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THE PROGINS VARIANT OF THE PGR GENE AND PLACENTAL ENDOCRINE FUNCTION AT RISK OF PRETERM LABOR: A PILOT STUDY

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Key words: *progins variant, PGR gene, placental endocrine function, preterm labor, progesterone deficiency, genetic association, hormonal regulation, preterm birth risk, endocrinology of pregnancy, genetic markers, progesterone treatment efficacy, placental function, personalized medicine, preterm labor prevention.*

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Resume. *Progesterone receptors, which are encoded by the PGR gene, mediate the main physiological effects of progesterone – the hormone that is required for a successful pregnancy. The PROGINS variant is one of the most common variants of the PGR gene. Due to genetic heterogeneity, the presence of inferior forms of progesterone receptors in women can be a clinical problem. In addition to fertility problems, such women may theoretically respond differently to progesterone replacement therapy.*

Aim of the study *to determine the effect of the PROGINS variant of the PGR gene on the hormonal status and results of progesterone deficiency treatment in pregnant women at risk of preterm labor.*

Material and methods. *The main group included 30 pregnant women with progesterone deficiency and the threat of preterm labor, and the comparison group included 30 pregnant women with a normal course of pregnancy. The concentrations of progesterone, estradiol, and placental lactogen were measured in the pregnant women of both groups. Genotyping was assayed by PCR.*

Results. *The genotypic frequencies of the PROGINS variant were not significantly different between the main and comparison groups. Pregnant patients in the main group with the T2T2 genotype after treatment had significantly lower progesterone levels compared to patients with the T1T1 and T1T2 genotypes. Pregnant women in the main group with the T2T2 genotype delivered at a shorter gestational age.*

Conclusion. *The results of our study showed the associations between the PROGINS variant of the PGR gene and the inefficacy of progesterone deficiency treatment in pregnant women at risk of preterm birth and shortened gestation.*

ВАРІАНТ PROGINS ГЕНА ПРОГЕСТЕРОНОВОГО РЕЦЕПТОРА PGR ТА ЕНДОКРИННА ФУНКЦІЯ ПЛАЦЕНТИ ПРИ ЗАГРОЗІ ПЕРЕДЧАСНИХ ПОЛОГІВ: ПІЛОТНЕ ДОСЛІДЖЕННЯ

П.Ю. Токар

Ключові слова: *варіант PROGINS, ген PGR, ендокринна функція плаценти, передчасні пологи, недостатність прогестерону, генетична асоціація, гормональна регуляція, ризик передчасних пологів, ендокринологія вагітності, генетичні маркери, ефективність лікування прогестероном, функція плаценти, персоналізована медицина, профілактика передчасних пологів.*

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Резюме. *Рецептори прогестерону, які кодуються геном PGR, забезпечують основні фізіологічні ефекти прогестерону – гормону, необхідного для успішної вагітності. Варіант PROGINS є одним з найпоширеніших варіантів гена PGR. Через генетичну гетерогенність наявність неадекватних форм рецепторів прогестерону у жінок може бути клінічною проблемою. Окрім проблем з фертильністю, такі жінки можуть теоретично по-різному реагувати на терапію заміщення прогестерону.*

Мета дослідження *- визначити вплив варіанта PROGINS гена PGR на гормональний статус та результати лікування прогестеронової недостатності у вагітних із загрозою передчасних пологів.*

Матеріал і методи. *Основна група включала 30 вагітних із недостатністю прогестерону та загрозою передчасних пологів, а група порівняння включала 30 вагітних із нормальним перебігом вагітності. У вагітних обох груп вимірювали концентрації прогестерону, естрадіолу та плацентарного лактогену. Генотипування проводили за допомогою ПЛР.*

Результати. *Генотипові частоти варіанта PROGINS не відрізнялися суттєво між основною групою та групою порівняння. Вагітні пацієнтки з основної групи з генотипом T2T2 після лікування мали значно нижчі рівні прогестерону порівняно з пацієнтками з генотипами T1T1 та T1T2. Вагітні з основної групи з генотипом T2T2 народжували на коротшому терміні гестації.*

Висновок. *Результати дослідження показали асоціації між варіантом PROGINS гена PGR і неефективністю лікування недостатності прогестерону у вагітних, які підлягають ризику передчасних пологів та скорочення терміну гестації.*

Introduction. Hormones are essential for the maintenance of pregnancy and harmonious fetal development. The placenta is one of the main endocrine organs in pregnancy, producing hormones and biologically active substances necessary for both the placenta itself and fetal development. However, it should be noted that the production of hormones during pregnancy is controlled by a complex system involving the mother, placenta, and fetus. The results of numerous studies in physiologic and complicated pregnancies indicate that disruptions in the endocrine activity of the placenta lead to a range of complications. These include preterm birth, the delivery of infants with low birth weight for their gestational age, preeclampsia, gestational diabetes, etc [1-3].

