BODY MASS INDEX, LIPID PROFILE, AND ENDOTHELIAL DYSFUNCTION GENE POLYMORPHISM IN WOMEN WITH EARLY-ONSET AND LATE-ONSET PREECLAMPSIA

Tetiana Loskutova, Albina Petulko, Yuliya Donskaya

The aim: to investigate and analyze clinical parameters, laboratory biomarkers of lipid metabolism and endothelial dysfunction gene polymorphisms in early-onset and late-onset preeclampsia and to identify potential risk factor(s) for the development of early-onset preeclampsia.

Materials and methods: a prospective case-control study included 133 women in the second half of pregnancy, including 46 with early-onset (EOP) and 87 with late-onset preeclampsia (LOP) and 34 conditionally healthy pregnant women with an uncomplicated obstetric history and no risk factors for preeclampsia. Concentrations of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides in blood plasma were determined. Genetic polymorphisms of endothelial dysfunction (192 Q→R PON-1, 677 C→ T MTHFR) were studied using allele-specific polymerase chain reaction.

Results: Early-onset preeclampsia is associated with an increased relative risk: preterm delivery by 2.08 times (95 % CI 1.48-2.93), operative delivery by 2.2 times (95 % CI 1.46-3.33), early operative delivery by 2.9 times (95 % CI 1.5-5.5), fetal distress during delivery by 3.78 times (95 % CI 1.2-11.9), a low score on the Apgar scale on the 1st minute, less than 6 points, by 2.59 times (95 % CI 1.84-3.66), on the 5th minute – 5.04 times (95 % CI 1.41-18.11), Grade III prematurity – 13.24 times (95 % CI 3.14-55.78) compared to women with late-onset preeclampsia. The study found that overweight was more often observed in patients with EOP (34.8 %) than in those with normal pregnancy (15.9 %) (p=0.02; OR=2.8; 95 % CI 1.03-7.7), obesity (BMI > 30 kg/m2) was more often recorded in those with LOP (33.33 %) than in the control group (3 (6.8 %)) (p=0.02; OR=6.8; 95 % CI 1.9-23.9). Patients in both groups with preeclampsia showed signs of dyslipidemia, but its significance in the development of early-onset or late-onset preeclampsia has not been separately proven. The study found that the number of carriers of MTHFR 677 TT in the group with EOP prevailed over the indicator of C group where there were no carriers of the pathological homozygote 677TT (p<0.05, OR=20.73 95 % CI 1.16-371.28), and the T allele in the EOP group occurs 1.78 times more often than in the LOP group (p<0.05, OR=2.22; 95 % CI 1.26-3.88) and 2.43 times more often than in the C group (P<0.05, or= 3.15; 95 % CI 1.54-6.45).

Conclusions: Factors of early onset of PE include pre-pregnancy, overweight, first pregnancy, a history of preeclampsia, and carrier of the 677T allele of the MTHFR gene.

Keywords: preeclampsia, lipids, body weight, genetic thrombophilia, pregnancy complications, prognosis, gene polymorphism


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1. Introduction

Hypertension disorders during pregnancy are the most common medical complications and occur in 5–10 % of pregnant women worldwide [1]. They remain the leading cause of morbidity and mortality in mothers, fetuses, and newborns.

Maternal risks include: premature abruption of the normally located placenta, stroke, multiple organ failure, and disseminated intravascular coagulation. The fetus has a high risk of intrauterine growth retardation (25 % of preeclampsia cases), prematurity (27 % of preeclampsia cases), and intrauterine death (4 % of preeclampsia cases).

According to the statistical and analytical guide "State of health of the female population in Ukraine for 2021", 21,190 cases of pregnancies complicated by edema, proteinuria and hypertensive disorders were registered, which was 81.88 per 1000 births, including 17687 cases of severe forms of preeclampsia and eclampsia, which was 6.52 per 1000 births [2].

Depending on the time of occurrence, PE is classified as early preeclampsia (EOP) and late preeclampsia (LOP). Early-onset preeclampsia is preeclampsia that
develops before 34 weeks of pregnancy. Late-onset preeclampsia is the one that develops after 34 weeks of pregnancy [3].

