Original research

ETIOPATHOGENESIS OF RECURRENT PREGNANCY LOSS DUE TO GENETIC FORMS OF THROMBOPHILIA

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Abstract: **The aim** of the study was to develop a concept of the etiopathogenesis of miscarriages due to the genetic form of thrombophilia.

Materials and methods. In a prospective cohort study, 143 pregnant women were examined, including 109 with pregnancy loss and genetic defects of hemostasis [main (M) group]; the control (K) group consisted of 34 relatively healthy pregnant women with a light history and pregnancy without risk factors for pregnancy loss. Genetic polymorphisms of coagulation factors and fibrinolysis (1691 G→A FVL, 20210 G→A prothrombin, 675 5G/4G PAI-1, 455 G→A fibrinogen β), endothelial dysfunction (677 C→T MTHFR) were studied with the help of allele-specific polymerase chain reaction.

Results. Based on a comprehensive clinical, laboratory, instrumental and statistical analysis, it has been determined the main risk factors for pregnancy loss. Pathological polymorphisms of hemostasis and endothelial dysfunction genes play an important role in the development of miscarriage, namely the following pathological genotypes: 1691 GA factor V Leiden - increases the risk by 5.3 times (95% CI 1.5-18.5), 20210 GA prothrombin - 26.47 times (1.6-445.7), 675 4G / 4G PAI-1 - 7.5 times (1.7-33.79), -455AA fibrinogen β - 9.7 times (1.3-74.16), 677 CT MTHFR - 2.6 times (1.0-6.2), 677TT MTHFR - 21.7 times (1.3-368.6). It has been found that multigenic forms of thrombophilia predominate in most patients with pregnancy loss - 76.1% ($p < 0.001$, OR = 12.31, 95% CI 4.8-31.55).

Conclusions. The obtained data allowed us to form a concept of the etiopathogenesis of recurrent pregnancy loss due to genetic thrombophilia and justify the need for a personalized approach in each case of pregnancy loss.

Keywords: pregnancy loss, genetic thrombophilia, pregnancy complications, hemostasis system, pregnancy management.

INTRODUCTION Recurrent pregnancy loss (RPL) is considered one of the major concerns in women's health. In women of reproductive age, 5% have a medical history of two or more miscarriages, and about 1% have that of three or more. According to ESHRE 2017 (European Society of Human Reproduction and Embryology), about 15% of pregnancies result in an inevitable miscarriage, and repeated miscarriages significantly aggravate the stress experienced by the family [1]. It is known that RPL has a multifactorial genesis, including genetic, immune, infectious, anatomical, endocrine, and thrombophilic components. None of them fully explain the episodes of reproductive wastage, and up to 40% of cases of NP remain uninterpreted after excluding all possible causes [1,2].

Thrombophilia is thought to be an etiologic factor of recurrent pregnancy loss (see RCOG 2011; ASRM 2012; ESHRE 2017; DGGG, OEGGG, and SGGG 2020), as well as the same for obstetric complications such as preeclampsia, fetal growth retardation, placental abruption [1,4-6]. Non-thrombogenic mechanisms of mutations and polymorphisms of thrombophilia genes disrupt normal implantation processes, creating conditions for the development of obstetric complications [7]. Nevertheless, the prevalence of such pathologies (type of pathological polymorphisms, combinations thereof) in women with recurrent pregnancy loss has not yet been definitively determined. Moreso, it is not yet clear how functionally

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impaired genes may behave in response to adverse exogenous and endogenous factors.
With that in mind, brand new research was desperately needed, thus outlining the relevance of our thesis and becoming its goal.

Aim: To develop a concept of the etiopathogenesis of miscarriage due to genetic thrombophilia.

MATERIALS AND METHODS The study was conducted at Dnipro State Medical University, Dnipro, Ukraine. A prospective cohort study covered 143 pregnant women, including 109 with pregnancy loss and genetic defects of hemostasis (main (M) group), control (C) group consisted of 34 relatively healthy pregnant women with a light history and pregnancy without risk factors for pregnancy loss (Table 1). When diagnosing recurrent pregnancy loss, they have been guided by Order №624 of the Ministry of Health of Ukraine dated 03.11.2008 and ESHRE, 2017 "Recurrent Pregnancy Loss" and determined that recurrent pregnancy loss is a consequence of two or more consecutive pregnancies that ended in pregnancy loss. Exclusion criteria have been the presence of antiphospholipid syndrome, isthmic-cervical insufficiency, anatomical malformations (intrauterine septum), submucosal leiomyoma of the uterine body (type 0-II according to FIGO classification of leiomyoma). 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.

