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ORIGINAL ARTICLE

The investigation of hereditary and acquired thrombophilia risk factors in the development of complications in pregnancy in Croatian women

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Abstract

Objectives: To investigate the genetic and acquired thrombophilic risk factors in pregnancy-associated complications and venous thromboembolism (VTE) and evaluate the association between particular thrombophilic risk factors and thromboembolic complications.

Methods: In this study, pregnant women with pregnancy complications and VTE ($N=101$) were the study group, and the control group were women with normal pregnancy ($N=102$). All women underwent testing for factor V Leiden mutation (FVL), mutation of the coagulation factors II (FII20210), methylenetetrahydrofolate reductase (MTHFR), plasminogen activator inhibitor-1, antithrombin III (ATIII), protein C (PC) and protein S, lupus anticoagulant (LAC) antibodies, anticardiolipin antibodies and anti-beta-2-glycoprotein-1.

Results: In this study group, mutations of the FVL was 15.8% (16/101), FII20210 5.9% (6/101) and the MTHFR at locus 677 was TT in 19.8% (20/101). Deficiency of ATIII and PC were rare: 3.0% and 1.0%, respectively. LAC were significantly higher in the study group than in the control group: 32.7% versus 3.9%; $p<0.0005$. Pregnant women with VTE have been more frequent for FVL (41.7%; $p<0.005$), PC deficiency (25.0%; $p<0.005$) and LAC (33.3%; $p<0.005$). Combination of FVL and MTHFR mutation was related to the risk of recurrent fetal death and habitual abortion.

Conclusion: The inherited and the acquired thrombophilic risk factors were found to be up to 10 times more common in the study group than in the control group.

Keywords

Antiphospholipid antibodies, genetic polymorphism, pregnancy complications, thrombophilia

History

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Introduction

Pregnancy is an independent, acquired risk factor for venous thromboembolism (VTE) and that risk is increased with the presence of hereditary thrombophilia. Among the pregnant women with thrombophilia, besides the increased risk of VTE, there is a risk of pregnancy complications such as: repeated early and late miscarriages, placental infarction, intrauterine fetal growth restriction, preeclampsia, placental abruption and fetal death [1,2].

One of the most common hereditary thrombophilias, which appears in 95% of cases, is the resistance to activated protein C (APC). APC resistance occurs due to the genetic mutations in the coagulation factor V gene locus 1691G/A or factor V Leiden mutation (FVL) [3]. The second most common cause of hereditary thrombophilia is the genetic mutation of the coagulation factors II at locus 20210G/A (FII20210GA), which causes hyperprothrombinemia [4]. In addition, there

are other known causes of this disorder, such as homozygous genetic mutation in the enzyme methylenetetrahydrofolate reductase (MTHFR) at the locus 677, which results in hyperhomocysteinemia [4]. Genetic changes that cause lack of the coagulation inhibitors are also important as the etiological causes of hereditary thrombophilia. Among them, the most important are mutations of antithrombin III (ATIII), protein C (PC) and protein S (PS). Polymorphism of plasminogen activator inhibitor-1 (PAI-1) 4G/5G gene, mostly the 4G allele responsible for the increase in PAI-1, inhibits the activity of plasminogen [5–8].

Acquired thrombophilia is caused by antiphospholipid antibodies: lupus anticoagulant (LAC), anticardiolipin (aCL) and anti-beta-2-glycoprotein-1 (aβ2GPI). It is considered that the antiphospholipid syndrome (APS) is confirmed if there is one clinical and one laboratory evidence of this disorder [9,10].

Methods

Study population and design

This study included a total of 203 pregnant women who were divided into two groups. The study group included 101 pregnant women, mean age 30 years (range 21–42 years),

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who had a history of VTE, such as deep vein thrombosis (DVT) and pulmonary embolism, or VTE in the immediate family members or pregnancy complications, such as recurrent fetal death, fetal growth restriction, preeclampsia, placental abruption and recurrent spontaneous abortions. The control group consisted of 102 pregnant women with normal pregnancies, the average age of 28 years (range 19–38 years) and no medical history of VTE. This two-year study was conducted from 2006 to 2008, and all study subjects were enrolled consecutively during the study timeline. All the subjects have signed informed consent for the inclusion in this study that was approved by the Ethics Committee of University Hospital Osijek and the Ethics Committee of the Faculty of Medicine, University of Osijek, as well.

