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The Relationship of the Factor V Leiden Mutation and Pregnancy Outcomes for Mother and Fetus

Donna Dizon-Townson, MD, Connie Miller, PhD, Baha Sibai, MD, Catherine Y. Spong, MD, Elizabeth Thom, PhD, George Wendel Jr, MD, Katharine Wenstrom, MD, Philip Samuels, MD, Margaret A. Cotroneo, RN, Atef Moawad, MD, Yoram Sorokin, MD, Paul Meis, MD, Menachem Miodovnik, MD, Mary J. O'Sullivan, MD, Deborah Conway, MD, Ronald J. Wapner, MD, Steven G. Gabbe, MD, and National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network*

National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network, Bethesda, Maryland

Abstract

Objective—We sought to estimate the frequency of pregnancy-related thromboembolic events among carriers of the factor V Leiden (FVL) mutation without a personal history of thromboembolism, and to evaluate the impact of maternal and fetal FVL mutation carriage or other thrombophilias on the risk of adverse outcomes.

Methods—Women with a singleton pregnancy and no history of thromboembolism were recruited at 13 clinical centers before 14 weeks of gestation from April 2000 to August 2001. Each was tested for the FVL mutation, as was the resultant conceptus after delivery or after miscarriage, when available. The incidence of thromboembolism (primary outcome), and of other adverse outcomes, was compared between FVL mutation carriers and noncarriers. We also compared adverse outcomes in a secondary nested carrier-control analysis of FVL mutation and other coagulation abnormalities. In this secondary analysis, we defined carriers as women having one or more of the following traits: carrier for FVL mutation, protein C deficiency, protein S deficiency, antithrombin III deficiency, activated protein C resistance, or lupus anticoagulant-positive, heterozygous for prothrombin G20210A or homozygous for the 5,10 methylenetetrahydrofolate reductase mutations. Carriers of the FVL mutation alone (with or without activated protein C resistance) were compared with those having one or more other coagulation abnormalities and with controls with no coagulation abnormality.

Results—One hundred thirty-four FVL mutation carriers were identified among 4,885 gravidas (2.7%), with both FVL mutation status and pregnancy outcomes available. No thromboembolic events occurred among the FVL mutation carriers (0%, 95% confidence interval 0–2.7%). Three pulmonary emboli and one deep venous thrombosis occurred (0.08%, 95% confidence interval 0.02–0.21%), all occurring in FVL mutation noncarriers. In the nested carrier-control analysis ($n = 339$), no differences in adverse pregnancy outcomes were observed between FVL mutation carriers, carriers of other coagulation disorders, and controls. Maternal FVL mutation carriage was not associated with increased pregnancy loss, preeclampsia, placental abruption, or small for gestational age births. However, fetal FVL mutation carriage was associated with more frequent preeclampsia among African-American (15.0%) and Hispanic (12.5%) women than white women (2.6%, $P = .04$), adjusted odds ratio 2.4 (95% confidence interval 1.0–5.2, $P = .05$).

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Corresponding author: Donna Dizon-Townson, MD, University of Utah Health Sciences Center, Department of Obstetrics and Gynecology, 50 North Medical Drive, Room 2B200, Salt Lake City, UT 84132; uvddizon@ihc.com.

*For a list of other members of the NICHD Maternal–Fetal Medicine Units Network, see the Appendix.

Conclusion—Among women with no history of thromboembolism, maternal heterozygous carriage of the FVL mutation is associated with a low risk of venous thromboembolism in pregnancy. Neither universal screening for the FVL mutation, nor treatment of low-risk carriers during pregnancy is indicated.

Pregnancy-related venous thromboembolism is the most common cause of maternal death and a significant cause of maternal morbidity¹⁻² in the United States. The factor V Leiden (FVL) mutation is the most common known genetic factor that predisposes to thrombosis.^{3,4} Retrospective studies have reported an increased risk of venous thromboembolism (10–25%) among pregnant women heterozygous for the FVL mutation.⁵⁻⁹ However, limited prospective data exist to define the risk of venous thromboembolism in gravid FVL mutation carriers without a history of prior venous thromboembolism.