Genetic polymorphisms of coagulation factors and fibrinolysis (1691 G→A FVL, 20210 G→A prothrombin, 675 5G/4G PAI-1, 455 G→A fibrinogen β), endothelial dysfunction (192 Q→R PON-1, 677 C→T MTHFR), blood pressure regulator (235 M→T angiotensinogen II) 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, Russian Federation), was used. DNA from blood leukocytes, which was isolated using the reagent "DNA-express blood" (Litech SPF, Russian Federation), was used for analysis.

The study of platelet aggregation and Willebrand factor activity was performed on an aggregometer AP 2110 "Solar" (Belarus). Adrenaline solution - 1x103 M and ristocetin (Technology-Standard, Russia) were used as stimulators of aggregation. Hemostasis parameters were determined on an automatic coagulometer, "Amelung Coagulometr KC 4A" (Trinity Biotech, Ireland). The state of the fibrinolytic system (natural convolution lysis and fibrin convolution retraction) was studied by Kotovshchikova and Kuznick's method. Determination of D-dimer in blood plasma was performed by immuno-turbidimetric analysis using the latex test "Tina-quant a D -Dimer" (Roche Diagnostics, USA) on the Roche / Hitachi Sobas c 6000 system.

Lipid metabolism and homocysteine levels were determined to evaluate the metabolic changes that lead to a thrombophilic state. The concentration of homocysteine in blood plasma was determined by ELISA using Axis reagents (Axis-Shield AS, Norway) on the device "Stat-Fax" (USA). Determination of the level of total cholesterol (CHC), high-density lipoprotein cholesterol (HDL cholesterol), low-density lipoprotein cholesterol (LDL cholesterol), and triglycerides (TG) in blood plasma was performed automatically on the analyzer "Biochemistry" La Test (Lachema-Pliva, Czech Republic). The formula calculated the coefficient of atherogenicity (CA): CA = (CHC - HDL cholesterol) / HDL cholesterol.

Statistical processing of the study materials has been performed using biostatistics methods implemented in the software packages STATISTICA v.6.1 (Statsoft Inc., USA) (licensed № AJAR909E415822FA) and MedCals (MedCalc Software, Belgium) v.9.6.4.0. 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, $\chi 2$ 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, relative risk (RR) and odds ratio (OR) assessments were performed at a 95% confidence interval (CI). The difference between the values was considered significant by $p<0.05$.

RESULTS The mean age of pregnant women in the M group was 30.7 ± 0.52 years (95% confidence interval (CI): 29.7-31.7), being higher than in the C-group - 25.8 ± 0.85 years (95% CI: 24.1-27.5) ($p = 0.001$). The phenomenon is due to the fact that the studied onset of pregnancy occurred after several unsuccessful ones and/or after infertility treatment. It was found that ages 35 years and upwards increase the chances of pregnancy loss by 5.43 times (95% CI 1.02-60.9) ($p = 0.042$).

Study group	Genotype			Alleles	
Prothrombin 20210 G→A					
	GG	GA	AA	20210G	20210A
M (n=109)	77 (70,6) *	30 (27,5) *	2 (1,8)	184 (84,8) *	34 (15,6) *
C (n=34)	34 (100,0)	0 (0,0)	0 (0,0)	68 (100,0)	0 (0,0)
Factor V Leiden 1691 G→A					
	GG	GA	AA	1691G	1691A
M (n=109)	71(65,1) *	37 (33,9) *	1 (0,9)	179 (82,1) *	39 (17,9) *
C (n=34)	31 (91,2)	3 (8,8)	0 (0,0)	65 (95,6)	3 (4,4)
PAI-1 5G/4G					
	5G/5G	5G/4G	4G/4G	5G	4G
M (n=109)	18 (16,5) *	56 (51,4)	35 (32,1)*	92 (42,2) *	126 (57,8) *
C (n=34)	19 (55,9)	13 (38,2)	2 (5,9)	5 (75,0)	17 (25,0)
Fibrinogen β 455 G→A					
	GG	GA	AA	-455G	-455A
M (n=109)	38 (34,9) *	44 (40,4)	27 (24,8)*	120 (55,0) *	98 (45,0) *
C (n=34)	25 (73,5)	8 (23,5)	1 (2,9)	58 (85,3)	10 (14,7)
MTHFR 677C→T					
	CC	CT	TT	677C	677T
M (n=109)	40 (36,7) *	48 (44,0) *	21 (19,3)*	128 (58,7) *	90 (41,3) *
C (n=34)	26 (76,5)	8 (23,5)	0 (0,0)	60 (88,2)	8 (11,8)

Table 1. Frequency of genotypes and alleles of thrombophilia and endothelial dysfunction genes in pregnant woman of study groups, n (%).