The evaluation of haemostatic factors: biochemistry and molecular testing

Samples of the peripheral blood were collected from all of the participants included in this study. Biochemistry tests were obtained to evaluate the antiphospholipid antibodies (LAC, aCL and a β 2GP1) and the coagulation inhibitors (ATIII, PC and PS).

Molecular analyses regarding the gene mutations were performed on samples of DNA isolated from the peripheral blood leukocytes. The analysis included genetic polymorphisms of FVL1691GA, FII20210GA and MTHFR677CT. Molecular analyses of PAI-1 4G/5G were introduced later, so this method tested only 60 pregnant women with complications in pregnancy and/or VTE and 32 pregnant women in the control group.

Statistical analysis

We analyzed all data using the Software Package for Social Sciences for windows version 15.0 (SPSS Inc. 2006, Chicago, IL). Descriptive procedure was used to evaluate patients' characteristics, and each variable is presented as frequencies. Chi-square (χ^2) or Fischer's exact test for crosstab data and relative risk, and 95% confidence interval were used wherever appropriate. p value of <0.05 was considered as statistically significant.

Results

This study included a group of 101 pregnant women with complications and VTE in pregnancy, mean age 30 years (21–42), and 102 women with normal pregnancies, mean age 28 years (19–38). The prevalence of certain diagnoses in this study group with VTE and complications in pregnancy is listed in Table 1.

In the group with complications and VTE, FVL1691GA was found in 15.8% (16/101) versus the control group, where 7.8% (8/102) of pregnant women had this genotype. The prevalence of FII20210GA in this study group was 5.9% (6/101), and in the control group, it was 2.9% (3/101). The prevalence of MTHFR677TT was 19.8% (20/101) in the group with complications and VTE, while in the control group it was 9.8% (10/102), which is notable difference, but not statistically significant. For the PAI-14G/5G genetic polymorphism, survey was carried out in 60 pregnant women

Table 1. The prevalence of venous thromboembolism and its complications in the study group ($N = 101$).

| Diagnoses | Prevalence (%) |
|--------------------------------------------|----------------|
| Venous thromboembolism | 11.9% |
| Preeclampsia, eclampsia and HELLP syndrome | 35.6% |
| Early pregnancy loss | 48.5% |
| Late pregnancy loss | 33.7% |
| Fetal growth restriction | 15.8% |
| Recurrent fetal death | 23.8% |
| Repeated miscarriages | 28.7% |
| Threatened miscarriage | 13.9% |

with VTE and complications, and 32 pregnant women were in the control group. In the first group, the prevalence of PAI-14G/5G was 55% (33/60), and PAI-14G/4G was 27% (16/60), whereas in the control group, PAI-14G/5G was 63% (20/32), and PAI-14G/4G was 25% (8/32), which is not a statistically significant difference. Deficiency of ATIII and PC were found in a small number of participants. PC deficiency was found in 3/101 women with complications and VTE and in 1/102 pregnant women in the control group. ATIII deficiency was found in one pregnant woman with complications. PS deficiency was found in relatively large number of participants in the study group (22/101) compared to the control group (12/102), and the incidence is nearly two times higher in women with complications (Table 2).

FVL, FII20210GA and MTHFR677TT were present in 36.6% (37/101) of the pregnant women with complications and VTE and in 20.6% (21/102) of healthy pregnant women, which is statistically significant difference ($p < 0.025$).

Fibrinolytic and coagulation inhibitor genetic polymorphisms that determine thrombophilia including PAI-14G/4G, PAI-14G/5G, ATIII deficiency, PC deficiency and PS deficiency were found in 64.4% (65/101) of the pregnant women with complications and VTE and in 39.2% (40/102) of healthy pregnant women, which is also statistically significant difference ($p < 0.005$).

