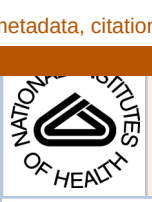

Published in final edited form as:

Obstet Gynecol. 2010 March ; 115(3): 521–525. doi:10.1097/AOG.0b013e3181d018a8.

Family History of Venous Thromboembolism and Identifying Factor V Leiden Carriers During Pregnancy

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Abstract

Objective—To estimate whether there is a correlation between family history of venous thromboembolism and factor V Leiden mutation carriage in gravid women without personal history of venous thromboembolism.

Methods—This is a secondary analysis of a prospective observational study of the frequency of pregnancy-related thromboembolic events among carriers of the factor V Leiden mutation. Family history of venous thromboembolism in either first- or second-degree relatives was self-reported. Sensitivity, specificity, and positive and negative predictive values of family history to predict factor V Leiden mutation carrier status were calculated.

Results—Women with a negative personal venous thromboembolism history and available DNA were included (n=5,168). One-hundred forty women (2.7%, 95%CI 2.3- 3.2%) were factor V Leiden mutation-positive. Four-hundred twelve women (8.0%, 95%CI 7.3–8.7%) reported a family history of venous thromboembolism. Women with a positive family history were twofold more likely to be factor V Leiden mutation carriers than those with a negative family history (23/412 (5.6%) versus 117/4,756 (2.5%), p<.001). The sensitivity, specificity and positive predictive value of a family history of a first or second degree relative for identifying factor V Leiden carriers were 16.4% (95%CI 10.7–23.6%), 92.3% (95%CI 91.5–93.0%) and 5.6% (95%CI 3.6–8.3 %), respectively.

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*For a list of other members of the NICHD who participated in this study, see the Appendix online at http://links.lww.com/xxx.

Dr. Spong, Associate Editor of *Obstetrics & Gynecology*, was not involved in the review or decision to publish this article.

Presented at the Society for Gynecologic Investigation, March 22, 2009, Glasgow, UK.

Financial Disclosure: The authors did not report any potential conflicts of interest.

Conclusion—While a family history of venous thromboembolism is associated with factor V Leiden mutation in thrombosis- free gravid women, the sensitivity and positive predictive values are too low to recommend screening women for the factor V Leiden mutation based solely on a family history.

INTRODUCTION

In the United States as well as the developed world, pregnancy-related venous thromboembolism (VTE) is the most common cause of maternal death(1,2). Compared with the non-pregnant state, the risk of VTE increases 4 to 5 fold during pregnancy. The overall incidence of VTE during pregnancy is estimated at 2 per 1000 deliveries (3,4).

One risk factor for VTE in pregnancy is thrombophilia (4,5). Almost half of cases of pregnancy-related VTE occur in women with an inherited or acquired thrombophilia(6). The Leiden mutation is the most common inherited thrombophilia, with a heterozygous carrier prevalence from 3–7% in the US and European populations(7). In its heterozygous form, it is associated with as much as an 8-fold increase in thrombotic risk (8). Homozygous inheritance, however, confers around a 30-fold increase in relative risk of thrombosis (8).

Universal screening for FVL has not been considered cost effective given the relatively high prevalence of inherited thrombophilias and the rarity of venous thromboembolism; nearly 8000 women would need to be screened for FVL to detect 400 mutations to prevent one episode of venous thromboembolism (9). Selective thrombophilia screening has been advocated in women with a personal or family history of VTE to identify those at increased risk of thrombotic complications during and outside of pregnancy (10). Despite the widespread acceptance of this recommendation, limited evidence exists on the reliability of family history to detect the most common thrombophilic defects (11–13).

To date, no study has evaluated the utility of a family history of VTE as a screening tool to identify women at risk for factor V Leiden (FVL) during pregnancy. The objective of this study was to estimate the sensitivity and positive predictive value of a positive family history of venous thromboembolism for FVL mutation among gravid women without a personal history of thrombosis.

MATERIALS AND METHODS

This is a secondary analysis of the *Eunice Kennedy Shriver* National Institutes of Child Health and Human Development Maternal-Fetal Medicine Units Network factor V Leiden (FVL) study. The FVL study was a prospective observational multicenter study of 5,168 women with a singleton pregnancy. Women with current or planned anticoagulation therapy, known factor V Leiden status, antiphospholipid syndrome, prior thrombosis, fetal demise, or planned pregnancy termination were excluded. Institutional Review board approval was obtained from the University of North Carolina. The primary objective was to estimate the frequency of pregnancy-related thromboembolic events among carriers of the FVL mutation without a personal history of thromboembolism. Full details on the study design, data collection, and results have been previously reported (14).

