



The obstetric complications in women with hereditary thrombophilia

Diana Mitriuc, Olga Popușoi, Rodica Catrinici, Valentin Criptu

Department of Obstetrics and Gynecology No. 1, Nicolae Testemitanu State University of Medicine and Pharmacy, Kishinev, Republic of Moldova

Abstract

All congenital thrombophilias are associated with an increased risk of venous thromboembolism (VTE) during pregnancy. Several studies have confirmed the increased risk of obstetric complications in women with congenital thrombophilias. Case-control, cohort and transversal studies have shown that hereditary thrombophilia is more prevalent in the cohorts of women with pregnancy losses, early onset preeclampsia, abruptio placentae and IUGR. However, despite the increase in the relative risk, the absolute risk of VTE and adverse pregnancy outcomes is low. There is convincing evidence that the deficiency of natural anticoagulants (AT, protein C, protein S) is a risk factor for late fetal loss. The mutations of the FVL (G1691A) gene and the prothrombin (G20210A) gene are associated with a double risk for unexplained RPL and non-recurrent late fetal loss. The association of congenital thrombophilia and preeclampsia is much more uncertain, being, probably, limited to the FVL G1691A gene mutation and more severe cases of preeclampsia. Fewer data are available for IUGR and abruptio placentae. In addition, genetic and epidemiological research suggest that obstetric complications during pregnancy have a polygenic multifactorial etiology, with a risk determined by the interaction of multiple genetic variants and other risk factors.

Keywords: hereditary thrombophilia, obstetric complications

The major forms of hereditary thrombophilia, currently recognized as independent risk factors for venous thromboembolism (VTE), include the anomalies of the procoagulant factors – the homozygous or heterozygous G1691A mutation of the factor V Leiden (FVL) gene (activated protein C resistance), homozygous or heterozygous G20210A mutation of the prothrombin gene (coagulation factor II), endogenous deficiency of anti-coagulants – antithrombin (AT), protein C and protein S and the C677T mutation in the methylenetetrahydrofolate reductase (MTHFR) gene (hyperhomocysteinemia). The most common forms of congenital thrombophilias are the heterozygous FVL G1691A and G20210A prothrombin gene mutations, while other congenital thrombophilias (AT deficiency, protein C deficiency and protein S deficiency) have a higher thrombogenic potential, but are less common [1,2,3,4,5].

The G1691A mutation of the factor V Leiden gene is the most common heterozygous or homozygous

form of hereditary thrombophilia, with a unique G→A substitution at nucleotide 1691 located on chromosome 1q23 and autosomal dominant inheritance. Because of this mutation, FVL becomes resistant to the action of activated protein C, is inactivated 10 times slower than normal, and persists longer in the circulation, being unable to act as a cofactor in factor VIII inactivation by activated protein C, leading to increased procoagulant activity, increased conversion of prothrombin to thrombin with increased thrombin generation, production of a hypercoagulable state and genetic predisposition to thrombosis [3,4,6,7].

The prevalence of FVL (G1691A) mutation is 1-15% in the general population [1] and 5-9% in the white Europeans, making it the most common congenital thrombophilia, covering approximately 40-50% of cases [2,6]. The mutation is almost absent in Africa and Asia, being present in 5.2% of white Americans and 3% of African Americans who are not recent immigrants. The rate of homozygosity, the more severe phenotype,

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Address for correspondence:
diana.mitriuc@gmail.com

is about 1% of people with the mutation [1,2,6,7].

The risk of developing VTE increases 2-7 times in people with the heterozygous FVL (G1691A) mutation and 40-80 times in people with homozygous FVL (G1691A) mutation [1]. Approximately 40-44% of the women who have VTE during the pregnancy or postpartum are carriers of the FVL (G1691A) gene mutation, most of them being heterozygous [2,7].

Data about the relationship between the FVL (G1691A) mutation and fetal loss are discordant. Generally, the mutation in the FVL G1691A gene contributes to a small increase in the risk of spontaneous abortion and recurrent pregnancy loss (RPL) [1,6,8,9]. Regarding other parameters of obstetric morbidity, a recent meta-analysis suggests that there is a significant increase in the frequency of obstetric complications, stillbirths, severe preeclampsia, intrauterine growth restriction (IUGR), small for gestational age (SGA) newborns and placental abruption in carriers of the FVL (G1691A) mutation [1,8].

Two recent and comprehensive literature reviews, which comprise case-control studies, prospective and retrospective cohort studies of moderate heterogeneity, have established that the FVL (G1691A) mutation carriers have a relatively high RPL risk (1.52-2.02 times higher). However, the absolute risk of pregnancy loss in women with the FVL (G1691A) mutation is low (4.2%) [10].

