ARTICLE TITLE

Risk of placenta-mediated pregnancy complications or pregnancy-related VTE in VTE-asymptomatic families of probands with VTE and heterozygosity for factor V Leiden or G20210 prothrombin mutation

SHORT TITLE

Pregnancy-related adverse events in asymptomatic carriers of factor V Leiden or G20210A prothrombin mutation

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ABSTRACT

Background: Few studies have evaluated the risk of placenta-mediated pregnancy complications or pregnancy-associated venous thromboembolism (VTE) in asymptomatic relatives of probands for VTE and factor V Leiden or the G20210A variant. The antepartum management of this population ranges from antepartum anticoagulation therapy to clinical surveillance.

Objective: To evaluate the risk of placenta-mediated pregnancy complications and pregnancy-related VTE in VTE-asymptomatic families of probands with VTE and who are heterozygous carriers of either factor V Leiden or G20210A prothrombin mutation.

Methods: One hundred and sixty-four relatives, who had 415 pregnancies, were retrospectively evaluated. Odds ratios and 95% confidence intervals were calculated to compare pregnancy outcomes between women with and without thrombophilia.

Results: In the factor V Leiden group, 22 placenta-mediated pregnancy events out of 152 pregnancies (14.4%) were reported, compared with 25 adverse events out of 172 pregnancies in the G20210A prothrombin group (14.5%) and 13 adverse events out of 91 pregnancies in the non-carrier group (14.2%). Carriers of factor V Leiden or G20210A prothrombin were not associated with a higher risk of pregnancy-adverse outcomes compared with non-carriers: OR 1.02 (95% CI, 0.46–2.27) and 1.15 (95% CI, 0.52–2.51), respectively. Four episodes of pregnancy-associated VTE out of 415 pregnancies (0.96%) were recorded. Two episodes of VTE in the G20210A group, one in the factor V Leiden group and one episode in the non-carrier group were noted.

Conclusions: In VTE-asymptomatic relatives of probands with VTE, the presence of factor V Leiden or the G20210A prothrombin mutation in heterozygosis should not lead to a decision to instigate antepartum prophylaxis.

INTRODUCTION

Inherited thrombophilias are a heterogeneous group of coagulation disorders that predispose individuals to thromboembolic events. Activated protein C resistance caused by factor V Leiden and the G20210 prothrombin mutation are the most common inherited thrombophilias. The prevalence in the Caucasian population is about 4% for factor V Leiden and 2–3% for the G20210 prothrombin mutation (1, 2)]. Pregnancy is also associated with an increased risk of venous thromboembolism (VTE) (3). The reported incidence of pregnancy-associated VTE ranges from 1 in 1000 to 1 in 2000 deliveries (4). Increased levels of prothrombotic factors, venous stasis and endothelial damage have been associated with an increased risk of VTE during pregnancy (5). Inherited thrombophilia may contribute to the hypercoagulable state during pregnancy. The prothrombin (OR 4.4; 95% CI 1.2–16.0) and factor V Leiden (OR 4.5; 95% CI 2.1–14.5) mutations were more common in women with pregnancy-associated VTE than in the general population (6, 7). In addition, the factor V Leiden and G20210A prothrombin mutation have also been implicated in a variety of adverse obstetric events, including pregnancy loss, preeclampsia, placental abruption, and small for gestational age (SGA) neonates (8-14). Therefore, some authors recommend that women with a strong family history of VTE or a personal history of adverse pregnancy events should be screened for inherited thrombophilia before attempting to become pregnant. However, other studies have failed to show this presumed increase in the risk of obstetric complications in carriers of factor V Leiden or G20210A prothrombin mutation (15-18). Thus, recommendations for the antepartum management of pregnant women with a known thrombophilia such as the factor V Leiden or the G20210A prothrombin mutation without a prior VTE variant, which range from antepartum therapy with prophylactic anticoagulants to clinical surveillance (19), do not have a sufficiently established evidential basis. The purpose of this study was to evaluate the risk of placenta-mediated pregnancy complications and pregnancy-related VTE in VTE-asymptomatic families of probands with VTE and heterozygous carriers of either factor V Leiden or G20210A prothrombin mutation. We compared women with single heterozygosis for either thrombophilia and those without thrombophilia.