The outcome of interest in this study was FVL heterozygous carriage in women who reported a positive family history (first or second degree relative) of a thromboembolic event in this cohort of women. In this registry, the presence of a positive family history of venous thromboembolism was based on self report at the time of study enrollment.

Women reported the presence or absence of a family history of VTE. If present, women then identified the affected family member and this relationship was documented in the study

record. A family history was regarded as positive if VTE was reported in at least one first-degree relative and/or second degree relative. Sensitivity, specificity, positive, and negative predictive values of family history to predict FVL carrier status and likelihood ratios were calculated by first degree and first or second degree relative history. With 140 FVL carriers, there was sufficient sample size to estimate sensitivity with a 95% confidence interval half-width no more than 8.3%. Likewise, with over 4700 non-carriers the precision in terms of 95% confidence interval half-width was 1.5%. Continuous variables were analyzed using Wilcoxon rank-sum test and categorical variables were analyzed using chi square. The association between FVL mutation carriage and family history of VTE were assessed using Pearson's chi square test and 95% CI for proportions were calculated. A p-value of <0.05 was considered significant.

RESULTS

A total of 5,168 women without a personal history of VTE had factor V Leiden DNA results available and were included in this analysis. FVL mutation heterozygous carrier status was identified in 140 women (2.7%, 95% CI 2.3 – 3.2%). Positive family history of venous thromboembolism was reported in 412 women (8.0%, 95% CI 7.3–8.7%). Of those who reported a positive family history, 23 women were found to be carriers of the FVL mutation. None of the 23 women found to be carriers of the FVL mutation developed VTE. Maternal demographic characteristics based on family history are presented in Table 1. Women with a positive family history were more likely to be Caucasian, smoke cigarettes, and have higher education levels in comparison to women with a negative family history.

Women with a positive family history of VTE were more likely to be FVL carriers than women with a negative family history (23/412 (5.6%) versus 117/4,756 (2.5%), p<0.001). Sensitivity, specificity, positive and negative predictive values of family history to predict FVL carrier status and likelihood ratios are shown in Table 2. For patients with positive family history of VTE patients, the probability of having FVL, the positive predictive value of the test, is 5.6% with 95% C.I 3.6, 8.3 % (Table 2). The positive predictive value was similar regardless of whether a first or first or second degree relative experienced VTE (5.0% with 95% C.I. 2.3, 9.3% and 5.6% with 95% C.I. 3.6, 8.3%, respectively).

Among Caucasian women, the prevalence of FVL was 6.1% (95% CI 5.0–7.4%). The sensitivity of a first or second degree relative to predict FVL mutation was 22.7% (95% CI 14.8– 32.3); the specificity was 84.3% (95% CI 82.4 – 86.1%) and likelihood ratio for positive family history of VTE was 1.4 (95% CI 1.0, 2.1). The positive predictive value remained poor (8.6%; 95%CI 5.4–12.7%).

DISCUSSION

Our analysis shows that a positive family history with at least one first or second degree relative with VTE is a poor predictor of FVL mutation carrier status in gravid women without a personal history of thrombosis. While this association between a positive family history and FVL carriage is significant, a positive family history does not appear to be a reliable screening method for FVL.

A personal history of thrombosis and the presence of a thrombophilia (7) are two of the risk factors with the highest association with venous thromboembolism.(5) Thrombophilia is present in up to 50% of women who experience VTE during pregnancy and postpartum.(15) While FVL is the most common inherited form of thrombophilia, universal screening is not recommended (10). To identify those women who are at increased risk of thrombotic

complications during and outside of pregnancy, selective screening based on personal and family history has been suggested by some(10).

