ISSN 2616-4868
ISSN 3041-1521 Online
UDC 614.21

КЛІНІЧНА ТА ПРОФІЛАКТИЧНА МЕДИЦИНА

НАУКОВИЙ МЕДИЧНИЙ ЖУРНАЛ

CLINICAL AND PREVENTIVE MEDICINE

SCIENTIFIC MEDICAL JOURNAL

№ 5 (43) / 2025

Адреса редакції:

01014, м. Київ, вул Верхня, 5, Україна
Тел. (044) 254-68-71, e-mail: mag.cp.medical@gmail.com
http://www.cp-medical.com

Address of the editorial office:

01014, Kyiv, Verkhnia st., 5, Ukraine
Tel. (044) 254-68-71, e-mail:mag.cp.medical@gmail.com
http://www.cp-medical.com

Періодичність виходу – 8 разів на рік

Свідоцтво про внесення суб'єкта господарювання до державного реєстру видавців, виготовлювачів і розповсюджувачів видавничої продукції ДК №8195

Рекомендовано до друку Вченою радою ДНУ «ЦІТОЗ» ДУС (протокол №3 від 17.04.25 р.)

Підписано до друку 2.06.2025 р.

Видавець – Державна наукова установа «Центр інноваційних технологій охорони здоров'я» Державного управління справами

Журнал входить до списку друкованих (електронних) періодичних видань, що включаються до Переліку наукових фахових видань України категорія «А» (Наказ МОН від 10.12.2024 року № 1721).

Ідентифікатор друкованого медіа в Реєстрі R30-02194

Periodicity – 8 times a year

Certificate of Inclusion of a Business Entity in the State Register of Publishers, Producers and Distributors of Publishing Products DK No. 8195

Recommended for printing by the Academic Council of the SIS «CINT» SAD (protocol No.3 dated 17.04.25).
Signed for printing 2.06.2025.

Publisher – State Institution of Science «Center of innovative healthcare technologies» State Administrative Department

The magazine is included in the list of printed (electronic) periodicals, included in the List of scientific professional editions of Ukraine category 'A' (Order of the Ministry of Education and Science of Ukraine dated 10.12.2024 No. 1721).

Print media identifier in the Register R30-02194

(ACCEPTED 06-JUL-2023)

Надруковано в типографії: ФОП Ліпак У.М., м. Чернівці, вул. Головна, 244/ 5. Свідоцтво: серія ДК-7505, від 8.11.2021 р.
Наклад 500 прим. Ум. друк. арк.: 25,5. Зам. №70-2025.

ЗМІСТ
№ 5 (43)

UDC 618.3-06-092-07:575.113:618.39-021.3-037
https://doi.org/10.31612/2616-4868.5.2025.02

PROGNOSIS OF RECURRENT PREGNANCY LOSS

Tetiana O. Loskutova, Albina P. Petulko

Dnipro State Medical University, Dnipro, Ukraine

Abstract

Aim. To develop a model for the prognosis of recurrent pregnancy loss (RPL) which is based on the determination of the polymorphism of genes 675 5G4/G plasminogen activator inhibitor – 1 (PAI-1) and fibrinogen β 455 G→A and to evaluate its effectiveness.

Materials and methods. A prospective case-control study included 109 women in the 1st trimester of pregnancy with RPL and 34 conditionally healthy pregnant women with an uncomplicated obstetric history and no risk factors for miscarriage. Genetic polymorphisms of coagulation and fibrinolysis factors 675 5G/4G PAI-1and fibrinogen β 455 G→A have been investigated using allele-specific polymerase chain reaction.