SUBJECTS AND METHODS

Subjects

The sample comprised 92 subjects with a documented history of symptomatic VTE and who were heterozygous carriers of either factor V Leiden or G20210A prothrombin mutation and who had been consecutively referred to the Thrombosis & Hemostasis Unit of the Hospital Universitario de Salamanca between May 2006 and October 2010. Probands with either homozygous or double heterozygous factor V Leiden and G20210A prothrombin mutation were excluded. The study cohort included first-degree relatives of these 92 probands with at least one pregnancy before thrombophilia screening and absence of VTE before pregnancy. We identified an initial study cohort of 164 women. Six women were excluded because they had received low molecular weight heparin as prophylaxis during at least one pregnancy. Therefore, 158 VTE-asymptomatic families of probands with VTE and factor V Leiden or G20210A prothrombin mutation were included in the study.

Outcomes

All patients were interviewed by two of the researchers (I.C. and G.H. No hay ningún autor que coincida con estas iniciales), who were unaware of the results of thrombophilia testing. Particular attention was paid to previous pregnancies, obstetric complications and thromboembolic events. Placenta-mediated pregnancy complications such as preeclampsia, small for gestational age (SGA) neonates, pregnancy loss and placental abruption were recorded. Preeclampsia was defined as high blood pressure (absolute blood pressure $\geq 140/90$ mm Hg) and excess protein in urine (urinary excretion of ≥ 0.3 g protein in a 24-hour specimen (20). SGA was defined as a birth weight less than the 10th percentile and less than the 5th percentile derived from sex- and race-specific growth curves (21). Pregnancy loss included those from first-trimester abortion until stillbirth. Abruption was considered to be present when there was a clinical suspicion, supported by written documentation, including excessive antepartum bleeding, treatment with blood products, and a description of delivery of the placenta or when there was confirmation by pathological examination of the placenta. The diagnosis of DVT was considered valid by venography or compression ultrasonography, according to standard methods. Pulmonary embolism (PE) was only accepted if it was demonstrated by a perfusion

lung scan or computerized tomography. Pregnancy-associated VTE was accepted if it was diagnosed during the pregnancy or during the puerperium.

Laboratory test

DNA from the entire study cohort was analyzed for the presence of prothrombin gene mutation and factor V Leiden by polymerase chain reaction-based assay systems (22, 23). Laboratory analyses included the assessment of antithrombin, protein C, protein S, anticardiolipin antibodies and lupus anticoagulant. The presence of these confounding factors was a cause for exclusion.

Statistical analysis

A descriptive statistical analysis was performed after including all the data in a Microsoft Excel spreadsheet. The results are expressed as percentages for categorical variables, and as medians (and standard deviations) for continuous variables. Differences in clinical measurements between groups were evaluated with SPSS 17.0 (SPSS, Chicago, IL, USA). The rates of obstetric complications and pregnancy-associated VTE were calculated from the total number of pregnancies. Odds ratios and 95% confidence intervals (CIs) were calculated to compare pregnancy outcomes between women with and without thrombophilia. Multivariable logistic regression analysis after adjustment for age and delivery by cesarean section was performed. Statistical significance in all tests was concluded for values of $p < 0.05$.

RESULTS

Forty-nine women with single heterozygous factor V Leiden, 67 with single G20210A prothrombin and 42 without thrombophilia made up the study cohort. By thrombophilia status there were 152 pregnancies in the factor V Leiden group, 172 in the G20210A prothrombin group and 91 in the non-carrier group. In total, 60 placenta-mediated pregnancy complications in the 415 pregnancies analyzed were recorded (14.4%). In the single heterozygous factor V Leiden group, 22 placenta-mediated pregnancy events out of 152 pregnancies (14.4%) were reported, compared with 25 adverse events out of 172 pregnancies in the single heterozygous G20210A prothrombin group (14.5%), and

13 adverse events out of 91 pregnancies in the non-carrier group (14.2%). In all groups the most frequent obstetric complication was pregnancy loss. The characteristics of the placenta-associated syndromes are summarized in Table 1.

