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Original Contribution

Neonatal Outcomes Associated With Placental Abruption

Katheryne L. Downes*, Edmond D. Shenassa, and Katherine L. Grantz

* Correspondence to Dr. Katheryne L. Downes, Maternal and Child Health Research Center, Department of Obstetrics and Gynecology, Perelman School of Medicine, University of Pennsylvania, 421 Curie Boulevard, 1351 BRB II/III, Philadelphia, PA 19104 (e-mail: katheryne.downes@gmail.com).

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Placental abruption (early separation of the placenta) is associated with preterm birth and perinatal mortality, but associations with other neonatal morbidities remain understudied. We examined the association between abruption and newborn outcomes. We analyzed 223,341 singleton deliveries from the Consortium on Safe Labor study, a retrospective, multisite, observational study (2002–2008) of electronic medical records in the United States. Adjusted relative risks, incidence rate ratios, and 99% confidence intervals were estimated. Direct effects attributable to abruption were examined by conditioning on intermediates (preterm birth and small for gestational age) with sensitivity analyses. Incidence of abruption was 1.6% (n = 3,619). Abruption was associated with an elevated risk of newborn resuscitation (relative risk (RR) = 1.5, 99% confidence interval (CI): 1.5, 1.6), apnea (RR = 5.8, 99% CI: 5.1, 6.5), asphyxia (RR = 8.5, 99% CI: 5.7, 11.3), respiratory distress syndrome (RR = 6.5, 99% CI: 5.9, 7.1), neonatal intensive care unit admission (RR = 3.4, 99% CI: 3.2, 3.6), longer intensive care length of stay (incidence rate ratio = 2.0, 99% CI: 1.9, 2.2), stillbirth (RR = 6.3, 99% CI: 4.7, 7.9), and neonatal mortality (RR = 7.6, 99% CI: 5.2, 10.1). In sensitivity analyses, there was a direct effect of abruption associated with increased neonatal risks. These findings expand our knowledge of the association between abruption and perinatal and neonatal outcomes.

abruption; apnea; neonatal morbidity; perinatal mortality; respiratory distress syndrome

Abbreviations: CI, confidence interval; LOS, length of stay; NICU, neonatal intensive care unit; SGA, small for gestational age.

Placental abruption, defined as the premature detachment of the placenta from the uterine wall, before birth and after 20 weeks' gestation, occurs in 0.6%–1% of all pregnancies in the United States (1, 2). The disorder is characterized by placental dysfunction which, with progression, can result in a decrease in the surface area available for oxygen exchange and nutrient supply to the fetus (3, 4). Abruption is well-established as a risk factor for growth restriction (5–11), prematurity (6–9, 11–15), and perinatal mortality (1, 11–13, 16–20). However, other adverse neonatal outcomes associated with hypoxia and prematurity—such as asphyxia, respiratory distress syndrome, and apnea—remain understudied. Furthermore, for neonates who survive the delivery, little is known about the extent of medical interventions used, such as admission to the neonatal intensive care unit (NICU), NICU length of stay (LOS), or newborn resuscitation in the delivery room. Finally, it is unclear how much of the risk of neonatal morbidity associated with abruption is attributable to preterm birth or being small for gestational age (SGA).

We examined the association between placental abruption and neonatal interventions, morbidities, and perinatal mortality and conducted sensitivity analyses to examine the role of prematurity and SGA in these relationships.

METHODS

Study population

This study used data from the Consortium on Safe Labor study (*Eunice Kennedy Shriver* National Institute of Child Health and Human Development) (21, 22). This retrospective, observational study includes electronic medical record data from 12 clinical centers containing 19 hospitals. In total, data on 228,438 deliveries occurring from 2002–2008 were collected

for the study, with 9.5% of women contributing more than 1 birth during the specified time period. All deliveries occurring at 23 weeks of gestation or later with the required electronic medical record data were included in the original study. We excluded multiple gestation pregnancies ($n = 5{,}044$), as they were likely to have a different risk profile for abruption (23), and women who were missing more than half of the specified covariates ($n = 53$), because the reliability of the imputed values would be questionable. After exclusions, 223,341 singleton delivery records remained for analysis. Analysis of resuscitation, NICU admission, respiratory distress syndrome, apnea, asphyxia, and neonatal death was restricted to live births ($n = 222{,}047$). Institutional review board approval was originally obtained from all participating institutions, and the present analysis received an exemption from the University of Maryland Institutional Review Board.

