

Frequency of selected thrombophilias in women with placental abruption

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Abstract

Objective: There is a growing view that inherited or acquired thrombophilia may predispose a woman towards an adverse pregnancy outcome. The aim of this study was to investigate whether risk factors for placental abruption because of such thrombophilias (such as carriership of factor V Leiden (FVL), prothrombin G20210A gene mutation and homozygous MTHFR C677T) might be used as a predictor for placental abruption.

Methods: A retrospective case-control study conducted at the University Hospital, Palacký University, Olomouc, Czech Republic. One hundred and eighty women with placental abruption out of 20 175 deliveries (0.79%) were compared to 196 unselected gravidae. A detailed medical history was taken with special reference to factors related to hypercoagulation and blood was drawn for polymerase chain reaction analysis. The prevalence of FVL, prothrombin G20210A and MTHFR C677T was related to placental abruption.

Results: The heterozygous form of FVL was present in 20 of 142 cases (14.1%) in the placental abruption group, compared to ten of 196 (5.1%) in the control group (odds ratio 3.0, 95% confidence interval 1.4–6.7).

Conclusions: We found that factor V Leiden is a significant risk factor for placental abruption.

Key words: factor V Leiden, MTHFR C677T, placental abruption.

Introduction

Premature separation of the placenta occurs in only 1% of all pregnancies, yet it is an important cause of stillbirth, preterm delivery, early neonatal death and even maternal death.¹ Placental abruption accounts for 20–25% of antepartum haemorrhages. The perinatal mortality rate varies between 2% and 67%, depending on gestational age, fetal weight, and the degree of abruption. Over 50% of all perinatal deaths occur before delivery.²

The role of maternal thrombophilia as a cause of placental abruption has recently come under scrutiny. Dahlbäck *et al.* identified activated protein-C resistance as a thrombophilic factor, as diagnosed by an activated prothrombin time-based test.³ A mutation in the factor V gene termed V Leiden (FVL or FVQ⁵⁰⁶) is the most common genetic cause for this haemostatic variation. The gene for FVL mutation results in the replacement of arginine (R) at position 506 by glutamine (Q).⁴ This affects one of the cleavage sites of FVL, rendering it resistant to proteolytic digestion by activated protein C. It is the most common known inherited risk factor for venous thrombosis in white European populations.⁴ Since 1996, a prothrombin gene mutation has been identified.

Nucleotide change (a G to A) within the '3 untranslated region causes impaired anticoagulation and increases the risk of venous thromboembolism.⁵

Increased plasma homocysteine concentrations have been associated with placental vascular thrombosis, particularly pre-eclampsia and placental abruption, as well as recurrent pregnancy loss.⁶ It has now been recognised that there are genetic polymorphisms of the enzymes involved in the metabolism of homocysteine. Methylenetetrahydrofolate reductase (MTHFR) is the enzyme required for the synthesis of 5-methyltetrahydrofolate; the methyl donor is required for the conversion of homocysteine to methionine. The homozygote thermolabile C677T variant of the gene for

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MTHFR has been associated with a tendency towards moderate hyperhomocysteinaemia.⁷

There is a growing view that both inherited or acquired thrombophilia may predispose a woman towards an adverse pregnancy outcome. The mechanism is thought to be thrombophilia-related uteroplacental insufficiency because of a compromised vascular support system.⁸ The exact role of each type of thrombophilia in the pathophysiology of the obstetric complications is unknown.⁹

The aim of our study was to determine if carriership of the abovementioned thrombophilias is associated with an increased risk of placental abruption.

Methods

We identified 180 women out of 20 175 deliveries (0.79%) with a confirmed diagnosis of placental abruption at the Department of Obstetrics and Gynaecology, University Hospital, Olomouc, during a 14-year period (January 1991 to July 2004). All 180 women were approached by letter to participate in the study, and 142 (79%), representing 154 babies, accepted. Women participating in the study were interviewed in person. A detailed history of the situation before the index pregnancy and a blood sample were taken. Also, all medical records were reviewed. Gestational age was routinely estimated by ultrasound examination. The interval between placental abruption and blood tests varied from 24 h to 14 years. The control group was collected between January 2003 and March 2004. Every tenth woman giving birth at the delivery unit was approached to participate in the study. Two hundred and six women with uncomplicated pregnancies were approached to participate in the study. Ten women declined to participate, and thus, 196 women were included in the control group. A detailed medical history of this group was also taken before delivery as part of the clinical routine and their medical records were reviewed. Blood was drawn within 72 h after delivery.

We defined placental abruption in terms of a clinical diagnosis, usually based on profuse vaginal bleeding appearing during the third trimester, painful contractions and clinical examination of the placenta. All placentas were examined macroscopically. Thrombosis heredity was defined as the presence of at least one first degree relative (parents or siblings) with anamnesis of venous thromboembolic events.

