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The Effect of Maternal Thrombophilia on Placental Abruption: Histologic Correlates

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Abstract

Objective—To determine if the histology of placental abruption differs by maternal thrombophilia status.

Study design—This was a multicenter, case-control study of women with abruption and delivering at ≥20 weeks' gestation, collected as part of the ongoing New Jersey-Placental Abruption Study. Women were identified by clinical criteria of abruption. Maternal blood was collected postpartum and tested for anticardiolipin antibodies, and mutations in the Factor V Leiden and prothrombin genes. Cases were comprised of women with an abruption and a positive thrombophilia screen. Controls were comprised of women with an abruption and a negative thrombophilia screen. All placental histology was systematically reviewed by two perinatal pathologists, blinded to the abruption status.

Results—A total of 135 women with placental abruption were identified, of which 63.0% (n=85) had at least one diagnosed maternal thrombophilia. There were increases in the rates of meconium-stained membranes (7.9% versus 2.1%, P=0.015) and decidual necrosis (4.5% versus 2.1%, P=0.023) when a maternal thrombophilia was diagnosed. Although there was no difference in the overall presence of infarcts between the 2 groups (27.0% versus 38.3%, P=0.064), the presence of an old infarct was more common among women with a positive thrombophilia screen (83.3% versus 44.4%, P=0.003).

Conclusion—Placental abruption with a positive maternal thrombophilia screen is associated with higher rates of old placental infarcts and decidual necrosis compared with abruption when thrombophilia is not diagnosed. These lesions suggest a chronic etiology of placental abruption in the presence of a maternal thrombophilia.

Maternal thrombophilia has been linked to an increased incidence of placental abruption,[1, 2] as well as other adverse pregnancy outcomes.[3, 4] It is believed that the increased obstetrical risk is mediated through placental vascular dysfunction.[5] Placental thrombosis can then result in subsequent ischemic complications, such as fetal loss, preeclampsia, and fetal growth restriction.[6–9] Placental abruption has been identified as being part of the spectrum

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of ischemic placental disease[10] and is postulated to be a chronic disease process.[11, 12] There is little histologic confirmation of this suggestion, however.[13, 14]

It is suspected that maternal thrombophilia predisposes women to placental abruption by causing chronic reduction in uteroplacental blood flow rather than an acute disruption of the maternal-fetal interface. Although similar histopathologic features of the placenta from different underlying conditions may indicate a common pathway, there are no microscopic features pathognomonic of the genetic thrombophilias, which are currently able to be diagnosed.[15] This multi-center, case-control study was designed to determine if placental histology in the setting of placental abruption differs based on maternal thrombophilia status.

Material and Methods

This was a case-control study of women with placental abruption collected as part of the ongoing New Jersey-Placental Abruption Study (NJ-PAS). NJ-PAS is a multi-center study, with subjects recruited from Saint Peter's University Hospital (since August 2002) and Robert Wood Johnson University Hospital (since July 2003) in New Brunswick, NJ. Institutional review board approval was obtained from both hospitals as well as that of the UMDNJ-Robert Wood Johnson Medical School.

Women with a clinical diagnosis of placental abruption were identified by the attending obstetrician either before or during delivery. Placental abruption was considered to have occurred if the classical clinical signs and symptoms were present (painful vaginal bleeding accompanied by non-reassuring fetal heart rate tracing, uterine tenderness or uterine hypertonicity). Placental abruption was also considered present if the delivered placenta showed gross signs of retroplacental bleeding/hematoma or if there was an antepartum sonographic diagnosis. Since even large marginal hematomas may not deform the placental surface, this was not considered a requirement for diagnosis. However, in the absence of a clinical diagnosis, a retroplacental hematoma was considered present only if adherent prior to formalin fixation. Pregnancies complicated by placental abruption were identified by reviewing daily delivery logs at both hospitals and/or by referral by the health care providers. Criteria for eligibility included women with an abruption that delivered at ≥20 weeks' gestation and that provided informed consent to participate in the study.