Four episodes of pregnancy-associated VTE out of 415 pregnancies (0.96%) were recorded; three of these occurred during pregnancy (third trimester) and one during puerperium (after delivery by cesarean section). Two women with G20210A prothrombin mutation and one non-carrier developed lower-limb DVT. One woman with factor V Leiden developed isolated PE. All cases of pregnancy-associated VTE were treated with a therapeutic dose of low molecular weight heparin.

We assessed the risk of placenta-mediated pregnancy complications and pregnancy-associated VTE considering all the pregnancies that occurred in the carrier and non-carrier groups. The age-adjusted OR for placenta-mediated pregnancy complications in women with single heterozygous factor V Leiden compared with those without thrombophilia was 1.02 (95% CI, 0.46–2.27). For single heterozygous carriers of G20210 prothrombin mutation the OR for placenta-mediated pregnancy complications was 1.15 (95% CI, 0.52–2.51). As noted in Table 2, there was no association between the factor V Leiden or G20210A prothrombin mutation and any individual adverse obstetric outcome. Similarly, there was no association between factor V Leiden or the G20210A prothrombin mutation and pregnancy-associated VTE in our model, with the OR adjusted for age and delivery by cesarean section.

DISCUSSION

According to the most commonly used guidelines for antithrombotic therapy (19), recommendations for the antepartum management of VTE-asymptomatic women and a known thrombophilic defect such as heterozygosity for factor V Leiden or G20210A prothrombin mutation, which ranges from prophylactic anticoagulation to clinical surveillance, does not have an evidentially sound basis. Our results show that the risk of placenta-mediated pregnancy complications or pregnancy-associated VTE in VTE-asymptomatic families who are heterozygous for factor V Leiden or G20210A prothrombin was similar

to that of relatives without these variants. Therefore, thrombophilia status should not be a factor influencing the decision to instigate antepartum prophylaxis in this population.

Studies that have assessed the relationship between factor V Leiden or G20210A prothrombin mutation and placenta-associated syndromes have yielded differing results (24). This wide variation probably reflects differences in the design of the studies (most of which are retrospective), the sample size and definition of the population studied. In a recent review (25), women with factor V Leiden or G20210A prothrombin had a greater relative risk of adverse pregnancy outcome, although the absolute risk of adverse outcomes remained low. In the most recent prospective study, of 2034 healthy nulliparous women, the presence of heterozygous factor V Leiden was not associated with preeclampsia or fetal growth restriction (26).

Few studies have evaluated the risk of placenta-mediated pregnancy complications in asymptomatic relatives of probands for VTE and factor V Leiden or the G20210A variant. Our findings are consistent with the results of Tormene et al (18), who found the overall RR of fetal loss in women belonging to families with VTE and isolated G20210A prothrombin to be 0.9 (95% CI, 0.7–1.4) (18). Coppens et al (25), in a retrospective study, showed that the outcome of the second pregnancy after a first loss in women who were first-degree relatives of probands with either the factor V Leiden or G20210A prothrombin mutation was similar, being generally excellent in women with and without thrombophilias. On the other hand, Villani et al (27) reported that, in family members of women with previous adverse obstetric outcomes who carry common inherited thrombophilias, relatives carrying factor V Leiden had a significant independent risk of obstetric complications (OR 1.98, 95% CI 1.03–3.83) but this risk was not observed in the presence of the G20210A prothrombin mutation (OR 1.03, 95% CI 0.46–2.32). Also, the presence of factor V Leiden or G20210A prothrombin mutation in heterozygosis was significantly associated with the occurrence of VTE (OR 5.2, 95% CI: 1.70–15.91). The differences between the populations studied —probands with VTE in our study and with adverse obstetric outcomes in Villani's study— could account for the contrary results.