Although the diagnostic criteria are the same for early-onset and late-onset preeclampsia, and maternal manifestations may be equally severe in both early-onset and late-onset preeclampsia, it has been suggested that maternal and perinatal morbidity and mortality are different in the two subgroups. EOP is considered to pose a high risk to both the mother and fetus, while LOP may have less pronounced clinical symptoms. There is an opinion that early-onset and late-onset preeclampsia have different etiologies, and clinical parameters and/or laboratory biomarkers indicate that early-onset preeclampsia and late-onset preeclampsia may be different forms of the disease, especially in cases of severe preeclampsia. Clinical parameters and corresponding prognostic consequences may reflect different mechanisms of this disease [1, 4].

The timing of the onset of preeclampsia is the most important factor in predicting pregnancy outcomes, as early preeclampsia with severe hypertension is associated with high rates of perinatal mortality and morbidity. A systematic examination and meta-analysis [5] suggested that dyslipidemia may play a role in the pathogenesis of preeclampsia, as mean serum lipid profiles were significantly higher in preeclamptic women than in normotensive pregnant women. Total cholesterol, triglycerides, LDL cholesterol, and VLDL cholesterol were significantly higher in women with preeclampsia than in pregnant women with normal blood pressure, and HDL cholesterol was lower in women with preeclampsia. At the same time, studies comparing clinical parameters or laboratory biomarkers between early-onset and late-onset preeclampsia are limited.

**The aim** – to investigate and analyze clinical parameters, laboratory biomarkers of lipid metabolism and endothelial dysfunction gene polymorphisms in early-onset and late-onset preeclampsia and to identify potential risk factor(s) for the development of early-onset preeclampsia.

2. Materials and methods

The study was conducted at Dnipro State Medical University, Dnipro, Ukraine, in 2018–2021. A prospective cohort study covered 176 women in a second half of pregnancy. The diagnosis of preeclampsia was based on Order No. 151 of the Ministry of Health of Ukraine, "Hypertensive disorders during pregnancy, childbirth and in the postpartum period", and criteria followed the guidelines of the International Society for the Study of Hypertension in Pregnancy (ISSHP) [6]. Early preeclampsia was defined as occurring before 34 weeks, and late preeclampsia was defined as occurring after 34 weeks of gestation. Mild preeclampsia was defined as maternal systolic blood pressure ≥140 mmHg but ≤160 mmHg and/or diastolic blood pressure ≥90 mmHg but ≤110 mmHg. Severe hypertension was defined as maternal systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥110 mmHg measured on two occasions, separated by at least 6 h, before 34 weeks of gestation of delivery.

All women who at the start of pregnancy may have had medical risk factors for developing preeclampsia such as pre-existing hypertension or other underlying medical disorders such as gestational or pre-existing diabetes, or autoimmune diseases were excluded from this study. No pregnancies conceived by in vitro fertilization were included.

Examination of patients was performed after written informed consent. The management of the study was conducted in full compliance with the ethical principles contained in the “Human Rights Declaration” adopted in Helsinki, which follows the Good Practice Rules in the Clinical Study and Legal Regulations and with the approval of the Ethics Committee of the Dnipro State Medical University (protocol No. 5 dated September 13, 2018).

The main cohort (M) consisted of 46 women with early-onset preeclampsia (EOP) and 87 with late-onset preeclampsia (LOP). Preeclampsia was diagnosed based on as described above. The control group (C) was formed by 44 conditionally healthy pregnant women with a non-complicated obstetrical anamnesis and without risk factors for preeclampsia. All women undergo clinical and laboratory examinations. Data recorded included maternal age, gestation week at diagnosis, gravidity, parity, previous preeclampsia, blood pressure, proteinuria, gestation weeks at delivery, birth weight, and stillbirth. Laboratory data at diagnosis included liver and renal function, platelet count, haematocrit, and haemoglobin. All the laboratory tests were done within 24 h after diagnosis of preeclampsia. Fetal growth restriction (FGR) was defined as birth weight below the 10th percentile for its.