All women eligible for enrollment were recruited immediately following delivery. A detailed medical and lifestyle interview was conducted. Maternal blood was then collected and tested for Factor V Leiden mutation, prothrombin gene mutation, lupus anticoagulant and anticardiolipin antibodies (IgG and IgM) using standard laboratory assays. For the purpose of this study, cases were comprised of women with placental abruption and a positive thrombophilia screen. Controls were comprised of women with placental abruption and a negative thrombophilia screen. All placentas were systematically evaluated by both gross and microscopic histology by one of two perinatal pathologists, whom were blinded to the placental abruption status. The lesions evaluated by the two pathologists were based on strict criteria and the findings were recorded on standardized data scoring sheets.

Histopathologic lesions

A histopathological evaluation of the placenta was performed. The examination included evaluation of the placental disc, maternal and fetal surfaces, evaluation of the umbilical cord, and membranes. A systematic examination was performed to evaluate the presence or absence of pathologic processes including chorioamnionitis, cord inflammation including funisitis, phlebitis and/or vasculitis, changes of decidual vasculopathy (mural hypertrophy, fibrinoid necrosis and atherosis), placental infarctions, intervillous thrombus, villous

maturation, perivillous fibrin deposition, villitis, villous edema and villous stromal hemorrhage. Villous maturation was evaluated by examining the size, stroma and blood vessel disposition of villi. A search for meconium stained membranes was made and associated changes such as amnion necrosis and pigmented macrophages were noted,[16, 17] since meconium induced myonecrosis is a feature of fetal thrombotic vasculopathy.[15] Chorioamnionitis was defined by the presence of inflammatory infiltrates of neutrophils at two or more sites on the chorionic plate and extra placental membranes. It was classified into one of four grades: none, mild, moderate and severe. Mild chorioamnionitis was defined by the presence of few scattered (5–10/high power field) neutrophils in the subchorionic space and adjacent chorion; moderate by many (11–30/high powered field) neutrophils in the lower half of the chorionic plate; and severe by dense infiltrates of neutrophils (>30/high powered field) throughout the chorionic plate into the amnion. Funisitis was diagnosed when neutrophils infiltrated the wall of at least one umbilical cord vessel. Infarctions were characterized as old or recent based on the gross examination. Recent infarctions were red, less indurated with a homogeneous cut surface while older infarctions were brown to white with a rather firm cut surface. The histological criteria for a diagnosis of placental abruption were: hematoma, fibrin, and compressed villi. In cases with older hematomas, hemosiderin-laden histiocytes were also searched for. Other lesions that were evaluated included chronic deciduitis (lymphocytic infiltration with or without plasma cell infiltrates), decidual necrosis, terminal villous hypoplasia, and hemosiderin deposition.[12, 18] Changes indicative of fetal thrombotic vasculopathy, including occlusive and mural thrombosis, avascular villi and hemorrhagic endovasculitis, were also searched for.

Statistical analysis

We examined the distributions of maternal socio-demographic characteristics between the two groups of women with placental abruption based on thrombophilia status. Potential differences between groups were evaluated by the Fisher's exact probability test for categorical variables and the t-test for continuous variables. Comparisons of histological lesions were made between women with and without thrombophilia among women diagnosed with placental abruption. The associations between each lesion and thrombophilia status were assessed based on odds ratio (OR) with 95% confidence interval (CI), derived from fitting multivariable logistic regression models.