Results. Pathological polymorphisms genes of hemostasis system play an important role in the development of miscarriage, namely such pathological genotypes as 675 4G/4G PAI-1 – increases the risk by 7.5 times (95% CI 1.7-33.79), -455AA fibrinogen β – by 10.87 times (95% CI 1.42-83.27). The combination of allelic variants of the PAI-1 genes 5G/4G, 4G/4G and fibrinogen β -455 GA, -455 A in women with RPL (53.2%) were significantly more common than in the control group (20.5%), ($p<0.05$, OR = 4.17, 95% CI 1.71-10.14). Pathogenetically grounded methods for predicting RPL have been developed. It is based on the determination of gene polymorphisms PAI-1 (675 5G/4G), fibrinogen β (-455 G→A) which consider the cumulative contribution each of the markers, and make it possible to determine the probability of miscarriage. Prognostic model has a sensitivity 69.72% (95% CI 60.19-78.16%), specificity– 76.47% (95% CI 58.83-89.25%).

Conclusions. The course of pregnancy against the background of pathological polymorphisms of genes of the hemostasis system significantly increases the risk of habitual miscarriage, which should be considered when planning pregnancy in such women.

Keywords: **habitual miscarriage, recurrent miscarriage, recurrent pregnancy loss, RPL, genetic thrombophilia, pregnancy complications, prognosis, gene polymorphism**

INTRODUCTION

Unfavorable dynamic changes in demographic indicators, especially during the war, make the problem of preserving the reproductive health of the population as one of the most important and prioritized areas of modern medicine. It was estimated that 23 million miscarriages occur every year worldwide. The pooled risk of miscarriage is 15,3% (95% CI 12,5-18,7%) of all recognized pregnancies. The frequency of one miscarriage is 10,8% (10,3-11,4%), two miscarriages is 1,9% (1,8-2,1%), and three or more miscarriages is 0,7% (0,5-0,8%) [1]. Although the prevalence of Recurrent Pregnancy Loss (RPL) is not very high among population in general, for a particular woman or a couple who suffers from pregnancy loss, it matters a lot.

Miscarriage has both physical and psychological impact on a woman's quality of life. Psychological consequences include increases in the risk of anxiety, depression, post-traumatic stress disorder and suicide. Miscarriage and especially recurrent pregnancy loss, is also a risk marker for obstetric complications, including preterm birth, fetal growth restriction [2], placental abruption, and stillbirth in future pregnancies, and a predictor of longer-term health problems, such as cardiovascular disease and venous thromboembolism [1].

At the same time, reducing the number of spontaneous miscarriages in the early stages of gestation should be considered one of the reserves for preventing perinatal losses and increasing the birth rate in our country.

According to ESHRE [3] a diagnosis of Recurrent Pregnancy Loss (RPL) could be considered after the loss

of two or more pregnancies. It is known that RPL has a multifactorial genesis that includes genetic, immune, infectious, anatomical, endocrine, and thrombophilic components [4, 5]. None of the factors can fully explain the occurrence of reproductive losses, and in 40% of cases, PL remains without an established cause after all possible factors have been excluded [6].

In turn, thrombophilia is attributed to the etiological factors of habitual miscarriage [3], as well as obstetric complications such as preeclampsia, fetal growth retardation, and placental abruption. Non-thrombogenic mechanisms of mutations and polymorphisms of thrombophilia genes disrupt normal implantation processes, which creates conditions for the development of obstetric complications. At the same time, the prevalence of this pathology (the type of pathological polymorphisms, their combinations) among women with repeated miscarriages has not been finally determined until today. It should also be borne in mind that the development, course, and complications of thrombophilia may depend on defects in various components of the hemostatic system, external factors, vary in degree of manifestation, and depend on the interaction and specifics of the combination of these disorders. The diagnostic approach and the management depend on the etiology and risk factors taken into consideration by a healthcare professional as a cause of recurrent miscarriage for a particular woman or couple. According to Musters, A. (2013) [7], «couples suffering from recurrent pregnancy loss require individualized management that includes appropriate support, and in this context, testing for relevant factors can help reduce anxiety and manage expectations.» All of the above determined the choice of the topic and purpose of the study.

