The HELLP syndrome. Clinical course, underlying disorders and long-term follow-up

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Prothrombin 20210 G-A mutation and Factor V Leiden mutation in women with a history of severe preeclampsia and (H)ELLP syndrome

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submitted for publication
Abstract

Objective

20210 G to A prothrombin gene variant and the factor V Leiden mutation are mutations associated with venous thrombotic risk. The aim of our study was to assess the prevalence of these specific mutations in women with a history of preeclampsia or (H)ELLP syndrome and their influence on perinatal outcome. In addition the association with venous thromboembolism was assessed.

Study Design

114 patients with a history of preeclampsia or (H)ELLP syndrome were investigated at least 3 months post partum for the presence of 20210 G to A prothrombin gene variant and factor V Leiden mutation.

Results

Seven of 114 women (6.1%) had at least one mutation, one woman carried both mutations. This is comparable with the prevalence in the general Dutch population. The odds ratio for thromboembolism for carriers versus non-carriers was 22 (95% CI 1.7-303). Perinatal mortality was not significantly higher in women with any mutation (odds ratio 1.5 (0.2-9.5)).

Conclusions

prothrombin 20210 G-A mutation and factor V Leiden mutation are associated with thrombotic risk, but most likely not with perinatal mortality in patients with severe preeclampsia or (H)ELLP syndrome.
Introduction

Women with inherited thrombophilia have an increased risk of preeclampsia and of perinatal mortality.\(^1\)\(^2\)\(^3\) The utero-placental vascular system appears to be compromised by disorders of hemostasis associated with a prothrombotic state. Two mutations, increased prothrombin associated with the prothrombin 20210 A allele and resistance to activated protein C associated with the factor V Leiden mutation, are the most prevalent thrombotic genetic risk factors. Together they can be found in up to 60% of the thrombophilia families.\(^4\) Both factors are more frequently coinherited in patients with venous thrombophilia.\(^5\)\(^6\) Several publications report a relation between factor V mutation and preeclampsia or pregnancy loss.\(^7\)\(^8\)\(^9\)\(^10\)\(^11\) The prothrombin 20210 G-A mutation in relation to complications of pregnancy was described only twice.\(^12\)\(^13\) The aim of our study was to look for the presence of both mutations in a cohort of women with a history of severe preeclampsia or (H)HELLP syndrome.

Material and Methods

Hundred and fourteen women who had been admitted between January 1984 and January 1996 because of severe preeclampsia or (H)HELLP syndrome were included. Severe preeclampsia was defined as a diastolic blood pressure of \(\geq 110\) mm Hg and proteinuria \(\geq 0.5\) g/L measured before 34 weeks gestation and delivered before 36 weeks gestation. The HELLP syndrome was defined as hemolysis (serum lactate dehydrogenase (LDH) \(\geq 600\) U/L), elevated liver enzymes (serum aspartate aminotransferase (ASAT) \(\geq 50\) U/L) and low platelet count (< 100.10\(^7\))L). Women with serum lactate dehydrogenase (LDH) < 600 U/L, but with elevated ASAT and low platelets were defined as incomplete HELLP i.e. ELLP.\(^14\) Patients with preexisting diseases such as hypertension, cardiac or renal disease and diabetes mellitus were excluded. Blood samples were obtained from all women at a minimum of 3 months post partum between April 1, 1995 and September 1, 1997 and were stored on filtering paper. At the same time the women were asked to fill out a questionnaire in order to obtain information on their personal and family history (1st and 2nd degree) relating to cardiovascular disease, medically treated hypertension, venous thromboembolism and smoking habits.

Informed consent was obtained from all participants and the study was approved by the Institutional Review Boards.

Laboratory tests

DNA was extracted and assayed in one batch. The status of the prothrombin 20210 G-A mutation was determined by the presence of a HindIII restriction site in the polymerase
chain reaction fragment according to the method of Poort et al.\textsuperscript{15} Genetic analysis of the factor V Leiden mutation (1691 G- A) was performed by standard polymerase chain reaction assay.\textsuperscript{16}

### Statistical analysis

Data were analyzed using Epi info (Centers for Disease Control, Atlanta, USA). Differences between groups were tested two-sided by use of chi-square test or Student's t-test as appropriate. Odds ratios and 95% confidence intervals were calculated. Statistical significance was considered at $p < 0.05$.

### Results

One hundred and fourteen women were analyzed for the presence of prothrombin 20210 G-A mutation and factor V Leiden mutation. The median time interval after delivery was 2.3 years (0.3-12.8). In Table 1 the most relevant obstetric, medical and family details of women with and without a mutation are presented. Gestational age at delivery, birth weight and perinatal mortality were comparable between women both with or without a mutation. Eight of 80 women with a history of (H)ELLP had experienced eclampsia. Three women (3.5\%) were heterozygous carriers of the prothrombin 20210 G-A mutation. Four women (3.5\%) had the factor V Leiden mutation, one of them homozygous. One