It has been further hypothesized that mothers or fetuses with an acquired or genetic predisposition may have abnormal thrombosis and infarction of the uteroplacental circulation that might manifest clinically as adverse pregnancy outcomes, such as preeclampsia, pregnancy loss, fetal growth restriction, and/or placental abruption. However, retrospective and cross-sectional studies in this regard have been conflicting.¹⁰⁻¹⁷

Accurate information regarding risks for thrombosis and adverse pregnancy outcome is important because of the increasing number of individuals who have been tested and treated with anticoagulation during pregnancy.^{10,18} Anticoagulation is costly and can cause significant morbidity.^{19,20,22} Our primary objective was to ascertain prospectively the risk of pregnancy-related venous thromboembolism among women who carry the FVL mutation but have no prior personal history of thromboembolism. Secondarily, we sought to evaluate the impact of maternal or fetal carriage of the FVL mutation (heterozygote or homozygote), or the presence of other thrombophilias, on the risk of adverse outcomes. This study was developed to assist in the design of a proposed interventional trial of prophylactic anticoagulation in pregnancy for FVL mutation carriers.

MATERIALS AND METHODS

This is the primary analysis of a prospective observational multicenter study conducted by the National Institute of Child Health and Human Development's Maternal–Fetal Medicine Units Network with institutional review board approval from each of 13 clinical centers and the Biostatistics Coordinating Center of George Washington University. Written informed consent was obtained for each subject. Women with a singleton pregnancy of 14 weeks of gestation or less (best estimate based on clinical or ultrasonographic findings) were considered eligible in the absence of any of the following exclusion criteria: multiple gestation, current or planned anticoagulation therapy, known factor V Leiden status, diagnosis of antiphospholipid syndrome, previous venous thromboembolism, known fetal demise, planned pregnancy termination, intention to deliver outside a Maternal–Fetal Medicine Units Network site, or participation in another research study that might influence the primary or secondary outcomes. The primary outcome was the occurrence of venous thromboembolism during the current pregnancy. Secondary outcomes included pregnancy loss, preeclampsia, placental abruption, and small for gestational age birth.

Each woman had a venous blood sample drawn and submitted to a central reference laboratory (DNA Diagnostic Laboratory, University of Utah), where analysis for the presence of the FVL mutation was performed. Two controls were selected randomly for each FVL mutation carrier, matched for clinical center, maternal age (± 5 years), and race/ethnicity. Carriers and controls had a second blood sample drawn, which was shipped to the Centers for Disease Control and Prevention and evaluated for protein C, protein S,

antithrombin III deficiencies, lupus anticoagulant, and activated protein C resistance. Separate aliquots were evaluated by the DNA Diagnostic Laboratory for prothrombin G20210A and 5,10 methylenetetrahydrofolate reductase (MTHFR) mutations. Patients, caregivers, and clinical research personnel were masked to the results of all research analysis.

For the purpose of this study, we defined antithrombin III, protein C, and protein S *deficiencies* as an activity or antigen value less than 2 standard deviations below the mean of the controls for the appropriate trimester. In the secondary nested carrier-control analysis, we defined *carriers* as women having a coagulation anomaly if one or more of the following were present: carrier for FVL mutation, protein C deficiency, protein S deficiency, antithrombin III deficiency, activated protein C resistance, lupus anticoagulant-positive, heterozygous carrier of prothrombin G20210A, or homozygote for the 5,10 methylenetetrahydrofolate reductase mutations. Controls were defined as women carrying none of the above protein deficiencies, lupus anticoagulant, or genetic predispositions to thrombosis. We compared maternal carriers of the FVL mutation alone (with or without activated protein C resistance) with those having at least one of the other coagulation abnormalities (including activated protein C resistance in the absence of FVL) and controls who had no abnormalities.