Genetic polymorphisms of endothelial dysfunction (192 Q→R PON-1, 677 C→T MTHFR) were studied with the help of allele-specific polymerase chain reaction, followed by detection by electrophoresis in 3 % agarose gel. A set of reagents “SNP-Express” (Litech SPF) was used. DNA from leukocytes of blood, which was isolated using the reagent "DNA-express blood" (Litech SPF,) was used for analysis.

Determination of the concentration of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG) in blood plasma was conducted in automatic mode on the "Biochemistry Analyzer 88" analyzer, using "Bio-La-Test" reagents (Lachema-Pliva, Czech Republic). Atherogenic index (AI) was calculated according to the formula: CA = (TC – HDL-C) / HDL-C.

Statistical processing of the study results was performed using licensed computer programs Microsoft Excel 2010 and Graph Pad Prism 5 using methods of parametric and nonparametric statistics. The normality of the distribution of quantitative traits was assessed using Shapiro-Wilk and Kolmogorov-Smirnov criteria, analysis of variance, odd t-test, Mann-Whitney test, χ² test with conjugation of conjugation tables and Yates correction, Fisher's exact test were used. Spearman and Pearson correlation coefficients (r) were used to assess the relationship between the indicators. To assess the relationship between impact and outcome, relative risk (RR) and odds ratio (OR) assessments were performed at 95 % confidence interval (CI). The difference between the values was considered significant by p<0.05.

3. Research results

The average age of women and the distribution by age category between groups practically did not differ...
and was 26.98±0.9 in the group with EOP, 28.98±0.65 in the group with LOP, and 26.7±0.8 years in the control group (p<0.05).

Studies of anthropometric data of women in the examined groups showed that women with PE were more likely to have excess body weight before pregnancy than representatives of the control group. The average prepregnancy body weight in the EOP and LOP groups was significantly higher than in the control group (p<0.05). The body mass index in the EOP group is 1.15 times higher (p<0.001), in the LOP group – 1.22 times (p<0.001) than in the control group (Table 1).

<table>
<thead>
<tr>
<th>Study group</th>
<th>Body weight, kg, M±m</th>
<th>Height, m, M±m</th>
<th>BMI, kg/m², M±m</th>
<th>BMI 25–30 kg/m², n, (%)</th>
<th>BMI≥30 kg/m², n, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EOP, n=46</td>
<td>71.9±2.54*</td>
<td>1.67±0.01</td>
<td>26.58±0.76*</td>
<td>16 (34.78)*</td>
<td>9 (19.57)</td>
</tr>
<tr>
<td>LOP, n=87</td>
<td>76.49±2.09*</td>
<td>1.64±0.01</td>
<td>28.27±0.71*</td>
<td>20 (22.99)</td>
<td>29 (33.33)*</td>
</tr>
<tr>
<td>C, n=44</td>
<td>61.8±1.5</td>
<td>1.63±0.01</td>
<td>23.05±0.5</td>
<td>7 (15.9)</td>
<td>3 (6.8)</td>
</tr>
</tbody>
</table>

Note. * – the statistical significance of differences of indicators relative to the C group (p<0.05)

Analysis of reproductive function showed that the number of women with a history of childbirth in the group with EOP was less than 11 (23.9 %) than in the group of LOP 43 (49.4 %) (P=0.005, OR=0.32; 95 % CI 0.14–0.71), and did not differ from the control group 14 (34.1 %). Accordingly, the number of first-born children in the EOP group is significantly higher, 35 (76.1 %), than in the LOP group 44 (50.6 %), (p<0.05, OR=3.1; 95 % CI 1.4–6.9). In the C group, this pregnancy was the first one in 50 % and childbirth in 65.9 %. PE equally often complicated obstetric history in the PE groups: in the group with EOP 5 (20.0 %), with LOP - 4 (7.4 %), respectively.