The genetic aspect plays a significant role in the development of placental endocrine disorders and preterm birth, although few studies have yielded contradictory findings [4]. In particular, these studies have analyzed the effect of progesterone receptor (PGR) gene variants on the development of preterm birth and the condition of newborns [5-7]. It is known that progesterone receptors mediate the main physiological effects of progesterone. It has been determined that high variability of the PGR gene is widespread among European populations, which is historically due to migration processes and natural selection [8]. The PROGINS variant is one of the most common variants of the PGR gene – according to the 1000 Genomes project, its frequency among Europeans is 18% [9]. The PROGINS variant of the PGR gene is formed due to the insertion of Alu in 306 bp in intron 7 and leads to a decrease in transcript stability and does not create splice variants [10, 11]. This, in turn, can lead to inferior forms of progesterone receptors with altered properties, in particular, with reduced sensitivity to progesterone [10]. It should be noted that the PROGINS variant (due to the presence of the Alu insertion) is in a strong nonequilibrium linkage with rs1042838 (Val660Leu) in exon 4 and rs1042839 (His770His) in exon 5 of the PGR gene, forming the haplotype of the same name [10, 12]. Due to genetic heterogeneity, the presence of inferior forms of progesterone receptors in women can be a clinical problem. In addition to fertility problems, such women may theoretically respond differently to progesterone replacement therapy.

Aim of the study to determine the effect of the PROGINS variant of the PGR gene on the hormonal status and results of progesterone deficiency treatment in pregnant women at risk of preterm labor.

Materials and methods.

Study groups

The main group included 30 pregnant women with progesterone deficiency and the threat of preterm labor, and the comparison group included 30 randomly selected pregnant women with a normal (physiological) course of pregnancy. Pregnant women in the main group received standard therapy for progesterone deficiency, including progesterone preparations. Criteria for inclusion and exclusion of study participants are depicted in Figure 1.

Baseline clinical characteristics and the condition of their children were analyzed in pregnant women of both groups. Table 1 presents the baseline clinical characteristics of pregnant women, as well as the gestational age of newborns, their weight and height.

When comparing clinical parameters, significant differences were found in the age of the examined women.

Table 1

Baseline characteristics of study groups

Characteristic		Main group (n=30)	Comparison group (n=30)	Statistical differences
Average age, years		31.8±6.7	25.9±4.7	p=0.001
BMI before pregnancy, kg/m^2		22.1±2.0	23.7±2.0	p=0.065
Gestational age of the newborn, weeks		36.8±2.3	39.4±0.9	p=0.0001
Conditions/diseases during pregnancy	Yes	14 (46.7%)	19 (63.3%)	p=0.19
	No	16 (53.3%)	11 (36.7%)	
The total number of pregnancies in the anamnesis		1 [0-2]	1 [0-1]	p=0.11
Number of live births		1 [0-2]	1 [0-1]	p=0.36
Extragenital pathology (before pregnancy)	Yes	23 (76.7%)	4 (13.3%)	p=0.00001
	No	7 (23.3%)	26 (86.7%)	
Weight of the newborn, g		2953.0±932.2	3405.5±413.9	p=0.027
Height of the newborn, cm		50.0±5.7	53.2±2.3	p=0.023

In the main group, women exhibited a notably higher average age and a significantly higher incidence of extragenital pathology. Women in the study group gave birth to newborns at an average gestational age of 36.8±2.3 weeks, with significantly lower weight and height than women in the comparison group.

This study conducted in accordance with the principles set forth in the Helsinki Declaration 2008. The study was approved by the Biomedical Ethics Committee of Bukovinian State Medical University (minutes No. 1 as of 09/15/2022) and all participants signed informed consent.

Assessment of the hormonal status of pregnant women

To assess the functional state of the hormonal function of the mother-placenta-fetus system in pregnant women, the concentrations of progesterone, estradiol, and placental lactogen were measured.