Recurrent pregnancy loss was defined as three or more first trimester losses, one second trimester fetal loss with subsequent two or more consecutive first trimester fetal loss(es), or at least two second trimester losses. Stillbirth, defined as intrauterine death after 24 weeks of gestation, occurred in four cases (2.8%) in the placental abruption group. Smoking habits and first degree heritage of thrombosis in the control group were recorded at the last antenatal visit. The data in the study group were based on detailed history-taking and retrospective review of the medical records. Gestational age was estimated by sonographic measurement at the end of the first trimester. Small for gestational age was defined as a newborn whose

birthweight was below the 5th percentile. Preterm delivery was defined as delivery before 37 weeks of gestation. Diagnosis of chorioamnionitis was based on the histopathological examination of the placenta and a combination of clinical signs (fever, pain, and fetal distress) and elevated inflammation markers (white blood cell count, C-reactive protein). Premature rupture of the membranes (PROM) was defined as rupture of membranes more than 24 h before delivery. The diagnosis of PROM was based on clinical signs (amniotic fluid index measured by ultrasound and detection of amniotic fluid microscopically and chemically). Pre-eclampsia was defined as hypertension in pregnancy (> 140/90) and proteinuria (> 300 mg/L). Pregnancy-induced hypertension was defined as hypertension in pregnancy measured on two occasions at an interval of at least five hours, and having developed after 20 weeks of gestation in a previously normotensive pregnancy.

The Ethics Committee of the Medical Faculty of Palacky University approved the study design, and informed consent was obtained from all participants.

Characteristics

The mean age for the study group and the control group was 27.5 years (± 5.4) and 28.8 years (± 5.1), respectively ($P = 0.02$). The neonates from the study group were at a significantly lower gestational age and had a lower birthweight than those from the control group (33.5 ± 4.8 and 39.1 ± 2.0 weeks, $P < 0.001$ and $2164 \text{ g} \pm 984$ and $3385 \text{ g} \pm 539$, $P < 0.001$, respectively). The pH of the umbilical artery was not statistically different between the two groups (7.30 ± 0.14 ($n = 106$) and 7.32 ± 0.06 ($n = 103$) cases, $P < 0.18$).

Coagulation methods

Carriership of FVL was defined as the presence of the FV:Q506 allele in either its heterozygous or its homozygous form. All women in both groups were tested with polymerase chain reaction-based analysis for the presence of FVL, prothrombin G20210 A gene mutation and MTHFR C677T polymorphism as previously described.^{10,11} The abovementioned genotypes were not known in any woman before this study.

Statistics

The χ^2 test or Fischer's exact test was used for analysis of categorical variables. All calculations were performed using STATISTIKA CZ (software system data analysis), version 6 (StatSoft, Inc., Tulsa, OK, USA). Values of $P < 0.05$ were considered statistically significant.

Results

Characteristics of pregnancies with placental abruption and controls that might affect the risk of placental abruption are given in Table 1. As expected, the prevalence of established risk factors such as maternal smoking, intrauterine growth

Table 1 Characteristics of women with placental abruption and controls

	Placental abruption (<i>n</i> = 142)		Control group (<i>n</i> = 196)		OR (95% CI)
Established risk factors for placental abruption					
Smokers	38	26.8%	25	12.7%	2.5 (1.4–4.4)
Intrauterine growth restriction	14	9.8%	7	3.6%	2.9 (1.2–7.5)
Pre-eclampsia	10	7.0%	2	1.0%	7.3 (1.6–34.1)
Chronic hypertension	5	3.5%	4	2.0%	1.7 (0.5–6.6)
Recurrent fetal loss	29	20.4%	4	2.0%	12.3 (4.2–35.9)
Premature rupture of membranes	37	25.3%	10	5.1%	6.5 (3.1–13.7)
Chorioamnionitis	10	7.0%	2	1.0%	7.3 (1.6–34.1)
Male fetal gender	78	55.9%	95	48.5%	1.3 (0.8–2.0)
Studied risk factors for placental abruption					
Factor V Leiden	20	14.1%	10	5.1%	3.0 (1.4–6.7)
Prothrombin gene mutation G20210A	0	0.0%	2	1.0%	na
MTHFR C677T homozygous	8	5.6%	7	3.6%	1.6 (0.6–4.7)
Recurrent fetal loss	29	20.4%	4	2.0%	12.3 (4.2–35.9)
Thrombosis heredity	24	16.2%	6	3.1%	6.4 (2.6–16.2)

Numbers, percentage and odds ratios (OR) with their 95% confidence intervals (CI) are given. na, not applicable.

restriction, pre-eclampsia, chorioamnionitis, and PROM was significantly greater in the study group compared to the control group.