A neonatal cord blood sample was obtained after delivery. If cord blood was not available, a neonatal buccal swab, a 2 × 2 cm portion of umbilical cord, or a 2 × 2 × 2 cm portion of placenta was collected. These samples were tested for the FVL mutation. Maternal and newborn medical records were reviewed for primary and secondary outcomes at hospital discharge after delivery. Maternal records were also reviewed 4–6 weeks postpartum, or if miscarriage occurred. At least 3 investigators, masked to carrier status, reviewed the medical records of those with suspected venous thromboembolism, preeclampsia, or placental abruption and reached a consensus opinion.

The diagnosis of pregnancy-related venous thromboembolism required clinical symptoms confirmed by objective testing that documented deep vein thrombosis, pulmonary embolus, or cerebral vein thrombosis. Deep vein thrombosis required confirmation by Doppler ultrasonography, venogram, or magnetic resonance imaging. Pulmonary embolism required confirmation by ventilation perfusion scan, pulmonary arteriogram, or spiral computer tomography. Cerebral vein thrombosis required confirmation by computer tomography or magnetic resonance imaging.

The diagnosis of preeclampsia required a diastolic blood pressure more than 90 mm Hg on 2 occasions 4 hours to 14 days apart, occurring within 4 hours to 14 days of evident significant proteinuria (> 300 mg protein in a 24-hour urine, urinary protein/creatinine ratio > 0.35, at least 2+ proteinuria from a single dipstick evaluation or 1+ proteinuria from 2 or more measurements obtained 4 hours to 14 days apart) in previously normotensive nonproteinuric patients. Women with incomplete findings of preeclampsia, as described, but who also had, concurrent with pulmonary edema or thrombocytopenia (< 100,000/mm³), eclampsia or the hemolysis elevated liver enzymes low platelets (HELLP) syndrome also qualified as having preeclampsia. Those with hypertension and/or proteinuria before 20 weeks of gestation needed to meet strict, predefined criteria to be diagnosed as having superimposed preeclampsia. In women with pre-existing proteinuria, a diagnosis of preeclampsia required new-onset, pregnancy-associated hypertension accompanied by “superimposed proteinuria.”²³

The diagnosis of placental abruption required a clinical suspicion that was supported by written documentation (excessive antepartum bleeding, treatment with blood products,

description of delivery and placenta) and/or confirmation by pathologic examination. A diagnosis of “pregnancy loss” required a first-trimester spontaneous abortion, a second-trimester fetal death, or a third-trimester stillbirth. Small for gestational age was defined as a birth weight less than the 10th percentile derived from gender- and race-specific growth curves.²⁴⁻²⁶

Deoxyribonucleic acid was extracted from whole blood (Puregene DNA extraction kit; Gentra System, Minneapolis, MN), and a 222-bp fragment containing the FVL mutation site specific was amplified by polymerase chain reaction (PCR). The amplicon was detected by fluorescence using hybridization probes (LightCycler FVL Mutation Detection Kit; Roche Diagnostics, Basel, Switzerland) that were used to determine the genotype by melting-curve analysis.²⁷