The quantitative assessment of the concentration of hormones in blood plasma was determined by the method of calorimetric enzyme-linked immunosorbent assay in the educational and scientific laboratory of Bukovinian State Medical University.

Hormone levels were determined using a competitive enzyme-linked immunosorbent colorimetric method. The following reagent kits were used: “Human PL (Placental Lactogen) ELISA Kit”, “Progesterone ELISA”, and “Estradiol ELISA”. Hormone levels were assessed during both the early (25-28 weeks of pregnancy) and late (30-40 weeks of pregnancy) fetal periods, and in the comparison group, post-treatment measurements were taken accordingly.

Molecular genetic studies

Genomic DNA for molecular genetic studies was isolated from the peripheral blood of the subjects using the “Quick-DNA Miniprep Plus Kit” (Zymo Research, USA) according to the instructions.

The PROGINS variant of the PGR gene was identified using the allele-specific polymerase chain reaction method. The “DreamTaq Green PCR Master Mix” (Thermo Scientific) and specific oligonucleotide primers (Metabion, Germany) were used for PCR: 5′-TAT GAG CTA TTT GAG TAA AGC CT-3′ and 5′-TTC TTG CTA AAT GTC TGT TTT AA-3′ [13].

The amplification products were separated by electrophoresis in a 2% agarose gel (agarose from Cleaver Scientific, UK) with ethidium bromide as a dye. To estimate the size of the fragments, the molecular weight marker O'GeneRuler Low Range (Thermo Scientific, USA) was added, and the distribution of fragments in the gel was visualized using a transilluminator (Figure 2).

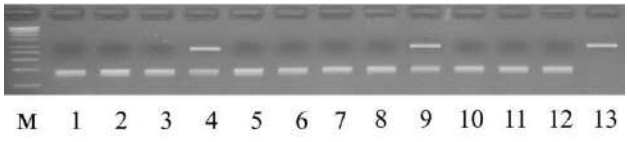

Fig. 2. Electrophoregram of amplified fragments of the PROGINS variant of the PGR gene. M – molecular weight marker; 1-3, 5-8, 10-12 – T1T1 genotype; 4, 9 – T1T2 genotype; 13 – T2T2 genotype

Statistical analysis

Descriptive, parametric, and nonparametric statistical methods were employed for data analysis using SPSS v.26. Quantitative parameters were expressed as mean ± standard deviation, while pregnancy characteristics such as the number of pregnancies and live births were presented as median within the 25th and 75th percentiles. Categorical variables were represented as percentages. Differences in the distribution of categorical variables among study groups and subgroups were evaluated using $\chi 2$ (or $\chi 2$ with Yates' correction). Normal distribution of quantitative characteristics among pregnant women was assessed using the Kolmogorov-Smirnov test, followed by ANOVA or Kruskal-Wallis test to determine the significance of differences. A significance level of $p<0.05$ was considered statistically significant.

Results. *Genetic risk of progesterone deficiency and preterm labor depending on the PROGINS variants of the PGR gene*

In the analysis of genotype frequencies concerning the PROGINS variant of the PGR gene among the groups of examined women (Table 2), a higher prevalence of T2T2 genotypes was observed among pregnant women in the main group, while T1T2 genotypes were more common in the comparison group. However, these differences were assessed as unreliable in the statistical analysis.

No genetic risk models for progesterone deficiency and preterm birth associated with the studied genetic factor were identified. Additionally, correlation analysis between the PGR gene variant and age or extragenital pathology revealed no significant associations. Consequently, the study continued within the comparison groups without excluding pregnant women from the main group based on factors such as overweight or obesity, extragenital pathology, or age exceeding 25 years.

Hormonal status of pregnant women, including the assessment of indicators before and after treatment of progesterone deficiency in the main group

In the main group of pregnant women, we determined the average levels of hormones before and after treatment and compared them with the average levels obtained for pregnant women in the comparison group (Table 3).

The average levels of hormones in the comparison group were within the range of reference values and corresponded to the gestational age.

A significant increase in the levels of progesterone, estradiol, and placental lactogen was observed in the examined pregnant women of the main group after treatment. It should be noted that in pregnant women after treatment, the levels of estradiol and placental lactogen were within the reference range and did not differ significantly from those of the comparison group. Despite the increase in the average progesterone level after treatment, the average progesterone level in the main group was low.

The hormone therapy used in pregnant women with threatened preterm labor and progesterone deficiency (in the main group) had a clinical effect – it prevented preterm labor in 76.6% of cases.