Abruption identification

A clinical diagnosis of placental abruption was abstracted from the prenatal history, labor, delivery, and discharge codes (*International Classification of Diseases*, *Ninth Revision*) portions of the electronic medical record. A patient was considered to have an abruption if there was a recorded diagnosis of antepartum or intrapartum abruption, abruption was recorded as the indication for cesarean delivery, or there was a discharge code for abruption.

Mediator and outcome definitions

For the mediation analysis described below, preterm birth was defined as delivery at <37 weeks of gestation, and SGA was defined as a birth weight below the tenth percentile for gestational age and fetal sex (24). Newborn resuscitation, NICU admission, NICU LOS, respiratory distress syndrome, apnea, asphyxia, antepartum or intrapartum stillbirth, and neonatal deaths (≤28 days of life) were all abstracted from electronic medical records (detailed description of methods previously published) (22). Because some overlap between outcomes is likely, a composite variable was also created to capture overall risk of having at least 1 of the specified outcomes.

Statistical analysis

Because approximately 10% of the women included in the study had more than 1 birth recorded during the study period, generalized estimating equation models were fitted to estimate the risk of all the outcomes of interest, while accounting for these instances of repeated observations. An exchangeable within-subject correlation structure was specified. A modified Poisson approach with a robust error variance estimator was fitted to estimate relative risk and 99% confidence intervals for all categorical neonatal outcomes (25). A negative binomial model was fitted to estimate incidence rate ratios and 99% confidence intervals for NICU LOS (26, 27). The incidence rate ratio for NICU LOS is interpreted as a relative increase in the rate (i.e., incidence rate ratio = 2.0 would be interpreted as the exposed group having a rate of NICU LOS that was twice as long as the unexposed group—2 days for every 1 day in the unexposed group). All models adjusted for maternal age, race/ethnicity, parity, prepregnancy body mass index, maternal comorbidities (chronic hypertension, gestational hypertension, preeclampsia, pregestational diabetes, and gestational diabetes), insurance, marital status, smoking, alcohol use, drug use, and study site. We imputed missing covariates using fully conditional specification, multiple imputation methods with SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina), using PROC MI and MIANALYZE. A total of 25 imputations were performed; the amount of missing data for the covariates that were imputed was as follows: maternal age (0.1%), race/ethnicity (4.1%), prepregnancy body mass index (33.6%), insurance status (10.4%), marital status (3.2%), and drug use (9.9%).

Preterm birth and fetal growth restriction are important risk factors for many poor neonatal outcomes (28–31); however, it is possible that these variables are on the causal pathway and serve as intermediates between abruption and the specified neonatal outcomes (Figure 1). Controlling for these types of variables can lead to inaccurate risk estimates if there is unmeasured confounding between the intermediate and the outcome, creating a collider bias. To estimate the direct effect of abruption independent of preterm birth and fetal growth restriction, we performed a sensitivity analysis conditioning on these intermediates, although using SGA as a proxy for fetal growth restriction (32). This approach was used to estimate direct effects, assess the potential impact of unmeasured confounding, and yield a range of bias-corrected risk estimates for individuals with preterm birth and SGA (32). For each variable, analyses are presented within each stratum, and sensitivity analyses were reported examining the impact of potential bias when the mediator was present (e.g., preterm/SGA). The analyses for this study were conducted using SAS software, version 9.4 (SAS Institute).

RESULTS

The incidence of placental abruption was 1.6% ($n = 3{,}619$ cases). Sample characteristics according to abruption group are presented in Table 1. Compared with women who had not had an abruption, women who had had an abruption were less likely to be white (46.6%), and more likely to be single (48.7%), be multiparous (64.3%), have public insurance (48.4%), and have a history of cesarean delivery if multiparous (26.2%). Neonates in pregnancies complicated by abruption weighed 695 grams less and were delivered 3 weeks earlier.

Descriptive statistics and results from adjusted regression analyses of the neonatal outcomes appear in Table 2. Overall, abruption was associated with a 1.9-fold risk of having at least 1 poor outcome, although risk estimates varied considerably according to outcome. Compared with neonates in pregnancies not complicated by abruption, the neonates in pregnancies complicated by abruption were more likely to need resuscitation in the delivery room (relative risk = 1.5, 99% confidence interval (CI): 1.5, 1.6) and to be admitted to the NICU (relative risk = 3.4, 99% CI: 3.2, 3.6). Among the neonates admitted to the NICU, abruption was also associated with a LOS nearly twice as long (incidence rate ratio = 2.0, 99% CI: 1.9, 2.2). Abruption was also associated with a 6.5-fold elevated risk of respiratory distress syndrome, 5.8-fold risk of apnea, 8.5-fold risk of asphyxia, 6.3-fold risk of stillbirth, and a 7.6-fold risk of neonatal mortality.