Total hereditary thrombophilia factors were found in 81.2% (82/101) of the pregnant women with complications and VTE and in 52.0% (53/102) of healthy pregnant women, which was statistically significant difference ($p < 0.0005$). Pregnant women with the hereditary thrombophilia factors are 2–4 times more likely to develop one of the complications of pregnancy compared to the women who do not have these factors (Table 2).

The overall prevalence of the LAC, a β 2GP1 and aCL was 37.6% (38/101) in the study group and 3.9% (4/102) in the healthy women, which were statistically significant at $p < 0.0005$. Similarly, prevalence of the LAC was 32.7% (33/101) in the study group opposite to the control group where it was 3.9% (4/101), which is also the significant difference ($p < 0.0005$). Furthermore, the difference in the prevalence of a β 2GP1 between groups was statistically significant ($p < 0.01$), whereas this was not the case with aCL ($p = 0.1213$; Table 2).

Overall number of inherited thrombophilic factors was significantly statically increased in the group of the pregnant women with gestational vascular complications ($p < 0.0005$), fetal loss ($p < 0.01$), the early loss of pregnancy ($p < 0.005$) and late loss of pregnancy ($p < 0.05$) compared to the healthy

Table 2. The frequency of hereditary and acquired thrombophilia factors among study participants.

| | Study group | | | Healthy pregnant women | | | <i>p</i> value | Relative risk (95% CI) |
|-----------------------------------|-------------|----|-------|------------------------|----|-------|----------------|------------------------|
| | <i>N</i> | P+ | % | <i>N</i> | P+ | % | | |
| Genetic polymorphism | | | | | | | | |
| FVL 1691GA heterozygote | | | | | | | | |
| Pregnant women with VTE | 12 | 5 | 41.67 | 102 | 8 | 7.84 | <0.005 | 5.5 (2.1–15) |
| Pregnant women with complications | 89 | 11 | 12.36 | | | | ns | – |
| F II 20210GA heterozygote | | | | | | | | |
| Pregnant women with VTE | 12 | 1 | 8.33 | 102 | 3 | 2.94 | ns | – |
| Pregnant women with complications | 89 | 5 | 5.62 | | | | ns | – |
| MTHFR 677TT homozygote | | | | | | | | |
| Pregnant women with VTE | 12 | 0 | 0.00 | 102 | 10 | 9.80 | ns | – |
| Pregnant women with complications | 89 | 20 | 22.47 | | | | <0.05 | 1.6 (1.1–2.1) |
| PAI-1 4G4G homozygote | | | | | | | | |
| Pregnant women with VTE | 5 | 0 | 0.00 | 32 | 8 | 25.00 | ns | – |
| Pregnant women with complications | 55 | 16 | 29.09 | | | | ns | – |
| PAI-1 4G5G heterozygote | | | | | | | | |
| Pregnant women with VTE | 5 | 4 | 80.00 | 32 | 20 | 62.50 | ns | – |
| Pregnant women with complications | 55 | 29 | 52.73 | | | | ns | – |
| AT III deficiency | | | | | | | | |
| Pregnant women with VTE | 12 | 1 | 8.33 | 102 | 0 | 0.00 | ns | 10.3 (5.9–18) |
| Pregnant women with complications | 89 | 0 | 0.00 | | | | ns | 2.1 (1.8–2.5) |
| PC deficiency | | | | | | | | |
| Pregnant women with VTE | 12 | 3 | 25.00 | 102 | 1 | 0.98 | <0.005 | 9.2 (3.9–21.3) |
| Pregnant women with complications | 89 | 0 | 0.00 | | | | ns | – |
| PS deficiency | | | | | | | | |
| Pregnant women with VTE | 12 | 1 | 8.33 | 102 | 12 | 11.76 | ns | – |
| Pregnant women with complications | 89 | 21 | 23.60 | | | | <0.05 | 1.5 (1.1–2) |
| Antiphospholipid antibodies | | | | | | | | |
| LAC – elevated | | | | | | | | |
| Pregnant women with VTE | 12 | 4 | 33.33 | 102 | 4 | 3.92 | | 6.6 (2.5–17.3) |
| Pregnant women with complications | 89 | 29 | 32.58 | | | | | 2.3 (1.8–2.9) |
| aCL – elevated | | | | | | | | |
| Pregnant women with VTE | 12 | 0 | 0.00 | 102 | 0 | 0.00 | | 9.5 (5.6–16.2) |
| Pregnant women with complications | 89 | 3 | 3.37 | | | | | 2.2 (1.9–2.6) |
| Aβ2GPI – elevated | | | | | | | | |
| Pregnant women with VTE | 12 | 0 | 0.00 | 102 | 0 | 0.00 | | 9.5 (5.6–16.2) |
| Pregnant women with complications | 89 | 9 | 10.11 | | | | | 2.3 (1.9–2.7) |