In these models, we considered several potential confounders for adjustment. These included hospital and year recruited to the study, maternal age (<25, 25–34 and ≥35 years), parity (parity 0, parity 1, and parity ≥2), maternal education (<12, 12, and ≥13 years of completed schooling), maternal race (Caucasian, African-American, Hispanic or other race/ethnicity), marital status (single or married), smoking during pregnancy (yes or no), and maternal prepregnancy body-mass index. Body-mass index was derived as weight (in kilograms) over squared-height (in inches), and was categorized as <18.5 (underweight), 18.5–24.9 (normal weight), 25.0–29.9 (overweight) and ≥30 (obese). In a separate analysis, both maternal age and BMI were analyzed as continuous variables. Since the results from the latter analysis were similar to those based on categorized maternal age and BMI, we present the former analysis. If inclusion of a confounder in the models changed the unadjusted odds ratio by 10% or more, the confounder was retained for adjustment.

Statistical analysis was performed using SAS (version 9.1; SAS Institute, Cary, NC). All statistical tests were two-tailed, and $P<0.05$ was considered to denote statistical significance.

Results

In the study period from August 2002 to December 2006, there were 196 deliveries complicated by placental abruption that occurred at ≥20 weeks' gestation. The prevalence of

placental abruption in both hospitals combined during the study period was 0.96%. Of these, 135 (68.9%) had completed information on maternal thrombophilia status and placental histology. Among the 135 placental abruption cases, the presence of any thrombophilia was detected in 85 women (63.0%). Table 1 depicts the demographic characteristics of the women included in the study population. There were no significant differences in maternal age, parity, race/ethnicity, maternal education, marital status, smoking status or body mass index.

The comparisons of placental lesions among abruptions with and without a positive maternal thrombophilia screen are presented in Table 2. Meconium-stained membranes (OR 7.7, 95% CI 2.4, 127.8) and decidual necrosis (OR 20.8, 95% CI 3.1, 393.5) were significantly more common when a thrombophilia was present. Acute deciduitis (the presence of acute inflammatory cells within the decidualized basal plate) on the other hand, occurred less commonly when a thrombophilia was present (OR 0.2, 95% CI 0.1, 0.7).

Although not statistically significant, there was a trend towards higher rates of decidual vasculopathy (P=0.069) and placental infarction (P=0.064) among abruption pregnancies with a negative thrombophilia screen. Interestingly, when a placental infarction was present (in 30% of abruptions), the presence of an old infarct was much more common among women with a diagnosed thrombophilia (83.3% versus 44.4%; P=0.003).

Discussion

Placental abruption has been identified to be in the spectrum of ischemic placental disease.[10] An increased incidence of ischemic placental disease has been noted in pregnancies complicated by a maternal thrombophilia. The hypothesized pathophysiology is one of increased clotting in the low-flow placental vasculature, leading to placental infarctions and other histologic lesions consistent with vascular stasis and hypoxia. This association of placental abruption and maternal thrombophilia supports the concept that abruption in this setting is the final clinical presentation of an underlying chronic placental disease process. Our study set out to determine the likelihood of this hypothesis. We found that there was a significant increase in meconium-stained membranes and decidual necrosis when an abruption occurs in the presence of a maternal thrombophilia. The increase in meconium-stained membranes is likely due to fetal distress associated with the changes as a result of the abruption. Such increase in meconium associated with placental abruption have been reported by Nagy et al.[19] Decidual necrosis is a chronic placental lesion often accompanied by a retroplacental hematoma, and was 20 times more likely to be found when a thrombophilia was present. In addition, among the 30% of placental abruption cases with a placental infarction, the presence of an old infarct with or without a recent infarct was significantly more common than the presence of a recent infarct alone. The trend towards higher rates of decidual vasculopathy in abruption cases without a diagnosed thrombophilia may indicate differing pathophysiology of ischemic placenta disease when a thrombophilia is or is not present. Decidual vasculopathy is a well-known finding, for example, among nulliparous preeclamptic pregnancies. In fact, our population of abruptions without a known thrombophilia was more likely to be nulliparous.