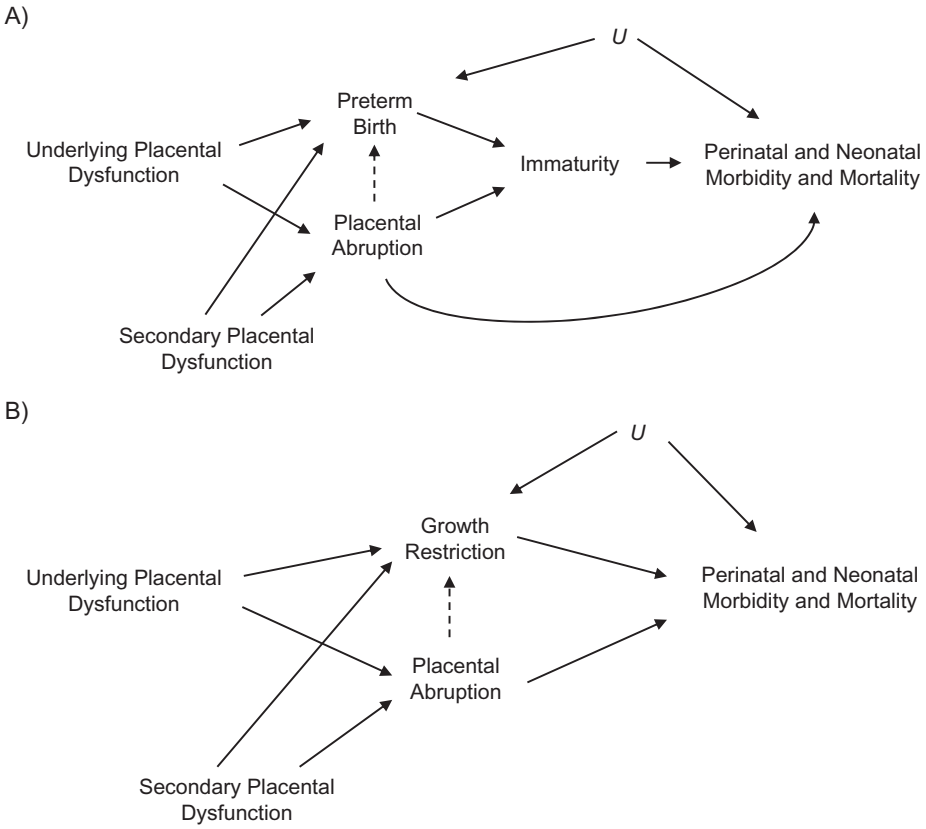

Figure 1. Directed acyclic graphs illustrating theoretical relationships between placental abruption, preterm birth, growth restriction, and perinatal and neonatal morbidity and mortality. Underlying placental dysfunction due to inadequate trophoblast invasion, inflammation, and/or abnormal remodeling of the spiral arteries could lead to placental abruption, preterm birth, and growth restriction. Potential direct, indirect (dashed line), and independent relationships are shown for preterm birth (A) and growth restriction (B). Both scenarios could be affected by secondary placental dysfunction resulting from maternal factors, such as smoking or chronic hypertension, as well possible unmeasured confounders (*U*).

To determine whether there was a direct effect attributed to abruption, beyond the risks associated with preterm birth and SGA as a proxy for fetal growth restriction, we conditioned on these intermediates with sensitivity analyses (32). For each variable, we have presented descriptive statistics and adjusted regression analyses of the neonatal outcomes within each stratum (Tables 3–4). Overall, when examining the stratified estimates, we did not observe any illogical protective effects associated with risk exposure, but there were some differences in magnitude of association. However, application of the correction factor resulted in only slight shifts in magnitude of association (Web Tables 1 and 2, available at https://academic.oup.com/aje), which would suggest the absence of substantial collider bias. The risk estimates within the term and non-SGA strata represent the natural direct effects for abruption and risk of neonatal morbidity. With the exception of NICU LOS among term deliveries, all other outcomes remained significant among the respective strata: term and preterm, SGA and non-SGA.