Blood for coagulation tests was collected in siliconized evacuated glass tubes (Vacutainer; Becton Dickinson, Franklin Lakes, NJ) containing 0.109 mmol/L sodium citrate, in a ratio of 1 volume to 9 volumes blood, and centrifuged at 1,600g at 4°C for 20 minutes followed by repeat centrifugation of plasma at 1,600g at 4°C for 20 minutes. The resulting plasma (0.5-mL aliquots) was frozen at -70°C and then shipped on solid CO₂ to the Centers for Disease Control and Prevention and stored at -70°C until tested by the Hemostasis Laboratory. Clotting and chromogenic tests (STA coagulation analyzer; Diagnostica Stago, Parsippany, NJ), enzyme-linked immunosorbent assays (ELISA: Tecan Genesis RMP 200; Tecan, Research Triangle Park, NC), protein C activity (clotting assay: Staclot C, Diagnostica Stago), protein C antigen (ELISA: Asserachrom; Diagnostica Stago), antithrombin III activity (chromogenic assay: Stachrom AT III, Diagnostica Stago), protein S activity (clotting assay: Staclot S, Diagnostica Stago), protein S free antigen and total antigen (ELISA: Asserachrom, Diagnostica Stago), lupus anticoagulants (activated partial thromboplastin time [APTT] using a lupus anticoagulant-sensitive thromboplastin and hexagonal phase phosphatidylethanolamine neutralization: Staclot Lupus Anticoagulant, Diagnostica Stago; and dilute Russell’s viper venom test [DRVV Test and DRVV Confirm]: American Diagnostica, Greenwich, CT) were performed in batch fashion. The activated protein C resistance test was performed by APTT, adding 50 µL of Platelin LS (Organon Teknika, Durham, NC) to 50 µL of plasma diluted 1:10 in factor V-deficient plasma (Helena, Beaumont, TX). The ratio of the APTT with addition of 25 µL activated protein C (Enzyme Research, South Bend, IN) at 2 µg/mL in bovine serum albumin buffer (0.1% bovine serum albumin, 10 mM TRIS HCl, 0.05 M NaCl, pH 7.5) to the APTT with 25 µL of buffer alone was calculated. The prothrombin G20210A genotype was determined using a LightCycler Prothrombin (G20210A) Mutation Detection Kit and a LightCycler thermocycler (Roche Applied Science, Nonnenwald, Germany). The 5,10-methylenetetrahydrofolate reductase (MTHFR) C677T genotype was determined by PCR of the C677T polymorphism region in the MTHFR gene, followed by enzymatic digestion and gel electrophoresis.

The sample size was based on the precision of the point estimate for the risk of thromboembolism among FVL mutation carriers. We considered a 95% confidence interval (CI) about the point estimate of within ± 10% to be acceptable. We expected that 10–25% of FVL mutation-positive women would experience a venous thromboembolism (Hastings S, Knowlton J, Nelson L, Reid J, Loucks C, Varner M, Ward K. Obstetrical and medical complications in women with the factor V Leiden mutation [abstract]. *Am J Obstet Gynecol* 1998; 178:S104),⁵ and that a cohort of 100 FVL mutation carriers would provide a 95% CI of ± 10% or narrower for this range of point estimates. Anticipating a carrier frequency for the FVL mutation of approximately 2%, we planned to enroll approximately 5,000 women to identify 100 FVL mutation carriers.

All data were collated and analyzed by the Biostatistics Coordinating Center of George Washington University. Relative risks and 95% CIs were calculated to compare pregnancy outcomes between FVL mutation carriers and noncarriers (mothers and fetuses). Proportions were compared using Fisher exact test or χ^2 analysis, and continuous variables were compared using the Mann Whitney test (SAS 8.0, SAS Institute, Cary, NC). Exact binomial confidence limits were calculated (Stat-Xact 5.0, Statistical Solutions, Saugus, MA) where indicated for small sample sizes.

RESULTS

Between April 2000 and August 2001, 5,188 eligible women were enrolled (Fig. 1). Maternal FVL mutation carrier status and pregnancy outcome data were available for 4,885 gravidas (94%), including 134 heterozygous carriers of the FVL mutation (2.7%). Fetal/neonatal samples were available for 4,033 infants, including 2,445 cord blood, 1,052 buccal, 480 umbilical cord, and 56 placental specimens. Maternal FVL mutation carrier rates varied by self-determined racial and ethnic classifications (Table 1). The carrier rate was 6.1% in whites, 0.8% in African Americans, 1.7% in Hispanics, and 1.9% in others. Carriers and noncarriers were similar with respect to age and parity.