AIM

To develop a model for the prognosis of habitual miscarriage based on the determination of the polymorphism of genes 675 5G4/G of plasminogen activator inhibitor – 1 (PAI-1) and fibrinogen β 455 G→A and to evaluate its effectiveness.

MATERIALS AND METHODS

The study was conducted at Dnipro State Medical University, Dnipro, Ukraine, in 2018-2020. A prospective cohort study covered 143 women in the first half of pregnancy. The diagnosis of RPL was based on Order No. 624 of the Ministry of Health of Ukraine and the ESHRE, 2023 guidelines «Recurrent Pregnancy Loss» and determined that habitual miscarriage is the result of two or more consecutive pregnancies that ended in miscarriage. The exclusion criteria for the study were the presence of Anti-Phospholipid Syndrome (APS), istmic-cervical insufficiency, anatomical malformations, and submucosal leiomyoma of the uterine body (FIGO type 0-II).

Examination of patients was performed if parents provided written informed consent. The study was conducted in full compliance with the ethical principles outlined in the Declaration of Helsinki, following Good Clinical Practice guidelines and applicable legal regulations, and was approved by the Ethics Committee of the Dnipro State Medical University (protocol No. 5 dated September 13, 2018).

The main cohort (M) consisted of 109 women with recurrent pregnancy loss. The control group (C) was formed by 34 conditionally healthy pregnant women with a non-complicated obstetrical anamnesis and without risk factors for miscarriage. All women were undergoing a clinical and laboratory examination, analysis of complaints, study of obstetric, gynecological, somatic, hereditary anamnesis, instrumental examination (ultrasound).

Genetic polymorphisms of coagulation factors and fibrinolysis 1691 675 5G/4G PAI-1, 455 G→A fibrinogen β 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.

Statistical processing of the study results was performed by 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, χ^2 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 odds ratio (OR) assessment was performed at 95% confidence interval (CI). The difference between the values was considered significant by $p<0.05$. Multiple regression analysis with logit transformation of the risk function was used for the prognostic model.

RESULTS

It was found that the average age of pregnant women in the main group (M) exceeded that of the control group and was 30.7±0.52 years (95% CI: 29.7-31.7) versus 25.8±0.85 (95% CI: 24.1-27.5) in the control group ($p=0.001$). This is because this pregnancy occurred after several unsuccessful pregnancies and/or infertility treatment.

The analysis of premorbid background, obstetric and gynecological and somatic anamnesis data revealed that the risk factors for miscarriage include age over 35 years (OR=5.43, 95% CI 1.02-60.9), history of preterm birth (5.22, 1.66-41.6), dysmenorrhea (18.39; 2.42-139.66),

background cervical disease (11.33; 3.27-39.27), overweight (7.88; 1.02-60.9), hypertensive disorders (8.74; 1.13-67.36), varicose veins of the lower extremities (9.74; 1.27-74.8). In addition, the data of hereditary history, namely hypertension in parents (OR=7.17, 95% CI 3.09-16.73), lipid metabolism disorders (32.4; 4.28-245.4), carbohydrate metabolism disorders (9.09; 2.62-31.5), cardiovascular incidents (heart attacks, strokes under the age of 50) in first-line relatives (21.5; 2.83-163.08), thyroid disease (16.27; 2.17-123.8), and miscarriage (3.81; 1.46-9.94). Patients with miscarriage more often ($p<0.05$) had the following gestational complications fetal growth retardation 26 (29.2%) (14.19, 1.85-109.08), oligohydramnios 22 (20.2%) (5.75, 1.05-31.44), preeclampsia 26 (23.9%) (21.9, 1.3-369.5), threatened miscarriage (230.6, 48.9-1086.11), surgical delivery (3.75, 1.29-10.89).