DISCUSSION

Among a large, population-based sample of US women, we found an association between placental abruption and elevated risk of neonatal asphyxia, respiratory distress syndrome, and perinatal mortality beyond what can be attributed to preterm birth or SGA. Additionally, abruption was associated with a greater need for neonatal resuscitation in the delivery room, NICU admission, and longer NICU LOS. Finally, abruption was also associated with elevated risk of apnea. Of particular note, the estimated risk of all neonatal outcomes remained elevated in the term group and the non-SGA group, which suggests that placental abruption had a direct negative effect on neonatal health and that there were additional risks for the neonate, such as apnea, that have not, to our knowledge, been previously documented.

Strengths and limitations of this study

Among the strengths of this study is that it was based on a large, demographically diverse, population-based, contemporary cohort with detailed clinical information that enabled adjustment for multiple confounders. Our study expanded knowledge of the occurrence of neonatal outcomes associated with abruption in multiple ways. Our sample, which included 3,619 cases of abruption, allowed estimation of infrequently reported outcomes, including neonatal delivery-room resuscitation,

NICU admission, and LOS, as well as asphyxia, apnea, and respiratory distress syndrome. Furthermore, we examined the direct effects of abruption, which furthers understanding of the associated risk beyond the mediators of preterm delivery and SGA.

The association between abruption and delivery-room resuscitation, NICU admission, and longer LOS in the NICU is in accord with extant research; however, the few previous reports are based on samples with fewer than 250 cases and primarily from single sites (9, 19, 33–35). A major strength of our study was the ability to report the incidence of rare outcomes in a large, multisite US cohort. Furthermore, confirmation of a previous report of elevated risk of respiratory distress syndrome among term deliveries (36), coupled with the novel finding of a 5.8-fold increased risk of apnea, suggests that abruption may be associated with a negative impact on the neonate that is not well recognized. Neonatal respiratory distress syndrome and neonatal apnea are both primarily associated with underdevelopment due to preterm birth (37, 38). In pregnancies complicated by abruption, it is possible that neonates experience chronic hypoxia that leads to underdevelopment even in the absence of prematurity. Hypoxia may also explain the elevated risk of poor outcomes even among term neonates. Early delivery may shorten

Table 1. Maternal, Pregnancy, and Neonatal Sample Characteristics According to Placental Abruption Exposure, Consortium on Safe Labor Study, United States, 2002–2008

	No Abruption (n = 219,722)		Abruption (n = 3,619)		P
	No.	%	No.	%	
Maternal age, years[a]	28 (6)		28 (6)		0.89
Maternal race/ethnicity					<0.001
White	114,283	52.0	1,688	46.6	
Black	51,190	23.3	1,171	32.4	
Hispanic	39,573	18.0	583	16.1	
Asian	9,324	4.2	109	3.0	
Multiple/other	5,352	2.4	68	1.9	
Prepregnancy BMI[b,c]	24.3 (21.1–28.9)		24.5 (21.1–29.3)		0.07
Comorbidity					
Chronic hypertension	4,242	1.9	120	3.3	<0.001
Gestational hypertension	5,991	2.7	87	2.4	0.24
Preeclampsia/eclampsia	12,282	5.6	395	10.9	<0.001
Pregestational diabetes	3,205	1.5	104	2.9	<0.001
Gestational diabetes	11,179	5.1	162	4.5	0.10
Smoking during pregnancy	14,457	6.6	468	12.9	<0.001
Alcohol use during pregnancy	3,955	1.8	134	3.7	<0.001
Drug use during pregnancy	4,614	2.1	266	7.4	<0.001
Insurance					<0.001
Private	136,857	62.3	1,805	49.9	
Public	79,050	36.0	1,751	48.4	
Self-pay/other	3,815	1.7	63	1.7	
Single marital status	86,302	39.3	1,764	48.7	<0.001
Nulliparous	87,722	39.9	1,293	35.7	<0.001
History of cesarean delivery[d]	30,879	23.4	610	26.2	<0.001
Cervical dilation at first exam, cm[c]	3 (2–4)		3 (1–4)		<0.001
Induction of labor	76,197	34.7	939	25.9	<0.001
Birth weight, g[c]	3,295 (2,970–3,619)		2,600 (1,710–3,185)		<0.001
Birth weight <2,500 g	17,151	7.8	1,663	45.9	<0.001
Small for gestational age	24,187	11.0	565	15.6	<0.001
Gestational age, weeks[c]	39 (38–40)		36 (32–38)		<0.001
Gestational age <37 weeks	24,192	11.0	1,931	53.4	<0.001

Abbreviation: BMI, body mass index.
[a] Data are given as mean values (standard deviations).
[b] BMI was calculated as weight (kg)/height (m)^2.
[c] Data are given as median values (interquartile ranges).
[d] Among multiparous women only.

