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Low Birthweight in Relation to Placental Abruption and Maternal Thrombophilia Status: A Case-Control Study

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Abstract

Objective: To evaluate whether the association between low birthweight and placental abruption is mediated through preterm birth or restricted fetal growth, and if these associations were influenced by maternal thrombophilia status.

Study design: Data were derived from the New Jersey-Placental Abruption Study, an ongoing, multicenter, case-control study conducted in New Jersey since August 2002. Abruption cases (n=156) were identified based on a clinical diagnosis, and controls (n=170) were matched to cases based on parity and maternal race. Low birthweight (<2500 g) was stratified based on preterm birth (<37 weeks gestation) and small for gestational age (birthweight <10th centile for gestational age). Maternal thrombophilia assessment was based on serum evaluation (Protein C and S deficiency, activated Protein C resistance ratio, and anticardiolipin antibodies) as well as genetic polymorphisms (methylenetetrahydrofolate reductase, prothrombin gene, and Factor V Leiden). Associations were expressed based on odds ratio (OR) with 95% confidence interval (CI).

Results: Among abruption cases, 60.3% (n=94) were low birthweight in comparison to 11.2% (n=19) of controls (OR 13.7, 95% CI 7.4, 25.2). Furthermore, placental abruption had a significantly increased association with preterm birth in both SGA (OR 17.4, 95% CI 4.6, 64.9) and appropriately grown fetuses (OR 15.8, 95% CI 8.4, 29.8). However, the association between abruption and low birthweight were similar between women with and without thrombophilia.

Conclusion: The association between placental abruption and low birthweight is chiefly mediated through preterm birth, and this association does not appear to be modified by maternal thrombophilia status.

Keywords

Placental abruption; fetal growth restriction; preterm birth; maternal thrombophilia

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Placental abruption is a major cause of perinatal morbidity and mortality, with mortality rates ranging between 2% and 67%, depending on factors such as the gestational age, fetal weight and degree of premature placental separation.¹ Several studies have reported that placental abruption is associated with low birthweight, preterm birth and intrauterine growth restriction.²⁻⁴ However, low birthweight, itself, is a heterogeneous pregnancy endpoint and may be the result of preterm birth or fetal growth restriction.⁵

Placental abruption has been associated with vascular placental or decidual lesions.⁶ These pathologic features have also been characterized in women with thrombophilia and placental abruption, again, by an increased rate of vascular lesions.⁷ The relationship between maternal thrombophilia and vascular underperfusion remains poorly defined. It has been hypothesized that complete thrombotic occlusion of an abnormally remodeled spiral artery may result in an overlying villous infarct, consistent with maternal underperfusion.⁸ If such an artery undergoes ischemia followed by reperfusion, rupture can occur leading to acute retroplacental hemorrhage and will clinically manifest as placental abruption.⁹ This proposed mechanism of maternal vascular underperfusion might be driven by the presence of a heritable thrombophilia, which may lead to placental abruption and fetal growth restriction.

We conducted a secondary analysis utilizing data from a large case-control study of placental abruption to examine if the association between low birthweight and placental abruption was mediated through preterm birth or fetal growth restriction. More precisely, we aimed to evaluate the extent of the association with preterm birth and restricted fetal growth. In addition, we further examined whether these associations were modified based on maternal thrombophilia status.

Materials and Methods

The New Jersey-Placental Abruption Study (NJ-PAS) is an ongoing, matched case-control study conducted at two hospitals in New Brunswick, New Jersey, since August 2002. Both Robert Wood Johnson University Hospital and Saint Peter's University Hospital are tertiary, level III, regional perinatal centers. The original study was undertaken to evaluate the association of maternal thrombophilia status and placental abruption. Each study participant was administered a structured in-person interview to elicit details regarding maternal and paternal demographic characteristics, lifestyle, and behavioral and general health conditions. In addition, each participant gave consent to abstract the medical and prenatal care records from the index and all previous pregnancies and outcomes.