The average weight of newborns in group M ((2744.0±83.0) g) was 1.27 times less than in group C ((3485.6±79.5) g, $p<0.05$). The height of newborns in the M group ((48.0±0.62) cm) is 1.09 times less compared to the C group ((52.1±0.39) cm, $p<0.05$). The Apgar score in the M group was significantly lower compared to the C group ($p<0.05$): at the 1st minute in the M group, 42.2% had a score of ≥7 points (C=85.3%, OR=7.32; 95% CI 2.73-19.63), and at the 5th minute in the M group – 71.6% (C=100%, OR 27.69, 95% CI 1.65-465.5). Miscarriage in past medical history has a significant effect on the weight and height of the newborn (r_{sp}=0.680, r_{sp}=0.636, respectively, $p<0.001$) and on the Apgar score (at the 1st minute r_{sp}=0.470, at the 5th minute r_{sp}=0.480, $p<0.001$), so the condition of children of mothers with miscarriage deserves attention both during intrauterine growth and after birth.

Analysis of the results of tests of genes that regulate the hemostasis system revealed a high frequency of pathological polymorphisms in patients with RPL (Table 1).

Table 1

Frequency of genotypes and alleles of thrombophilia and endothelial dysfunction genes in pregnant women from study groups, n (%)

Genotype	C group (n=34)	M group (n=109)	Sum (n=143)	P	OR	95% CI
PAI-1 5G/4G						
5G/5G PAI-1, n	19	18	37	<0,0001	0,16	0,07-0,36
%	55,9%	16,5%	25,9%			
5G/4G PAI-1, n	13	56	69	0,238	1,71	0,78-3,75
%	38,2%	51,4%	48,2%			
4G/4G PAI-1, n	2	35	37	0,0015	7,57	1,72-33,38
%	5,9%	32,1%	25,9%			
Fibrinogen β –455 G→A						
455 GG, n	25	38	63	<0,0001	0,19	0,08-0,45
%	73,5%	34,9%	44,0%			
455 GA, n	8	44	52	0,102	2,2	0,91-5,30
%	23,5%	40,4%	36,4%			
455 AA, n	1	27	28	0,005	10,87	1,42-83,27
%	2,9%	24,8%	19,6%			

Note: * – the statistical significance of differences of indicator relative to the C group ($p<0.05$), the $\chi 2$ test and Fisher's exact test are used.

The following factors were considered as markers for predicting RPL: polymorphisms in the 675 5G4/G plasminogen activator inhibitor – 1 (PAI-1) and in the fibrinogen gene β 455 G→A. The choice was based on the following facts.

Comparing the frequencies of PAI-1 5G/4G genotypes, it has been determined that the 5G/5G genotype has protective properties against the development of RPL and is 3.4 times more common in pregnant women of group C ($p<0.001$, OR = 0.16, 95% CI 0.07-0.36) than in the M group. Carriers of the pathological homozygote of the PAI-1 4G/4G gene have been registered 5.4 times more often in the M group ($p<0.05$, OR = 7.57; 95% CI 1.72-33.38). The correlation between PAI-1 5G/4G and RPL was r = 0.438 ($p<0.05$).

The number of normal homozygotes of the 455 GG fibrinogen β (FGB) gene in the O group (44.1%) was reduced by 1.67-fold compared to the control group (73.5%, $p< 0.05$) (OR=0.19, 95% CI 0.08-0.45), the number of heterozygotes of 455 GA FGB in the M group (36.4%) was significantly indistinguishable from the C group (23.5%, $p>0.05$). The number of pathological homozygotes of 455 AA FGB in the M group (19.6%) significantly exceeded that of the main group (2.9%, $p<0.05$, OR=10.87, 95% CI 1.42-83.27). The rank coefficient of Spearman's correlation between RPL and polymorphism in the FGB 455 G→A gene is 0.344 ($p<0.05$).

It was found that the combination of allelic variants of the PAI-1 genes 5G/4G, 4G/4G and fibrinogen β –455 GA, –455 A in women with RPL (53.2%) was significantly more common than in the C group (7 (20.5%), $p<0.05$, OR = 4.17, 95% CI 1.71-10.14).