In a systematic review to determine the risk of pregnancy-associated VTE (28), the ORs for factor V Leiden in heterozygosis were 8 (95% CI 5–12) and 6 (95% CI 2–18) for those heterozygous for

G2021A prothrombin. However, the absolute risk of pregnancy-associated venous thrombosis in women with heritable thrombophilia with no previous history was small (18). Here, the occurrence of pregnancy-associated VTE was similar in carriers and non-carriers. In the factor V Leiden carriers the estimated risk of pregnancy-associated VTE compared with non-carriers was 0.96 (0.05–16.54), while in the G20210 group the OR was 1.49 (0.12–17.54). As factor V Leiden or G20210A prothrombin did not increase the risk of adverse pregnancy outcome or pregnancy-associated VTE, the routine screening of fertile VTE-asymptomatic women from families of probands with VTE and who were heterozygous for factor V Leiden or G20210A prothrombin is not justified. In line with our results, a UK National Health Service economic evaluation of screening for the factor V Leiden in pregnant women showed this approach not to be cost-effective. Alternative risk factors should be considered to better account for the pregnancy-related risk of placenta-mediated pregnancy complications or VTE. In this context, VTE-asymptomatic pregnant women with a family history of VTE, aged over 35 years, with comorbidities or a body mass index greater than 30 would benefit from prophylaxis with heparin (29–31). In summary, for pregnant women with no history of VTE but who are heterozygosity of factor V Leiden or the G20210A prothrombin mutation, the risk of placenta-mediated pregnancy complications or pregnancy-associated VTE is similar to that of non-carriers. Therefore, the hereditary thrombophilia status of this population should not be a factor influencing clinical antepartum management.

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Pregnancy-related adverse events in asymptomatic carriers of factor V Leiden or G20210A prothrombin mutation

Table 1.-

Table 1.- Obstetric complications and pregnancy-associated VTE of the study cohort by thrombophilia status

	Single heterozygous for Factor V Leiden	Single heterozygous for G20210A prothrombin	Non-carrier
Women, n	49	67	42
Pregnancies	152	172	91
Age at first pregnancy (median $\pm$ SD)	26 $\pm$ 5.4	25 $\pm$ 3.9	27 $\pm$ 0.9
Number of pregnancies per woman (range)	4 (1–8)	4 (1–7)	3 (1–8)
Number of obstetric complications (%)			
Preeclampsia	0 (0)	1 (0.6)	1 (1.2)
SGA neonates	4 (2.6)	5 (2.9)	2 (2.2)
Pregnancy loss	17 (11.1)	19 (11.0)	9 (10.0)
Placental abruption	1 (0.6)	0 (0)	1 (1.1)
Number of deliveries after cesarean section (%)	14 (9.0)	18 (10.0)	10 (10.0)
Number of pregnancy-associated VTEs (%)	1 (0.6)	2 (1.1)	1 (1.1)

Pregnancy-related adverse events in asymptomatic carriers of factor V Leiden or G20210A
prothrombin mutation

Table 2.- Risk of obstetric complications and pregnancy-associated VTE in carriers of factor V Leiden or the prothrombin G20210A mutation compared with non-carriers

	Pregnancy loss	SGA neonates	Preeclampsia	Placental abruption	Pregnancy-associated VTE
Non-carrier	Reference	Reference	Reference	Reference	Reference
Single Factor V Leiden	0.99 (0.40–2.74)	0.94 (0.14–6.95)	0.01 (0.00–0.02)	0.01 (0.00–0.02)	0.96 (0.05–16.54)
Single G20210A	0.87 (0.35–2.19)	1.41 (0.25–7.80)	0.50 (0.02–8.91)	0.01 (0.00–0.02)	1.49 (0.12–17.54)
prothrombin					

TABLE AND FIGURE LEGENDS

Table 1.-

Header. Obstetric complications and pregnancy-associated VTE of the study cohort by thrombophilia status

Foot. SGA: small for gestational age; VTE: venous thromboembolism.

Table 2.-

Header: Risk of obstetric complications and pregnancy-associated VTE in carriers of factor V Leiden or the prothrombin G21021A mutation compared with non-carriers

Foot. SGA: small for gestational age; VTE: venous thromboembolism.