Risk factors for blood transfusion in patients undergoing high-order Cesarean delivery

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BACKGROUND: The objective was to identify risk factors associated with blood transfusion in patients undergoing high-order Cesarean delivery (CD).

STUDY DESIGN AND METHODS: This was a retrospective cohort study of patients undergoing third or more CD by a single maternal-fetal medicine practice between 2005 and 2016. We compared risk factors between women who did and did not receive a red blood cell transfusion during the operation or before discharge. Repeat analysis was performed after excluding women with placenta previa.

RESULTS: A total of 514 patients were included, 18 of whom (3.5%; 95% confidence interval [CI], 2.2%-5.5%) received a blood transfusion. Placenta previa was the most significant risk factor for transfusion (61.1% of patients who received a transfusion vs. 1% of patients who did not; $p < 0.001$). Patients with a placenta previa had a 68.8% likelihood of requiring a blood transfusion. After women who had placenta previa were excluded, the incidence of blood transfusion was seven of 498 (1.4%; 95% CI, 0.7%-2.9%). Risk factors significantly associated with blood transfusion in the absence of previa were prophylactic anticoagulation during pregnancy and having labored. The incidence of transfusion in patients with no placenta previa, no anticoagulation, and no labor was 0.7% (95% CI, 0.3%-2.1%). Placenta previa was the most predictive risk factor for transfusion with a positive predictive value of 68.8% and a negative predictive value of 98.4%.

CONCLUSION: In patients undergoing a third or more CD, only placenta previa, prophylactic anticoagulation during pregnancy, and having labored are independently associated with requiring a blood transfusion. These data can be used to guide physician ordering of prepared blood products preoperatively.

Many obstetric complications, including postpartum hemorrhage (PPH), are more common after Cesarean delivery (CD) than after vaginal delivery. In fact, many of the risk factors for Cesarean are themselves risk factors for PPH.[1] PPH is one of the most common reasons for maternal intensive care unit admissions each year and remains a leading cause of maternal mortality in the United States.[2] The rate of obstetric transfusion has increased by 33% between 2001 and 2014, largely due to PPH.[3]

Cesarean delivery is common in the United States, increasing from 22% of all deliveries in 1990 to 32% in 2014.[4] Multiple CDs are associated with increased short- and long-term maternal morbidity including blood transfusion, cystotomy, hysterectomy, postoperative ventilator use, longer operative time and hospital stay, endometritis, and future placenta previa and accreta.[5,6] The composite maternal morbidity has also been shown to increase with increasing number of CDs, and this risk has been found to be significantly higher beginning at the third CD.[7,8]

ABBREVIATIONS: CD(s) = Cesarean delivery(-ies); IVF = in vitro fertilization; PPH = postpartum hemorrhage.

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Given the increasing complexity and complication rate of higher-order CD, proper planning for these cases is imperative for patient safety.[9-11] Proper preparation may include delivering at an institution with a blood bank, crossmatching units of blood in advance, bringing crossmatched units to the operating room before surgery, or placing additional intravenous lines, among others. Often these measures are labor- or cost-intensive and, in institutions with smaller blood banks, may pull essential units out of the bank unnecessarily.

In this study, we sought to determine which specific risk factors were independently associated with blood transfusion in the third or more CD. With better understanding of the factors that contribute to blood transfusion in these patients, prudent preoperative planning can be undertaken for those women at highest risk.

MATERIALS AND METHODS

After Biomedical Research Alliance of New York Institutional Review Board approval was obtained, the charts of all patients undergoing CD by a single maternal-fetal medicine practice between July 2005 (when our computerized medical record was created) and June 2016 were reviewed. We included any patient undergoing a third or more CD, due to the known baseline increased risk of complications in this cohort. For each patient, we reviewed the computerized medical record, hospital inpatient records, operative reports, anesthesia records, and discharge summaries. We recorded maternal baseline characteristics, delivery information, operative details, and intra- and postoperative complications.

