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Placenta Previa and Maternal Hemorrhagic Morbidity

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Abstract

Objective: Placenta previa is associated with maternal hemorrhage, but most literature focuses on morbidity in the setting of placenta accreta. We aim to characterize maternal morbidity associated with previa and to define risk factors for hemorrhage.

Methods: This is a secondary cohort analysis of the NICHD Maternal-Fetal Medicine Units Network Cesarean Section Registry. This analysis included all women undergoing primary Cesarean delivery without placenta accreta. 496 women with previa were compared to 24,201 women without previa. Primary outcome was composite maternal hemorrhagic morbidity. Non-hemorrhagic morbidities and risk factors for hemorrhage were also evaluated.

Results: Maternal hemorrhagic morbidity was more common in women with previa (19 vs 7%, aRR 2.6, 95% CI 1.9-3.5). Atony requiring uterotonics (aRR 3.1, 95% CI 2.0-4.9), red blood cell transfusion (aRR 3.8, 95% CI 2.5-5.7), and hysterectomy (aRR 5.1, 95% CI 1.5-17.3) were also more common with previa. For women with previa, factors associated with maternal hemorrhage were pre-delivery anemia, thrombocytopenia, diabetes, magnesium use, and general anesthesia.

Conclusion: Placenta previa is an independent risk factor for maternal hemorrhagic morbidity. Some risk factors are modifiable, but many are intrinsic to the clinical scenario.

Keywords

placenta previa; obstetric hemorrhage; maternal morbidity

Introduction

The rate of placenta previa is increasing [1], accounting for 1.3% of pregnancies in 2007 [2]. This increase has coincided with the crescendo in Cesarean deliveries (CD) [3, 4]. Placenta previa necessitates delivery via CD, often at preterm gestations. Deliveries complicated by

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placenta previa are at high risk for obstetric hemorrhage prior to, during, and after delivery [1, 5]. For example, placenta previa or abruption have adjusted odds ratio of 7.0 (95% CI 6.6-7.3) for severe postpartum hemorrhage [6]. Hemorrhage is associated with increased risk of maternal morbidity, the need for additional medications and procedures to staunch bleeding and the sequelae of overwhelming hemorrhage such as coagulopathy [1, 2, 5, 7].

Previous studies characterizing hemorrhage and morbidity due to placenta previa have focused on those that are also complicated by placenta accreta or morbidly adherent placenta [2, 8, 9, 10]. Thankfully, most placenta previas are not comorbid with accreta. However, few data are available to counsel women diagnosed with placenta previa and no accreta. One prior study evaluating morbidity of previa in Australia found a 14% rate of major morbidity in these women, however a large proportion of women in this study delivered at hospitals without 24 hour blood banks [11]. Improved knowledge of the true morbidity of placenta previa will also allow us to justify, plan, and adequately power intervention trials to effectively decrease this morbidity.

Thus, our objectives were to characterize the maternal morbidity associated with placenta previa without accreta and to define maternal and obstetric risk factors that increase the odds of maternal morbidity.

Materials and Methods

This is a secondary analysis of the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units (MFMU) Network Cesarean Section Registry (CSR). The CSR was a prospective registry from 1999 to 2002 conducted in 19 academic medical centers participating in the MFMU Network. The original cohort included women undergoing CD or vaginal birth after at least one previous CD (VBAC). For 1999 and 2000, patients were eligible if they delivered via primary or repeat CD or VBAC. Starting in 2001, only repeat CD and VBAC were included. The original registry included only deliveries of infants of at least 500 grams birthweight or 20 weeks gestational age by best estimate using standard obstetric dating criteria. Nurse coordinators and all study nurses assigned to the study underwent a certification process for data abstraction using a sample chart to prove adequacy of chart abstraction and coding. Data were obtained from review of the patient's medical record. Chart abstraction forms were provided by the MFMU.

This analysis is a cohort study with placenta previa as the exposure and post-operative maternal morbidity as the outcome. All women in the CSR who underwent primary CD were included. Only primary CDs were included in order to control for the additional morbidity associated with repeat CD. Women were excluded if the number of previous CDs was not recorded, even if the indication for current CD was listed under "primary c-section indications." The previa cohort (cases) was defined as women undergoing CD with the indication for CD coded as "previa with hemorrhage" or "previa without hemorrhage." The no previa cohort (controls) included all other CDs in the dataset. Morbidly adherent placentae (placenta accreta, placenta increta, or placenta percreta) were excluded from both cohorts. Accreta was coded as present if the placenta was adherent to the uterine wall. When

pathologic report of the uterus was available, pathologic assessment of adherent placenta took precedence over clinical suspicion.