To predict RPL based on the dependent predictor variables of PAI-1 and fibrinogen polymorphisms β was used binary logistic regression analysis with logit

transformation. Thanks to logit transformation, the result of the equation will always be in the range from 0 to 1, and instead of the assumed binary variable (either 0 or 1), we can predict a continuous variable y from 0 to 1 for any values of the independent variables. Thus, the equation of the RPL predictive model is as follows:

$$P = 1/1 + exp^{-y} = 1/1 + exp^{-(0,08047+0,2019\times xPAI+0,1585\times xFIB)} \quad (1)$$

where xPAI is the value of PAI – 1, *xFGB* is the value of FGB. The value of *xPAI* is 1 if the gene is normal, equal to 2 if the gene is heterozygous, and equal to 3 if the gene is mutant (pathological) homozygous; similarly, *xFGB* takes the values 1, 2 and 3. Each pregnant woman is assigned a vector of factors: $x = (xPAI, x\text{FGB}_j$ – the results of her laboratory examination.

The statistical significance of the equation was verified using the coefficient of determination and the Fisher test. It was found that in 22.82% of the total variability y is explained by the change in the factors Xj.

To determine how well the proposed model of dependence of the probability of developing RPL on the factors of *xPAI, xFGB*, we ordered the values of the risk function of all pregnant women (group M and group C) from minimum to maximum and divided the obtained values into eight parts according to the critical values of the risk function (Table 2). The first group included the part of pregnant women whose values of the risk function are minimal, in the second – the next part of pregnant women with a higher value of risk functions, in the last – the part of pregnant women with maximum values of the risk function. For each group, the actual and predicted number of pregnant women with RPL was calculated, as well as the actual and predicted number of pregnant women with a normal course of pregnancy (Table 2).

Analysis of the data shows that at the value of $P\ (0.801) = 0.699$, the number of pregnant women with the actual and predicted amount of RPL increases sharply, and the number of healthy ones decreases, so the value $of\ P\ (0.801) = 0.699$ is determined as critical. Exceeding this value indicates that the pregnant woman should be classified as a high-risk group for developing RPL. The sensitivity of the proposed model is 69.72% (95% CI: 60.19-78.16%), specificity – 76.47% (95% CI: 58.83-89.25%), positive predictive significance (PPV) – 90.48% (83.66-94.66), negative predictive value (NPV) – 44.07% (35.92-52.55).

Table 2

The actual and predicted number of miscarriages

Serial number	The value of the risk function y	The value of the risk function after logit transformation $P(y)$	The number of pregnant women				Total amount
			With RPL		Normal pregnancy		
			actual	predicted	actual	predicted	
1	0,44	0,6084	8	15	17	10	25
2	0,599	0,6455	7	6	2	3	9
3	0,643	0,6555	15	14	7	8	22
4	0,758	0,6808	3	2	0	1	3
5	0,801	0,6994	39	31	6	14	45
6	0,959	0,723	17	13	1	5	18
7	1,003	0,7316	13	12	1	4	14
8	1,161	0,7616	7	5	0	2	7

As a consistency between the real distribution of observations in the presence of RPL and the distribution obtained from the logistic regression equation, the percentage of concordance was used – the proportion of correctly requalified using the observational equation. The higher this figure is up to 100%, the higher the quality of the model. Considering the value of the concordance percentage of 89.9%, it can be argued that in the vast majority of cases, the logistic model consisting of the selected variables correctly predicts the RPL.

Considering the data obtained, algorithms for predicting RPL have been developed depending on the probability RPL calculated by the logistic equation by mathematical modeling using binary logistic regression. This is a convenient method that allows to determine the risk of miscarriage in a particular patient based on data on the presence of polymorphisms in the genes PAI-1 675 5G/4G and fibrinogen β 455 G→A.