In our practice, patients undergoing a third or more CD are delivered at approximately 37 to 39 weeks or earlier as indicated. All patients were delivered at Mount Sinai Hospital, which is a large tertiary academic medical center in New York City. The decision regarding exact timing of delivery (before or after 39 weeks, for example) was not uniform over the study period and was individualized based on clinical circumstances and contemporary management guidelines. Gestational age was determined by last menstrual period and confirmed by ultrasound in all patients. The pregnancy was redated if there was a more than 5-day discrepancy up to 14 weeks or a more than 7-day discrepancy after 14 weeks. If the pregnancy was the result of in vitro fertilization (IVF), gestational age was determined from IVF dating.

We identified which patients received a blood transfusion before discharge to estimate the rate (and 95% confidence interval [CI]) of blood transfusion in this population. We then compared baseline characteristics between women who did and did not receive a blood transfusion. Baseline characteristics examined included maternal age, body mass index before pregnancy and at delivery, number of previous CDs, gestational age, IVF, use of prophylactic anticoagulation during pregnancy, maternal medical problems, race, fibroids, prior myomectomy, uterine anomalies, the number of attending surgeons (two attending or one attending plus one resident), whether the patient was in labor at the time of the operation, and whether there was a placenta previa or accreta suspected preoperatively. The purpose of the study was to identify preoperative risk factors for blood transfusion; therefore, we did not consider placenta accretas noted at delivery that were not suspected preoperatively. Patients in labor included women who intended to labor (planned vaginal birth for women with two prior CDs) as well as women who presented in labor or ruptured membranes before a scheduled CD. Over the course of the study period, the decision to administer a blood transfusion was made clinically and not standardized.

We compared baseline characteristics between women who did and did not receive a blood transfusion before discharge using nonparametric testing (Fisher's exact test and Mann Whitney U test, as appropriate, IBM SPSS for Windows 22.0, IBM Corp.). For all risk factors associated with transfusion at a p value of less than 0.10, we repeated the analysis excluding all women with a placenta previa, as this was by far the risk factor most strongly associated with transfusion. For the outcome of transfusion, we calculated the sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios of placenta previa, as well as all the variables that remained significantly associated with transfusion in the absence of placenta previa.

RESULTS

Over the course of the study period there were 514 patients who underwent a third or more CD and data were available for 100% of patients. Of the 514 patients, 261 (50.8%) were undergoing their third CD, 138 (26.8%) their fourth CD, 74 (14.4%) their fifth CD, 28 (5.4%) their sixth CD, 10 (1.9%) their seventh CD, and three (0.6%) their eighth CD. The overall incidence of blood transfusion in the population was 18 of 514 (3.5%; 95% CI, 2.2%-5.5%). The details of the transfusions are listed in Table 1.

We compared baseline characteristics between the 18 women who received a blood transfusion and the 496 women who did not and the results are shown in Table 2. Placenta previa was the risk factor most significantly associated with transfusion, present in 11 of 18 (61.1%) of patients who received a transfusion and in five of 496 (1.0%) patients who did not receive a transfusion (odds ratio, 154.3; 95% CI, 42.3-562.8; $p < 0.001$). Other variables that were significantly associated with transfusion were gestational age at delivery, maternal age, prophylactic anticoagulation use during pregnancy, diabetes, and suspected placenta accreta. Of note, there were an additional five patients with placenta accreta diagnosed at or after

TABLE 1. Characteristics of patients receiving a transfusion*

Number of patients	18
Indication for transfusion	
Placenta previa or accreta	11 (61.1)
Uterine atony	2 (11.1)
Placental abruption	2 (11.1)
Dense adhesions	2 (11.1)
Uterine rupture	1 (5.6)
Antibody status	
Negative	15 (83.3)
Positive	3 (16.7)
Products transfused	
RBCs	18 (100)
FFP	10 (55.6)
Cryoprecipitate	5 (27.8)
PLTs	7 (38.9)
Number of units transfused (range)	
RBCs	2-27
FFP	0-12
Cryoprecipitate	0-10
PLTs	1-4
Timing of transfusion	
Intraoperative	15 (83.3)
Postoperative	7 (38.9)

* Data are reported as number (%) or range.

the time of delivery, three of whom had a placenta previa. Of the two patients with placenta accreta that was not suspected, one required a blood transfusion.

