
Clinical signs			
Systolic BP, mm Hg*	145 (140,0; 153,5)	115 (110,0; 120,0)	0,001
Diastolic BP, mm Hg*	90 (86,0; 100,0)	70 (60,0; 75,0)	0,001
Proteinuria, g/L*	0,65 (0,30; 1,65)	—	—
Edema, *n* (%)	24 (57,1)	2 (10,0)	<0,001
IUPBF, *n* (%)	3 (7,1)	0 (0,0)	0,545
Delivery and perinatal outcomes			
Term of delivery, weeks*	38,43 (36,07; 40,40)	40 (39,18; 40,54)	0,018
Preterm labor, *n* (%)	10 (23,8)	0 (0,0)	0,001
Cesarean section, *n* (%)	16 (38,1)	0 (0,0)	<0,001
Weight of the child at birth, g*	3145 (2485,0; 3572,5)	3690 (3440,0; 3982,5)	<0,001
Apgar score, *n* (%):			<0,001
8–10 points	22 (52,4)	20 (100,0)	
⩽6–7 points	20 (47,6)	0 (0,0)	
FGR, *n* (%)	8 (19,0)	0 (0,0)	0,044
Neonatal RDS, *n* (%)	4 (9,5)	0 (0,0)	0,295

Note. Data are presented as the absolute number and proportion (%) of patients, Fisher's exact test, and Z-test for proportions adjusted for endpoints (0%). *Data are presented as median with interquartile range (Mann–Whitney test). BMI, body mass index; FGR, fetal growth restriction; NMPC, disturbance of uteroplacental and fetal blood flow; RDS, respiratory distress syndrome.

Table 3. Comparative analysis of the expression levels of microRNAs in the blood plasma of patients in the study groups

MicroRNA	FC (study group/ control group)	*p* (study group/ control group)
hsa-miR-20a-5p	1,62	0,440
hsa-miR-143-3p	1,51	0,272
hsa-miR-146a-5p	0,28	0,011
hsa-miR-181a-5p	0,34	0,015
hsa-miR-210-3p	0,31	0,031
hsa-miR-320a-3p	0,73	0,271
hsa-miR-375-3p	1,14	0,524
hsa-miR-517a-3p	0,07	0,004
hsa-miR-517c-3p	0,14	0,007
hsa-miR-574-3p	0,32	0,048
hsa-miR-574-5p	0,05	0,003
hsa-miR-1304-5p	0,03	<0,001
hsa-miR-4498	0,58	0,591
hsa-miR-210-5p	NA	
hsa-miR-1972	NA	

Note. FC — fold change in microRNA levels between groups. NA — absence of expression in one of the compared groups.

migration and proliferation (hsa-miR-146a-5p, hsa-miR-181a-5p, and hsa-miR-210-3p), trophoblast migration and proliferation (hsa-miR-146a-5p, hsa-miR-181a-5p, hsa-miR-210-3p, hsa-miR-517a-3p, hsa-miR-517c-3p, hsa-miR-574-5p, and hsa-miR-1304-5p), angiogenesis (hsa-miR-181a-5p, hsa-miR-517a-3p, hsa-miR-517c-3p, and hsa-miR-574-3p), maintenance of vascular tone (hsa-miR-574-3p and hsa-miR-574-5p), redox balance (hsa-miR-181a-5p, hsa-miR-210-3p, hsa-miR-517a-3p, and hsa-miR-517c-3p), immune tolerance (hsa-miR-517a-3p and hsa-miR-517c-3p), and epithelial–mesenchymal transition (hsa-miR-146a-5p) through post-transcriptional effects on the expression of their target genes [21–40].

Implantation and further development of maternal–fetal interaction depend on the differentiation of placental cytotrophoblasts into villous and extravillous cells [44]. According to studies, among the microRNAs identified in this study as prognostic markers for PE development, the functional potential of hsa-miR-146a-5p is of particular interest. This molecule has been shown to have suppressive activity against epithelial–mesenchymal transition [23] through inhibition of the Wnt2/β-catenin pathway.

Hypoxia was found to play a pivotal role in the development of the placenta, with its impact varying depending on the gestational age. In the first trimester of pregnancy, hypoxia stimulates cytotrophoblast invasion and angiogenesis [45], whereas prolonged hypoxic conditions in the second and third trimesters impede the syncytialization of trophoblast cells, invasion of trophoblast cells, and vascular remodeling, which collectively results in placental dysfunction and hypertension. Among the aberrantly expressed molecules identified, some belong to the family of microRNAs sensitive to hypoxia. In particular, under hypoxia conditions, HIF-1α enhances miR-210 expression, which can lead to blockade of cell proliferation and DNA repair, inhibition of mitochondrial respiration and ATP synthesis, and inhibition of angiogenesis [27]. Hypoxia-induced overexpression of this microRNA in PE was determined to result in damage to the endothelium of trophoblast vessels and trophoblast cells themselves [28]. Our findings revealed that the absence of miR-210 overexpression in patients with PE indicates a potential for this molecule to exhibit broader functional capabilities, which remain to be investigated.

Furthermore, a reduction in placental perfusion in PE results in the release of antiangiogenic factors into the maternal bloodstream, which contributes to generalized endothelial dysfunction. Regarding the molecules miR-517a/b and miR-517c, data from previous studies show their ability to increase the synthesis of anti-angiogenic protein sFlt1. This protein binds circulating angiogenic factors and blocks their ability to induce angiogenesis [47].