Placental abruption cases were identified, with gestational age ≥ 20 weeks based on clinical criteria which comprised of painful vaginal bleeding or hemorrhage, uterine pain or tenderness, uterine hypertonicity, retroplacental clot or hematoma on the placental surface or based on prenatal sonographic diagnosis.¹⁰ Control patients were women that delivered at ≥ 20 weeks' gestation and had no evidence of abruption and were matched to cases based on maternal race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic or other) and parity (0, 1, ≥ 2). Women with placenta previa in the present pregnancy or with a history of abruption were excluded from the control pool. Abruption cases were enrolled during the delivery hospitalization after informed consent and were matched to controls. Controls were enrolled on an ongoing basis following the recruitment of a case. Further detail of the NJ-PAS is described elsewhere.¹¹

Low birthweight was defined as live born infants that weight below 2,500 g, and was stratified as following shortened gestation (i.e., preterm birth defined as delivery between 20 and 36 weeks gestation), or restricted fetal growth (i.e., small for gestational age infants identified as those with birthweight $< 10^{\text{th}}$ centile of for-gestational age based on the criteria of Alexander

et al.¹²) The thrombophilia assessment was performed at the time of recruitment and included an assessment of serum (Protein C and S deficiency, activated Protein C resistance ratio, and anticardiolipin antibodies) as well as genetic polymorphisms (Prothrombin gene, Factor V Leiden, and methylenetetrahydrofolate reductase).

Other factors that were considered to potentially influence the risk of abruption included maternal age (<20, 20-24, 25-29, 30-34, and ≥ 35 years), maternal education (<12 vs. ≥ 12 years of completed schooling), marital status (married or unmarried), prenatal care (initiated in the first 2 trimesters or late initiation/no care), maternal smoking (yes or no), and cocaine use (yes or no). Cocaine and tobacco use was based on maternal self-report, or was abstracted from the medical record.

Ethics approval was received from the institutional review boards of both hospitals, as well as by the Institutional Review Board of UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ.

Statistical analysis

Distributions of maternal sociodemographic and behavioral characteristics were examined according to preterm birth status for both cases and controls. Fisher's exact test was used to evaluate the associations between placental abruption and low birthweight. Categorical variables were compared using the Chi-square test.

The association between placental abruption and low birthweight was quantified based on odds ratio with 95% confidence interval, and these analyses were further stratified based on preterm birth and small for gestational age status. These odds ratios were adjusted for potential confounders through multivariate logistic regression models. These models were adjusted for race, marital status, parity, education, and smoking status. Finally to evaluate the strength of association between abruption and low birthweight differed based on maternal thrombophilia status, stratum-specific odds ratios (by the presence and absence of thrombophilia status) were compared using the Breslow-Day test (in the crude analysis) and by a Wald Chi-square test for interaction (between abruption and thrombophilia) in the regression model. All statistical analyses were performed with the use of SAS version 9.1 (SAS Institute, Cary, NC).

Results

Differences in maternal sociodemographic and behavioral characteristics were compared based on low birthweight status (Table 1). Significant differences between the groups included parity, with LBW associated with nulliparity. Low birthweight births were more likely to be associated with preeclampsia, earlier gestational age at delivery, and placental abruption. The demographic characteristics for abruption cases and controls have been described previously.¹¹

The rates of low birthweight among abruption cases and controls were 60.3% and 11.2%, respectively (Table 2). This strong association between placental abruption and low birthweight was largely mediated through preterm birth (OR 14.8, 95% CI 8.3, 26.7) rather than through small for gestational age (OR 1.3, 95% CI 0.7, 2.6). The distribution of the frequency of maternal thrombophilia was similar between abruption cases and controls (OR 0.9, 95% CI 0.6, 1.4). Preterm birth was more common in abruption cases among both small for gestational age (OR 15.8, 95% CI 8.4, 29.8) and among births with appropriately grown infants (OR 17.4, 95% CI 4.6, 64.9).

To evaluate the contribution of maternal thrombophilia status on the associations between placental abruption and low birthweight, we further stratified our findings based on

thrombophilia status (Table 3). For this analysis, the following thrombophilias and genetic polymorphisms were identified in cases and controls: Protein C deficiency (cases=6; controls=15) and S deficiency (cases=0; controls=0), activated Protein C resistance ratio (cases=63; controls=69), and anticardiolipin antibodies (cases=1; controls=7); methylenetetrahydrofolate reductase (homozygous cases=19; controls=26; heterozygous cases=56; controls=61), Prothrombin gene (heterozygous cases=3; controls=2), and Factor V Leiden (heterozygous cases=1; controls=2). Although the association between abruption and preterm, small for gestational age was not different based on maternal thrombophilia status ($P=0.551$), the association between abruption and preterm, small for gestational age birth was particularly striking (OR 29.6, 95% CI 3.1, 277.5).

Comment

Our findings clarify the etiology of low birthweight in relation to placental abruption, with the association largely stemming from shortened gestation (preterm birth). This contradicts other studies which have placed small for gestational age in the causal pathway that leads to abruption, with a roughly three-fold increased risk of abruption associated with small for gestational age.² In fact, we found no association between abruption and small for gestational age births. Moreover, thrombophilia status does not clearly influence this association, but shows a remarkable trend for small for gestational age births at preterm gestations.