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

Analysis of reproductive function showed that the M groupd no women with the first pregnancy, while in the control group, the numbers were 58.8%. Among women of the M group, the average pregnancy count was G3 (ranging from the third one to the fourteenth one), and the expected delivery was the first (P1) in 75 (68.8%) women, significantly differentiating from the control group ($p < 0.001$). In the C-group, the parity of future deliveries was the first (P1) in 24 (70.6%) and fluctuated to the third (P3) in 2.9%. Premature deliveries occurred in 14 women (13%) in the study group, but none in the control group ($p < 0.001$, odds ratio (OR) 5.22; 95% CI: 1.66-41.10). Our findings thus align with the ones made by Magnus et al., 2019, confirming the risk of losing the next pregnancy increases with each recurrent loss: approximately 11% in women without a medical history of delivery, up to 40% after three or more losses. Thus, the PL risk factors are as follows: female age and the number of previous pregnancies [8].

While examining extragenital pathology in patients of the main group, it was found that somatic pathology was 1.93 times higher (87 (79.8%)) than that of the C-group (14) (14.2%) ($p = 0.0001$; OR = 5.65; 95% CI: 2.47-12.95). The overweight women were 3.2 times more likely to get the pathology [21 (19.3%) ($p = 0.021$; OR = 7.88; 95% CI: 1.02-60.91)]. Our data confirm that obesity is often associated with thrombophilic complications and must be considered a risk factor for pregnancy loss and thromboembolic complications during pregnancy, delivery, and postpartum [9].

In case of hypertensive disorders in women, the chances of developing the PL increased 8.74 times [22 (20.2%)] ($p = 0.004$; 95% CI: 1.13-67.36). Lower extremity varicose vein disease occurred in 24 (22%) of women in the S-group but in none in the C-group ($p <0.05$, OR 9.74, 95% CI: 1.27-74.83).

The analysis of hereditary anamnesis revealed the following findings: increased blood pressure was more common in relatives of women in the study group [89 (81.7%)], being 2.4 times higher than the same indicator of the control group [13 (38.2%)] ($p = 0.001$; OR = 7.17; 95% CI: 3.09-16.73).

Seventy-two (66.1%) of women of the M-group and 8 (23.5%) ones of the C-group had a positive family history of cardiac pathologies ($p = 0.001$; OR = 6.32; 95% CI: 2.61-15.34), being almost equally distributed between fathers - 43 (39.4%) and mothers - 44 (40.4%). The parents of women in the M group had indications for an increase in cholesterol levels in 54 cases (49.5%), while those of women in the control group had them in 1 case (2.9%) ($p <0.05$). Fifty-one (46.8%) women of the M group and 3 (8.8%) of the C group had a positive family history of carbohydrate metabolism disorders ($p = 0.001$; OR = 9.09; 95% CI: 2.62-31.51). Cardiovascular catastrophes, namely heart attacks and strokes in the ages under 50, were observed in 43 (39.4%) of first-degree relatives of women in the study group and in 1 (2.9%) first-degree relative of those in the control group ($p = 0.001$; OR = 21.5; 95% CI: 2.83-163.08). The data obtained indicate the need for a more in-depth study of the data on thromboembolic hereditary history and additional examinations to determine genetic thrombophilia in patients of this type.

Features of such pregnancies, deliveries and postpartum period in women with PLs showed a significant percentage of perinatal complications, namely: women in the study group more often ($p <0.05$) had cases of fetal growth retardation - 26 (29.2%) (OR = 14.19, 95% CI: 1.85-109.08), oligohydramnios - 22 (20.2%) (OR = 5.75, 95% CI: 1.05-31.44), preeclampsia - 26 (23.9%) (OR = 21.9, 95% CI: 1.3-369.5) compared with the control group with none such complications. Pregnancies of the M-group had 6.68 times more complications of the threatened abortion (OR = 230.6, 95% CI: 48.9-1086.11). Our results confirm the data on the genetic and/or acquired forms of thrombophilia possibly associated with a high risk of recurrent pregnancy loss, preeclampsia, fetal growth retardation (FGR), antenatal fetal death, premature placental abruption, and other complications [3,7].

