Published in final edited form as:

Obstet Gynecol. 2010 January ; 115(1): 14–20. doi:10.1097/AOG.0b013e3181c88918.

Prothrombin Gene *G20210A* Mutation and Obstetric Complications

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Abstract

OBJECTIVE—To estimate whether maternal carriage of the prothrombin gene *G20210A* mutation is associated with pregnancy loss, preeclampsia, placental abruption, or small for gestational age (SGA) neonates in a low-risk, prospective cohort.

METHODS—This was a secondary analysis of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development factor V Leiden study, a multicenter, prospective, observational cohort of 5,188 unselected singleton gestations. A total of 4,167 first-trimester samples were available for analysis and were tested for the prothrombin *G20210A* mutation. Obstetric complications were compared between women with and without the prothrombin *G20210A* mutation by univariable and multivariable analysis.

RESULTS—A total of 157 (3.8%) women had the prothrombin gene mutation (156 heterozygous and one homozygous). Carriers of the prothrombin *G20210A* mutation had similar rates of pregnancy loss, preeclampsia, SGA neonates, and abruption compared with noncarriers. Results were similar in a multivariable analysis controlling for age, race, prior pregnancy loss, prior SGA neonates, and family history of thromboembolism. Three thromboembolic events occurred in women testing negative for the mutation.

CONCLUSION—There was no association between the prothrombin *G20210A* mutation and pregnancy loss, preeclampsia, abruption, or SGA neonates in a low-risk, prospective cohort. These

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Financial Disclosure

The authors did not report any potential conflicts of interest.

data raise questions about the practice of screening women without a history of thrombosis or adverse pregnancy outcomes for this mutation.

LEVEL OF EVIDENCE—II

Inherited thrombophilias are a heterogeneous group of coagulation disorders that predispose individuals to thromboembolic events. They are major risk factors for thromboembolism during pregnancy and the puerperium. In addition, thrombophilias have been implicated in a variety of adverse obstetric events, including pregnancy loss (especially fetal death), preeclampsia, placental abruption, and small for gestational age (SGA) neonates.¹ The pathophysiology is uncertain but is thought to involve thrombosis in the uteroplacental circulation leading to infarction and placental insufficiency.² Thus, anticoagulant therapy has the potential to improve obstetric outcomes in women with heritable thrombophilias. This has led to widespread screening for and treatment of women with thrombophilias in hopes of improving obstetric outcomes. However, efficacy remains uncertain.³

The vast majority of data linking thrombophilias, including the prothrombin *G20210A* mutation, to adverse obstetric events are derived from case-control studies.⁴⁻¹¹ Such studies are subject to bias and may overestimate the risk of adverse obstetric outcomes in women with thrombophilias.^{12,13} It is noteworthy that in two large cohorts of unselected pregnant women, maternal carriage of the factor V Leiden mutation was not associated with an increased risk of any adverse pregnancy outcome.^{14,15}

Few prospective cohort studies have been performed in unselected populations for the prothrombin *G20210A* mutation. This mutation is second only to the factor V Leiden mutation with regard to frequency in women with thromboembolism associated with pregnancy.¹⁶ It is present in about 2% to 3% of Europeans and about 17% of women with thromboembolism in pregnancy.¹⁷ Our objective was to estimate whether maternal heterozygosity of the prothrombin gene *G20210A* mutation is associated with pregnancy loss, preeclampsia, or SGA neonates in a prospective, low-risk cohort.

MATERIALS AND METHODS

This is a secondary analysis of a prospective, observational, multicenter, cohort study conducted by the Maternal-Fetal Medicine Units Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development conducted from April 2000 through August 2001. The methods have been described previously.¹⁵ The cohort included women from 13 clinical centers who had uncomplicated singleton pregnancies at 14 weeks of gestation or less (best estimate based on clinical or ultrasonographic findings). Exclusion criteria included multiple gestation, current or planned anticoagulation therapy, known factor V Leiden status, antiphospholipid syndrome, previous thromboembolism, fetal demise, planned pregnancy termination, planned delivery at an institution not included in the Maternal-Fetal Medicine Units Network, and participation in another research study that might influence the risk of venous thromboembolism or perinatal outcome. Written informed consent was obtained from each participant, and institutional review board approval was obtained from each of the 13 clinical centers as well as the Data Coordinating Center at the George Washington University.