The primary outcome was maternal hemorrhagic morbidity, defined as mortality, blood product transfusion, atony requiring uterotonics, uterine or hypogastric artery ligation, hysterectomy, coagulopathy, and/or exploratory laparotomy. A separate analysis of the primary outcome was performed excluding atony requiring uterotonics since this outcome is more common and less morbid than the others in the composite. Severe maternal morbidity was defined per the Joint Commission policy as ICU admission or receipt of 4 units of blood products. The decrease in hemoglobin prior to and after delivery was compared. Rates of emergent delivery and emergent delivery for antenatal hemorrhage were compared as well. The frequency of hemorrhagic morbidity was compared between women with and without any antenatal bleeding leading to delivery. Other maternal outcomes examined included mortality, cystotomy or ureteral injury, bowel injury, venous thromboembolic disease, postpartum endometritis, wound complication, necrotizing fasciitis, maternal sepsis, acute respiratory distress syndrome, cardiopulmonary arrest, pulmonary edema, septic pelvic thrombophlebitis, and readmission for any reason.

A case-control analysis also was conducted in the cohort of women with placenta previa to evaluate potential risk factors for hemorrhagic morbidity, as defined above. Cases were those who experienced hemorrhagic morbidity, and controls were those who did not. We evaluated the following exposures: maternal age, race, education, modality of healthcare payment, body mass index (BMI) (pre-delivery and at delivery), number of fetuses, parity, anemia (hematocrit <33%), thrombocytopenia (platelets <150,000/ μ L), gestational age at delivery, emergent delivery, neonatal birthweight, neonatal sex, maternal health comorbidities (diabetes, asthma, thyroid disease, seizure disorder, hypertension, renal disease, heart disease, and connective tissue disease), previous myomectomy, tobacco use, alcohol use, drug use, presence of preterm premature rupture of membranes (PPROM), preterm labor, bleeding as indication for delivery, meconium, hypertensive disease of pregnancy, magnesium administration, placental abruption, chorioamnionitis, general anesthesia, and vertical uterine incision.

In order to be sure that we could address the primary research question, a sample size estimate was calculated based on the assumption of a 25% frequency of postpartum hemorrhage in the previa group [2, 12]. If we assume a 10% or lower rate of postpartum hemorrhage in the no previa group [6], power of 90%, and a two-sided alpha of 0.05, 146 subjects per group would be required.

The primary outcomes are reported with numbers, rates, relative risks, 95% confidence intervals, and p-values. Secondary outcomes are presented as numbers, means, rates, and standard deviations as appropriate. Comparisons were conducted using the Wilcoxon rank-sum test, chi-square test, and risk ratios as appropriate. Logistic or Poisson linear regression models were fitted for these outcome variables as well. Regression models were built by selecting variables using backwards-stepwise elimination testing statistically different variables into the model first. Analysis was conducted using Stata version 13.1 (StataCorp LP, College Station, TX).

Results

54,458 women underwent CD and did not have a placenta accreta in the MFMU CSR. 196 women with placenta accreta were excluded. 24,697 underwent primary CD, of which 496 had placenta previa and 24,201 had no placenta previa. Demographics of the study cohort are presented in Table 1. Women with previa were 3.3 years older, had a lower pre-conception BMI by 2.1 points, and were more likely to use tobacco than women without previa. Women with previa had a higher median number of previous births >20 weeks (1 vs 0, $p<0.001$). Women with previa were significantly less likely to have undergone labor or induction of labor than women without previa (22.8% vs 74.1%, $p<0.001$). Births complicated by previa occurred earlier in gestation (35.1 vs 37.6 weeks, $p<0.001$) and had lower birth weight (2503 vs 2987 grams, $p<0.001$). Each of these demographic and obstetric factors were considered for the regression models.