Analysis of the method of delivery revealed some specific findings: the frequency of term deliveries in both clinical groups had no significant differences, and the percentage of operative deliveries was significantly higher in the study group [35.5% vs. 11.8% ($p = 0.015$)] due to the higher number of positive obstetric and somatic anamnesis, longer infertility periods, as well as due to the use of assisted reproductive technologies, thus, RPL may be considered increasing the chances of operative delivery by 3.75 times (95% CI: 1.29-10.89).

The average weight of newborns in the M-group ((2,744.0 ± 83.0) g) was 1.27 times less than that in the C-group ((3,485.6 ± 79.5) g, $p < 0.05$). The height of newborns in the M-group ((48.0 ± 0.62) cm) was 1.09 times less than that in the control group ((52.1 ± 0.39) cm, $p < 0.05$). The Apgar score in the M-group was significantly lower compared to the same indicator of the C-group ($p < 0.05$): at 1st minute, the 42.2% of the newborns of the M-group had a score of ≥7 points (C = 85.3%, OR = 7.32; 95% CI: 2.73-19.63), and

at 5th minute, 71.6% of them had shown the same result (C = 100%, OR 27.69, 95% CI: 1.65-465.5). A RPL had a significant effect on the weight and height values in the newborns (r = 0.680, r = 0.636, respectively, p < 0.001), as well as on the Apgar score (at 1st minute, r = 0.470, at 5th minute, r = 0.480, p < 0.001), as evidenced by the specified values of Spearman correlation coefficients; thus, the condition of newborns born from the mothers with thrombophilia deserves special attention both during fetal development and after delivery.

It has been found that the coefficient of atherogenicity in group M exceeded the same indicator of group C 1.09 times in the 1st trimester (p<0.05) and 1.13 times in the second (p<0.05).

Analysis of the coagulation hemostasis in the first trimester has revealed the following differences in the M group compared with the C group. There was a significant decrease in the average value of the international normalized ratio by 7 % (0.93 ± 0.01 vs. 1.026 ± 0.008, p = 0.002), prothrombin index - by 5.9 % (91.01 ± 1.16 % vs. 97.0 ± 1.1 %, p =0.021), APTT by 16.8 % (25.7 ± 0.33 sec vs. 31.2 ± 0.5 sec, p <0.001), and an increase in the average level of D-dimer by 22 % (0.90 [0.60-1.175] vs. 0.50 [0.40-0.50] µg FEU/ml, p <0.001). Levels of fibrinogen, fibrinolytic activity between the groups had no significant differences.

Analysis of platelet aggregation (main group 23, control 28 studies) showed that they were distributed differently by type [10]. Thus, the two-phase type of aggregation occurred in 43.5% of cases (C = 71.4%, p<0.05), the irreversible type in 26% (C = 28.6%) in the main group. The reverse type was observed in 17.5% of pregnant women with PL, and platelet hypoaggregation was 13%. The last two types in group C did not occur at all. Regarding platelet hypoaggregation, it is likely that this type of platelet aggregation masks hyperaggregation, i.e., the presence of an increased number of aggregation inducers. In this case, the effect of the aggregation stimulant, which is added, cannot be manifested because the platelets are altered by the action of the previous activator of aggregation. The activity of intravascular coagulation in this subgroup is evidenced by the fact that the level of SFMC was 15.3 ± 1 µg/ml. This fact is also confirmed by the inverse correlation between the degree of platelet aggregation and the number of platelets r = -0.359 (p<0.001).

Analysis of Willebrand factor activity, which reflects the condition of the endothelial wall, that increases with its damage, have shown an increase in Willebrand factor activity in pregnant women of the main group 173.4 ± 7.19 (C = 147.7 ± 5.03, p <0.05) 1.17 times. There was a strong bond between the activity of the Willebrand factor and the degree of platelet aggregation, r = 0.850 (p <0.001), and a medium-strength feedback r = -0.440 (p <0.001) with the number of platelets.