The association of placental infarction and thrombophilia status has previously been evaluated. Maternal vascular lesions, in particular multiple villous infarcts, has been shown to be more common in maternal thrombophilia cases.[15,20] The placental pathology of women who experienced an adverse pregnancy outcome (severe preeclampsia, fetal growth restriction, fetal demise or abruption) was compared in those with and without a thrombophilia by Many et al.[13] The presence of a thrombophilia was associated with an increased incidence of both a single villous infarct (72% versus 39%; P<0.01) and multiple

infarcts (44% versus 14%; P<0.05). In another study, placental infarction was the most common lesion found in pregnancies complicated by either preeclampsia, placental abruption, fetal growth restriction or unexplained stillbirth, found in 48% of the study population.[14] Although no differences were identified in the presence of infarctions in women with or without a thrombophilia, only 19 women with an abruption were included and no distinction was made between old and recent infarction.[14]

To the best of our knowledge, this is perhaps the largest series to report the associations between maternal thrombophilia and histologic lesions among pregnancies complicated by placental abruption. Most previous studies have combined multiple adverse pregnancy outcomes (such as placental abruption, preeclampsia, and restricted fetal growth and stillbirth), thereby masking the associations between thrombophilia and placental lesions. The larger study size allowed a more detailed evaluation of placental lesions. Other strengths include the blinding of the two perinatal pathologists to either the abruption or thrombophilia status, and careful adjustments for a variety of potential confounding factors through multivariable modeling. Nonetheless, our findings also warrant some caution in interpretation. Many of the associations reported herein had fairly wide confidence intervals. The New Jersey-Placental Abruption Study was not originally designed to examine these associations.

This study supports the concept that placental abruption is an acute clinical presentation of a chronic disease process. When an abruption occurs in the setting of a known maternal thrombophilia, it is more likely to be associated with decidual necrosis. In addition, when infarctions are found in placental abruption cases, they are more likely to be old infarcts when a maternal thrombophilia screen is positive. This supports the presence of chronic placental lesions in the setting of a maternal thrombophilia. Future studies are needed, however, to determine whether an exact causal link between inherited thrombophilia and adverse pregnancy outcomes exists. Although the current data is not consistent in determining the benefit of thrombo-prophylaxis in women with inherited thrombophilia and poor pregnancy histories,[21] randomized trials evaluating this management strategy should include the risk of recurrent placental abruption.

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APPENDIX

Investigators currently participating or who have been previously involved in the New Jersey—Placental Abruption Study include Cande V. Ananth, PhD, MPH (Principal investigator), Darios Getahun, MD, MPH, Neela Srinivas, MD, MPH, Celeste DeMarco, RN, BSN, Denise Elsasser, MPH, Yu-Ling Lai, RN and Shelby Pitts, RN (Division of Epidemiology and Biostatistics), John C. Smulian, MD, MPH, Wendy L. Kinzler, MD, Morgan R. Peltier, PhD, and Marian Lake, RN, MPH (Division of Maternal-Fetal Medicine), Department of Obstetrics, Gynecology, and Reproductive Sciences; Claire Philipp, MD (Department of Medicine), all at UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ; and George G. Rhoads, MD, MPH (Department of

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Other investigators that were involved with the study included Jacques Genest, MD (McGill University, Montreal, Canada), Susan Shen-Schwarz, MD (Department of Pathology, Saint Peter's University Hospital, New Brunswick, NJ), and Vinay Prasad, MD (Department of Pediatric Pathology, Nationwide Children's Hospital, Ohio State University, Columbus, OH).