Moreover, miR-574 molecules are generally considered as key modulators of endothelial dysfunction in PE [37]. In particular, the experimental study of Ura et al. [46] demonstrated the antiangiogenic effect of miR-574-5p, which is evidenced by the reduced ability to repair damaged tissue, migration suppression, and endotheliocyte proliferation. Given that miR-574-3p and miR-574-5p are among the most frequently identified microRNAs in cardiovascular diseases, particularly in ischemic heart disease, myocardial infarction, and heart failure, an imbalance in the expression levels of these microRNAs may play a crucial role in the development and progression of cardiovascular disorders in PE.

Hypoxia/ischemia in the placenta has been shown to be a potent generator of oxidative stress, to stimulate increased secretion of pro-inflammatory cytokines, and to induce apoptosis in placental tissue [48]. Oxidative stress has been shown to affect the expression levels of certain microRNAs, and microRNAs have been observed to alter the production of cellular antioxidants and cytokines [49]. Previously, miR-181a was found to play a unique role in the development and activation of T cells. Its expression decrease leads to defects in adaptive immunity, which significantly contributes to the pathogenesis of PE. In this regard, published data on the possibility of correcting mitochondrial dysfunction by inhibiting miR-181a are of interest [50].

A comparative analysis of 15 microRNA expression levels in pregnant women with different clinical phenotypes of PE revealed no significant differences between subgroups with

Table 4. Comparative analysis of the expression levels of microRNAs in the blood plasma of the main group depending on the PE phenotype

MicroRNA	FC (PE with FGR/ without FGR)	*p*	FC (severe/ moderate PE)	*p*	FC (early/late PE)	*p*
hsa-miR-20a-5p	0,39	0,049	0,52	0,256	0,86	0,313
hsa-miR-143-3p	0,71	0,05	0,81	0,252	1,07	0,351
hsa-miR-146a-5p	0,57	0,076	0,96	0,400	1,75	0,327
hsa-miR-181a-5p	0,64	0,130	0,84	0,336	1,56	0,363
hsa-miR-210-3p	1,00	0,632	1,00	0,630	1,71	0,251
hsa-miR-320a-3p	0,84	0,336	0,84	0,469	2,30	0,173
hsa-miR-375-3p	0,01	0,379	0,002	0,428	6,71	0,433
hsa-miR-517a-3p	0,60	0,342	5,00	0,450	5,00	0,333
hsa-miR-517c-3p	0,38	0,214	1,38	0,409	1,43	0,442
hsa-miR-574-3p	0,97	0,216	2,45	0,313	2,87	0,186
hsa-miR-574-5p	0,88	0,352	5,29	0,317	2,95	0,222
hsa-miR-1304-5p	1,02	0,397	0,78	0,301	6,47	0,295
hsa-miR-4498	NA	NA	NA	NA	3,73	0,248
hsa-miR-210-5p	NA	NA	NA	NA	NA	NA
hsa-miR-1972	NA	NA	NA	NA	NA	NA

Note. FC, fold change in microRNA levels between subgroups; NA, absence of expression in one of the compared groups.

moderate and severe and early and late PE. This indicates that the final stage of PE development may be characterized by a certain commonality of pathogenetic processes.

The differential expression of miR-20a-5p and miR-143-3p was observed, with significantly lower levels in patients with PE and fetal growth retardation than in those PE and no growth retardation. Studies have indicated that these microRNAs are associated with cardiovascular and cerebrovascular diseases [51]. miR-20a-5p plays a critical role in the pathogenesis of acute kidney injury caused by ischemia/reperfusion [52] and suppresses proliferative and invasive activity of trophoblast cells by repressing the transcription factor FOXA1, which has a direct effect on the laying down and development of organs and tissues. The lower expression levels of miR-20a-5p and miR-143-3p in pregnant women with PE and fetal growth retardation may be compensatory in placental dysfunction.

As outlined in the literature, microRNAs are present in human blood as both free molecules and in extracellular membrane vesicles (apoptotic corpuscles, microvesicles, and exosomes), extracellular complexes with RNA-binding proteins, and complexes with high-density lipoproteins. The concentration of exosomes, including various microRNAs, in maternal blood increases almost 50-fold in the early uncomplicated pregnancy. This increase is progressive as the pregnancy progresses and more than doubles closer to term [53]. However, it has been observed that the contribution of placental exosomes to the total number of plasma exosomes and their bioactivity decreases toward term. This may further explain the decrease in differentially expressed microRNAs just before delivery detected in this study.

MicroRNAs whose regulation is impaired in PE potentially influence a multitude of signaling pathways. These include pathways regulating hormonal and metabolic processes (e.g., HIF-1-, TGF-b-, and p53-signaling pathways), carcinogenesis, infectious processes of various localizations, cell proliferation and differentiation, embryogenesis, oxidative stress, immune response reactions, cell cycle, and others. This fact reiterates the multifaceted nature of disorders of molecular and cellular processes in the development of PE and, as a consequence, makes it challenging to predict and diagnose PE at an early stage using a single biomarker.

CONCLUSIONS

Pregnancy complicated by PE is accompanied by significant epigenetic changes. In particular, changes are noted in the expression profile of microRNAs associated with cardiovascular and cerebrovascular diseases and placental abnormalities.

The results indicate the need for further molecular genetic studies in this area to expand the understanding of the

molecular genetic pathophysiological mechanisms of PE development and search for biomarkers and targeted therapeutic agents.

ADDITIONAL INFO

Author 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.

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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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