N, total number of subjects; P+, number of pregnant women with positive test; %, frequency of positive test; VTE, venous thromboembolism; FVL, factor V Leiden; FII, coagulation factor II; MTHFR, methylenetetrahydrofolate reductase; PAI-1, plasminogen activator inhibitor-1; ATIII, antithrombin III; PC, protein C; PS, protein S; LAC, lupus anticoagulant antibodies; aCL, anticardiolipin antibodies; aβ2GPI, anti-beta-2-glycoprotein-1; CI, confidence interval; and ns, no significance.

pregnant women. On the contrary, in the group of pregnant women with preeclampsia, eclampsia and HELLP (H-hemolysis, EL- elevated liver enzymes, LP- low platelets counts) syndrome, the difference was not statistically significant compared to the control group of the healthy women with the regard to the hereditary thrombophilic factors (Table 3). Antiphospholipid antibodies were significantly more frequent in the women with complications and VTE ($p < 0.0005$), in the group of pregnant women with gestational vascular complications ($p < 0.0005$), fetal loss ($p < 0.0005$), preeclampsia, eclampsia and HELLP syndrome ($p < 0.005$), early pregnancy loss ($p < 0.0005$) and late pregnancy loss ($p < 0.0005$) compared to the control group, respectively.

The prevalence of heterozygous FVL in pregnant women with VTE was significantly higher than in the control group ($p < 0.005$) as well as the prevalence of homozygous MTHFR677TT in pregnant women with complications ($p < 0.05$).

PC deficiency was significantly more common in the group with VTE compared to the control group ($p < 0.005$), while deficiency of PS was significantly more common in the pregnant women with complications in pregnancy compared

to the control group ($p < 0.05$). Prevalence of the antiphospholipid antibodies was significantly higher in the group with complications and VTE than in the control group. Similarly, LAC antibodies were more common in the group with VTE ($p < 0.005$) and in the pregnant women with complications ($p < 0.0005$), and the antibodies aβ2GPI were more common only in the pregnant women with complications ($p < 0.005$), which is listed in Table 3.

Discussion

Pregnant women with thrombophilia have a higher risk for VTE, and they are at the increased risk for developing complications of pregnancy due to the pathological changes in the uteroplacental circulation.

Although the prevalence of the inherited thrombophilia factors in high-risk pregnancies is approximately two times higher than in the normal pregnancies, none of the genetic polymorphisms showed no statistically significant difference in the prevalence compared to the control group. The results of the prevalence of these genetic polymorphisms in the group of the pregnant women with VTE and complications and in the control group of healthy women are in line with the results

Table 3. The frequency of hereditary and acquired thrombophilia factors in pregnant women with gestational vascular complications, loss of pregnancy and VTE compared to the control group.

