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# Thrombophilia in Women with Pregnancy-Associated Complications: Fetal Loss and Pregnancy-Related Venous Thromboembolism

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**Key Words**
Recurrent pregnancy loss · Thrombophilia · Venous thromboembolism, pregnancy related

**Abstract**
***Backgound/Aims:*** Existing data regarding the prevalence of thrombophilia in women with pregnancy complications are conflicting. ***Methods:*** To investigate the relationship between pregnancy-associated complications and the presence of thrombophilia, we studied the records of 453 women with pregnancy-associated complications. In 55 women, intrauterine fetal death (fetus mortus in utero, FMU) after 20 weeks of gestation was recorded, in 231 two or more consecutive recurrent fetal losses (RFL) were recorded, while 167 had a venous thromboembolism (VTE) during one of their pregnancies. The control group consisted of 128 healthy women, with no previous history of thrombotic events or miscarriages. ***Results:*** In the FMU group we found 54.5% of women had thrombophilia, in the RFL group 38%, and in the VTE group 52.7%. The most frequent thrombophilia in the VTE group was the FV Leiden (OR 17.9, 95% CI 4.2–75.9). The most frequent thrombophilia in the FMU group was the FII G20210A (OR 7.09, 95% CI 1.8–27.9). Statistical difference between RFL and the control group was observed only for FV Leiden (OR 6.8, 95% CI 1.6–29.7). ***Conclusion:*** Thrombophilia was found to be considerably more common in women with pregnancy-associated complications in comparison with the women with normal pregnancies, most frequently in patients with VTE or FMU.


## Introduction

Pregnancy is accompanied by hypercoagulation changes that may interact with thrombophilia as additional risk factors and thus threaten the pregnancy [1]. These changes include increased production of clotting factors, decreased production of natural coagulation inhibitors and changes in the fibrinolytic activity [2–5]. Presence of inherited thrombophilia represents an additional risk factor for maternal thromboembolism and certain adverse pregnancy outcomes, including second and third trimester fetal loss, placental abruption, severe intrauterine growth restriction and early onset of severe pre-eclampsia, due to vascular uteroplacental insufficiency [6–11]. The data regarding the prevalence of thrombophilia in pregnancy complications are conflicting. The frequency of thrombophilia is dependent on the study inclusion criteria and the ethnic origin of the study population [7]. The frequency of FV Leiden mutation in

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women with recurring fetal loss (RFL) varies from 3.7% in the study of Carp et al. [12] (which did not confirm the correlation between thrombophilia and RFL in the first and the second trimesters) up to 32% in the study of Brenner et al. [10] (which points to the significant association between thrombophilia and RFL). The data regarding thrombophilia presence among women with pregnancy-related venous thromboembolism (VTE) point to the significant correlation between thrombophilia presence and VTE during pregnancy or the postpartum period, but vary among women of different ethnicity [13–15]. The purpose of our study was to investigate the relationship between pregnancy-associated complications and the presence of thrombophilia among women who had fetal loss or pregnancy-related VTE in a Serbian population.

## Materials and Methods

*Patients*

The study encompassed 453 women, 286 with pregnancy complications [RFL or intrauterine fetal death (fetus mortus in utero, FMU)] and 167 with pregnancy-related VTE. They were referred to the thrombosis and hemostasis units in 2 centers in Serbia, the National Blood Transfusion Institute Belgrade and the Clinical Centre Novi Sad, for the evaluation of thrombophilia, from 1998 to 2008. We excluded women with chromosomal abnormalities in both parents, anatomic malformations of the uterus, reproductive hormone dysfunction, diabetes mellitus, thyroid disorders, chronic hypertension, auto-immune and infective disorders. Out of 286 women with pregnancy complications, we evaluated a group of 231 women with 2 or more pregnancy losses before the 20th gestation week (RFL group), and 55 with intrauterine fetal deaths after the 20th week of gestation (FMU group). In the group with VTE we evaluated only women who had a thrombotic process during pregnancy or after delivery (6 weeks). Of 167 women with a history of VTE, 135 had vaginal delivery and 32 delivered by cesarean section. All the women with a history of VTE had an objectively diagnosed episode of deep venous thrombosis or pulmonary embolism. Deep venous thrombosis was diagnosed by Doppler sonography during pregnancy and after delivery by Doppler sonography or scintigraphy in case of pulmonary embolism. All women provided blood samples at least 3 months after delivery.

The control group consisted of 128 healthy women, with no previous history of miscarriages or thrombotic events. Six of them had three deliveries, 79 of them had two and 43 had one.

None of the investigated women were pregnant at the time of investigation, none of them were using oral contraceptives.