In the group with EOP, maternal or fetal complications were significantly more likely to occur, which complicated the course of gestation. These are premature abruption of the normally located placenta – 4 (8.7 %), eclampsia – 1 (2.17 %), HELLP – syndrome – 1 (2.17 %), intrauterine growth restriction – 23 (50 %), intrauterine fetal death – 6 (13.04 %), fetal distress during pregnancy – 21 (45.65 %).

The average period of disease onset in the group with EOP was (29.02±0.55) weeks, which is 1.18 times less than in the LOP group (31.17±0.52) weeks (p<0.001), and the duration of the existence of PE in the group with EOP (4.48±0.47) weeks was 1.7 times longer than in the LOP group (2.63±0.18 weeks, p<0.001).

The average gestational age at the time of delivery in the EOP group (33.50±0.57) was 3.44 weeks less than in the comparison group of 36.94±0.27 (p<0.001), which is associated with the severity of preeclampsia and its complications, which required early delivery. In the control group, labour occurred at 38.69±0.22 weeks, which is significantly more than in the study groups (p<0.05).

In the EOP group, 7 (15.22 %) women had moderate preeclampsia, which is mostly less than in the LOP group (24.35 %), p<0.001; OR=0.32; 95 % CI 0.14–0.71). 39 (84.78 %) women in the EOP group had severe preeclampsia, which is more than in the LOP group - 30 (65.52 %) (p<0.001; OR=0.09; 95 % CI 0.04–0.25). 39 (84.78 %) women in the EOP group had severe preeclampsia, which is more than in the LOP group - 30 (65.52 %) (p<0.001; OR=0.09; 95 % CI 0.04–0.25).

The period of pregnancy during which childbirth took place in the EOP group was mainly 1.1 times less (33.5±0.57) weeks than in the LOP group (36.94±0.22) weeks (p<0.001). The presence of complications that occur more frequently in EOP correlates with the term of delivery (p<0.001). Full-term delivery in the EOP group occurred 2.28 times less frequently than in the LOP group (p<0.001, OR=0.22, 95 % CI 0.1-0.48, RR=0.41, 95 % CI 0.25–0.67). Preterm birth prevailed 2.1 times in the EOP group (33 (71.4 %)), compared to the LOP group (30 (34.48 %)) (p<0.001, OR=4.68, 95 % CI 2.11-9.98, RR=2.08, 95 % CI 1.48–2.93). In the EOP group, childbirth at 32-34 weeks was recorded 2.52 times more often (p<0.05, OR=3.0, 95 % CI 1.17-7.9, RR=2.52, 95 % CI 1.15-5.54), at 29-31 weeks – 6.14 times more often than in the 2D group (p<0.001, OR=8.17, 95 % CI 2.48-26.91, RR=6.15 95 % CI 2.12-17.78) (table 2). In C group, all deliveries were urgent.

Operative deliveries in the EOP group 28 (60.9 %) were registered 2.2 times more than in the LOP group (24 (27.6 %)) (p<0.001, OR=4.0, 95 % CI 1.9-8.7) and 2.04 times more often compared to controls (13 (29.5 %)) (p<0.001, OR=3.7, 95 % CI 1.5-8.9). The high rate of operative deliveries in the EOP group is associated with the physiological unpreparedness of the birth canal, lack of effect from treatment, progressive deterioration of the condition of the fetus and/or mother, the addition of complications requiring emergency delivery (premature placental abruption, fetal distress), as evidenced by the presence of an inverse correlation between the frequency of operative interventions and the term of delivery (r=-0.328, p<0.001). The number of premature births by Caesarean section prevails in the EOP group (by 2.94 times) compared to the LOP group (p<0.001, OR=14.57, 95 % CI 3.7-57.73).

Delivery in 8 (17.39 %) women in the EOP group was complicated by fetal distress 3.78 times more often than in the LOP group - 4 (4.6 %) (p<0.05, OR=4.37, 95 % CI 1.24-15.41, RR=3.78, 95 % CI 1.2-11.9) and premature abruption of the normally located placenta in 4 (8.7 %) (p<0.001, OR=18.53, 95 % CI 0.97-352.4).