The effect of the PROGINS variant of the PGR gene on

hormone levels in the examined pregnant women, including the dynamics of indicators in the main group

Taking into account the main objective of the study and the low average progesterone level in the main group after treatment, we analyzed the effect of the PROGINS variant of the PGR gene on hormone levels in the examined pregnant women (Table 4).

As can be seen from the data presented in the table, in the comparison group and the main group (before treatment), there was no significant effect of the PROGINS variant of the PGR gene on hormone levels.

At the same time, it is noteworthy that pregnant patients in the main group with the T2T2 genotype after progesterone treatment had significantly lower progesterone levels compared to patients with the T1T1 and T1T2 genotypes, indicating reduced effectiveness of progesterone deficiency treatment in pregnant women with threatened miscarriage and risk of preterm birth in the presence of the T2T2 genotype.

Association of the PROGINS variant of the PGR gene with gestational age of newborns

It is well known that the hormonal status of a pregnant woman and the results of treatment of progesterone deficiency at risk of preterm birth determine the outcome of delivery and the condition of the newborn, including weight and growth parameters. Our study revealed a notable impact of the PROGINS variant of the PGR gene on delivery outcomes, particularly on the height and weight of newborns (see Table 5). Interestingly, among pregnant women in the main group, despite receiving standard treatment for progesterone deficiency and the risk of preterm labor, those with the T2T2 genotype delivered at a shorter gestational age.

Table 2

Distribution of genotype frequencies by the *PGR* gene in the study groups

Variant, genotype		Main group (n=30)	Comparison group (n=30)	Statistical differences
PROGINS	T1T1	21 (70.0%)	18 (60.0%)	p=0.48
	T1T2	7 (23.3%)	11 (36.7%)	
	T2T2	2 (6.7%)	1 (3.3%)	

Table 3

Hormonal status of pregnant women

Hormone	Main group (n=30)		Comparison group (n=30)	Statistical differences
	Before treatment	After treatment		
Progesterone, nmol/L	108.3±28.9	174.7±14.1	301.9±84.7	p<0.0001
Estradiol, nmol/L	27.1±7.2	65.1±17.0	66.7±16.4	p=0.89
Placental lactogen, mg/L	1.4±0.4	8.1±2.1	7.7±2.2	p=0.38

Table 4

Hormonal status of pregnant women depending on PGR gene genotypes

Study group	Hormone	T1T1 genotype	T1T2 genotype	T2T2 genotype	Statistical differences
Comparison group (n=30)	Progesterone, nmol/L	290.3±91.6	321.9±76.5	288.6	p=0.65
	Estradiol, nmol/L	63.0±16.7	72.7±15.5	66.6	p=0.39
	Placental lactogen, mg/L	7.4±2.4	8.3±2.0	7.4	p=0.65
Main group (n=30) (before treatment)	Progesterone, nmol/L	108.9±28.4	105.3±36.2	112.4±5.1	p=0.85
	Estradiol, nmol/L	27.2±7.1	26.3±9.1	28.1±1.3	p=0.85
	Placental lactogen, mg/L	1.4±0.4	1.3±0.5	1.4±0.1	p=0.85
Main group (n=30) (after treatment)	Progesterone, nmol/L	174.4±13.6	180.8±13.9	156.6±0.1	p=0.043
	Estradiol, nmol/L	65.3±17.0	63.6±20.6	67.4±3.1	p=0.85
	Placental lactogen, mg/L	8.2±2.1	8.0±2.6	8.4±0.4	p=0.85

Table 5

Gestational age and weight-growth characteristics in newborns depending on maternal genotypes by *PGR* gene

Study group	Characteristic	T1T1 genotype	T1T2 genotype	T2T2 genotype	Statistical differences
Comparison group (n=30)	Weight of the newborn, g	3445.8±349.7	3358.2±528.6	3200.0	p=0.82
	Height of the newborn, cm	53.4±1.9	52.9±2.9	52.0	p=0.56
	Gestational age, weeks	39.2±0.9	39.6±0.5	41.0	p=0.08
Main group (n=30)	Weight of the newborn, g	2977.1±986.3	3027.1±654.6	2410.0±1412.2	p=0.87
	Height of the newborn, cm	50.0±6.0	50.7±635	47.5±12.0	p=0.97
	Gestational age, weeks	36.8±2.1	37.4±1.3	32.8±4.1	p=0.048

Our findings indicate an association between the T2T2 genotype and a decrease in the gestational age of newborns during the treatment of progesterone deficiency in pregnant women following the standard regimen. Additionally, pregnant women in the main group with the T2T2 genotype showed a tendency to deliver infants with lower weight and height, although this difference was not significant.