*Laboratory Testing*

The laboratory analyses for thrombophilia testing included the assessment of antithrombin, protein C, protein S, activated protein C resistance, while the presence of lupus anticoagulant was tested by activated partial thromboplastin time, dilute Russell's-viper-venom time and silica clotting time assays. In all women, the functional activity of antithrombin, protein C and protein S was performed. After 2 consecutively obtained pathological results, the diagnosis of inhibitor deficiency was made. Following the current recommendations [16] if lupus anticoagulant or anticardiolipin antibodies were present, repeated testing at least 6–12 weeks apart was performed. Only women with 2 consecutively obtained clearly positive tests were considered as APL antibody positive.

For the detection of thrombophilia, IL tests (Instrumentation Laboratory, Milan, Italy) were used, and analyses were performed on IL Coagulometers ACL 6000 and Elite Pro. DNA analyses for FV Leiden, FII G20210A and MTHFR C677T mutations were conducted by PCR as previously described [17]. The serum anticardiolipin IgG and IgM antibody titer were determined by ELISA assay using Bindazyme Human Anti IgG and IgM (Binding Site, Birmingham, UK).

Institutional approval for the study was granted by the local research ethics committee in accordance with the internationally accepted ethical standards and each patient had signed the informed consent form.

*Statistical Analysis*

The prevalence of each thrombophilia was compared between patients and controls with the use of Fisher's exact and $\chi^2$ test. $p < 0.05$ was considered to be statistically significant. Univariate odds ratio (OR) and 95% CI were estimated separately for each mutation.

## Results

The characteristics of all women included in the study are presented in table 1. No statistical difference was observed between study and control groups regarding the age.

Of a total of 918 pregnancies among the women from the study group, 655 were recorded as fetal loss. In the control group, 219 successful pregnancies and no fetal loss were recorded. Regarding the outcomes of pregnancies a significant difference was observed, $p < 0.0001$. In the study group, in 55 women, intrauterine fetal death after the 20th week of gestation was recorded, in 114 women two consecutive RFL were recorded, and in 117 women more than three consecutive RFL before the 20th week of gestation. Venous thromboembolism during one of their pregnancies was observed in 167 women from the study group (table 1).

Presence of thrombophilia was found in 45% of women in the study group and in 8.6% of women from the control group ($p < 0.0001$). In the study group, 14.3% of women had FV Leiden/heterozygous, 8.8% had FII G20210A/heterozygous, 6.7% MTHFR C677T/homozygous mutations, 5.7% of women had deficiency of the nat-

**Table 1.** Characteristics of the study population

| | Women with pregnancy-associated complications (n = 453) | Control group (n = 128) | p |
|---|---|---|---|
| Median age (range), years | 29.7 (18–42) | 28 (19–40) | n.s. |
| Pregnancies | 918 | 219 | |
| Successful pregnancies, n (%) | 263 (28.6) | 219 (100) | |
| Unsuccessful pregnancies | 655 (71.4) | 0 | <0.0001 |
| One | 59 | | |
| Two | 228 | | |
| ≥Three | 368 | | |
| History of VTE | 167 | 0 | |
| Thrombophilia presence, n (%) | 204 (45.0) | 11 (8.6) | <0.0001 |
| FV Leiden | 65 (14.3) | 2 (1.6) | |
| FII G20210A | 40 (8.8 ) | 3 (2.3) | |
| MTHFR C677T[a] | 30 (6.7) | 6 (4.7) | |
| AT, PC, PS def. | 26 (5.7) | 0 | |
| Combined | 24 (5.3) | 0 | |
| APL | 19 (4.2) | 0 | |

[a] Homozygous. AT = Antithrombin; PC = protein C; PS = protein S; n.s. = not significant.

**Table 2.** Prevalence of thrombophilia among women with pregnancy-related VTE and control group

| Thrombophilia | VTE group, n (%) (n = 167) | Controls, n (%) (n = 128) | p | Odds ratio | 95% CI |
|---|---|---|---|---|---|
| FV Leiden | 37 (22) | 2 (1.6) | <0.000001 | 17.9 | 4.2–75.9 |
| FII G20210A | 16 (9.6) | 3 (2.3) | 0.01536 | 4.4 | 1.3–15.5 |
| MTHFR C677T[a] | 7 (4.2) | 6 (4.7) | 1.0 | 0.9 | 0.3–2.7 |
| AT, PC, PS def. | 10 (6) | 0 | 0.00588 | n.a. | |
| Combined | 16 (9.6) | 0 | 0.000102 | n.a. | |
| APL | 2 (1.2) | 0 | 0.507 | n.a. | |
| Total | 88 (52.7) | 11 (8.6) | <0.0001 | 11.84 | 5.9–23.6 |

[a] Homozygous. APL = Antiphospholipid antibodies (lupus anticoagulant/anticardiolipin antibodies); AT = antithrombin; PC = protein C; PS = protein S; n.a. = not applicable.

ural anticoagulants, 5.3% had combined thrombophilia and 4.2% had APL antibodies (table 1).