After backwards-stepwise elimination, the Poisson regression model for the primary outcome of hemorrhagic morbidity included the following variables: presence of any labor or induction attempt, admission hematocrit, pre-conception BMI, maternal age, diabetes, number of fetuses, meconium, placental abruption, chorioamnionitis, neonatal weight, years of schooling, use of tocolysis, diagnosis of preeclampsia or gestational hypertension, and prior vaginal delivery

The primary outcome of maternal hemorrhagic morbidity was higher in women with previa (19% vs 7%; aRR 2.6, 95% CI 1.9-3.5) (Table 2). When we compared hemorrhagic morbidity without including use of uterotonics for atony in the composite outcome, it remained higher in women with previa (14.7% vs 4.2%; aRR 2.6, 95% CI 1.8-3.7). Individual factors of the hemorrhagic morbidity composite that were more common in the previa cohort included atony requiring uterotonics (10.5% vs 6.4%; aRR 3.1, 95% CI 2.0-4.9), red blood cell transfusion (12.9% vs 3.1%; aRR 3.8, 95% CI 2.5-5.7), and hysterectomy (2% vs 0.3%; aRR 5.1, 95% CI 1.5-17.3). Severe maternal morbidity (as defined by ICU admission or receipt of 4 or more units of packed red blood cells) was not increased with presence of previa (2.6 vs 1.5%; aRR 1.1, 95% CI 0.4-3.0). In women with previa, hemorrhagic morbidity was more common in women with bleeding as the indication for delivery than in women with other indications for delivery (24.2 vs 11.2%, $p<0.001$). Non-hemorrhagic morbidity was rare in both cohorts and not statistically different (Table 3).

The previa cohort was more likely to receive 4 units of red blood cells (2.2% vs 0.7%) but this did not persist after adjustment (aRR 2.1, 95% CI 0.8-5.8). Additionally, women with previa had a hemoglobin decrease of 2.3 g/dL surrounding delivery, which was 0.4 g/dL more than the no previa cohort ($p<0.001$).

More women with previa underwent emergent delivery than women without previa (23.8 vs 17.6%). However, after adjustment for confounders, there was no difference in emergent delivery for those with previa compared to those without (aRR 1.1, 95% CI 0.8-1.5). Of women with previa, 20.4% of women with previa underwent emergent delivery for antenatal hemorrhage.

Of the 496 women with primary CD for placenta previa, 92 (19%) had adverse hemorrhagic outcomes and 404 (81%) did not (data not shown). In univariate analysis, exposures more common in women with maternal hemorrhagic morbidity were anemia on admission, thrombocytopenia, prematurity <34 weeks, low birth weight, diabetes, drug use, preterm labor requiring tocolysis, emergent delivery, bleeding as indication for cesarean, and general anesthesia. After adjustment for education, diabetes, drug use, pre-delivery hematocrit, magnesium administration, and general anesthesia, only anemia on admission (aOR 2.49, 95% CI 1.36-4.56), thrombocytopenia (aOR 3.78, 95% CI 1.2-11.86), diabetes (aOR 3.47, 95% CI 1.2-10.06), magnesium (aOR 4.72, 95% CI 1.33-16.7), and general anesthesia (aOR 4.29, 95% CI 2.25-8.16) remained as risk factors for maternal hemorrhagic morbidity. There were 23 women with a diagnosis of preeclampsia or gestational hypertension, and 22/23 received magnesium. Conversely, all women who received magnesium also had a diagnosis of preeclampsia or gestational hypertension.

Discussion

In this cohort 20% (or 1 out of 5) women with previa underwent emergent delivery for antenatal hemorrhage. The burden of this morbidity is substantial. Placenta previa was associated with an overall increased risk of maternal hemorrhagic morbidity (aRR 2.6, 95% CI 1.9-3.5), with 18.6% of women with previa suffering the composite primary outcome. Three percent of women suffered severe hemorrhagic morbidity, and 2% underwent hysterectomy, presumably due to persistent hemorrhage. In contrast, women did not suffer additional non-hemorrhagic morbidity, suggesting our focus should be identifying women with previa at risk for hemorrhage and finding ways to staunch hemorrhage. A previous series of 147 cases of placenta previa from 1975 to 1982 noted a high maternal morbidity rate, with 5.4% undergoing hysterectomy and three quarters meeting the definition for postpartum hemorrhage[7]. 11 of these women had a placenta accreta, and previous cesarean was a risk factor for hysterectomy. Although our results show a lower rate of hysterectomy, we excluded accretas and analyzed a more modern cohort.

Factors associated with hemorrhage in our cohort included pre-delivery anemia, thrombocytopenia, diabetes, magnesium, and general anesthesia. Pre-delivery anemia increases the chances of signs and symptoms of blood loss such as tachycardia, thus increasing the chances of being diagnosed with hemorrhage using our criteria. Thrombocytopenia may diminish the effectiveness of clotting and thus increase blood loss. Diabetes may be a marker for poor maternal health, abnormal uterine neurovascular function, and inability to tolerate hemorrhage (similar to pre-delivery anemia). We suspect that magnesium is a marker for preeclampsia with severe features, as all women who received magnesium also had preeclampsia. General anesthesia increases uterine atony and thus likely increases hemorrhage. However, it may also simply be a marker of emergent delivery and thus a clinical situation at increased risk of bleeding. Regardless, these risk factors warrant clinical vigilance and preparation for hemorrhage.