DISCUSSION

Thus, considering the current data and the results of many studies, it should be clear that although thrombophilia is not the main cause of pregnancy complications, it still contributes to the risks of pregnancy loss and habitual miscarriage, as well as worsening the possible effects of other concomitant pathology during pregnancy, and therefore should be considered in the context of examinations of such patients [8]. This assumption is confirmed by the recent meta-analysis of 89 studies with 30,254 participants involved, which suggested that hereditary thrombophilia is associated with RPL [9]. The most prevalent types of thrombophilia associated with RPL are hereditary (factor V Leiden, genetic polymorphism of methylenetetrahydrofolate reductase (MTHFR) enzyme, prothrombin gene mutation, protein C deficiency, etc.) or acquired (antiphospholipid syndrome). It was found a significant difference between

RPL and the control group for *PAI-1* 4G/5G mutation and *PAI-1* 4G/4G mutation variants. The authors concluded that patients with three or more abortions had a higher ratio than those with two abortions ($p < 0.05$) [10].

In [11] was established that the PAI-1 4G /4G homozygous mutation was significantly associated with early pregnancy loss (14.6% in the early loss group vs. 1.9% in the late loss group, $p = 0.014$). Late pregnancy loss associated with β-Fibrinogen 455 G>A heterozygous mutation with an OR of 2.20 (p-value = 0.002) [11].

According to the latest guidelines on RPL [3], routine screening for genetic thrombophilia is not performed except for women with miscarriage and thrombotic risks, as well as for scientific purposes. This approach is explained by the fact that currently there is no method of medical treatment for RPL and genetic forms of thrombophilia with proven effectiveness. The use of heparin and aspirin is not routinely indicated but is used only in the context of thromboprophylaxis among the women who are at risk for thromboembolic complications.

Although there is no reasonable treatment for RPL, couples are evaluating opportunities for subsequent pregnancy. Before attempting conception, couples and clinicians aim to identify the cause of pregnancy loss and choose appropriate treatment tactics to prevent its recurrence, especially in cases with modifiable risk factors such as thyroid disorders and APS. That is why most recommendations advise investigating the causes of miscarriage. However, there is no consensus on when to investigate risk factors in spouses with RPL.

According to Musters A. (2013) [7], couples suffering from RPL need individualized management that includes appropriate support and, in this context, testing for relevant factors can help reduce anxiety and manage expectations. Therefore, at this stage of scientific development, screening for polymorphisms in the genes for thrombophilia and endothelial dysfunction is a matter of personalized medicine.

Our findings suggest the potential value of a selective approach for patients with recurrent losses or those with familial histories of thrombotic events. This strategy may uncover actionable thrombophilia disorders, enabling personalized interventions that could mitigate the risk of future pregnancy losses, such as a personalized approach to antithrombotic prophylaxis in pregnancy. Our data underscore the importance of careful evaluation and management of pregnant patients who may potentially benefit from prophylactic anticoagulation [11].

CONCLUSIONS

Thus, molecular diagnostics in the case of RPL can predict the possibility of this pathology in a particular patient, i.e. to predict the development of miscarriage and create a personalized management algorithm to prevent pregnancy complications.

Pathological polymorphisms of the genes of the hemostasis system play a significant role in the development of miscarriage, namely such pathological genotypes as 675 4G/4G PAI-1 – increases the risk by 7,5 times (1,7-33.79), –455AA fibrinogen β – by 9.7 times (1.3-74.16).

Substantiated pathogenetic methods for predicting pregnancy loss, based on the determination of gene polymorphisms PAI-1 (675 5G/4G), fibrinogen β (–455 G → A), which take into account the total contribution of each of the markers, make it possible to determine the probability of pregnancy loss and have a sensitivity of 69.72 (95% CI 60.19-78.16%), specificity – 76.47% (95% CI 58.83-89.25%).

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 miscarriage and the creation of a personalized management algorithm to prevent pregnancy complications.