When we excluded the 16 women with a placenta previa, the incidence of blood transfusion was seven of 498 (1.4%; 95% CI, 0.7%-2.9%). Among these women, the only two risk factors significantly associated with transfusion were prophylactic anticoagulation use during pregnancy and labor at the time of CD (Table 3). Due to the small sample size of patients receiving transfusion, a regression analysis was not performed.

As expected, operative time and estimated blood loss were both associated with transfusion. However, neither of these are preoperative risk factors, but rather intraoperative risk factors.

Of the seven patients without placenta previa who had a transfusion, two women had both labor and prophylactic anticoagulation, one woman had labor and no anticoagulation, one woman had prophylactic anticoagulation and no labor, and three women had neither labor nor anticoagulation. Therefore, there were only three women in the entire cohort who had a blood transfusion without a placenta previa, prophylactic anticoagulation

TABLE 2. Risk factors for blood transfusion in patients undergoing third or more CD*

Risk factor	Blood transfusion (n = 18)	No blood transfusion (n = 496)	p value
Preoperative Hb (g/dL)	11.4 (9.9, 12.0)	11.6 (10.3, 12.9)	0.620
Preoperative Hct	33.8 (29.3, 38.2)	34.1 (30.3, 37.9)	0.825
Placenta previa	11 (61.1)	5 (1.0)	<0.001
Suspected placenta accreta	4 (22.4)	1 (0.2)	<0.001
Gestational age at delivery (weeks)	35.4 (26.1, 39.1)	37.6 (36.1, 39.3)	<0.001
Preterm (<37 weeks)	13 (72.2)	139 (28.0)	<0.001
Labored	4 (22.2)	42 (8.5)	0.080
Maternal age (years)	37.3 (30.0, 43.6)	34.7 (28.3, 41.4)	0.023
Advanced maternal age	14 (77.8)	243 (49.0)	0.028
Maternal BMI prepregnancy (kg/m^2)	25.6 (17.1, 32.6)	24.9 (19.8, 35.5)	0.688
Maternal BMI prepregnancy $\geq$ 30 kg/m^2	6 (33.3)	110 (22.2)	0.259
Maternal BMI at delivery (kg/m^2)	32.3 (20.3, 36.2)	30.2 (24.3, 39.2)	0.907
Maternal BMI at delivery $\geq$ 30 kg/m^2	11 (61.1)	255 (51.4)	0.478
Number of previous CDs			0.145
2	14 (77.8)	247 (49.8)	
3	0 (0)	137 (27.6)	
4 or more	4 (22.2)	112 (22.6)	
IVF	2 (11.1)	31 (6.3)	0.327
White race	16 (88.8)	472 (95.2)	0.229
Prophylactic anticoagulation during pregnancy	5 (27.8)	37 (7.5)	0.011
Chronic hypertension	0 (0.0)	18 (3.6)	0.999
Gestational hypertension	0 (0.0)	11 (2.3)	0.999
Diabetes (any)	4 (23.5)	40 (8.1)	0.049
Fibroids	1 (5.6)	19 (3.8)	0.517
Prior myomectomy	0 (0.0)	11 (2.2)	0.999
Uterine anomaly	1 (5.6)	38 (7.7)	0.999
Surgeon skill level			0.999
Two attendings	10 (55.6)	272 (55.3)	
One attending, one resident	8 (44.4)	220 (44.7)	
Operative time (min)	103 (52, 164)	59 (42, 83)	<0.001
Estimated blood loss (mL)	2250 (1160, 4550)	800 (800, 1000)	<0.001

* Data are reported as median (10, 90) or number (%).
BMI = body mass index.