Four women experienced a pregnancy-related venous thromboembolic event, including 3 pulmonary emboli (1 antepartum, 2 peripartum) and 1 deep venous thrombosis (1 intrapartum). None of the 4 thromboembolic events occurred in FVL mutation carriers (0%, 95% CI 0–2.7%). The total population risk of venous thromboembolic events was 4/4,885 (0.08%, 95% CI 0.02–0.21%). We found no significant differences in the risks of adverse pregnancy outcomes between FVL mutation carriers and noncarriers (Table 2). Adverse pregnancy outcomes for women whose conceptus was a carrier for the FVL mutation are summarized in Table 3. A marginally increased risk ($P = .06$) of maternal preeclampsia was observed among fetal FVL carriers. Further analysis revealed a statistically significant racial disparity for preeclampsia among fetal FVL carriers. Among mothers of fetal carriers of the FVL mutation, preeclampsia was more common in African Americans (15.0%) and Hispanics (12.5%) when compared with whites (2.6%, $P = .04$). Correspondingly, among African-American and Hispanic women, there was an increased risk for preeclampsia in fetal FVL mutation carriers compared with noncarriers ($P = .04$ and 0.03, respectively, Table 4). We found no association between carrier status and preeclampsia among the white women, despite nearly 90% power to detect the 4-fold increased risk seen in nonwhite women ($\alpha = 0.05$, 2-sided). After adjusting for maternal race, the adjusted odds ratio for preeclampsia among all mothers of fetal carriers of the FVL mutation was 2.4 (95% CI 1.0–5.2, $P = .05$).

Coagulation assay testing was performed for 380 women (122 carriers who agreed to a second blood draw and their 244 matched controls, and also 14 additional controls who were subsequently replaced by another candidate for matching or who matched carriers refused a second blood draw). DNA testing for prothrombin G20210A and 5, 10 methylenetetrahydrofolate reductase was performed for 388 women (140 FVL mutation carriers, 244 controls, and 4 additional noncarriers who were subsequently replaced by matching candidates). Of these, 113 FVL mutation carriers and 226 controls had complete assay and outcome data available for analysis.

Functional assay samples were collected at a mean gestational age of 23 ± 6 weeks for carriers and 25 ± 6 weeks for controls. Results of these analyses are summarized by FVL carrier status and trimester in Table 5. As anticipated, activated protein C resistance was significantly higher among carriers of the FVL mutation (91.8% versus 4.7%, $P < .001$,

Table 6). The frequency of abnormalities among the other coagulation factors was not different between carriers and controls.

The results of our comparisons among maternal carriers of the FVL mutation alone, those having at least one of the other coagulation abnormalities (including activated protein C resistance in the absence of FVL), and controls are presented in Table 7. We found no significant differences in adverse pregnancy outcomes among these groups.

DISCUSSION

We have found women who carry the FVL mutation but who have no history of venous prior thromboembolism to be at low risk of thromboembolic events in pregnancy (0%, 95% CI 0–2.7%). This finding occurred in the context of a total cohort risk of 0.8 per 1,000 pregnancies, which is consistent with prior reports (0.5–3.0 per 1,000).² We found no increase in the risk of thromboembolism among FVL mutation carriers. The risk of thromboembolism in our study is much less than in prior retrospective or case-control studies.^{5–9} Those studies included women without regard to their thromboembolic history and suffered inclusion bias because symptomatic women would be more likely to be tested for and carry the mutation. Our study is strengthened by its large size and prospective observational study design. The 2 other prospective studies were substantially smaller, were published after the initiation of our study, and had findings consistent with our results. Middeldorp and colleagues¹⁸ studied 470 asymptomatic male and female FVL mutation carriers who were first-degree relatives of 247 symptomatic probands. Of only 17 full-term pregnancies, 9 received heparin thrombo-prophylaxis, and none was complicated by an objectively confirmed thromboembolism (95% CI 0.0–41.0). Clark and colleagues,²¹ in a prospective study of 967 unselected gravidas and 113 selected based on risk factors or a positive family history, found 30 of 967 to carry the FVL mutation, and one of these had a venous thromboembolism.