For this secondary analysis, the outcome variables of interest included preeclampsia, SGA neonates, pregnancy loss, and placental abruption. Preeclampsia was defined as a diastolic blood pressure more than 90 mm Hg on two occasions 4 hours to 14 days apart occurring within 4 hours to 14 days of evident significant proteinuria (more than 300 mg protein in a 24-hour test, urinary protein/creatinine ratio more than 0.35, at least 2+ proteinuria from a single dipstick evaluation or 1+ proteinuria from two or more measurements obtained 4 hours to 14

days apart) in previously normotensive nonproteinuric patients. Women also were considered to have preeclampsia if they were diagnosed with eclampsia; hemolysis, elevated liver enzymes, low platelets syndrome; or if they met the blood pressure criteria and had pulmonary edema or thrombocytopenia (less than 100,000/mm³). Women with chronic hypertension or proteinuria or both needed to meet strict, predefined criteria to be considered to have superimposed preeclampsia. For women with preexisting proteinuria, new-onset, pregnancy-associated hypertension as well as superimposed proteinuria was required for the diagnosis of preeclampsia.¹⁸

Small for gestational age 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.¹⁹ Pregnancy loss included first-trimester spontaneous abortion, fetal death between 14 and 20 weeks of gestation, and stillbirth, defined as fetal demise after 20 weeks of gestation. Abruption was considered present when there was clinical suspicion that was 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 pathologic examination of the placenta.

Each participant had venous blood obtained and submitted to the DNA diagnostic laboratory at the University of Utah School of Medicine. The DNA was extracted from whole blood (Puregene DNA extraction kit, Gentra System, Minneapolis, MN). Genotype results were obtained using a Taqman Assay (Applied Biosystems, Inc., Foster City, CA) designed to detect the prothrombin *G20210A* mutation. This allele discrimination assay used PCR amplification and a pair of fluorescent dye detectors that target the *G20210A* mutation. One fluorescent dye is attached to the detector that is a perfect match to the wild type allele (G), and a different fluorescent dye is attached to the detector that is a perfect match to the mutant allele (A). During PCR, the polymerase will release the fluorescent probe into solution, where it is detected using an Applied Biosystems 7900HT Real-Time instrument (Applied Biosystems, Inc.). Genotypes were determined using Applied Biosystems automated Taqman genotyping software SDS 2.1 (Applied Biosystems, Inc.).

Data were collected and analyzed by the Biostatistics Center of the George Washington University—the data-coordinating center for the Maternal-Fetal Medicine Units Network. Relative risks and 95% confidence intervals (CIs) were calculated to compare pregnancy outcomes between women with and without the prothrombin *G20210A* mutation. Multivariable logistic regression analysis was performed, controlling for age, race, prior pregnancy loss, prior SGA neonates, and family history of thromboembolism. Proportions were compared using the Fisher exact test or χ^2 test as appropriate; continuous variables were compared using the Wilcoxon rank-sum test. Exact binomial confidence limits were calculated when indicated owing to small sample size.

RESULTS

The flow of patients through the study is shown in Figure 1. Of the original 5,188 women enrolled in the study, 4,167 had pregnancy outcome data and prothrombin *G20210A* mutation status available. A total of 157 (3.8%) of the women tested positive for the prothrombin *G20210A* mutation; 156 were heterozygous and one was homozygous for the mutation. Table 1 depicts demographic characteristics of patients stratified by prothrombin *G20210A* mutation status. Based on self-determined racial and ethnic classification, the carrier rate of the mutation was 4.4% in white women, 3.2% in African-American women, 3.8% in Hispanic women, and 4.3% in others. Women with and without the prothrombin *G20210A* mutation were of similar age and parity.

Pregnancy outcome for the cohort comparing carriers of the prothrombin *G20210A* mutation with noncarriers is shown in Table 2. There were no differences among groups for any individual adverse obstetric outcome including preeclampsia, SGA neonates, pregnancy loss, abruption, and oligohydramnios. Gestational age at delivery also was similar among groups.