Although hemorrhagic morbidity was more common in women with previa who had bleeding as an indication for delivery than in women with previa with a non-bleeding indication for delivery, it is impossible to know if a woman will bleed or not when you are

diagnosing her with a previa and developing a plan of care. Thus, it is important to consider all women with placenta previa at increased risk for hemorrhagic morbidity.

Several investigators have tried to predict which women with placenta previa are at risk for hemorrhage or early delivery. One group developed a risk score for emergency delivery in women with placenta previa and bleeding. They found presence of previa, 3 or more episodes of antepartum bleeding, and first bleed prior to 29 weeks associated with an increased risk of emergent cesarean [13]. This model is useful to practitioners and researchers trying to elucidate the benefit of prolonged hospitalization for a woman who has ceased bleeding after her first or second antenatal bleeding episode and remains pregnant. However, the study was limited to women with antenatal bleeding, which is not true of all women with previa. The main limitation of our study was variables of interest that were not collected in the original dataset. It would be ideal to query the relationship between hemorrhage and variables such as placental location, previous antenatal bleed, and whether women were hospitalized prior to delivery, but these data were not available. Lack of detailed ultrasound data requires us to use clinician diagnosis of placenta previa recorded in the chart as opposed to ultrasound images or recorded measurements. Additionally, the data are now historic, as this cohort finished collection in 2002. Also, since we are using women undergoing primary CD (including emergent cesareans) as controls, we selected a control group that is also at increased risk for morbidity when compared to women undergoing spontaneous vaginal delivery, for example. This increases our risk of type 2 error. Additionally, the generalizability of this dataset is limited, as the majority of included centers are tertiary care centers.

Our strengths include the nature of the dataset – The MFMU Network's CSR was prospectively collected in a rigorous fashion by trained research nurses. Also, by limiting the entire cohort to women with primary CD, we are able to focus on the additional morbidity associated with previa alone, as opposed to muddying the waters with morbidity associated with CD or repeat CD. This is the first comprehensive analysis to report these outcomes in women with previa but without accreta.

In case reports and small series, numerous strategies to decrease postpartum hemorrhage associated with previa have been reported. Interventions described include compression sutures [14, 15], Foley catheter placement [16], postpartum hemorrhage specific intrauterine balloon [17], hemostatic gel [18], local injection of vasopressin [12], temporary internal iliac artery balloon occlusion [19], and even suturing the cervix to the placental bed [20]. However, no randomized-controlled trials have been conducted.

In conclusion, in this large cohort of women, placenta previa is an independent risk factor for maternal hemorrhagic morbidity. Nineteen percent of women with previa experienced hemorrhagic morbidity, 20% were delivered emergently for antenatal bleeding, and 2% required hysterectomy (even in the absence of accreta). These data will be useful in counseling, management, and planning future intervention trials and cost-effectiveness analysis. In the meantime, clinicians managing these pregnancies should remain vigilant for antenatal and postpartum hemorrhage.

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Table 1.

Demographics of women undergoing cesarean delivery with and without placenta previa.

Characteristic	Previa N=496	No Previa N=24,201	p-value
Maternal Age (years)	30.1 (6.4)	26.8 (6.5)	<0.001
Race	148 (29.8)	7404 (30.6)	0.021
African-American	221 (44.6)	10466 (43.3)	
Caucasian	92 (18.6)	5060 (20.9)	
Hispanic	18 (3.6)	395 (1.6)	
Asian	1 (0.2)	41 (0.2)	
Native American	16 (3.2)	835 (3.5)	
Other/Unknown			
Schooling (years)	12.5 (2.6)	12.4 (2.7)	0.360
Payment	187 (39.5)	9242 (40.4)	0.37
Government funded	225 (48.1)	10609 (46.4) >	
Private Insurance	56 (12.0)	3013 (13.2)	
Self-pay/None			
Tobacco Use	90 (18.2)	3373 (14.0)	0.008
Alcohol Use	18 (3.6)	821 (3.4)	0.778
Drug Use	16 (3.2)	820 (3.4)	0.840
Prenatal Care	482 (97.2)	23628 (97.7)	0.462
# of previous pregnancies >20 weeks Median (range)	1 (0-8)	0 (0-14)_	<0.001
BMI pre-conception	24.5 (4.8)	26.6 (6.8)	<0.001
BMI at delivery	29.1 (5.2)	32.5 (7.1)	<0.001
Any labor or attempted induction	113 (22.8)	17922 (74.1)	<0.001
Gestational age of delivery (weeks)	35.1 (3.5)	37.6 (3.9)	<0.001
Birthweight (grams)	2503.4 (805.8)	2987.9 (964.2)	<0.001
Sex of neonate	269 (54.3)	13053 (53.9)	0.860
Male	226 (45.7)	11144 (46.1)	
Female			