The average weight of newborns in the EOP group was 3.76 kg (29.5 %) (p<0.001) more often compared to controls (13 (29.5 %)) (p<0.001, OR=3.7, 95 % CI 1.5-8.9). The high rate of operative deliveries in the EOP group is associated with the physiological unpreparedness of the birth canal, lack of effect from treatment, progressive deterioration of the condition of the fetus and/or mother, the addition of complications requiring emergency delivery (premature placental abruption, fetal distress), as evidenced by the presence of an inverse correlation between the frequency of operative interventions and the term of delivery (r=-0.328, p<0.001). The number of premature births by Caesarean section prevails in the EOP group (by 2.94 times) compared to the LOP group (p<0.001, OR=14.57, 95 % CI 3.7-57.73).

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The average weight of newborns in the EOP group was 1.79 times less, the growth of newborns was 1.18 times less than in the LOP group (p<0.005) and 2.09 and 1.22 times less, respectively, than in the C group (p<0.05) (Table 2). Apgar score at the 1st and the 5th minutes in the EOP group was significantly lower than in the LOP and control groups (p<0.05).
Analysis of newborn state in study group

<table>
<thead>
<tr>
<th>Indicator</th>
<th>EOP, n=46</th>
<th>LOP, n=87</th>
<th>C, n=44</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, gr M±m</td>
<td>1647±103.2</td>
<td>2931±71.68</td>
<td>3440±71.54</td>
</tr>
<tr>
<td>Height, cm M±m</td>
<td>42.5±0.85</td>
<td>50.25±0.41</td>
<td>51.93±0.35</td>
</tr>
<tr>
<td>Weight &lt;10th percentile for gestational age, n (%)</td>
<td>23 (50.0)*</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Apgar score at 1 minute, points, M±m</td>
<td>5.1±0.32*</td>
<td>5.53±0.24</td>
<td>6.95±0.09</td>
</tr>
<tr>
<td>Apgar score at 1 minute, ≤6 points, n (%)</td>
<td>37 (80.43)*</td>
<td>27 (31.63)</td>
<td>7 (15.91)</td>
</tr>
<tr>
<td>Apgar score at 5 minutes, points, M±m</td>
<td>6.07±0.36*</td>
<td>7.64±0.06</td>
<td>7.98±0.08</td>
</tr>
<tr>
<td>Apgar score at 5 minute ≤6 points, n (%)</td>
<td>8 (17.39±5.6)*</td>
<td>3 (3.45±1.9)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Note: * p<0.05 compared with the control group by Student’s (t) or Mann-Whitney (U) test for independent samples.

Analysis of lipid metabolism indicators did not reveal significant differences between the groups with preeclampsia (Table 3). The level of total cholesterol (TC) in the group with EOP was 1.13 times higher than the value of the control group in the LOP group – by 1.1 times, respectively (p<0.05), LDL-C in the EOP group by 1.16, in the LOP group by 1.12 times, VLDL-C in the EOP group by 1.27 times exceeded the corresponding values of the C group (p<0.05).

An integral indicator of lipid metabolism and the risk of damage to the vascular wall is the atherogenic index. The value of AI in the EOP group was 1.26 times, and in the LOP group, 1.2 times higher than the indicator of the control group (p<0.05).