Table 2. Adjusted Relative Risk for Neonatal Outcomes According to Presence or Absence of Placental Abruption, Consortium on Safe Labor Study, 2002–2008

Neonatal Outcome	No Abruption (n = 219,722)		Abruption (n = 3,619)		RR	99% CI[a]
	No.	%	No.	%		
Composite perinatal-neonatal outcome[b]					1.9	1.8, 2.0
No	152,234	69.3	1,195	33.0		
Yes	67,488	30.7	2,424	67.0		
Newborn resuscitation[c]					1.5	1.5, 1.6
No	168,614	77.1	2,084	59.8		
Yes	49,948	22.9	1,401	40.2		
NICU admission[c]					3.4	3.2, 3.6
No	193,186	88.4	1,796	51.5		
Yes	25,376	11.6	1,689	48.5		
NICU LOS, days[c,d]	7 (3–17)		20 (7–48)		2.0[e]	1.9, 2.2[e]
Respiratory distress syndrome[c]					6.5	5.9, 7.1
No	212,145	97.1	2,599	74.6		
Yes	6,417	2.9	886	25.4		
Apnea[c,f]					5.8	5.1, 6.5
No	193,982	97.9	2,854	84.9		
Yes	4,180	2.1	507	15.1		
Asphyxia[c]					8.5	5.7, 11.3
No	218,051	99.8	3,408	97.8		
Yes	511	0.2	77	2.2		
Antepartum or intrapartum stillbirth					6.3	4.7, 7.9
No	218,562	99.5	3,485	96.3		
Yes	1,160	0.5	134	3.7		
Neonatal mortality ≤28 days[c]					7.6	5.2, 10.1
No	217,932	99.7	3,395	97.4		
Yes	630	0.3	90	2.6		

Abbreviations: CI, confidence interval; LOS, length of stay; NICU, neonatal intensive care unit; RR, relative risk.

[a] Relative risk estimated with modified Poisson model adjusting for maternal age, race/ethnicity, parity, prepregnancy body mass index, maternal comorbidities (chronic hypertension, gestational hypertension, preeclampsia, pregestational diabetes, and gestational diabetes), insurance, marital status, smoking status, alcohol use, drug use, and study site. All models were significant at $P < 0.001$.

[b] Composite outcome included resuscitation, NICU admission, respiratory distress syndrome, apnea, asphyxia, stillbirth, and neonatal mortality.

[c] Excluding antepartum and intrapartum stillbirths.

[d] Data are given as median values (interquartile ranges) among those admitted to NICU; excludes sites 4 and 8, which did not report NICU LOS.

[e] Incidence rate ratio estimated with negative binomial model.

[f] Excluding site 6, which did not report neonatal apnea.

the duration of hypoxic conditions among preterm neonates and thereby allow better outcomes. It is also possible that abruptions associated with term delivery are distinct disorders from abruptions that trigger preterm delivery.

Analytically, it is important to acknowledge that our choice of method to examine "direct effects" attributed to abruption, by performing stratified analyses, assumed that there was no interaction between gestational age and abruption or SGA and abruption. Our choice of methodology also assumed that there was no uncontrolled confounding of the mediator-outcome association. To address this second issue, we performed sensitivity analyses, which suggested low likelihood of significant confounding effects. However, that possibility cannot be ruled out.

Another limitation of our study was that gestational age at diagnosis of antepartum abruption was not available, so we were unable to determine elapsed time between the abruption and delivery. Gestational timing of the abruption is likely an important determinant of the impact on the neonate. The severity of the abruption (either through percentage detachment or pathological examination) was also unavailable to us. This

Table 3. Adjusted Relative Risk for Neonatal Outcomes According to Presence or Absence of Placental Abruption, Conditioned on Gestational Age at Delivery, Consortium on Safe Labor Study, 2002–2008[a]