There is no significant association between the FVL (G1691A) mutation and preeclampsia, the FVL (G1691A) mutation and IUGR or SGA newborns [10]. The association between abruptio placentae and the FVL (G1691A) gene mutation is also poor [3].

The connection between severe preeclampsia and the FVL G1691A gene mutation was assessed in a meta-analysis of case-control studies, which did not find a strong association – the Odds Ratio (OR) ranging from 1.23 to 3.36 [9]. A more recent case-control study, despite the confirmation of the lack of correlation with abruptio placentae, found an increase in the placenta-related factors that induce fetal hypoxia in mothers with the FVL G1691A gene mutation, compared to the control group with the similar age range [3].

A systematic review of the literature and a meta-analysis of 42 recent case-control and cohort studies, published in 2016, found a significant association of the FVL (G1691A) mutation with SGA newborns (OR=1.40) and a lack of association of the FVL (G1691A) gene mutation with premature births [11].

The G20210A mutation of the prothrombin gene is a coagulation defect of the factor II at 20210 gene position, inherited as a dominant autosomal trait, located on chromosome 11, the 11 β 11-Q12 position, and is the second most widespread thrombophilic genetic anomaly [1,3,4]. Factor II converts fibrinogen into fibrin to form the thrombus, stimulates platelet aggregation, activates the factors V, VIII, XIII and protein C, thus inhibiting

coagulation [1,4]. The mutation of the prothrombin G20210A gene results in elevated serum prothrombin concentrations – by 30% in heterozygous bearers and by 70% in homozygous carriers [1].

The prevalence of the G20210A mutation of the prothrombin gene is 1-3% in the general population [1], 2-6% in the European population and very rare in the African or Asian ones [1,2,6]. The mutation of the G20210A prothrombin gene is found in 1-2% of the asymptomatic population, 4-7% of thrombotic patients, 18% of thrombophilic families, and 17% of pregnant women with VTE during the pregnancy [1,2,7].

The risk of VTE in carriers of the G20210A prothrombin gene mutation is 2-5 times higher and combined with the FVL G1691A gene mutation – 20 times higher [1]. The heterozygous type of mutation of the prothrombin G20210A gene has a 3-8 times higher risk and the homozygous type – a 18-80 times higher risk for thromboembolic events [4].

A systematic review of the literature found an OR of 2.49 for early pregnancy loss, 2.70 for early RPL, 2.66 for late pregnancy loss, 2.54 for preeclampsia, 2.92 for SGA newborns and 7.71 for placental abruption in pregnant women with the G20210A mutation of the prothrombin gene compared to pregnant women without this form of congenital thrombophilia [9].

Cumulative data from several studies indicate a significant association between the G20210A mutation of the prothrombin gene and RPL, preeclampsia and severe preeclampsia. Although the relationship between the G20210A mutation of the prothrombin gene and VTE during the pregnancy is clear, the results of studies do not confirm the impact of G20210A prothrombin gene mutation on obstetric complications: early RPL, preeclampsia, including early or severe onset, placental abruption, IUGR and SGA newborns [1,3,6,8,10].

Most of the data that predict the association of congenital thrombophilias, including the association of the G20210A mutation of the prothrombin gene, with adverse obstetric effects, are derived from case-control studies. Such studies are subjected to bias and may overestimate the risk of obstetric complications in pregnant women with congenital thrombophilias [12].

The protein C deficiency contains over 160 distinct mutations of the protein C gene, inherited as a dominant autosomal disorder, located on chromosome 2 (2q13-14) [6,7].

Protein C is synthesized in the liver and is a vitamin K-dependent natural anticoagulant. When activated by thrombin, protein C inactivates factor V and factor VIII, which leads to the prevention of factor X activation by limiting the prothrombin conversion to thrombin and fibrinogen to fibrin, correspondingly. Protein S is an important cofactor in the inhibitory effect of protein C [1,2,3,6].

The prevalence of protein C mutation is estimated at 0.2-1.5% in the general population, is more common

among Asian or African descendants [2,6,13] and is found in 2.5-6% of the patients with the first episode of VTE [1]. The risk of primary VTE with protein C deficiency during the pregnancy varies within the range of 0.1-0.8% [7], while the risk of recurrent VTE varies within the range of 4-17% [2].

Protein C deficiency includes two distinct subtypes. Type I is more common and results in the decrease of the amount and functional activity of the protein C. Type II results in decreased functional activity with a normal protein C level [1,6].

Overall, the conducted studies did not find a clear association between protein C deficiency and RPL [1,2,6], but in the case of association of the protein S deficiency and protein C deficiency, there is a correlation with an increased incidence of stillbirth [2].

There are no studies finding an association between protein C deficiency and early pregnancy loss, IUGR or abruptio placentae. Protein C deficiency was associated with an increased risk of spontaneous abortions during the second trimester and stillbirth [3].