### Table 3

Analysis of lipid indicators in pregnant women with early and late preclampsia

<table>
<thead>
<tr>
<th>Indicators</th>
<th>EOP (n=46)</th>
<th>SD</th>
<th>LOP (n=87)</th>
<th>SD</th>
<th>C (n=44)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG, mmol/l</td>
<td>Mean: 3.51</td>
<td>1.08</td>
<td>3.42</td>
<td>1.03</td>
<td>3.2</td>
<td>0.79</td>
</tr>
<tr>
<td>TC, mmol/l</td>
<td>7.03*</td>
<td>1.87</td>
<td>6.87*</td>
<td>1.6</td>
<td>6.2</td>
<td>1.18</td>
</tr>
<tr>
<td>HDL-C, mmol/l</td>
<td>1.45</td>
<td>0.4</td>
<td>1.48</td>
<td>0.5</td>
<td>1.61</td>
<td>0.4</td>
</tr>
<tr>
<td>LDL-C, mmol/l</td>
<td>4.09*</td>
<td>1.4</td>
<td>3.94*</td>
<td>1.12</td>
<td>3.54</td>
<td>0.86</td>
</tr>
<tr>
<td>VLDL-C, mmol/l</td>
<td>1.46*</td>
<td>0.6</td>
<td>1.42</td>
<td>0.65</td>
<td>1.15</td>
<td>0.5</td>
</tr>
<tr>
<td>AI</td>
<td>3.97*</td>
<td>1.14</td>
<td>3.79*</td>
<td>0.93</td>
<td>3.16</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Note: * p<0.05 compared with the control group by Student’s (t) or Mann-Whitney (U) test for independent samples.

Table 4

Frequencies of genotypes and alleles of MTHFR gene (polymorphism 677C→T) and paraoxonase -1 (polymorphism 192 Q→R) in pregnant women with early and late preeclampsia, n (%)

<table>
<thead>
<tr>
<th>Study group</th>
<th>CC</th>
<th>CT</th>
<th>TT</th>
<th>677C</th>
<th>677T</th>
</tr>
</thead>
<tbody>
<tr>
<td>EOP (n=46)</td>
<td>21 (45.65)%,*</td>
<td>17 (36.96)</td>
<td>8 (17.39)%*</td>
<td>59 (64.13)%*</td>
<td>33 (35.87)%*</td>
</tr>
<tr>
<td>LOP (n=87)</td>
<td>60 (68.97)</td>
<td>19 (21.84)</td>
<td>8 (9.2)</td>
<td>139 (79.89)</td>
<td>35 (20.11)</td>
</tr>
<tr>
<td>C (n=44)</td>
<td>31 (70.45)</td>
<td>13 (29.54)</td>
<td>0</td>
<td>75 (85.23)</td>
<td>13 (14.77)</td>
</tr>
</tbody>
</table>

Paraoxanase-1 192 Q→R

<table>
<thead>
<tr>
<th>Study group</th>
<th>QQ</th>
<th>QR</th>
<th>RR</th>
<th>192Q</th>
<th>192R</th>
</tr>
</thead>
<tbody>
<tr>
<td>EOP (n=46)</td>
<td>28 (60.87)</td>
<td>13 (28.26)</td>
<td>5 (10.87)</td>
<td>69 (75.0)</td>
<td>23 (25.0)</td>
</tr>
<tr>
<td>LOP (n=87)</td>
<td>41 (47.13)</td>
<td>31 (35.63)</td>
<td>15 (17.24)</td>
<td>113 (64.94)</td>
<td>61 (35.06)</td>
</tr>
<tr>
<td>C (n=44)</td>
<td>29 (65.91)</td>
<td>8 (18.18)</td>
<td>7 (15.91)</td>
<td>66 (75.0)</td>
<td>22 (25.0)</td>
</tr>
</tbody>
</table>

Note: * – the difference in indicators is statistically likely with LOP (p<0.05) by Criterion χ², including the Yates correction; * – the difference in indicators is statistically likely with C group (p<0.05) by Criterion χ², including the Yates correction.

Analysis of allele and genotype frequencies MTHFR 677 C→T revealed a decrease in the frequency of the normal CC genotype in the EOP group (Table 4). Its frequency is reduced by 1.5 times compared to the LOP group (p<0.05, OR= 0.38, 95 % CI 0.18-0.79) and 1.54 times compared to the control group (p<0.05, OR= 0.35, 95 % CI 0.15-0.84).

The number of MTHFR 677 TT carriers in the group with EOP prevailed over the indicator of the C group, where there were no carriers of the pathological
The number of heterozygotes is 677 St MTHFR, and pathological homozygotes are 677 TT between groups with PE.

Comparing the frequencies of alleles C and T, it was noted that the T allele in the group with EOP occurs 1.78 times more often than in the group with LOP (p<0.05, OR=2.22; 95 % CI 1.26-3.88) and 2.43 times more often than in the C group (P<0.05, or= 3.15; 95 % CI 1.54-6.45).