Neonatal Outcome	Term, ≥37 Weeks (n = 197,218)						Preterm, <37 Weeks (n = 26,123)					
	No Abruption		Abruption		RR	99% CI[b]	No Abruption		Abruption		RR	99% CI[b]
	No.	%	No.	%			No.	%	No.	%		
Composite perinatal-neonatal outcome[c]					1.4	1.3, 1.5					1.3	1.3, 1.4
No	143,412	73.4	939	55.6			8,822	36.5	256	13.3		
Yes	52,118	26.6	749	44.4			15,370	63.5	1,675	86.7		
Newborn resuscitation[d]					1.3	1.3, 1.4					1.3	1.2, 1.4
No	152,757	78.3	1,070	64.5			15,857	67.6	1,014	55.5		
Yes	42,349	21.7	589	35.5			7,599	32.4	812	44.5		
NICU admission[d]					1.9	1.6, 2.2					1.5	1.5, 1.6
No	181,549	93.0	1,412	85.1			11,637	49.6	384	21.0		
Yes	13,557	7.0	247	14.9			11,819	50.4	1,442	79.0		
NICU LOS, days[d,e]	3 (2–7)		4 (2–7)		1.0[f]	0.7, 1.2[f]	15 (6–34)		26 (10–52)		1.4[f]	1.3, 1.5[f]
Respiratory distress syndrome[d]					3.3	2.0, 4.6					2.1	1.9, 2.2
No	193,886	99.4	1,615	97.4			18,259	77.8	984	53.9		
Yes	1,220	0.6	44	2.6			5,197	22.2	842	46.1		
Apnea[d,g]					2.6	1.2, 4.1					1.9	1.7, 2.1
No	175,089	99.5	1,578	98.5			18,893	85.0	1,276	72.5		
Yes	850	0.5	24	1.5			3,330	15.0	483	27.5		
Asphyxia[d]					7.3	2.8, 11.9					3.7	2.2, 5.1
No	194,805	99.9	1,639	98.8			23,246	99.1	1,769	96.9		
Yes	301	0.1	20	1.2			210	0.9	57	3.1		
Antepartum or intrapartum stillbirth					9.4	4.4, 14.3					1.7	1.3, 2.2
No	195,106	99.8	1,659	98.3			23,456	97.0	1,826	94.6		
Yes	424	0.2	29	1.7			736	3.0	105	5.4		
Neonatal mortality (≤28 days)[d]					–[h]	–[h]					2.4	1.6, 3.1
No	194,968	99.9	1,655	99.8			22,964	97.9	1,740	95.3		
Yes	138	0.1	4	0.2			492	2.1	86	4.7		

Abbreviations: CI, confidence interval; LOS, length of stay; NICU, neonatal intensive care unit; RR, relative risk.

[a] The stratified risk estimates did not show evidence for potential collider bias, and therefore uncorrected estimates were reported here. Corrected estimates for the preterm stratum are available in Web Table 1.

[b] Relative risk estimated with modified Poisson model adjusting for maternal age, race/ethnicity, parity, prepregnancy body mass index, maternal comorbidities (chronic hypertension, gestational hypertension, preeclampsia, pregestational diabetes, and gestational diabetes), insurance, marital status, smoking status, alcohol use, drug use, and study site. All comparisons significant at $P < 0.001$, except NICU LOS in the term group.

[c] Composite outcome included resuscitation, NICU admission, respiratory distress syndrome, apnea, asphyxia, stillbirths, and neonatal mortality.

[d] Excluding antepartum and intrapartum stillbirths.

[e] Data are given as median values (interquartile ranges) among those admitted to NICU; excludes sites 4 and 8, which did not report NICU LOS.

[f] Incidence rate ratio estimated with negative binomial model.

[g] Excluding site 6, which did not report neonatal apnea.

[h] Too few neonatal deaths among abruption group for model convergence.

information could help elucidate the relationship between abruption, growth restriction, and the course of pregnancy. However, these limitations are not unique to our study. A related issue was our use of SGA as a proxy for intrauterine growth restriction; the former is a classification based on failure to achieve a specific weight for a particular gestational age and fetal sex, whereas the latter is defined as a failure to reach growth potential or reduced growth velocity (the specific definition of which has continued to be debated) (39, 40). Although they are highly related, these conditions are not identical and do not always overlap. Some neonates classified as SGA may simply be constitutionally small rather than growth restricted. Although intrauterine growth restriction would have been the preferable variable, the Consortium on Safe Labor study does not include sufficient detail to determine it, and thus we used SGA as a proxy. It is also important to note that severe cases of abruption are associated with an elevated incidence of stillbirth (41, 42), and so a fetus must have first survived the

Table 4. Adjusted Relative Risk for Neonatal Outcomes According to Presence or Absence of Placental Abruption, Conditioned on Birth Weight for Gestational Age and Fetal Sex, Consortium on Safe Labor Study, 2002–2008[a]