Our design limited bias of preconceived theories based on retrospective information of thrombophilia risk. Masking of care providers to mutation status avoided surveillance bias and unnecessary anticoagulation. An additional strength is the objective confirmation of the primary outcome and adherence to strict disease definition of secondary outcomes by investigators masked to mutation status. Our investigators often found that review of medical record coding only was insufficient and did not correlate with clinical diagnosis or disease severity.

Our initial goal was to conduct a prospective trial of heparin prophylaxis for gravidas with the FVL mutation who had no other risk factors for thrombosis. However, we found accurate information regarding the risk of thrombosis among these women to be limited. The current study was designed to estimate with precision the actual risk of venous thromboembolism among carriers of the FVL mutation during pregnancy. We excluded candidates for anticoagulation therapy, as determined by the women's caregivers. As such, this study was not designed to compare the risks of pregnancy-associated thromboembolism between all FVL mutation carriers and noncarriers. Given the observed incidence (0.84/1,000 noncarriers), over 77,000 women would need to be studied to evaluate a 4-fold increase in risk ($\alpha = 0.05$, power 0.80) with FVL mutation carriage, and many more would be needed to evaluate smaller incremental risks.

This study was not designed to study the rates of other adverse pregnancy outcomes among FVL mutation carriers, and thus the power of our findings regarding these is limited. Further, we did not test the entire cohort for the other inherited thrombophilias evaluated in nested carrier-control study. Nonetheless, this study provides accurate estimates regarding

the risks of adverse pregnancy outcomes among asymptomatic heterozygote FVL mutation carriers. Although we had hoped to evaluate potential interactions among maternal FVL mutation carriage, fetal FVL mutation carriage, other coagulation abnormalities, described genotypes, and the occurrence of venous thrombotic events, we were unable to because of the rarity of thromboembolism in these women.

Our findings suggest a possible association between fetal FVL mutation carriage and preeclampsia in African-American and Hispanic women, emphasizing the potential importance of both maternal and fetal contributions to obstetric disease. It is plausible that, through intimate juxta-position of maternal and fetal tissues in the human placenta, maternal and/or fetal genotype could actively modulate normal or abnormal pregnancy conditions. The evident racial differences in response to carriage of the FVL mutation seen in this study suggest that maternal and/or fetal race could contribute to the different frequencies of preeclampsia observed in different racial groups. It is plausible that the different carriage rates among whites (6.1%), African Americans (0.8%), and Hispanics (1.7%) reflects differential predisposition to diseases such as preeclampsia among these groups. We recognize that our findings in this regard could be attributable to type I error and that further study of the role of fetal genotype on maternal preeclampsia is warranted to provide better understanding of this finding.

This prospective analysis provides strong evidence that the risk of thromboembolic events in untreated heterozygotes for the FVL mutation without evident risk factors for thrombosis is low and is not different from noncarriers. Universal screening for FVL mutation and prophylactic anticoagulation treatment of the heterozygote carrier without a prior venous thromboembolism is unwarranted. We suggest caution in the implementation of prophylactic interventions for potentially treatable risk factors that are plausibly related to adverse events in pregnancy, but that have not been prospectively evaluated.