Currently, no consensus agreement exists on the value of family history for the selection of patients who should be screened for an inherited thrombophilia. Our finding of a poor sensitivity and positive predictive value of a positive family history is consistent with available literature in nonpregnant individuals (11–13). Cosmi et al prospectively evaluated 479 thrombosis- free women prior to the initiation of oral contraceptives (12). In this study, the sensitivity and positive predictive value for a positive family history of a first degree relative predict FVL carrier status was 6.7% (95% CI 0– 32%), and 3.1 % (95% CI 0–16%), respectively. When first or second degree relatives were combined, the sensitivity and positive predictive value for a positive family history to predict FVL carrier status were similar 6.7% (95% CI 0–32%) and 2.1% (95% CI 0–11%), respectively (12). Our results may actually overestimate the association, as there may have been women who enrolled in the FVL study motivated to participate in study due to a relative with a prior VTE and underlying thrombophilia.

There are several limitations to our study which warrant discussion. Family history of VTE was self-reported and not confirmed through objective documentation in medical records. Family history of VTE was not further defined to distinguish between superficial or deep vein thrombosis or pulmonary embolism. Age and the number of affected family members were also not taken into account. We considered a family history as positive when only 1 first or second degree relative was reported to have had a VTE. Although second degree relatives were included in the analysis, they were not analyzed separately. Second degree and further distant relatives likely have a lower baseline risk of VTE through a dilution of effect of other inherited predispositions.(16) To date, a uniform definition of a positive family history has not been established.

In this analysis, our interest was the use of a positive family history of VTE as a screening tool to identify carriers of FVL, the most common inherited thrombophilia. We further evaluated the role of a positive family history among Caucasians, given its highest prevalence in this racial category, and found similar results when compared to the entire cohort of women. Other thrombophilias, such as the prothrombin G20210A mutation, protein C deficiency, and protein S deficiency were not included in this analysis and therefore the utility of family history to determine risk for these inherited thrombophilias cannot be extrapolated from our data.

How should these findings be incorporated into clinical practice? This study was prompted by the question of whether clinicians can identify gravid women who should be screened for FVL on the basis of a positive family history of VTE. The results indicate that selective screening for FVL based on family history fails to identify a substantial number of women who are carriers of this common thrombophilia. Given the high specificity, women with a negative family history can be reassured it is unlikely they are carriers of the FVL mutation. As the risk of thromboembolic events in untreated heterozygotes for the FVL mutation without evident risk factors for thrombosis is low, neither universal nor selective screening based on a positive family history for the FVL mutation is warranted during pregnancy.

Acknowledgments

Supported by grants from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (HD27860, HD36801, HD27917, HD21414, HD27861, HD27869, HD27905, HD34208, HD34116, HD21410, HD27915, HD34136, HD34122, HD34210)

The authors wish to thank the Elizabeth Thom, Ph.D. for protocol/data management and statistical analysis, and Michael W. Varner, M.D. for protocol development and oversight.

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Table 1

Demographic characteristics of the study population

	Negative Family History N= 4756	Positive Family History N= 412	P value*
Maternal age (years)	24 [21–29]	25 [21–29]	0.04
Race (%)			<0.001
Caucasian	1340 (28.2)	257 (62.4)	
African American	1701 (35.8)	134 (32.5)	
Other	1715 (36.1)	21 (5.1)	
Pregravid BMI (kg/m2)	25.0 [21.7–29.5]	24.5 [21.0–30.7]	0.59
Smoker (%)	588 (12.4)	79 (19.2)	<0.001
Primigravida (%)	1461 (30.7)	128 (31.1)	0.88
Education (years)	12 [10–14]	12 [11–13]	<0.001
Married (%)	2766 (58.3)	260 (63.1)	0.06

Data presented as median and intraquartile range or n (%)

*Wilcoxon rank-sum test or chi square, as appropriate

Table 2

Predictive Value of Family History for Factor V Leiden carrier status

	Factor V Leiden carrier (%)	95% CI
First Degree Relative*		
Sensitivity	6.4	3.0–11.9
Specificity	96.6	96.1–97.1
Positive Predictive Value	5.0	2.3–9.3
Negative Predictive Value	97.4	96.9–97.8
Likelihood Ratio (positive)	1.9	1.0–3.6
Likelihood Ratio (negative)	1.0	0.9–1.0
First or Second Degree Relative		
Sensitivity	16.4	10.7–23.6
Specificity	92.3	91.5–93.0
Positive Predictive Value	5.6	3.6–8.3
Negative Predictive Value	97.5	97.1–98.0
Likelihood Ratio (positive)	2.1	1.4–3.1
Likelihood Ratio (negative)	0.9	0.8–1.0

* This category includes all women with at least one first degree relative with a history of VTE and may also include second degree relatives (data not shown)