The one patient who was homozygous for the prothrombin *G20210A* mutation delivered at 34 weeks of gestation secondary to preeclampsia. Her neonate was appropriately grown for gestational age, and there were no other obstetric complications. There were five patients who were heterozygous for both the prothrombin *G20210A* and factor V Leiden mutations. One had an SGA neonate with oligohydramnios. The other four had entirely uncomplicated term pregnancies.

Odds ratios (ORs) for obstetric complications in women with and without the prothrombin *G20210A* mutation after controlling for maternal age, race, parity, prior pregnancy loss, prior SGA neonates, and family history of thromboembolism are shown in Table 3. There was no association between the prothrombin *G20210A* mutation and any individual adverse obstetric outcome in the model.

There were three thromboembolic events during pregnancy and the postpartum period, including two pulmonary emboli and one deep venous thrombosis. All occurred in women who tested negative for the prothrombin *G20210A* mutation. These women also tested negative for the factor V Leiden mutation. It is unknown whether they have other thrombophilias.

DISCUSSION

There was no association between the prothrombin *G20210A* mutation and any individual obstetric complication, including pregnancy loss, preeclampsia, abruption, and SGA neonates in this low-risk, prospective cohort of more than 4,000 women. In addition, there was no difference in the gestational age at delivery among carriers and noncarriers of the mutation.

These data differ from previous reports linking the prothrombin *G20210A* mutation and each of these complications.⁴⁻¹¹ In a systematic review, Robertson and colleagues report an OR of 2.49 (95% CI 1.24–5.00) for early pregnancy loss, 2.70 (95% CI 1.37–5.34) for recurrent early pregnancy loss, and 2.66 (95% CI 1.28–5.53) for late loss for women with the mutation compared with those without.¹ The ORs and 95% CIs for the prothrombin *G20210A* mutation and preeclampsia, SGA neonates, and abruption were 2.54 (1.52–4.23), 2.92 (0.62–13.70), and 7.71 (3.01–19.76), respectively.¹ All of these were retrospective studies, often including small numbers of women.

It is noteworthy that not all retrospective studies showed a relationship between the prothrombin *G20210A* mutation and obstetric complications. Several case–control studies failed to show an association between this mutation and abruption,²⁰ SGA neonates,²¹ recurrent pregnancy loss,²² preeclampsia,^{23,24} and other adverse obstetric outcomes.²⁵ Explanations for differences in results among studies may include different ethnic populations, different definitions for adverse outcomes, combining thrombophilias or adverse outcomes or both into summary statistics, incomplete data regarding the gestational age of lost pregnancies, the inclusion of “explained” pregnancy losses (eg, aneuploidy), and the variable but relatively small size of most studies. Each of these factors introduces potential bias. It is striking that the only large case–control study, including almost 1,000 women, showed no association between the prothrombin *G20210A* mutation and SGA neonates.²¹

There are few data from prospective cohort studies assessing the relationship between adverse obstetric outcomes and the prothrombin gene *G20210A* mutation. Recently, Coppens and colleagues performed a retrospective cohort study of women who were first-degree relatives

of probands with either the factor V Leiden or prothrombin *G20210A* mutation.²⁶ They assessed subsequent pregnancy outcomes in 918 women with and without these thrombophilias. Subsequent pregnancy outcome was similar and generally excellent in women with and without thrombophilias. Regardless of thrombophilia status, women with a pregnancy loss in their first pregnancy were more likely to suffer a loss in their next pregnancy (25%) than were those with live births in their first pregnancy (12%). The overall cohort included 118 women who were heterozygous and four who were homozygous for the prothrombin gene *G20210A* mutation.²⁶ Recently, Kocher and colleagues assessed a large cohort of unselected pregnant women for the factor V Leiden and prothrombin *G20210A* mutations.²⁷ The factor V Leiden mutation was associated with an increased risk of stillbirth (OR 11.6, 95% CI 1.93–69.43). In contrast, the prothrombin *G20210A* mutation was not associated with stillbirth, preeclampsia, SGA neonates, miscarriage, or abruption. However, prothrombin the *G20210A* mutation was associated with an increased risk of preterm delivery (OR 3.17, 95% CI 1.08–9.30).²⁷