The frequency and structure of genetic polymorphisms and mutations in genes that regulate the hemostasis system and endothelial dysfunction in pregnant women with pregnancy loss have been studied. Analyzing the frequency of prothrombin gene genotypes (20210 G → A), it has been found that the heterozygous variant 20210 GA is unique to the group with RPL (p <0,001, OR = 26,47; 95% CI 1,6-445,7), and the homozygous variant 20210 GG has projective properties (p <0.001, OR = 0.03; 95% CI 0.002-0.58). Similar changes apply to the polymorphism of factor V Leiden. Carriers of the heterozygous variant 1691 GA factor V Leiden were 3.8 times more likely to be observed in group M (p <0.05, OR = 5.3; 95% CI 1.5-18.5), and genotype 1691 GG in 1, 4 times more often registered in group C (p <0.05, HS = 0.18; 95% CI 0.05-0.63). The correlation between RPL and mutation of the prothrombin gene was r = 0.361, with the mutation of factor V Leiden - r = 0.287 (p <0.05). 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, HS = 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 = 7.5; 95% CI 1.7-33.39). The correlation between PAI-1 5G / 4G and RPL is r = 0.438 (p <0.05). Regarding the polymorphism of the fibrinogen gene β -455 G → A, the carriers of the genotype -455 AA were 8.55 times more often registered in the M group (p<0.001, OR = 9.7, 95% CI 1.3-74.16).

Analysis of the frequencies of MTHFR 677 C → T genotypes revealed a decrease in the frequency of the normal CC genotype in the M group. Its frequency is reduced by 2.1 times compared with the K group (p <0,001, OR = 0,18, 95% CI 0,07-0,43). The number of heterozygotes 677 CT MTHFR in the M group exceeded the value of the K group 1.9 times (p <0.05, OR = 2.6; 95% CI 1.0-6.2). Carriers of pathological homozygote 677 TT were registered only in group M (p <0.05, OR = 21.7; 95% CI 1.3-368.6). The correlation between the polymorphisms of the fibrinogen gene β -455 G → A, MTHFR 677 C → T, and RPL was r = 0.399 and r = 0.409, respectively (p <0.05).

Analysis of homocysteine levels revealed significant differences between the control (7.11 ± 0.56, n = 15) and the main groups (11.75 ± 0.54, n = 109) (p <0.05). In addition, in group M in a significantly larger number of women, the level of homocysteine exceeded 15 µmol / l - 35 (53.3%) compared with control 0 (0%, p <0,001, OR 32,88, 95% CI: 1,96 -551.77). The cause of hyperhomocysteinemia is a mutation in MTHFR 677 C → T, which is confirmed by the correlation (r = 0.267, p = 0.042) between the level of homocysteine and the polymorphic variant of the gene. RPL is a multifactorial disease and not only pathological polymorphisms of individual genes but also their combined effect, which reveals the potentiation of their action play a role in its occurrence. As combinations of unfavorable genotypes have been considered: homo- and heterozygous mutations of the prothrombin gene 20210 GA, AA, gene FV Leiden 1691 GA, AA, homo and heterozygous polymorphisms PAI-1 genes 5G / 4G, 4G / 4G, FGB -455 GA, AA, monozygous PON - 1 192RR and MTHFR 677 TT. Analyzing the distribution of combinations of pathological variants of genes, we have found that they were more common in pregnant women with RPL. The simultaneous existence of two or more pathological polymorphisms has been determined in 83 (76.1%) women of group M against 7 (20.5%) of group K (p <0.001, OR = 12.31, 95% CI 4.8-31.55). The presence of two pathological polymorphisms (33% vs. 14.7%) increases the chances of pregnancy loss by 2.66 times (95% CI 1.02-7.19), and the presence of three pathological polymorphisms (28, 4% vs. 5.9%) increases the chances of developing RPL by 4.99 times (p <0.05, 95% CI 1.29-19.29). There was a significant difference in the combinations of allelic variants of the genes PAI-1 5G / 4G, 4G / 4G, and FGB -455 GA, -455 AA between women with RPL and the control group, which separately (25.7% vs. 14.7%) or in combination with other pathological polymorphisms in women of group M 58 (53.2%) were probably more common than in group K (7 (20.5%), p <0.05, OR = 4.17, 95% CI 1,71-10,14). The combination of PAI-1 5G / 4G or 4G / 4G with MTHFR 677 TT and other polymorphisms was more likely to occur more frequently in the main group 16 (14.7% vs. 0% in K, p = 0.039), which increases the chances of pregnancy loss in 12,18 times (95% CI 7.1-208.5).