Our results indicate that preterm birth is the intermediary between placental abruption and low birthweight. Since placental vasculopathy has been implicated as a likely mechanism in the pathway that leads to placental abruption, we attempted to evaluate the interaction of thrombophilia and its association with growth restriction and preterm birth. Because this was a secondary analysis, our findings may not have been sufficiently powered to make any definitive conclusions regarding thrombophilia status, as evidenced by a post-hoc power analysis ($P=0.74$).

We were particularly interested in defining the magnitude of the association between abruption and low birthweight, and whether the presence of a thrombophilia would influence this association. It has been shown that a history of placental dysfunction, identified by previous small for gestational age or preterm birth, is associated with an increased risk of placental abruption.¹³ Similarly, a pregnancy following placental abruption has an increased risk of recurrence, with an excess risk of small for gestational age, preterm birth.¹⁴ Placentas of thrombophilic women have been characterized by an increased rate of vascular damage, multiple infarcts and fibrinoid necrosis.⁷

Several thrombophilic mutations have been identified in women with serious complications of pregnancy, including abruption placenta and fetal growth restriction as well as severe preeclampsia and stillbirth.^{11, 15-19} Recent studies indicate that several thrombophilias such as activated protein C resistance and the associated Factor V Leiden mutation, Prothrombin gene mutation, MTHFR have a high prevalence in women with placental abruption.^{16, 17, 20} Facchinetti and colleagues¹⁸ reported an association between Factor V Leiden mutation (9.1-fold) and the Prothrombin gene mutation (12.3-fold). A similar finding was reached in a systematic review, with heterozygous Factor V Leiden mutation and heterozygous Prothrombin gene mutation, respectively conferring an overall 4.7-fold and 7.7-fold increased risk for abruption.¹⁹

Besides placental changes related to thrombophilia, there is considerable evidence that indicates that abnormalities in trophoblast invasion, are associated with preterm birth and uteroplacental diseases such as preeclampsia and intrauterine growth restriction.²¹ Decreased serum levels of pro-angiogenic factor placental growth factor (PIGF) and increased anti-

angiogenic soluble fms-like tyrosine kinase 1 (sFlt-1) leading to an increased sFlt-1/PlGF ratio have been associated with IUGR and the development of preeclampsia, as a result of abnormal trophoblast invasion.^{22, 23}

Signore and colleagues²⁴ found that women who developed placental abruption had lower PlGF and higher sFlt-1 concentrations and higher sFlt-1/PlGF ratios. In addition, the angiotensinogen Thr235 mutation, which is associated with abnormal remodeling of the spiral arteries, has been observed more frequently in placental abruption.²⁵ Both of these findings present another mediator by which angiogenic and anti-angiogenic factors may lead to the pathologic changes that result in placental vascular underperfusion, and potentially leading to placental abruption.

In our study, we were able to better define the associations among placental abruption, low birthweight, preterm birth and thrombophilia status. Our study has several strengths, which are the result of our study design. Because our original study was undertaken to evaluate the association of maternal thrombophilia status and risk of placental abruption, we had extensive information on thrombophilia status. In addition, the data came from a well-designed, matched case-control study, with every abruption case being clinically confirmed.

Despite these strengths, a few limitations of this study remain. Our main limitation was that there was insufficient power to detect differences in the thrombophilia analysis. Although the presence of thrombophilia appears to be associated with a greater risk of preterm small for gestational age births, in relation to abruption, we are limited by the data in this secondary analysis. In general, our population was diverse, but heritable thrombophilias are known to be more prevalent in the Caucasian population, whereas this sample included only a minority of Caucasians (16.3%), and a preponderance of Hispanics (31.6%) and African-Americans (36.8%). It would be important to have a better knowledge of the background prevalence of these polymorphisms in our population to make conclusions, which can be generalized to other populations. Furthermore, our study population was recruited from 2 high-risk tertiary referral centers, which may not be representative of a normal obstetric population with respect to risk for preterm birth, low birthweight, and the presence of a thrombophilia and other ischemic placental diseases.

In conclusion, our findings clarify the association between low birthweight and placental abruption, with preterm birth identified as the intermediary. This is extremely relevant, as other studies have identified fetal growth restriction in the causal pathway that leads to abruption. With respect to the impact of thrombophilia and placental abruption, future studies are needed in order to address the interaction of thrombophilias and other angiogenic and anti-angiogenic factors in the development of placental abruption.