Neonatal Outcome	Not Small for Gestational Age and Fetal Sex (n = 198,589)						Small for Gestational Age and Fetal Sex (n = 24,752)					
	No Abruption		Abruption		RR	99% CI[b]	No Abruption		Abruption		RR	99% CI[b]
	No.	%	No.	%			No.	%	No.	%		
Composite perinatal-neonatal outcome[c]					1.9	1.9, 2.0					1.6	1.5, 1.8
No	136,076	69.6	1,007	33.0			16,158	66.8	188	33.3		
Yes	59,459	30.4	2,047	67.0			8,029	33.2	377	66.7		
Newborn resuscitation[d]					1.6	1.5, 1.6					1.5	1.3, 1.7
No	149,709	76.9	1,770	59.8			18,905	79.3	314	59.8		
Yes	45,024	23.1	1,190	40.2			4,924	20.7	211	40.2		
NICU admission[d]					3.7	3.5, 3.9					2.1	1.8, 2.4
No	173,484	89.1	1,518	51.3			19,702	82.7	278	53.0		
Yes	21,249	10.9	1,442	48.7			4,127	17.3	247	47.1		
NICU LOS, days[d,e]	6 (3–17)		22 (7–49)		2.1[f]	2.0, 2.3[f]	7 (3–20)		14 (5–37)		1.4[f]	1.1, 1.7[f]
Respiratory distress syndrome[d]					7.2	6.5, 7.9					3.5	2.7, 4.4
No	189,256	97.2	2,184	73.8			22,889	96.1	415	79.0		
Yes	5,477	2.8	776	26.2			940	3.9	110	21.0		
Apnea[d,g]					6.7	5.8, 7.6					2.5	1.6, 3.3
No	173,944	98.0	2,404	84.2			20,038	96.7	450	89.1		
Yes	3,487	2.0	452	15.8			693	3.3	55	10.9		
Asphyxia[d]					8.9	5.6, 12.1					–[h]	–[h]
No	194,302	99.8	2,896	97.8			23,749	99.7	512	97.5		
Yes	431	0.2	64	2.2			80	0.3	13	2.5		
Antepartum or intrapartum stillbirth					7.1	5.0, 9.2					4.4	2.5, 6.3
No	194,733	99.6	2,960	96.9			23,829	98.5	525	92.9		
Yes	802	0.4	94	3.1			358	1.5	40	7.1		
Neonatal mortality (≤28 days)[d]					8.8	5.5, 12.2					4.6	1.8, 7.4
No	194,292	99.8	2,892	97.7			23,640	99.2	503	95.8		
Yes	441	0.2	68	2.3			189	0.8	22	4.2		

Abbreviations: CI, confidence interval; LOS, length of stay; NICU, neonatal intensive care unit; RR, relative risk.

[a] The stratified risk estimates did not show evidence for potential collider bias, and therefore uncorrected estimates were reported here. Corrected estimates for the low birth weight stratum are available in Web Table 2.

[b] Relative risk estimated with modified Poisson model adjusting for maternal age, race/ethnicity, parity, prepregnancy body mass index, maternal comorbidities (chronic hypertension, gestational hypertension, preeclampsia, pregestational diabetes, and gestational diabetes), insurance, marital status, smoking status, alcohol use, drug use, and study site. All comparisons significant at $P < 0.001$.

[c] Composite outcome included resuscitation, NICU admission, respiratory distress syndrome, apnea, asphyxia, stillbirths and neonatal mortality.

[d] Excluding antepartum and intrapartum stillbirths.

[e] Data are given as median values (interquartile ranges) among those admitted to NICU; excludes sites 4 and 8, which did not report NICU LOS.

[f] Incidence rate ratio estimated with negative binomial model.

[g] Excluding site 6, which did not report neonatal apnea.

[h] Model for risk of asphyxia in low–birth weight neonates would not converge due to small sample sizes at some of the individual study sites.

gestation and delivery to be at risk of neonatal morbidities. A complete understanding of the neonatal morbidity associated with abruption must be viewed in the context of elevated perinatal mortality.

Delivery mode is another important variable that was ultimately excluded from the analyses presented here for several reasons. It is reasonable to suspect that, in the setting of abruption, vaginal delivery may lead to prolonged exposure to acute hypoxic conditions for the neonate, which could increase risk of apnea and asphyxia as well as admission to NICU and longer LOS—and potentially even death. Abruption is also associated with significant maternal morbidity (primarily in the form of blood loss) (9, 11, 43), so it would be reasonable to conclude that cesarean delivery may be advisable to limit maternal blood loss as well as neonatal exposure to hypoxia. However, cesarean delivery is a major surgical procedure that presents risks both in the short term and in subsequent pregnancies (44). Thus, it is difficult to weigh whether vaginal or cesarean delivery is the

best option when considering both neonatal and maternal health in the index pregnancy as well as the health of potential future pregnancies. Analytically, mode of delivery is on the causal pathway and may mediate the association between abruption and neonatal (and maternal) outcomes and, as such, would be a candidate for the type of analysis we performed with preterm birth and being SGA. However, the analysis is also likely subject to substantial confounding by indication, because the most severe cases of abruption are probably more likely to be delivered by cesarean than vaginally, and vice versa. The alternative of including mode of delivery as a covariate is also problematic, because it could lead to biased estimates.