Thus, the association of the T2T2 genotype with decreased effectiveness of progesterone deficiency treatment in pregnant women, leading to shortened gestation (preterm birth), was identified. Therefore, the presence of the T2T2 genotype in pregnant women with progesterone deficiency and the risk of preterm labor is a promising indicator of the ineffectiveness of standard treatment.

Discussion. In our study, we observed that pregnant women in the main group experiencing hormone level issues were generally older compared to those in the control group. This finding aligns with existing scientific literature, which highlights a woman's age as a contributing factor influencing hormone production during pregnancy [14,15]. However, upon conducting correlation analysis, we did not reveal any significant relationship between the studied gene variant and women's age, along with other clinical characteristics such as the presence of extragenital pathology. Consequently, these features of pregnant women in the main group did not exert any influence on the outcomes of genetic risk assessment.

The results of our study have shown that the T2T2 genotype is associated with ineffective treatment of progesterone deficiency and a corresponding reduction in the gestational age of newborns (preterm birth) among treated pregnant women.

Insufficiency of the hormonal response in pregnant women at risk of preterm labor is characterized by a decrease in the concentration of all hormones produced by the placenta. This presentation indicates the presence of severe long-term disorders within the fetoplacental system, often culminating in placental insufficiency. To address such pathological conditions, progesterone drugs are commonly prescribed to pregnant women as a primary intervention. However, the efficacy of progesterone treatment in prolonging pregnancy remains uncertain, and the results of large-scale studies on the effectiveness of this type of drug in pregnant women with threatened premature birth/miscarriage are still controversial for unknown reasons [16]. Consequently, questions persist regarding the optimal dosage and administration routes of progesterone drugs [17]. Our findings directly highlight the necessity for such optimization in pregnant women with progesterone deficiency and a predisposition to preterm birth, accounting for genetic factors like the presence of the T2T2 genotype. It is worth noting that this study is preliminary and constrained by the limited number of patients included in genotyping and subsequent statistical analysis. Therefore, further large-scale research is required to explore the associations of the PROGINS variant of the PGR gene with the efficacy of progesterone treatment in reducing the risk of preterm birth.

Studies of the effect of the PROGINS variant of the PGR gene on hormone levels in pregnant women with progesterone deficiency are few, especially in the context of treatment. For example, the study by Mir et al. identified a significant association between the PROGINS haplotype and lower serum progesterone levels [18]. Meanwhile, our study demonstrated for the first time that the presence of the PROGINS variant of the PGR gene is associated with lower efficacy of progesterone-based medical correction in pregnant women at risk of preterm labor. The obtained results confirm the findings of the study by Romano et al. where they determined the functional characteristics of the PROGINS variant using various in vitro approaches [10]. It should be noted that this result has an extraordinary potential for use in medical practice, which will allow us to identify a group of patients resistant to standard corrective drug therapy among pregnant women with threatened

preterm labor at the diagnostic stage.

In our study, we identified the association of the PROGINS variant of the PGR gene with a shortened gestation period in newborns. Similar results were obtained by other research groups. For example, Ehn et al. proved that the presence of variants of the PGR gene (including PROGINS) in the mother can provoke preterm birth [19]. A study by Tiwari et al. indicated that the presence of the PROGINS variant is a genetic risk factor associated with a tendency to preterm birth, negative pregnancy outcome, and low birth weight [7]. It should be noted that some studies have refuted this claim, finding no significant relationship between the presence of the PROGINS variant in the mother and the risk of preterm birth [20,21,22], which may be due to population genetic differences, and this should be taken into account when planning further large-scale work in this area.

Further exploration into the significant correlations identified in this study will serve as the foundation for the implementation of personalized approaches to address and overcome this medical problem.

Conclusions. The results of our study showed the associations between the PROGINS variant of the PGR gene and the inefficacy of progesterone deficiency treatment in pregnant women at risk of preterm birth and shortened gestation.

Prospects for further research. Further research into the significant patterns we have identified-specifically, the association of the PROGINS variant of the PGR gene with treatment inefficacy in cases of progesterone deficiency in pregnant women at risk of preterm labor and shortened gestational duration—will form the basis for implementing personalized approaches to address this prevailing medical issue.

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