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APPENDIX

Investigators currently participating or who have participated 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, Marian Lake,

RN, MPH (Division of Maternal-Fetal Medicine), all in the Department of Obstetrics, Gynecology, and Reproductive Sciences, UMDNJ-Robert Wood Johnson Medical School; Claire Philipp, MD (Department of Medicine), UMDNJ-Robert Wood Johnson Medical School; and George G. Rhoads, MD, MPH (Department of Epidemiology) and Dirk F. Moore, PhD (Department of Biostatistics) at UMDNJ-School of Public Health.

Other investigators that were involved with the study included Rima Rozen, PhD and 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, Arkansas Children's Hospital, University of Arkansas Medical Sciences, Little Rock, AR)

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Table 1

Clinical and demographic characteristics of women that delivered a low birthweight and appropriate-for-gestational age infants

	Low birthweight % (n=113)	Normal birthweight % (n=213)	P value
Maternal age (years)			0.092
< 20	2.7	1.9	
20-24	21.2	16.0	
25-34	54.0	52.4	
≥35	22.1	29.7	
Maternal race/ethnicity			0.294
Caucasian	22.1	13.2	
African-American	29.2	40.6	
Hispanic	36.3	28.8	
Others	12.4	17.4	
Parity			0.045
Para 0	42.5	31.6	
Para 1	34.5	37.7	
Para 2+	23.0	30.7	
Gestational age (weeks)	30.6 ± 4.3	38.3 ± 1.9	<0.001
Single marital status	62.0	74.1	0.024
Education below high school	53.1	67.0	0.014
Smoking during pregnancy	9.7	5.7	0.173
Prepregnancy BMI	25.2 ± 5.2	24.7 ± 5.4	0.483
Preeclampsia	13.3	4.2	0.003
Placental abruption	83.2	28.6	<0.001

Table 2

Birthweight characteristics, including preterm birth status and thrombophilia status for cases and controls

	Cases % (n=156)	Controls % (n=170)	Unadjusted OR (95% CI)	Adjusted OR [†] (95% CI)
Low birthweight	60.3 (93)	11.2 (19)	12.3 (6.9, 21.9)	13.7 (7.4, 25.2)
SGA	15.4 (24)	11.2 (19)	1.5 (0.8, 2.8)	1.3 (0.7, 2.6)
Preterm birth	67.3 (104)	14.1 (24)	12.9 (7.4, 22.2)	14.8 (8.3, 26.7)
Thrombophilia	43.0 (67)	45.9 (78)	0.9 (0.6, 1.3)	0.9 (0.6, 1.4)
Term, AGA	27.6 (43)	76.9 (145)	1.0 (Reference)	1.0 (reference)
Term, SGA	5.1 (8)	8.9 (15)	1.6 (0.6, 4.1)	1.7 (0.6, 4.3)
Preterm, AGA	57.1 (89)	12.4 (21)	12.8 (7.1, 23.1)	15.8 (8.4, 29.8)
Preterm, SGA	10.3 (16)	1.8 (3)	16.1 (4.5, 58.0)	17.4 (4.6, 64.9)

OR, odds ratio; CI, confidence interval; SGA, small for gestational age; AGA, appropriate-for-gestational age

[†] Odds ratios were adjusted for race, parity, marital status, parity, education, and smoking status

Table 3
Associations between placental abruption and low birthweight stratified on thrombophilia status

	Unadjusted odds ratio (95% CI)		P-val [†]	Adjusted odds ratio (95% CI) ^{††}		P-val [†]
	Thrombophilia (+)	Thrombophilia (–)		Thrombophilia (+)	Thrombophilia (–)	
LBW	8.4 (3.6, 19.5)	15.9 (7.2, 35.1)	0.275	12.1 (4.5, 32.0)	20.0 (8.4, 47.6)	0.247
Term, AGA	1.0 (reference)	1.0 (reference)	—	1.0 (reference)	1.0 (reference)	—
Term, SGA	0.9 (0.2, 4.9)	2.2 (0.7, 6.9)	0.565	0.9 (0.1, 8.6)	2.8 (0.8, 9.8)	0.447
Preterm, AGA	9.4 (4.0, 22.2)	16.4 (7.3, 37.0)	0.356	12.5 (4.7, 33.1)	25.4 (9.7, 66.6)	0.278
Preterm, SGA	25.0 (3.0, 208.5)	11.5 (2.2, 59.6)	0.400	29.6 (3.1, 277.5)	12.1 (2.1, 70.1)	0.551

[†] P-value denotes significance testing for differences in odds ratios

^{††} Odds ratios were adjusted for race, parity, marital status, parity, education, and smoking status