In Table 1, the relationship between the primarily studied variables and placental abruption is shown. None of the women in our series exhibited homozygous FVL or homozygous prothrombin mutation G20210A. We therefore present only carriers and non-carriers. In the placental abruption group, we found 14.1% to be carriers of FVL, as compared to 5.1% in the control group (OR 3.0, 95% CI 1.4–6.7). There were only two cases of heterozygous prothrombin mutation G20210A, both in the control group. Heterozygous MTHFR C677T was present in 61 women (43.0%) in the study group and 84 (42.9%) in the control group. For the purpose of analysis, homozygous carriers were compared to others. We found a non-significant increased risk of being a homozygous MTHFR C677T carrier in the study group as compared to the control group (5.6% vs. 3.6%, respectively, OR 1.6, 95% CI 0.6–4.7). Notably four of five women with a combination of FVL and homozygous form of MTHFR C677T polymorphism had placental abruption.

Also, placental abruption showed a sixfold higher prevalence among women with first-degree relatives with anamnesis of thromboembolic events and 12-fold higher prevalence of prior recurrent fetal loss.

Discussion

In this retrospective case-control study, we found carriership of FVL, prior recurrent fetal loss, and first degree heritage of thrombosis to be significant risk factors for developing placental abruption.

Other conditions known to have an increased risk of placental abruption were at similar risk as usually reported

(ie smokers, intrauterine growth restriction, pre-eclampsia, and chronic hypertension). We confirmed the recent report stating an increased risk for women with first-degree heritage of venous thromboembolism.¹² In addition, we found prior repeated fetal loss as a significant risk factor for placental abruption, which is in accordance with a prior recent report.¹³

A strength of our study was that it is one of the largest focusing on FVL and placental abruption and that the reported ORs for placental abruption among FVL carriers was not in disagreement with other reports (Table 2).^{12,14,15,16} The major weakness was the retrospective nature of this study with all possible bias. The anamnesis in the control group was taken at the end of the index pregnancy, while the study group was interviewed several years later. This may have introduced recall bias. However, we were able to confirm the number of recurrent fetal losses in the review of medical records and we only included anamnestic variables present at time of the index pregnancy. Another possible shortcoming is that the blood samples from the control group were taken the first post-partum days. It is known that carriers of FVL have lower blood loss at delivery and have shorter time in hospital.¹⁰ Thus, the inclusion of hospitalised women in the control group might have introduced selection bias towards a low prevalence of FVL in the control group. Our reported prevalence of FVL in the Czech population (5.1%) is consistent with the proportion of FVL found in a previous study of 448 oral contraceptive users in the Czech Republic (6.5%),¹⁷ but considerably lower than in a Hungarian (9.8%) or German population (7.5%).^{18,19}

We found the prevalence of prothrombin gene mutation G20210A in the Czech population to be lower than expected (1.0 vs 2–3%) and, in fact, there were no carriers in the study group. Thus, our results are not in agreement with the previously published high prevalence of G20210A mutation (20%) among women with placental abruption.¹⁴ We found

Table 2 Studies investigating the association between FV Leiden and abruptio placentae**

	Placental abruption FV Leiden +/-	Control group FV Leiden +/-	OR (95%CI)	Power*
Wiener-Megnagi <i>et al.</i> , 1998	8/27	1/29	11.8 (1.4–102)	8%
Kupferminc <i>et al.</i> , 1999	5/20	7/110	4.9 (1.4–17.4)	18%
Alfirevic <i>et al.</i> , 2001	0/23	3/44	na	14%
Procházka <i>et al.</i> , 2003	16/102	270/2366	1.5 (0.9–2.6)	73%
Present study	20/142	10/196	3.0 (1.4–6.7)	37%

*Power to detect a doubled prevalence of FV Leiden among pregnancies with abruptio placentae, as compared to given controls.

**Study and control groups expressed as number of carriers of FV Leiden/non-carriers.

Odds ratios (OR) and 95% confidence intervals (95%CI) are given.

the homozygous form of the C677T in 5.6% of the study group and 3.6% of the control group (OR 1.6). This is partly in agreement with Kupferminc *et al.*, who reported homozygous MTHFR in 15% of patients in study and 8.2% in the control group (OR 2.2, 95% CI 0.4–11.6).¹⁴ Although not significant, our finding that four of five carriers of both FVL and homozygous MTHFR mutation were in the placental abruption group may partly explain the heterogenic results regarding FVL and placental abruption, that is, the prevalence of combined thrombophilias might vary (Table 2). Preston *et al.* also reported a high prevalence of combined thrombophilic defects in women with stillbirth.⁸ In addition, our data support the established risk factors related to placental abruption. Also, the predominance of male fetal gender is in agreement with that in study by Kramer *et al.*¹

We conclude that FVL is a significant risk factor for placental abruption and that several anamnestic factors such as thrombosis heredity and prior recurrent fetal loss might be used to identify cases at higher risk for late pregnancy haemorrhage or premature contractions.

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