Data represented as mean(SD) or n(%) as appropriate

Table 2.

Maternal hemorrhagic morbidity in women undergoing cesarean delivery with and without placenta previa.

Variable	Previa N=496	No Previa N=24,201	RR (95% CI)	aRR* (95% CI)
Emergent delivery	118 (23.8)	4270 (17.6)	1.35 (1.15-1.58)	1.12 (0.83-1.50)
Maternal hemorrhagic morbidity	92 (18.6)	1585 (6.6)	2.67 (2.21-3.22)	2.57 (1.87-3.53)
ICU admission and/or 4 units packed red blood cells	13 (2.6)	354 (1.5)	1.79 (1.04-3.10)	1.14 (0.44-2.96)
Atony requiring uterotonics	52 (10.5)	1557 (6.4)	1.63 (1.25-2.11)	3.11 (1.97-4.91)
Uterine Artery Ligation	14 (2.8)	218 (0.9)	3.13 (1.84-5.34)	1.62 (0.63-4.21)
Hypogastric Artery Ligation	0 (0)	6 (0.02)	---	---
Red Blood Cell Transfusion	64 (12.9)	754 (3.1)	4.14 (3.26-5.26)	3.80 (2.51-5.74)
Transfusion of FFP/Cryo/Platelets	1 (0.2)	21 (0.1)	2.32 (0.31-17.24)	---
Coagulopathy	4 (0.8)	171 (0.7)	1.14 (0.43-3.06)	0.74 (0.10-5.71)
Unplanned Exploratory Laparotomy	2 (10)	67 (6.2)	1.63 (0.43-6.18)	1.04 (0.26-4.10)
Hysterectomy	10 (2)	60 (0.25)	8.13 (4.19-15.79)	5.14 (1.53-17.28)
Maternal Mortality	1 (5)	20 (1.8)	2.72 (0.38-19.33)	---

* Adjusted for presence of any labor or induction attempt, admission hematocrit, pre-conception BMI, maternal age, diabetes, number of fetuses, meconium, placental abruption, chorioamnionitis, neonatal weight, years of schooling, use of tocolysis, diagnosis of preeclampsia or gestational hypertension, and prior vaginal delivery.

Table 3.

Maternal non-hemorrhagic morbidity in women undergoing cesarean delivery with and without placenta previa.

Variable	Previa N=496	No Previa N=24,201	RR (95% CI)	aRR* (95% CI)
Genitourinary Injury	0 (0)	45 (0.2)	---	---
Bowel Injury	0 (0)	14 (0.1)	---	---
Venous Thromboembolic Disease	3 (0.6)	143 (0.6)	1.02 (0.33-3.20)	---
Endometritis	24 (4.8)	2229 (9.2)	0.53 (0.35-0.78)	0.41 (0.17-0.98)
Sepsis	0 (0)	54 (0.2)	---	---
Pulmonary Edema	1 (0.2)	180 (0.7)	0.27 (0.04-1.93)	---
ICU Admission	2 (0.4)	238 (1.0)	0.41 (0.10-1.64)	---
Acute Respiratory Distress Syndrome	0 (0)	24 (0.1)	---	---
Necrotizing Fasciitis	0 (0)	5 (0.02)	---	---
Cardiopulmonary Arrest	0 (0)	7 (0.03)	---	---
Readmission	7 (1.4)	378 (1.6)	0.90 (0.43-1.90)	0.23 (0.03-1.69)
Wound Complication	4 (0.8)	335 (1.4)	0.58 (0.22-1.55)	0.40 (0.05-3.11)

* Adjusted for presence of any labor or induction attempt, admission hematocrit, pre-conception BMI, maternal age, diabetes, number of fetuses, meconium, placental abruption, chorioamnionitis, neonatal weight, years of schooling, use of tocolysis, diagnosis of preeclampsia or gestational hypertension, and prior vaginal delivery.