The most frequent thrombophilia in the group with VTE was the FV Leiden mutation, and the difference between VTE women and the control group was statistically significant ($p < 0.000001$, OR 17.9, 95% CI 4.2–75.9). The statistical differences between VTE and the control group were also observed for the prevalence of FII G20210A mutation (p = 0.01536, OR 4.4, 95% CI 1.3–15.5), deficiency of inhibitors (p = 0.00588) and combined defects (p = 0.000102; table 2).

In the FMU group, the most frequent thrombophilia was the FII G20210A mutation (p = 0.00331, OR 7.1, 95% CI 1.8–27.9). The statistical differences between the FMU and control groups were also observed for the prevalence of the FV Leiden mutation (p = 0.00983, OR 7.71, 95% CI 1.5–39.5), deficiency of inhibitors (p = 0.00004) and APL antibodies (p = 0.0075; table 3).

The incidence of mutations was almost equally frequent in the RFL group. However, the statistical difference between RFL women and the control group were observed for FV Leiden (p = 0.00194, OR 6.8, 95% CI 1.6–

**Table 3.** Prevalence of thrombophilia among women with FMU and the control group

| Thrombophilia | FMU group, n (%) (n = 55) | Controls, n (%) (n = 128) | p | Odds ratio | 95% CI |
|---|---|---|---|---|---|
| FV Leiden | 6 (11.0) | 2 (1.6) | 0.00983 | 7.7 | 1.5–39.5 |
| FII G20210A | 8 (14.5) | 3 (2.3) | 0.00331 | 7.1 | 1.8–27.9 |
| MTHFR C677T | 3 (5.5) | 6 (4.7) | 1.0 | 1.1 | 0.3–4.9 |
| AT, PC, PS def. | 8 (14.5) | 0 | 0.00004 | n.a. | |
| Combined | 1 (1.8) | 0 | 0.2849 | n.a. | |
| APL | 4 (7.3) | 0 | 0.0075 | n.a. | |
| Total | 30 (54.5) | 11 (8.6) | <0.0001 | 12.76 | 5.6–28.8 |

AT = Antithrombin; PC = protein C; PS = protein S; n.a. = not applicable.

**Table 4.** Prevalence of thrombophilia among women with RFL before the 20th week of gestation and the control group

| Thrombophilia | Women with RFL ≥2 n (%) (n = 231) | Controls, n (%) (n = 128) | p | Odds ratio | 95% CI |
|---|---|---|---|---|---|
| FV Leiden | 22 (9.5) | 2 (1.6) | 0.00194 | 6.8 | 1.6–29.7 |
| FII G20210A | 16 (7.0) | 3 (2.3) | 0.08341 | 3.2 | 0.9–11.2 |
| MTHFR C677T | 20 (8.6) | 6 (4.7) | 0.20298 | 1.9 | 0.8–5.1 |
| AT, PC, PS def. | 10 (4.3) | 0 | 0.01579 | n.a. | |
| Combined | 7 (3.0) | 0 | 0.05128 | n.a. | |
| APL | 13 (5.6) | 0 | 0.00286 | n.a. | |
| Total | 88 (38) | 11 (8.6) | <0.0001 | 6.8 | 3.5–13.0 |

AT = Antithrombin; PC = protein C; PS = protein S; n.a. = not applicable.

29.7). The statistical differences between the RFL and the control group were also observed for deficiency of inhibitors (p = 0.01579) and APL antibodies (p = 0.00286; table 4).

## Discussion

Venous thromboembolism and pregnancy loss are nowadays the most frequent pregnancy complications. Heritable prothrombotic factors lead to an increased risk of thromboembolism and play a considerable role in the pathogenesis of spontaneous abortions [18]. Results of studies on pregnancy complications in women with thrombophilia are conflicting and dependent on the criteria of inclusion into the study and the ethnic origin of the study population [7].

In our 10-year follow-up study, the prevalence of thrombophilia was investigated among women who had unexplained fetal loss or pregnancy-related VTE. In the whole study group, the presence of thrombophilia was observed in 45% of participants, with the most frequent presence of FV Leiden in 14.3% of women. In the similar Denmark study of Hvas et al. [19] the presence of FV Leiden was observed in 12.5% of women who had pregnancy-associated complications, fetal loss or pregnancy-related VTE.