Consequently, although thrombophilia is not considered a major cause of pregnancy complications, it may still contribute to the risks of pregnancy loss and habitual miscarriage, exacerbating the possible consequences of other concomitant pathologies during pregnancy and must be considered in the context of examinations of such female patients. According to the data obtained, we hereby propose the RPL model (Fig.1).

DISCUSSION.

According to the latest recommendations of the RCOG 2011, ASRM 2012, ESHRE 2017, DGGG, OEGGG, and SGGG 2018 on RPL, routine screening for genetic thrombophilia is not to be performed, except for women with pregnancy loss risks and thrombotic risks, as well as for scientific purposes [1,4-6]. Said recommendations are explained by the fact that currently, there are no effective procedures for drug treatment in RPLs, nor genetic forms of thrombophilia. Routine use of heparin and aspirin is not indicated but may be used only in the context of thromboprophylaxis in women at risk for thromboembolic complications.

Although RPL cases lack sufficient treatment, the couples may evaluate the possibility of the next pregnancy. Before the pregnancy, couples and clinicians are to try to find the causes for pregnancy loss and choose appropriate treatment tactics that may prevent the recurrence of PL, especially in cases with modifying risk factors such as thyroid disorders and antiphospholipid syndrome. That is why most guidelines are recommended further analysis of the causes of miscarriage. However, there is no consensus on the time of such analysis of risk factors in spouses with RPL.

According to Musters A. (2013), couples with RPL need individual follow-up, including appropriate support, so - in the context of this thesis - the testing for relevant factors may help reduce anxiety and manage expectations [11]. Therefore, at this stage of the development of science, screening for the polymorphisms in the genes of thrombophilia and endothelial dysfunction must be considered as a matter of personalized medicine.

Thus, molecular diagnostics may be considered the most promising in the modern world because it, given the individual structure of the human genome, as well as the peculiarities of metabolic processes of the human body, may provide clear and specific information on the possible course of the disease. In the case of a certain disease (in our case, in the event of PL), several genes may have a different effect on its course. Still, with their role combined, we may predict such pathology in a particular female patient, i.e., predict the development of pregnancy loss, and create a personalized follow-up algorithm to prevent pregnancy complications.

CONCLUSION.

1. It has been determined that the risk factors for pregnancy loss include: the age of the woman over 35 years (OR = 5.43, 95% CI 1.02-60.9), premature birth in the anamnesis (5.22, 95% CI 1.66-41.6), overweight (7.88;