COMPLIANCE WITH ETHICAL REQUIREMENTS

The study was conducted in full compliance with the ethical principles outlined in the Declaration of Helsinki, following Good Clinical Practice guidelines and applicable legal regulations, and was approved by the Ethics Committee of the Dnipro State Medical University (protocol No. 5 dated September 13, 2018). Examination of patients was performed if parents provided written informed consent.

FUNDING AND 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 the results presented in this article.

No external financial support was provided to the study.

AUTHOR CONTRIBUTIONS

Loskutova T. O.[A, B, C, D, F]

Petulko A. P.[B, D]

REFERENCES

1. Quenby, S., Gallos, I. D., Dhillon-Smith, R. K., Podesek, M., Stephenson, M. D., Fisher, J., Brosens, J. J., Brewin, J., Ramhorst, R., Lucas, E. S., McCoy, R. C., Anderson, R., Daher, S., Regan, L., Al-Memar, M., Bourne, T., MacIntyre, D. A., Rai, R., Christiansen, O. B., Sugiura-Ogasawara, M., … Coomarasamy, A. (2021). Miscarriage matters: the epidemiological, physical, psychological, and economic costs of early pregnancy loss. Lancet (London, England), 397(10285), 1658-1667. https://doi.org/10.1016/S0140-6736(21)00682-6
2. Fawzy, M., Saravelos, S., Li, T. C., & Metwally, M. (2016). Do women with recurrent miscarriage constitute a high-risk obstetric population?. Human fertility (Cambridge, England), 19(1), 9-15. https://doi.org/10.3109/14647273.2016.1142214
3. ESHRE Guideline Group on RPL, Bender Atik, R., Christiansen, O. B., Elson, J., Kolte, A. M., Lewis, S., Middeldorp, S., Mcheik, S., Peramo, B., Quenby, S., Nielsen, H. S., van der Hoorn, M. L., Vermeulen, N., & Goddijn, M. (2023). ESHRE guideline: recurrent pregnancy loss: an update in 2022. Human reproduction open, 2023(1), hoad002. https://doi.org/10.1093/hropen/hoad002
4. Jackson, T., & Watkins, E. (2021). Early pregnancy loss. JAAPA: official journal of the American Academy of Physician Assistants, 34(3), 22-27. https://doi.org/10.1097/01.JAA.0000733216.66078.ac
5. Turesheva, A., Aimagambetova, G., Ukybassova, T., Marat, A., Kanabekova, P., Kaldygulova, L., Amanzholkyzy, A., Ryzhkova, S., Nogay, A., Khamidullina, Z., Ilmaliyeva, A., Almawi, W. Y., & Atageldiyeva, K. (2023). Recurrent Pregnancy Loss Etiology, Risk Factors, Diagnosis, and Management. Fresh Look into a Full Box. Journal of clinical medicine, 12(12), 4074. https://doi.org/10.3390/jcm12124074
6. van Dijk, M. M., Kolte, A. M., Limpens, J., Kirk, E., Quenby, S., van Wely, M., & Goddijn, M. (2020). Recurrent pregnancy loss: diagnostic workup after two or three pregnancy losses? A systematic review of the literature and meta-analysis. Human reproduction update, 26(3), 356-367. https://doi.org/10.1093/humupd/dmz048
7. Musters, A. M., Koot, Y. E., van den Boogaard, N. M., Kaaijk, E., Macklon, N. S., van der Veen, F., Nieuwkerk, P. T., & Goddijn, M. (2013). Supportive care for women with recurrent miscarriage: a survey to quantify women's preferences. Human reproduction (Oxford, England), 28(2), 398-405. https://doi.org/10.1093/humrep/des374
8. Thrombophilia and the predisposition to improper coagulation can affect chorionic blood flow and cause vasculopathy leading to pregnancy loss Alecsandru, D., Klimczak, A. M., Garcia Velasco, J. A., Pirtea, P., & Franasiak, J. M. (2021). Immunologic causes and thrombophilia in recurrent pregnancy loss. Fertility and sterility, 115(3), 561-566. https://doi.org/10.1016/j.fertnstert.2021.01.017
9. Liu, X., Chen, Y., Ye, C., Xing, D., Wu, R., Li, F., Chen, L., & Wang, T. (2021). Hereditary thrombophilia and recurrent pregnancy loss: a systematic review and meta-analysis. Human reproduction (Oxford, England), 36(5), 1213-1229. https://doi.org/10.1093/humrep/deab010
10. Barut, M. U., Bozkurt, M., Kahraman, M., Yıldırım, E., Imirzalioğlu, N., Kubar, A., Sak, S., Ağaçayak, E., Aksu, T., & Çoksüer, H. (2018). Thrombophilia and Recurrent Pregnancy Loss: The Enigma Continues. Medical science monitor: international medical journal of experimental and clinical research, 24, 4288-4294. https://doi.org/10.12659/MSM.908832
11. Borsi, E., Potre, O., Ionita, I., Samfireag, M., Secosan, C., & Potre, C. (2024). Risk Factors of Thrombophilia-Related Mutations for Early and Late Pregnancy Loss. Medicina (Kaunas, Lithuania), 60(4), 521. https://doi.org/10.3390/medicina60040521