| | Pregnant women with complications | | | Healthy pregnant women | | | <i>p</i> value | Relative risk (95% CI) |
|------------------------------------------------------------|-----------------------------------|----|------|------------------------|----|------|----------------|---------------------------|
| | <i>N</i> | P+ | % | <i>N</i> | P+ | % | | |
| Genetic polymorphism | | | | | | | | |
| Pregnant women with complications in the pregnancy and VTE | | | | | | | | |
| A | 101 | 37 | 36.6 | 102 | 21 | 20.6 | <0.025 | 1.4 (1.1–1.9) |
| B | 101 | 65 | 64.4 | 102 | 40 | 39.2 | <0.005 | 1.7 (1.2–2.3) |
| [A + B] | 101 | 82 | 81.2 | 102 | 53 | 52.0 | <0.0005 | 2.2 (1.4–3.3) |
| Gestational vascular complications | | | | | | | | |
| [A + B] | 41 | 36 | 87.8 | 102 | 53 | 52.0 | <0.0005 | 4.4 (1.8–10.4) |
| Loss of fetus | | | | | | | | |
| [A + B] | 56 | 42 | 75.0 | 102 | 53 | 52.0 | <0.01 | 2 (1.2–3.3) |
| Preeclampsia, eclampsia and HELLP syndrome | | | | | | | | |
| [A + B] | 36 | 23 | 63.9 | 102 | 53 | 52.0 | ns | – |
| Early pregnancy loss | | | | | | | | |
| [A + B] | 49 | 40 | 81.6 | 102 | 53 | 52.0 | <0.005 | 2.8 (1.5–5.3) |
| Late pregnancy loss | | | | | | | | |
| [A + B] | 34 | 25 | 73.5 | 102 | 53 | 52.0 | <0.05 | 2.1 (1–4.1) |
| Antiphospholipid antibodies | | | | | | | | |
| Pregnant women with complications in the pregnancy and VTE | | | | | | | | |
| Gestational vascular complications | 41 | 13 | 31.7 | 102 | 4 | 3.9 | <0.0005 | 3.4 (2.3–5.2) |
| Loss of fetus | 56 | 25 | 44.6 | 102 | 4 | 3.9 | <0.0005 | 3.6 (2.6–5) |
| Preeclampsia, eclampsia and HELLP syndrome | 36 | 8 | 22.2 | 102 | 4 | 3.9 | <0.005 | 3 (1.8–5) |
| Early pregnancy loss | 49 | 19 | 38.8 | 102 | 4 | 3.9 | <0.0005 | 3.5 (2.4–5.1) |
| Late pregnancy loss | 34 | 13 | 38.2 | 102 | 4 | 3.9 | <0.0005 | 4.3 (2.7–6.9) |

N, total number of subjects; P+, number of pregnant women with positive test; %, frequency of positive test; A, hereditary thrombophilic factors: FVL, FII20210GA and MTHFR677TT; B, hereditary thrombophilic factors: PAI-14G4G, PAI-14G5G, ATIII deficiency, PC deficiency, PS deficiency; VTE, venous thromboembolism; and ns, no significance.

of the prevalence of these genetic polymorphisms in comparable populations of Central and Southern Europe [11–15]. However, when the total prevalence of all three genetic polymorphisms observed in the group with complications and VTE, which was 36.6%, was compared with the control group, where it was 20.6%, statistically significant difference at the level of $p < 0.025$ was obtained, indicating a significant accumulation of the hereditary thrombophilia factors in the risk pregnancies resulting in a significant burden of thrombophilia in pregnancy.

Overall, 81.2% (82/101) of the pregnant women with complications and VTE and 52.0% (53/102) of the healthy pregnant women had one or more genetic factors for thrombophilia ($p < 0.0005$). The most common factor for acquired thrombophilia in pregnancy is APS, which is associated with the occurrence of placental vascular thrombosis and placental infarction [16,17]. Our study has shown 2–6 times (95% CI: 2.17–13.42) more often positive APS in the pregnancies with complications, compared to the control group.

In the group with complications, 11.9% developed DVT. In this group, heterozygous FVL and lack of PC were significantly more common. FVL was found in 41.7% of patients ($p < 0.005$) compared with the control group where the prevalence was only 7.8%. Our results have shown that the pregnant women with VTE have an average of 5.6 times (95% CI: 2.1–15.0) more frequent FVL compared to the women with normal pregnancies. Literature data indicate that the prevalence of FVL in the group with inherited thrombophilia ranges from 20% to 40% [4,8,18,19]. PC deficiency is poorly represented in the population with thrombophilia (3%)

[13,14]. In the group with VTE, PC deficiency was found in 25% of the women ($p < 0.005$), which was statistically significant compared to the control group as well as the prevalence of LAC in the pregnant women with VTE, which was 33.3% compared to the 3.9% in the control group ($p < 0.005$).