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APPENDIX

Members and institutions participating in the Maternal-Fetal Medicine Units Network include University of Utah: M. Varner, K. Anderson, K. Jolley, A. Guzman, J. Parsons; University of Alabama at Birmingham: D. Rouse, A. Northen, K. Bailey; George Washington University Biostatistics Center: V. Momirova, A. Arrieta, L. Leuchtenburg; National Institute of Child Health and Human Development: M. Klebanoff, S. Pagliaro, D. McNellis, K. Howell; University of Chicago: P. Jones, G. Mallett; University of Pittsburgh Magee-Womens Hospital: K. Lain, T. Kamon, S. Caritis; University of Texas Southwestern Medical Center: K. Leveno, J. McCampbell, S. Williams; Wayne State University: M. Dombrowski, G. Norman, P. Lockhart, C. Sudz; University of Cincinnati: T. Siddiqi, H. How, N. Elder, W. Knox; Wake Forest University: M. Harper, M. Swain, K. Lanier; Ohio State University: J. Iams, F. Johnson, C. Latimer; University of Miami: F. Doyle; University of Tennessee: W. Mabie, R. Ramsey; University of Texas at San Antonio: O. Langer, D.

Dudley, S. Barker, D. Skiver; Thomas Jefferson University: A. Sciscione, M. Talucci, M. DiVito.

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Fig. 1.
Flow of patients through the study.

Table 1
Maternal Demographic Characteristics of Enrolled Patients

Characteristic	Maternal FVL Carriers n = 140	Maternal Noncarriers (n = 5,028)
Maternal age (y)	26.5 ± 5.7	25.1 ± 5.6
Primigravida	47 (33.6)	1542 (30.7)
African American	14 (10.0)	1821 (36.2)
Hispanic	27 (19.3)	1596 (31.7)
White	97 (69.3)	1505 (29.9)
Asian	1 (0.7)	42 (0.8)
Native American	0 (0)	12 (0.2)
Other	1 (0.7)	52 (1.0)

FVL, factor V Leiden mutation.

Data are presented as n (%) or mean ± standard deviation.

Table 2
Adverse Pregnancy Outcome in Maternal Carriers of the Factor V Leiden Mutation
Compared With Noncarriers

	FVL Carriers	FVL Noncarriers	Relative Risk (95% CI)	P
Pregnancy loss	8/134 (6.0)	264/4,751 (5.6)	1.1 (0.5–2.2)	.84
Preeclampsia	5/134 (3.7)	141/4,751 (3.0)	1.3 (0.4–2.8)	.60
Abruption	0	31/4,751 (0.7)	0	1.00
SGA < 5th percentile *	6/124 (4.8)	173/4,428 (3.9)	1.2 (0.5–2.6)	.64
SGA < 10th percentile *	10/124 (8.1)	403/4,428 (9.1)	0.9 (0.5–1.7)	.69

FVL, factor V Leiden mutation; CI, confidence interval; SGA, birth weight small for gestational age.

Data are presented as n/N (%) or relative risk (95% confidence interval).

* Based on live-born singletons.

Table 3
Association Between Conceptus Factor V Leiden Mutation Carrier Status and Adverse Pregnancy Outcomes

	FVL Carriers	FVL Noncarriers	Relative Risk (95% CI)	P
Preeclampsia	8/121 (6.6)	121/3,912 (3.1)	2.1 (1.0–4.1)	.06
Pregnancy loss	0/121 (0)	35/3,912 (0.9)	0	.63
Abruption	2/121 (1.7)	22/3,912 (0.6)	2.9 (0.3–10.7)	.16
SGA < 10th percentile*	10/20 (8.3)	352/3,857 (9.1)	0.9 (0.5–1.6)	.77

FVL, factor V Leiden mutation; CI, confidence interval; SGA, birth weight small for gestational age.

Data are presented as n/N (%) or relative risk (95% confidence interval).

* Based on live-born singletons.

Table 4
Frequency of Preeclampsia Based on Predominate Maternal Ethnic/Racial Groups and
Conceptus Factor V Leiden Mutation Carrier Status

Ethnicity/Race	FVL Carriers	FVL Noncarriers	Relative Risk (95% CI)	P
African American (n = 1,381)	3/20 (15.0)	52/1,361 (3.8)	3.9 (1.3–9.9)	.04
Hispanic/Other (n = 1,256)	3/24 (12.5)	32/1,232 (2.6)	4.8 (1.6–12.8)	.03
White (n = 1,396)	2/77 (2.6)	37/1,319 (2.8)	0.9 (0.2–3.3)	1.00

FVL, factor V Leiden mutation; CI, confidence interval.