Резюме

ПРОГНОЗУВАННЯ ЗВИЧНОГО НЕВИНОШУВАННЯ ВАГІТНОСТІ

Тетяна О. Лоскутова, Альбіна П. Петулько

Дніпровський державний медичний університет, м. Дніпро, Україна

Мета. Розробити модель прогнозу звичного невиношування вагітності на підставі визначення поліморфізму генів 675 5G/4G інгібітора активатора плазміногена – 1 (PAI-1) та фібриногену β 455 G→A та оцінити її ефективність.

Матеріали та методи. Проспективне дослідження випадок-контроль включало 109 жінок в 1 триместрі вагітності зі звичним невиношуванням вагітності та 34 умовно здорових вагітних з неускладненим акушерським анамнезом та без факторів ризику невиношування вагітності. Генетичні поліморфізми факторів згортання та фібринолізу 675 5G/4G PAI-1, 455 G→A фібриногену β досліджували за допомогою алель-специфічної полімеразної ланцюгової реакції.

Результати. У розвитку невиношування вагітності вагому роль мають патологічні поліморфізми генів системи гемостазу, а саме такі патологічні генотипи, як 675 4G/4G PAI-1 підвищує ризик в 7,5 рази (1,7-33,79), -455AA фібриногену β – в 9,7 рази (1,3-74,16). Поєднання алельних варіантів генів PAI-1 5G/4G, 4G/4G та фібриногену β -455 GA, -455 A у жінок зі звичним невиношуванням вагітності (53,2%) зустрічались вірогідно частіше, ніж в контрольній групі (7 (20,5%), p<0,05, ВШ= 4,17, 95% ДІ 1,71-10,14). Розроблені патогенетично обґрунтовані способи прогнозування невиношування вагітності, що засновані на визначенні генних поліморфізмів PAI-1 (675 5G/4G), фібриногену β (-455 G→A), які враховують сукупний внесок кожного з маркерів, дають змогу визначити ймовірність розвитку невиношування вагітності та мають чутливість – 69,72 (95% ДІ 60,19-78,16%), специфічність – 76,47% (95% ДІ 58,83-89,25%).

Висновки. Перебіг вагітності на тлі патологічних поліморфізмів генів системи гемостазу значно збільшує ризик звичного невиношування вагітності, що має бути враховано при плануванні вагітності.

Ключові слова: **невиношування вагітності, генетична тромбофілія, ускладнення вагітності, прогноз, поліморфізм генів**

Received: 14.01.2025
Accepted: 11.04.2025