In the group of pregnant women with complications, 33.7% had a history of late pregnancy loss and only statistically significant finding were confirmed LAC in 32.4% of cases ($p < 0.0005$). According to the research of Preston et al., hereditary thrombophilia factors such as FVL, ATIII, PC and PS deficiency were associated with late loss of pregnancy, but the results of our study did not confirm these observations [20–22].

Intrauterine growth restriction (IUGR) as a complication of pregnancy had 15.9% of pregnant women included in our study. In this group, we found a high prevalence of MTHFR677TT (31.3%, $p < 0.05$) and presence of LAC (25.0%, $p < 0.01$). De Vries et al. have showed high prevalence of hyperhomocysteinemia, PS deficiency and FVL in the group with IUGR [23]. Our results have showed a statistically significant representation of the MTHFR677TT, in contrast to the studies that did not identify the association between the inherited thrombophilia factors and IUGR [24–26].

In the group of pregnant women with complications, 35.6% (36/101) had clinically expressed pre-eclampsia, eclampsia and HELLP syndrome. Kupfermanc showed more often homozygous mutation of MTHFR677TT, lack of PS, PC and ATIII in pregnant women with preeclampsia. Robertson et al. found that the heterozygous mutations FII20210GA and FVL are more often found in the preeclamptic patients [27].

The results of our study showed no statistically significant difference in the prevalence of FVL and FII20210GA compared to the control group. Statistically significant difference was found only in the MTHFR677TT (22.2%, $p < 0.05$) and PS deficiency (30.6%, $p < 0.025$). The most likely cause of the difference in results lies in the nature of this disease, which depends on the different demographic parameters such as ethnic origin, age of pregnant women, lifestyle and diet and other medical reasons [28,29].

In the researched study group, medical history of recurrent fetal death had 23.8% and recurrent miscarriage had 28.7% of the pregnant women. In this group, we have found significant differences in the prevalence of associated hereditary thrombophilia factors, FVL1691GA and MTHFR677TT as compared to the control group. Some studies have suggested the association between FII20210GA and the death of the fetus, but other studies could not confirm this association [30]. In the group of pregnant women with repeated fetal death, we have found a high prevalence of the LAC 41.7% ($p < 0.0005$), which also have shown in the studies of Randa et al. and Salvagano et al. [14]. The presence of LAC, a β 2GP1 and aCL was the main finding in the group of women with medical history of early spontaneous abortion, recurrent miscarriage and late pregnancy loss in the clinically expressed APS. The pathogenesis of early fetal loss is assumed to have antiphospholipid antibodies responsible for trophoblast dysfunction and poor embryo implantation.

In the pregnant women research study group, statistically significant difference in the prevalence was found for the MTHFR677TT ($p < 0.025$) and PS deficiency ($p < 0.005$) compared to the control group. These factors of thrombophilia were averaged 4.4 times (RR = 1.8–10.4, 95% CI) more common in pregnancies with gestational vascular complications related to the pregnancy without complications. The presence of LAC and a β 2GP1 ($p < 0.0005$ and $p < 0.025$, respectively) was averaged 3.4 times higher in this type of pregnancy complications compared to the control group of women with the normal pregnancy (RR = 2.3–5.2, 95% CI). This study showed that the pregnancy with VTE and complications in pregnancy were 10 times more frequently associated with the inherited and acquired thrombophilia factors compared with the normal pregnancies.

In conclusion, the evaluation of hereditary and acquired thrombophilia factors in the pregnancy complications is of particular importance because of the possibility that the anticoagulation prophylaxis and therapy may provide the protection of the pregnant women and the unborn child. Criteria for the prophylaxis and treatment should be based on medical history, clinical and laboratory indicators of hereditary and acquired risk factors of thrombophilia. It is therefore of particular interest to control the coagulation status of the pregnant women with history of previous VTE and complications in the pregnancy to determine the degree of risk that a particular genetic and acquired thrombophilia factors could have in the development of pregnancy complications.

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Declaration of interest

The authors report no declarations of interest.

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