Data are presented as n/N (%) or relative risk (95% confidence interval).

Table 5
Coagulation Assays Among Maternal Factor V Leiden Mutation Carriers and Noncarriers in the First and Second or the Third Trimesters

Assay	FVL Carriers		FVL Noncarriers	
	Trimester 1&2 (n = 79)	Trimester 3 (n = 43)	Trimester 1&2 (n = 132)	Trimester 3 (n = 126)
Antithrombin III activity	103.6 (7.7)	105.4 (7.4)	103.0 (8.2)	105.5 (8.2)
Protein C activity	118.0 (20.3)	113.5 (24.0)	118.7(24.1)	108.4 (24.3)
Protein C antigen	110.1 (17.8)	111.9 (22.3)	110.2 (18.3)	106.3 (19.9)
Protein S activity	44.5 (11.3)	36.6 (8.8)	50.4 (13.6)	41.7(13.2)
Protein S total antigen	98.0 (16.8)	100.5 (19.6)	98.8 (19.2)	94.0 (19.7)
Protein S free antigen	61.7(14.0)	51.2 (10.4)	60.6 (14.0)	52.3 (14.0)

FVL, factor V Leiden mutation.

Data are presented as mean (SD).

Table 6
Occurrence of Coagulation Abnormalities Among Maternal Factor V Leiden Mutation Carriers and Noncarriers

	FVL Carrier	FVL Noncarrier	P
Lupus anticoagulant	1/121 (0.8)	4/255 (1.6)	1.00
Antithrombin III activity	3/122 (2.5)	8/258 (3.1)	1.00
Protein C activity	1/122 (0.8)	6/258 (2.3)	.44
Protein C antigen	2/122 (1.6)	3/258 (1.2)	.66
Protein S activity	3/122 (2.5)	5/258 (1.9)	.72
Protein S total antigen	1/122 (0.8)	2/258 (0.8)	1.00
Protein S free antigen	2/122 (1.6)	2/258 (0.8)	.60
APCR abnormal *	112/122 (91.8)	12/258 (4.7)	< .001
Homozygote carrier MTHFR (C677T)	16/133 (12.0)	30/241 (12.5)	.52
Heterozygote carrier prothrombin G20210A	5/138 (3.6)	9/243 (3.7)	1.00

FVL, factor V Leiden mutation; APCR, activated protein C resistance test; MTHFR (C677T), 5,10-methylenetetrahydrofolate reductase (MTHFR) C677T genotype.

Data are presented as n/N (%)

* Adjusted for factor V.

Table 7
**Adverse Pregnancy Outcomes Among Maternal Factor V Leiden Mutation Carriers,
 Those With Other Coagulation Abnormalities, and Noncarriers**

	FVL Carriers [*]	Other Coagulation Abnormalities [†]	Noncarriers [‡]	P
Preeclampsia	3/86 (3.5)	4/87 (4.6)	7/166 (4.2)	1.00
Abruption	0/86	0/87	2/166 (1.2)	.50
SGA < 5th percentile [§]	5/85 (5.9)	3/87 (3.5)	7/164 (4.3)	.74
SGA < 10th percentile [§]	7/85 (8.2)	11/87(12.6)	14/164 (8.5)	.53

FVL, factor V Leiden mutation; SGA, birth weight small for gestational age.

Data are presented as n/N (%).

^{*}Includes FVL carriers with and without activated protein C resistance.

[†]Includes those with activated protein C resistance not attributable to the factor V Leiden mutation.

[‡]Women with neither factor V Leiden mutation nor other coagulation abnormalities.

[§]Based on live-born singletons.