A review of the literature, published in 2002, included 3-5 pertinent studies and found an increased risk of preeclampsia in pregnant women with protein C deficiency (21.5 times higher) with an absolute risk of 1.4% [3].

Protein S deficiency. Protein S is a vitamin K-dependent glycoprotein, a protein C cofactor, and is synthesized in the liver. It is found in the plasma in an active free form (40%) or bound to an inactive protein (60%). When it is functional, protein S accelerates the effect of protein C on factor V and factor VIII, suppressing thrombin formation. More than 130 autosomal dominant mutations of the gene located on chromosome 3q11.2, with variable expressions [1,2,4,7], are identified.

Protein S deficiency is less common, with a prevalence of 0.03-1.3% in the general population [1,7,13], 0.03-0.13% among the white population [2,6] and 1.1-5% in patients with VTE. VTE develops in up to 20% of the women with protein C deficiency or protein S deficiency during the pregnancy and postpartum [7].

The protein S deficiency is divided into 3 major subtypes: the classic type I protein S deficiency with low functional activity and low level of free and total S protein (approximately 50% of the normal quantity); type II with reduced functional activity and normal free and total protein S level; type III with reduced functional activity and low level of free protein S [1,6].

A review of the literature, published in 2002, evaluating 3-5 pertinent studies, revealed an increased risk of preeclampsia in pregnant women with protein S deficiency (12.7 times higher) with an absolute risk of 12.3%. The same study suggested an increase of stillbirths in pregnant women with protein S deficiency (16.2 times higher) with an absolute risk of 6% [3].

There are no studies that have found an association

between protein S deficiency and early pregnancy loss, IUGR or abruptio placentae [3].

Given the small prevalence and limited data, conclusions about the effect of protein C and protein S on RPL and other pregnancy complications cannot be drawn, and further investigations are needed [6,13].

Antithrombin deficiency. AT glycoprotein is synthesized in the liver and is the most important physiological inhibitor of thrombin and activated coagulation factors [1]. AT, being one of the most important physiological regulators of fibrin formation, has an inhibitory effect on thrombin, the transformation process of fibrinogen into fibrin and coagulation factors IX, X, XI, XII, VIII [6,7].

Although AT deficiency is the rarest hereditary thrombophilia, over 250 AT gene mutations, located on chromosome 1q23-25, are known. The mutation is inherited as a dominant autosomal trait, which, by direct binding to factors XI, X and thrombin, decreases the level and activity of AT or modifies the structure and function of AT, causing its activity to be reduced [1,2,7].

The AT deficiency was the first identified hereditary thrombophilia that significantly increases the risk of VTE; it is the most thrombogenic and presents the highest risk for VTE among hereditary thrombophilias and often requires long-term anticoagulant therapy. The lifetime risk of VTE is 70-90%. The risk of VTE is particularly high in pregnancy, post-partum and after major surgery [1].

There are 2 types of AT deficiency: type I deficiency is a quantitative dysfunction with the reduction of functional activity and protein level of about 50% in heterozygous women, and type II deficiency – a qualitative dysfunction with low functional activity and normal protein level [1,6].

The prevalence of AT gene mutation is 0.02-0.20% in the general population [13], 0.02-1.15% among white Europeans, 2-5% among Asians [6] and 0.5-8.0% in patients with VTE [7]. However, up to 60% of the pregnant women during pregnancy and 33% of the post-partum women with this thrombophilia make VTE. The absolute risk of VTE in pregnant women is 31% if anticoagulation prophylaxis is not administered and increases up to 49% in pregnant women with a history of VTE [7].

Data regarding the role of AT deficiency in fetal loss (spontaneous abortion, RPL) are inconsistent. Some studies have found that women with AT-III deficiency have an increased risk of embryonic death and fetal death, compared to the general population [1,3]. The results obtained from other studies suggest an association between AT deficiency and pregnancy loss, but the final causal relationship is not yet established. AT-III deficiency is rarely associated with severe preeclampsia, IUGR or abruptio placentae, but this fact could be “falsely negative”, because of the low prevalence of this thrombophilia [1].

MTHFR C677T gene mutation. MTHFR is one of the three enzymes involved in the

metabolism of the folic acid. In the hepatic cell, MTHFR reduces 5,10-methylenetetrahydrofolates to 5-methyltetrahydrofolates, which by remethylating converts homocysteine into methionine. The MTHFR gene is located on chromosome 1, position 1p36.3. The mutation of this gene, inherited as a recessive autosomal trait, can cause increased levels of homocysteine, and the homozygosity of the MTHFR C677T gene mutation is the most common cause of hyperhomocysteinemia [1, 3, 6].