Table 1

Distribution of maternal characteristics of women with placental abruption based on the presence and absence of maternal thrombophilia

Maternal characteristics	Thrombophilia present (n=85)		Thrombophilia absent (n=50)		P-value
	n	%	n	%	
Maternal age (years)‡					0.793
<25	16	18.8	10	20.0	
25–34	42	49.4	27	54.0	
≥35	27	31.8	13	26.0	
Parity					0.095
Nulliparous	27	31.8	24	48.0	
Primiparous	37	43.5	13	26.0	
Parity ≥2	21	24.7	13	26.0	
Maternal race/ethnicity					0.586
Caucasian	13	15.3	12	24.0	
African-American	29	34.1	15	30.0	
Hispanic	31	36.5	15	30.0	
Other race/ethnicity	12	14.1	8	16.0	
Education below high school	33	38.8	23	46.0	0.471
Single marital status	25	29.4	10	20.0	0.309
Smoking during pregnancy	11	12.9	7	14.0	0.999
Pre-pregnancy BMI†	25.0 ± 5.7		26.4 ± 7.2		0.282
Chronic hypertension	6	7.1	2	4.0	0.710
Preeclampsia	13	15.3	5	10.0	0.443
Insulin-dependent diabetes	2	2.4	1	2.0	0.999
Placental weight (g)†	409 ± 134		371 ± 159		0.161
Gestational age (weeks)†	33.5 ± 4.6		32.3 ± 5.4		0.209

†Data reported as mean (standard deviation)

BMI, body-mass index; SD, standard deviation

Table 2

Comparison of placental histologic lesions among deliveries complicated by placental abruption in the presence and absence of a maternal thrombophilia

Histologic lesions	Thrombophilia		Adjusted odds ratio (95% CI)	P-value
	Present (%) (n=85)	Absent (%) (n=50)		
Chorioamnionitis (n=46)	35.3	32.0	0.7 (0.2, 2.2)	0.539
Funisitis (n=28)	24.7	14.0	4.1 (1.0, 17.1)	0.055
Acute deciduitis (n=13)	7.1	14.0	0.2 (0.1, 0.7)	0.013
Meconium stained membranes (n=8)	7.1	4.0	7.7 (2.4, 127.8)	0.015
Villous hemorrhage (n=11)	5.9	12.0	0.3 (0.1, 1.5)	0.151
Villous edema (n=13)	9.4	10.0	2.0 (0.4, 9.3)	0.375
Acute villitis (n=3)	2.4	2.0	1.1 (0.1, 20.2)	0.950
Chronic deciduitis (n=39)	23.5	38.0	0.6 (0.2, 1.7)	0.342
Decidual necrosis (n=5)	4.7	2.0	20.8 (3.1, 394)	0.023
Decidual vasculopathy (n=14)‡	8.2	14.0	0.2 (0.03, 1.1)	0.069
Placental infarction (n=42)	28.2	36.0	0.4 (0.2, 1.1)	0.064
Recent infarction (n=14)	16.7	55.6	1.0 (0.3, 3.5)	0.998
Old and/or recent infarction (n=28)	83.3	44.4	15.5 (2.6, 91.3)	0.003
Infarctions <25% (n=30)	62.5	83.3	0.3 (0.1, 0.9)	0.033
Infarctions ≥25% (n=12)	37.5	16.7	1.0 (0.2, 5.2)	0.975
Advanced villous maturation (n=19)	15.3	12.0	2.5 (0.6, 10.7)	0.201
Villous dysmaturity (n=48)	29.4	46.0	0.5 (0.2, 1.3)	0.178
Hemosiderin deposition (n=4)	3.5	2.0	0.9 (0.1, 16.8)	0.923
Perivillous fibrin deposition (n=6)	4.7	4.0	2.5 (0.2, 26.2)	0.444
Intervillous thrombus (n=6)††	4.7	4.0	2.8 (0.2, 37.4)	0.443
Villitis (n=7)	3.5	8.0	0.1 (0.06, 2.1)	0.150

CI, confidence interval

Odds ratios were adjusted for hospital and year recruited to study, maternal age, parity and maternal race, and smoking in addition to every lesion listed in the table

‡Decidual vasculopathy includes muscular thickening and/or atherosis

††Intervillous thrombus includes lesions associated with feto-maternal hemorrhage, and large placentas of diabetes or erythroblastosis