Our study confirmed high prevalence of inherited thrombophilia among women who experienced VTE during pregnancy or postpartum. On the basis of our results, where the presence of the FV Leiden mutation was found in 22% of women in the study group versus 1.6% of the control group (OR 17.9), FV Leiden represents an important inherited risk factor which could be connected to the elevated risk for development of preg-

nancy-related VTE. The prevalence of FII G20210A of 9.6 versus 2.3% in the control group (OR 4.4) was also observed as an important inherited risk factor of VTE during pregnancy/puerperium. In our prior investigation we reported that only patients with FII G20210A mutation developed the transverse sinus venous thrombosis, where pregnancy was just an additional risk factor in developing thrombosis process [20]. Likewise, deficiency of inhibitors and the presence of combined defects were important risk factors, while the MTHFR C677T gene variant and the presence of APL had no influence on the risk of pregnancy-related thrombosis. The OR estimated for each tested mutation in our group was higher in comparison to other studies, possibly due to the inclusion of criteria for the control group. Women in the control group had no previous miscarriages, no thrombotic episodes and the majority had 2 or 3 deliveries. Prevalence of thrombophilia in the control group in the present study was actually lower compared with the general population in Serbia [21].

Martinelli et al. [22] showed similar prevalence of inherited thrombophilia in their study. In the study of Gerhardt et al. [23], the prevalence of hereditary coagulation defects is much higher than in our study, with a prevalence of 43.7% for FV Leiden and 16.9% for the G20210A mutation.

Among FMU women in our study, a high prevalence of thrombophilia (54.5%) was found. This study demonstrates that women who are carriers of prothrombin or FV Leiden mutations are at high risk of late fetal death (OR 7.1, 95% CI 1.8–27.9, and OR 7.7, 95% CI 1.5–39.5, respectively). Due to a low incidence of thrombophilia presence among the control group and a relatively high incidence among the study women, we have a wide confidence interval in our statistical calculations of OR for mutations, especially for FV Leiden. This mutation was observed in 1.6% of women from the control group, while among the study groups the figures were 22% in VTE, 11% in FMU and 9.5% in RFL. Similarly, a wide confidence interval for prothrombin mutation in the FMU group was recorded, with regard to the relatively high incidence of mutation in the study women (14.5%), contrary to the relatively low incidence in the control group (observed in 2.3%). The deficiency of natural inhibitors and APL antibodies were also important risk factors of FMU, while the MTHFR C677T genotype and combined defects had no influence on the risk of late fetal death in our study.

Likewise, an association between the presence of MTHFR C677T polymorphism and late fetal loss was not found in the study of Martinelli et al. [24], but they found a lower prevalence of mutations for FV Leiden and for prothrombin, with an equal relative risk of late fetal loss (RR of 3.2 and 3.3, respectively). In the study by Kupferminic et al. [25], the prevalence of FV Leiden among FMU women was much higher (25%), while the presence of prothrombin was not found.

The FV Leiden mutation was statistically significantly more frequently observed in the RFL than in the control group women, with a frequency of 9.5% in participants versus 1.6% in the control group (OR 6.8, 95% CI 1.6–29.7). The significant difference between participants and the control group was also observed for prevalence of inhibitors deficiency and APL antibodies. The data obtained from similar investigations have given conflicting results. The frequency of FV Leiden in women with RFL varies from 3.7% in the study of Carp et al. [12] to 4.8% in the study of Pasquier et al. [26] and did not confirm the association between thrombophilia and the RFL at or before the 20th gestation week. On the other hand, Grandone et al. [27], who investigated an Italian population, found the prevalence of FV Leiden of 16%, while in the study of Sarig et al. [28] it was 18%, and even up to 32% in the study of Brenner et al. [10].

Antiphospholipid antibodies are widely accepted as established risk factors for pregnancy loss in general. In our study, the presence of APL antibodies was observed in 5.6% of investigated women and, along with the FV Leiden mutation, represented the most important risk factor. In the Danish study by Hvas et al. [19], which was similar to our study regarding the number of investigated women and the study design, the observed prevalence of APL was more than twice as high. In our study, the determination of immunoglobulin G and M antibodies against $\beta_2$-glycoprotein1 was not performed, which might have had possible influence on the prevalence of APL in our population.

Among the limitations of this study, we should consider that our patient population was selected, since the women were referred to 2 centers specialized in the diagnosis of thrombophilia. As our study is retrospective, all data were collected and classified according to medical records, and a recall bias cannot be excluded. This retrospective study performed on a considerable sample size should be considered as a hypothesis-generating one, and further prospective studies for confirmation of our observations should be performed.

## Conclusion

Thrombophilia was found to be considerably more common in women with pregnancy-associated complications in comparison with the general population, and most frequently in those with VTE or FMU. The most prevalent inherited thrombophilia was the FV Leiden mutation, which was found in 22% of women in the group with pregnancy-related VTE and 9.5% in the RFL group. The prothrombin mutation was the most frequent in the FMU group, while the presence of APL antibodies was found to be considerable only in women with pregnancy complications. Our investigation justified the investigation of thrombophilia presence among women with pregnancy-associated complications in the Serbian population.


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