It is remarkable that two large cohort studies of unselected women showed no association between the factor V Leiden mutation and adverse obstetric outcomes.^{14,15} Our results were similar with the prothrombin *G20210A* mutation. On balance, prospective cohort studies are considered to be less prone to bias than are retrospective case–control studies. Indeed, in a recent meta-analysis of the association between thrombophilias and intrauterine growth restriction, Facco and colleagues conclude that the association can be discerned only in case–control studies and is largely a result of publication bias.¹³

Another possible explanation for the discrepant results in retrospective and prospective studies is that women with thrombophilias and prior adverse pregnancy outcomes are different than those with no prior adverse pregnancy outcomes. The vast majority of women with thrombophilias have normal pregnancies, and thrombophilias alone are insufficient to cause adverse pregnancy outcomes. Perhaps other yet unidentified factors, genes, or environmental triggers are required for pregnancy complications to occur in women with thrombophilias.

The lack of an association between the prothrombin *G20210A* mutation and individual adverse pregnancy outcomes in this prospective study raises concern about the strength of the relationship between this mutation and pregnancy complications. For example, antiphospholipid antibodies have been associated with pregnancy loss and obstetric complications in both case–control and prospective cohort studies.^{28,29} One would anticipate the same to be true for thrombophilias if the relationship between these conditions and obstetric complications was as robust as that noted with antiphospholipid antibodies.

Our observations have important clinical implications. A major drawback of widespread testing for thrombophilias is that a relatively large percentage of healthy individuals will test positive. This is especially true when testing for a large number of thrombophilias or a “thrombophilia panel.” In one case–control study, a positive test result for a thrombophilia was found in 39% of participants in the control group who were healthy and had normal pregnancy outcomes.³⁰ Accordingly, there is the potential to diagnose a large number of asymptomatic, healthy individuals with thrombophilias.

In turn, this creates a dilemma as well as anxiety for patients and clinicians. Many physicians are treating women with thrombophilias with heparin or low molecular weight heparin during pregnancy in hopes of improving obstetric outcomes and reducing the risk of thrombosis. However, there is little evidence to guide the treatment of such women.³ There is one randomized trial reporting improved pregnancy outcomes in women with thrombophilias and prior fetal death treated with low molecular weight heparin compared with low-dose aspirin.

³¹ Concerns have been raised about the generalizability of this study owing to an extremely

high rate of pregnancy loss (71%) in women in the control group as well as some methodological flaws.³ There are no data from properly designed clinical trials regarding women with thrombophilias and no prior adverse pregnancy outcomes. A recent nonrandomized cohort showed no benefit from thromboprophylaxis in women with thrombophilias, regardless of whether they had prior pregnancy complications.³²

There are meaningful drawbacks to using heparin and low molecular weight heparin during pregnancy. Complications include bleeding, osteopenia, skin reactions, allergy, and thrombocytopenia.³³ Heparins are also inconvenient, requiring subcutaneous injections, and they are costly, especially low molecular weight heparins. Finally, they may interfere with the safe use of neuraxial analgesia. Thus, ideally, benefit should be demonstrated in appropriately designed trials before the adoption of widespread treatment during pregnancy of women with thrombophilias.

Our study had several limitations. First, samples were unavailable for some patients, introducing a possible source of bias. Indeed, patients with analyzable samples were less likely to be African American and to have SGA neonates and were more likely to have pregnancy loss, preeclampsia, and oligohydramnios than were those without analyzable samples. However, DNA degradation was the reason most patients were not included, making systematic bias less likely. Second, there was limited power to detect small differences in the risk of some obstetric complications among carriers of the prothrombin *G20210A* mutation. Third, we excluded women who were candidates for anticoagulant therapy. Thus, we may have limited our ability to detect an association between the prothrombin *G20210A* mutation and obstetric complications in an at-risk population. Finally, we did not assess fetal mutation status. Thus, we cannot comment on whether there is an association between fetal prothrombin *G20210A* mutation and obstetric complications.