The polymorphism in the paraoxonase-1 192 Q→R gene has no proven influence on the development of preeclampsia (p>0.05).

4. Discussion

During the last decades, preeclampsia has remained the leading cause of maternal and fetal complications worldwide. Early-onset preeclampsia is associated with an increased relative risk (RR): preterm delivery by 2.08 times (95 % CI 1.48-2.93), operative delivery by 2.2 times (95 % CI 1.46-3.33), early operative delivery by 2.9 times (95 % CI 1.5-5.5), fetal distress during delivery by 3.78 times (95 % CI 1.2-11.9), a low score on the Apger scale on the 1st minute, less than 6 points, by 2.59 times (95 % CI 1.84-3.66), on the 5th minute – 5.04 times (95 % CI 1.41-18.11), Grade III prematurity – 13.24 times (95 % CI 3.14-55.78) compared to women with late-onset preeclampsia. It was determined that the onset of preeclampsia at 28 weeks of gestation or earlier increases the relative risk of complications by 34.04 times (p<0.001, RR=34.04, 95 % CI 4.69-247.1), and the duration of the existence of PE more than 5 weeks increases the relative risk of developing complications by 3.57 times (95 % CI 1.73-7.38).

Previous studies have shown that obesity is a significant independent risk factor for gestational hypertension [7], but data that relate specifically to the risk of early-onset or late-onset preeclampsia have not been found. Adipose tissue is known to be associated with metabolic syndrome, obesity, and dyslipidemia, which can induce inflammatory changes and subsequently lead to increased oxidative stress. This leads to endothelial dysfunction, prothrombotic changes, and pathological hozygous 677TT. In our study, it was determined that the number of MTHFR 677 TT carriers in the group with EOP was greater than the indicator of the C group (p<0.05, OR= 20.73 95 % CI 1.16-371.28), and the T allele in the EOP group was 1.78 times more frequent than in the LOP group (p<0.05, OR=2.22; 95 % CI 1.26-3.88) and 2.43 times more often than in the C group (p<0.05, OR= 3.15; 95 % CI 1.54-6.45). Our data are consistent with a study [16] that indicated that MTHFR 677TT homozygous were present only in early-onset PE, and hyperhomocysteinemia created a threefold increased risk of early preeclampsia. The obtained data are also consistent with [17], where it was determined that the proportion of TT genotype MTHFR in women with preeclampsia was 25.53 %, which significantly exceeded the indicator in the group with physiological pregnancy (7.84 %, p<0.05). Thus, it can be hypothesized that the combination of the MTHFR 677TT mutation, overweight, or obesity is a risk factor for early-onset preeclampsia.

Study limitations:
1. Small sample size.
2. Different distribution of genetic forms of thrombophilia depending on the region of residence.

Prospects for further research. The results of the study can be used to develop a model for predicting
preeclampsia and create a personalized management algorithm to prevent pregnancy complications.

5. Conclusions
Early-onset preeclampsia is associated with an increased relative risk (RR): preterm delivery by 2.08 times (95 % CI 1.48–2.93), operative delivery by 2.2 times (95 % CI 1.46–3.33), early operative delivery by 2.9 times (95 % CI 1.5–5.5), fetal distress during delivery by 3.78 times (95 % CI 1.2–11.9), a low score on the Apgar scale on the 1st minute, less than 6 points, by 2.59 times (95 % CI 1.84–3.66), on the 5th minute – 5.04 times (95 % CI 1.41–18.11), Grade III prematurity – 13.24 times (95 % CI 3.14–55.78) compared to women with late-onset preeclampsia.

Factors of early onset of PE include pre-pregnancy, overweight, first pregnancy, a history of preeclampsia, and carrier of the 677T allele of the MTHFR gene.

Conflict of interest
The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this article.

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Data availability
Data will be made available on reasonable request.

Use of artificial intelligence
The authors confirm that they did not use artificial intelligence technologies when creating the current work.

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