Finally, there is known error in the classification of cases of abruption. Among our sample, abruption was classified based on 2 sources of information—electronic medical records and discharge codes—that are both subject to error, although the direction is unclear. In some studies, abruption is classified only in the presence of certain maternal symptoms (such as vaginal bleeding, abdominal pain, or both) or fetal signs (such as low birth weight or perinatal mortality). However, because there is a spectrum of abruption cases, excluding women that did not present with vaginal bleeding could have resulted in the exclusion of 30%–50% of cases exhibiting concealed abruption, which is typically associated with worse perinatal outcomes (45, 46). Likewise, limiting cases only to low–birth weight outcomes might have excluded acute cases that occurred toward the end of pregnancy. These exclusions could plausibly bias morbidity estimates in either direction, depending on the criteria applied. We did not apply any further criteria for the diagnosis of abruption, which may have resulted in the inclusion of milder cases of abruption, which likely led to an underestimation of associated risk. However, these methodological quandaries are present in most studies of abruption.

Comparison with other studies

To our knowledge, this is the first study to examine the association between abruption and risk of neonatal apnea. It is also the largest study to examine the association between abruption and respiratory distress syndrome, as well as the need for medical intervention. Previous reports of the association between abruption and need for medical intervention are limited by small sample sizes or focused on specific high-risk subpopulations, such as neonates requiring positive pressure ventilation at birth (34) or pregnancies complicated specifically by chronic abruption-oligohydramnios sequence (35). Furthermore, in contrast to the majority of existing studies of abruption, which have controlled for gestational age and birth weight in the analyses, we also estimated risk of poor outcomes conditioned on preterm birth and SGA. This analysis yielded valuable information about the direct effects of abruption on neonatal outcomes that were not attributable to the association with preterm birth or being SGA. Our results also confirmed the previous reports of an association between abruption and elevated risk of respiratory distress syndrome, among both preterm and term neonates (36).

Implications and conclusion

Our findings suggest that placental abruption is associated with an elevated risk of need for neonatal delivery-room resuscitation, NICU admission, and longer NICU LOS. Additionally, our finding of elevated risk of both respiratory distress syndrome and apnea among both preterm and term neonates suggests that abruption may be associated with physiologic underdevelopment, which has not been previously recognized. Together, our results suggest that neonates in pregnancies complicated by abruption are vulnerable beyond the immediate perinatal time frame. The discovery of the elevated risk of neonatal apnea may also be key to understanding the mechanism behind the association between abruption and sudden infant death syndrome (47–49).

Our findings also point toward the need for changes in the way information about placental disorders is clinically collected and documented. There is a notable paucity of the detailed information about the timing and nature of placental events during pregnancy that is vital for understanding both the epidemiology of the diseases as well as its likely impact on both the mother and the neonate. Likewise, assessment of placental health and functioning during pregnancy is an area in need of further development, as reflected in the establishment of the National Institute of Health's Human Placenta Project. The invention of new, noninvasive surveillance methods for the placenta and implementing routine, detailed documentation of placental disorders are vital first steps toward furthering our understanding of placental function and disease.

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Author affiliations: Epidemiology Branch, Division of Intramural Population Health Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Bethesda, Maryland (Katheryne L. Downes, Katherine L. Grantz); Maternal and Child Health Program, Department of Family Science, School of Public Health, University of Maryland, College Park, Maryland (Katheryne L. Downes, Edmond D. Shenassa); Maternal and Child Health Research Center, Department of Obstetrics and Gynecology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania (Katheryne L. Downes); Department of Epidemiology and Biostatistics, School of Public Health, University of Maryland, College Park, Maryland (Edmond D. Shenassa); Department of Epidemiology and Biostatistics, School of Medicine, University of Maryland, Baltimore, Maryland (Edmond D. Shenassa); and Epidemiology Department, School of Public Health, Brown University, Providence, Rhode Island (Edmond D. Shenassa).

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