| **Table 1**. Obstetric, medical and family characteristics of the study group of 114 women specified for both prothrombin 20210 G-A and factor V Leiden mutation. |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| **N**           | Entire group    | No mutation     | Mutation        | OR              |
| Age (years) *   | 114             | 107 (94\%)      | 7 (6\%)         |                 |
| (H)ELLP syndrome (n) | 33 (21-47)      | 33 (21-47)      | 33 (29-46)      |                 |
| Severe preeclampsia (n) | 80 (70\%)       | 75 (70\%)       | 5 (71\%)        |                 |
| Gestational age (weeks) * | 34 (30\%)       | 32 (26-41)      | 31 (27-35)      |                 |
| Birth weight (grams) * | 1265 (400-3710) | 1265 (400-3710) | 1310 (460-2420) |                 |
| Perinatal mortality (n) | 25 (22\%)       | 23 (22\%)       | 2 (29\%)        | 1.5 (0.2-9.5)   |
| Thromboembolism (n) | 4 (3.5\%)       | 2 (1.9\%)       | 2 (29\%)        | 22 (1.7-303)    |
| Smoking (n)      | 46 (40\%)       | 42 (39\%)       | 4 (57\%)        |                 |
| Hypertension (n) | 14 (12\%)       | 13 (12\%)       | 1 (14\%)        | 1.2 (0.0-12)    |
| Family thromboembolism (n) | 17 (15\%)       | 17 (16\%)       | 0               | --              |

* = median (range)
woman was heterozygous for both mutations. The obstetric characteristics of the seven women with mutations are specified in Table 2.

The woman with heterozygosity of both factor V Leiden and the 20210 G-A mutation experienced deep venous thrombosis of the left leg three weeks after a spontaneous vaginal delivery. Two years later she had deep venous thrombosis in the left arm after having blood taken. The woman homozygous for factor V Leiden experienced deep venous thrombosis of the left upper leg 4 months after cesarean section on starting oral contraceptives. Two women without either mutation reported venous thrombosis not associated with pregnancy. Lung embolism did not occur in the study group. Women with a mutation had an odds ratio of 22 (1.7-303) for venous thromboembolism.

None of the women with a mutation reported thromboembolic disease in their family, while this occurred in 17 (16%) of the women without mutation.

Table 2. Obstetric and thromboembolic characteristics in women with prothrombin 20210 G-A mutation (FII) and/or factor V Leiden mutation (FV)

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<th>BW</th>
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</tr>
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</table>

DVT = deep venous thrombosis, PE = pulmonary embolism, HT = treated hypertension, GA = gestational age (days), BW = birth weight (grams), he = heterozygous, ho = homozygous.

Discussion

Early-onset preeclampsia, fetal growth retardation and fetal death are related obstetric complications and are associated with inherited thrombophilia. This study was restricted to the prothrombin 20210 G-A and factor V Leiden mutations because these genetic defects are highly prevalent and can be found in 63% of the families affected by thrombophilia. No investigations with respect to other thrombophilia defects such as protein S, protein C or antithrombin III deficiency and anticardiolipin antibodies were performed in these women. In a Dutch study, prothrombin 20210 G-A mutation was detected in 29 of 471 (6.1%) patients, who had suffered a venous thrombosis, in 5 of 28 (18%) probandi with a personal and family history of venous thrombosis compared to 11 of 474 (2.3%) control subjects.
Comparing our study population with the Dutch control population shows an odds ratio of 1.5 (0.35-5.29) for women with a history of early preeclampsia or (H)ELLP of having a prothrombin 20210 G-A mutation. Factor V mutation occurs in 3% of the Dutch population. In an earlier study we detected factor V mutation in 1.5% of women who were selected because they had had at least one normal pregnancy while they never suffered from pregnancy loss or other obstetric complications. In comparison with this control group patients with a history of early preeclampsia or (H)ELLP syndrome have an odds ratio of 2.4 (0.23-120) of having the factor V Leiden mutation. Although this odds ratio is not statistically significant and the 95% confidence interval is largely due to a low prevalence, it is comparable to an odds ratio of 2.2 (0.98-4.89) determined by Dizon-Townson et al in a case-control study of patients with severe preeclampsia.

One woman had both prothrombin 20210 G-A mutation and factor V Leiden mutation. Comparing her obstetric outcome with that of the other women with a mutation (Table 2) does not show a more adverse effect of a combined mutation on pregnancy outcome. The number of women in this study is insufficient to determine if combined mutation is more frequent in women with a history of preeclampsia or (H)ELLP syndrome. Interestingly, the woman with a combined mutation and the woman with a homozygous factor V Leiden mutation (Table 2, A and C) both had venous thromboembolism, while their obstetric and medical history did not differ from that of other women. Although several reports demonstrated an increased risk of cardiovascular disease in women with these mutations, we did not observe this.

Gestational age, birth weight and perinatal mortality between women with and without prothrombin 20210 G-A or factor V Leiden mutation were comparable. The prothrombin 20210 G-A mutation in relation to complications of pregnancy has been described only twice. In the first study the prothrombin mutation was seen to be significantly more frequent in women with abruptio placentae and fetal growth retardation, than in those with severe preeclampsia. Fetal outcome was not described in this study. The second study focused on thrombophilic disorders and late fetal loss. The frequency of prothrombin 20210 G-A mutation was not increased in women with late fetal loss.

Although our study confirms that prothrombin 20210 G-A mutation and factor V Leiden mutation are important genetic factors associated with thrombotic risk, they are of minor importance in the perinatal outcome in women with preeclampsia or (H)ELLP syndrome.
References