The homozygosity of the MTHFR C677T gene mutation is present in 10-16% of Europe's population. Carriers of the C677T allele have a frequency from 7% in sub-Saharan Africa to 44% in Italy. When homocysteinemia is present, it acts as a procoagulant, affecting the vascular endothelium and leading to placental vasculopathy with impaired development of the embryo [1,6].

Hyperhomocysteinemia is an independent risk factor for VTE. Although several studies did not find a strong relationship between the homozygous mutation of the MTHFR C677T gene or elevated homocysteine levels [1,6] and the adverse outcomes of the pregnancy, a recent meta-analysis revealed an association of the MTHFR C677T gene mutation with severe preeclampsia [8].

A meta-analysis, which included 26 case-control studies with 2,120 cases and 2,949 controls (1997-2005), along with other recent studies, has found that the mutation of the MTHFR C677T gene is a genetic risk factor for inexplicable RPL (2 or more consecutive pregnancy losses) only in the Chinese and Iranian populations, but not in the population of the European countries [14,15].

Two more recent meta-analyses, which included 27 and 37 studies (1997-2011 and 1997-2012), 2,427 and 3,559 cases and 2,202 and 5,097 controls (published in 2012 and 2013), identified a significant association between the MTHFR C677T gene mutation and inexplicable RPL (2 or more consecutive pregnancy losses) in the East Asian subgroup (Chinese, Japanese and Korean population) and in the mixed subgroup (Indian, Brazilian, Bahraini, Mexican and Egyptian populations) but not in the Caucasian population, including Caucasians of European origin. In addition, the study found a genetic heterogeneity among ethnic groups [16,17].

Three recent meta-analyses, published in 2014 and 2015, which included a substantial number of cases and controls, revealed statistically significant results on the relationship between the MTHFR C677T gene mutation and high blood pressure in the general population, high blood pressure in pregnancy and preeclampsia, especially among Asians and Caucasians. The authors believe that this polymorphism is an independent risk factor for hypertension and preeclampsia [18,19].

The results of the Hordaland Homocysteine Study, conducted among 5,883 women aged 40-42 years with 14,492 pregnancies and published in 2004, revealed that the MTHFR C677T maternal polymorphism is associated

with increased pregnancy complications overall, increased risk of placental abruption and, possibly, IUGR or SGA newborns [20].

In conclusion, all congenital thrombophilias are associated with an increased risk of VTE during the pregnancy. Numerous studies have confirmed the increased risk of obstetric complications during the pregnancy in women with congenital thrombophilias. Case-control, cohort and transversal studies have shown that hereditary thrombophilia is more prevalent in cohorts of women with pregnancy losses, early-onset preeclampsia, abruptio placentae and IUGR. However, despite the relative risk increase, the absolute risk of VTE and negative pregnancy outcomes is low. Moreover, the risk assessment largely depends on the type of hereditary thrombophilia, the methodological criteria applied for the selection of patients, the ethnic groups included in the study, the differences in the sensitivity and specificity of the laboratory methods for the detection of thrombophilia. All these factors produce, in some cases, ambiguous results. There is convincing evidence that the deficiency of natural anticoagulants (AT, protein C, protein S) is a risk factor for late fetal loss. The FVL (G1691A) gene mutation and the G20210A prothrombin gene mutation are associated with a double risk for unexplained RPL and for non-recurrent late fetal loss. The association of congenital thrombophilia and preeclampsia is much more uncertain, being probably limited to the cases of FVL (G1691A) gene mutation with severe preeclampsia. Fewer data are available for IUGR and placental abruption.

According to more recent opinions of some researchers, hereditary thrombophilia may be poorly associated with pregnancy loss and, probably, poorly associated with severe forms of preeclampsia, abruptio placentae and IUGR. Concluding evidence suggests that hereditary thrombophilia is not associated with non-severe placentally mediated complications. Associations between more severe congenital thrombophilias (AT deficiency, protein C deficiency and protein S deficiency, double heterozygosity or homozygosity for mutation of the FVL G1691A gene or G20210A prothrombin gene mutation) and placentally mediated complications remain uncertain, because these thrombophilic defects are rare and poorly represented in studies.

The combination of two or more forms of hereditary thrombophilia (FVL G1691A gene mutation, G20210A prothrombin gene mutation, MTHFR C677T gene mutation), particularly the combination of the FVL gene mutation and MTHFR gene mutation, revealed their significant correlation with the early RPL.

In addition, genetic and epidemiological studies suggest that the obstetric complications during the pregnancy are of a polygenic multifactorial etiology, with the risk determined by the interaction of multiple genetic variants and environmental factors. The risk factors involved in

the recurrence of complications include the maternal age, race, ethnicity, number of previous spontaneous abortions and type of prior medical care during the pregnancy. The prevalence of congenital thrombophilias among the population is low, and women with these defects may have normal pregnancies, due to the little impact on the absolute risk of developing complications.

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