The study also had numerous strengths. We had a very large number (more than 4,000) of racially diverse, prospectively ascertained patients. There was more than adequate power to detect differences in outcomes of the order of magnitude seen in previous studies. For example, for an outcome rate of 6%, such as that observed with pregnancy loss, there was more than 95% power to detect a 2.5-fold increase in the carrier group. Similarly, for an outcome rate of 12%, such as that observed for preterm delivery, there was more than 95% power to detect a twofold increase in risk. Care providers were unaware of mutation status, avoiding potential confounding due to altered obstetric care such as increased fetal surveillance in prothrombin gene *G20210A* carriers. Strict definitions were used to define adverse obstetric outcomes, and medical records were abstracted by trained investigators blinded to mutation status.

In summary, there was no association between the prothrombin *G20210A* mutation and pregnancy loss, preeclampsia, abruptio, or SGA neonates in a low-risk, prospective cohort. These data raise questions about the practice of screening women without a history of thrombosis or adverse pregnancy outcomes for this mutation.

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 thank Margaret Cotroneo, RN, for central outcome review; Valerija Momirova, MS, and Elizabeth Thom, PhD, for data management and statistical analysis; and Michael Varner, MD, and Donna Dizon-Townson for protocol development and oversight.

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Fig. 1.

Availability of data and samples.

Silver, Prothrombin Gene G20210A Mutation. Obstet Gynecol 2010.

Table 1**Maternal Demographics and Characteristics of Enrolled Patients**

Characteristic	Prothrombin <i>G20210A</i> Mutation Status		<i>P</i>
	Carrier (n=157)	Noncarrier (n=4,010)	
Maternal age (y)	25 (22–29)	24 (21–29)	.225
Primigravida	48 (30.6)	1235 (30.8)	.952
White	57 (36.3)	1244 (31.0)	.432
African American	45 (28.7)	1368 (34.1)	
Hispanic	51 (32.5)	1309 (32.6)	
Other race	4 (2.5)	89 (2.2)	
Prior pregnancy loss	37 (23.6)	928 (23.1)	.902
Prior SGA	1 (0.6)	48 (1.2)	1.000*
Family history of thromboembolism	17 (10.8)	311 (7.8)	.161

SGA, small for gestational age.

Data are median (interquartile range) or n (%) unless otherwise specified.

* Fisher exact test.

Adverse Pregnancy Outcomes in Maternal Carriers of the Prothrombin Gene *G20210A* Mutation Compared With Noncarriers (Univariable Analysis)

Table 2

	Carrier (n=157)	Noncarrier (n=4,010)	RR	95% CI	P
Pregnancy loss	9 (5.7)	238 (6.0)	0.96	0.50–1.84	.907
Preeclampsia	6 (3.8)	123 (3.1)	1.25	0.56–2.78	.487*
SGA 5%	8 (5.4)	151 (4.0)	1.35	0.68–2.70	.394
SGA 10%	17 (11.6)	338 (9.0)	1.28	0.81–2.03	.291
Abruption	2 (1.27)	24 (0.6)	2.13	0.51–8.93	.257*
Oligohydramnios	8 (5.1)	177 (4.4)	1.15	0.58–2.30	.684
Preterm delivery	23 (15.3)	458 (12.1)	1.27	0.86–1.86	.239
GA at delivery	39.0 (37.5–40.0)	39.0 (37.0–40.0)	—	—	.424 [†]

RR, relative risk; CI, confidence interval; SGA, small for gestational age; GA, gestational age.

Data are n (%) or median (interquartile range) or unless otherwise specified.

* Fisher's exact test.

[†] Wilcoxon test.

Table 3

Adverse Pregnancy Outcomes in Maternal Carriers of the Prothrombin Gene *G20210A* Mutation Compared With Noncarriers

	Odds Ratio	95% CI	P
Pregnancy loss	0.98	0.49–1.95	.951
Preeclampsia	1.30	0.56–3.02	.536
SGA 5%	1.39	0.67–2.89	.377
SGA 10%	1.34	0.80–2.25	.267
Abruption	2.23	0.52–9.58	.280
Oligohydramnios	1.18	0.57–2.44	.659
Preterm delivery	1.39	0.87–2.21	.165
GA at delivery	—	—	.941

CI, confidence interval; SGA, small for gestational age; GA, gestational age.

Multivariable analysis adjusted for maternal age, race, parity, prior pregnancy loss, prior SGA neonates, and family history of thromboembolism.