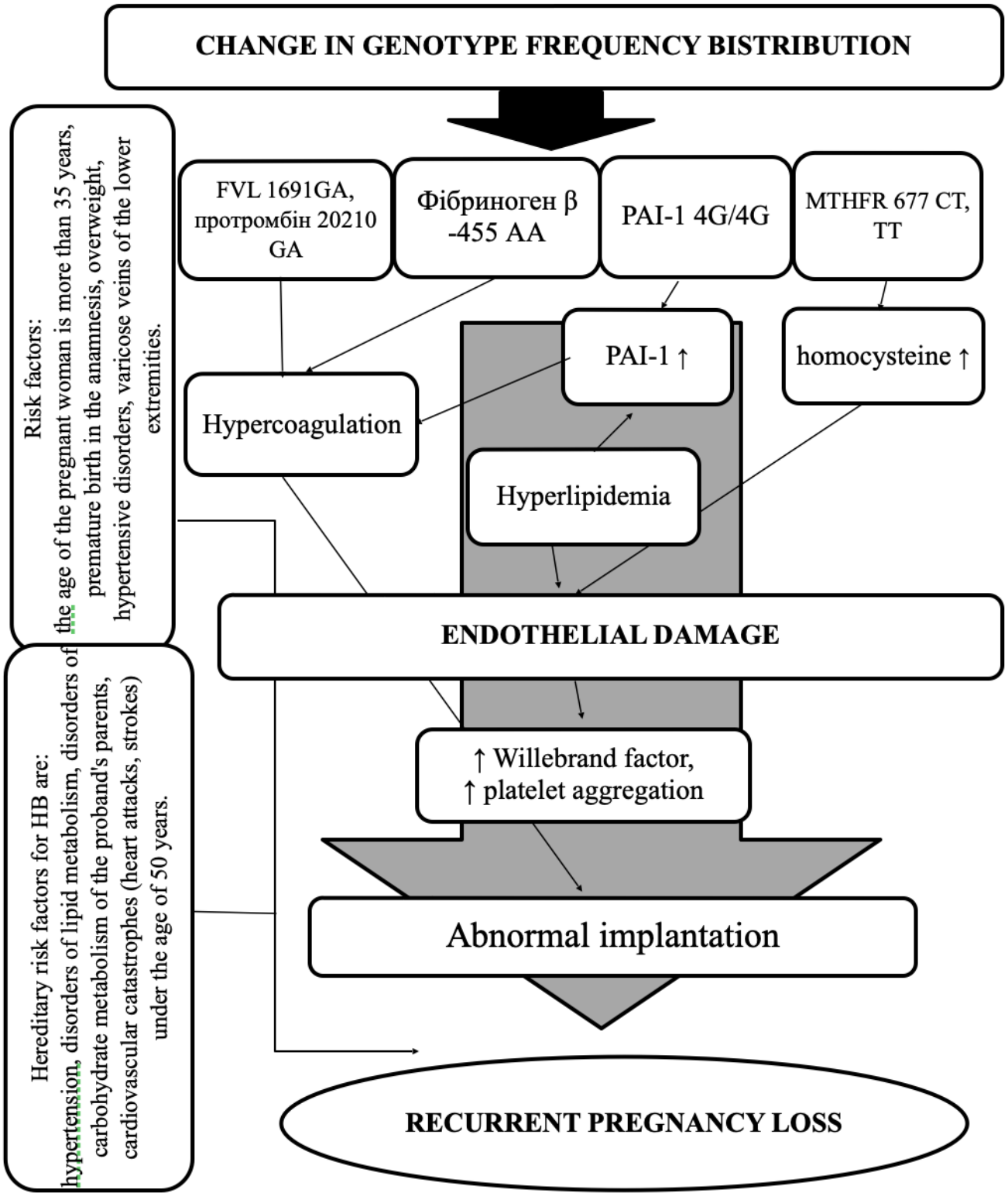

Figure 1. Model of etiopathogenesis of recurrent pregnancy loss due to genetic thrombophilia.

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, it has been considered hereditary history: hypertension in parents (OR = 7.17, 95% CI 3.09-16.73), disorders of lipid metabolism (32.4; 4.28-245.4), disorders of carbohydrate metabolism (9.09; 2.62-31,5), cardiovascular catastrophes (heart attacks, strokes under the age of 50) in closest relatives (21.5; 2.83-163.08).

2. It was determined that in pregnant women with PL, due to genetic forms of thrombophilia, changes in lipid metabolism are more common in the form of an increase in atherogenic factor in the first trimester by 1.09 times, in the second trimester - by 1.13 times ($p < 0.05$), as well as an increase in the level of homocysteine by 1.65 times, resulting in conditions for the development of the acquired thrombophilic state.

3. The state of the hemostasis system in pregnant women with pregnancy loss due to genetic thrombophilia is characterized by activation of vascular-and-platelet and coagulation links of the hemostasis system in the presence of intact fibrinolysis. The obtained data showing increased activity of Willebrand factor in pregnant women with pregnancy loss by 1.17 times show damage to the endothelial wall, becoming an additional stimulus to the activation of platelet hemostasis ($g = 0.850$ in the presence of platelet aggregation, $p < 0.05$).

4. Pathological polymorphisms of hemostasis system genes, as well as those of the endothelial dysfunction genes, play an important role in the development of RPL cases (namely, the following pathological genotypes: 1691 GA factor V Leiden - increases the risk by 5.3 times (95% CI: 1.5-18.5), 20210 GA of prothrombin - by 26.47 times (1.6-445.7), 675 4G/4G PAI-1 - by 7.5 times (1.7-33.79), -455AA of fibrinogen β - by 9.7 times (1.3-74.16), 677 CT MTHFR - by 2.6 times (1.0-6.2), 677TT MTHFR - by 21.7 times (1.3-368.6)).

5. The obtained data allows us to put together a concept of the etiopathogenesis of pregnancy loss due to the genetic form of thrombophilia, as well as to justify the need for a personalized approach in each individual case of pregnancy loss.

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