TABLE 3. Risk factors for blood transfusion in patients undergoing third or more CD, excluding women with a placenta previa*

Risk factor	Blood transfusion (n = 7)	No blood transfusion (n = 491)	p value
Maternal age (years)	35.4 (29.6, 39.3)	34.7 (28.2, 41.4)	0.398
Advanced maternal age	5 (71.4)	241 (49.1)	0.280
Gestational age at delivery (weeks)	36.6 (26.3, 40)	37.6 (36.1, 39.3)	0.231
Preterm (<37 weeks)	4 (57.1)	135 (27.5)	0.099
Prophylactic anticoagulation during pregnancy	3 (42.9)	36 (7.3)	0.013
Diabetes (any)	0 (0.0)	40 (8.2)	0.999
Labored	3 (42.9)	42 (8.6)	0.019
Suspected placenta accreta	0 (0)	1 (0.2)	0.999
Operative time (min)	75 (56, 173)	59 (42, 83)	0.031
Estimated blood loss (mL)	1500 (800, 2600)	800 (800, 1000)	<0.001

* Data presented as median (10, 90) or number (%).

TABLE 4. Prediction of blood transfusion in women undergoing third or more CD

Predictor	Sensitivity	Specificity	PPV	NPV	+LR	–LR
Placenta previa	61.1%	99.0%	68.8%	98.6%	61.1	0.39
Labored	22.2%	91.5%	8.7%	97.0%	2.61	0.85
Prophylactic anticoagulation	27.8%	92.5%	11.9%	97.2%	3.71	0.78

+LR = positive likelihood ratio; –LR = negative likelihood ratio; NPV = negative predictive value; PPV = positive predictive value.

TABLE 5. Neonatal outcomes based on maternal blood transfusion in patients undergoing third or more CD*

Outcome	Blood transfusion (n = 18)	No blood transfusion (n = 496)	p value
Birthweight (g)	2620 (920, 3290)	3085 (2490, 3700)	0.001
1-min Apgar score < 7	5 (27.8)	13 (2.6)	<0.001
5-min Apgar score < 7	1 (5.6)	5 (1.0)	0.194
Death	0	0	NA

* Data are reported as median (10, 90) or number (%).

during pregnancy, or labor (risk of transfusion, 3/417; 0.7%; 95% CI, 0.3%-2.1%).

The predictions of transfusion using the risk factors of placenta previa, prophylactic anticoagulation use in pregnancy, and labor are shown in Table 4. Placenta previa was the most predictive risk factor with a positive predictive value of 68.8% and a negative predictive value of 98.6%.

Neonatal outcomes are shown in Table 5. The transfusion group delivered smaller infants with lower 1-minute Apgar scores, which was not unexpected given the earlier gestational ages at delivery. There were no intrauterine or neonatal deaths in the cohort.

DISCUSSION

Although the Cesarean section rate in the United States has plateaued over the past several years, it remains significantly higher than in previous decades. The ubiquity of this procedure has spurred a large amount of research dedicated to its implications. A history of Cesarean section has been found to be the main risk factor for many obstetric complications, including uterine rupture, morbidly adherent placenta, peripartum hysterectomy, and severe blood loss at delivery.[12] Silver and colleagues[13] found that maternal morbidity increases with increasing number of CDs. In their study, increasing number of CDs led to increased risks of placenta accreta, hysterectomy, transfusion of 4 or more units of red blood cells (RBCs), bladder, bowel or ureteral injury, ileus, intensive care unit admission, and longer operative time. Given this potential for serious complications in higher-order Cesareans, preoperative planning is essential. For example, at our institution all tertiary Cesarean sections or higher are crossmatched for 2 units of RBCs. These are often brought to the operating room before the start of surgery. However, it is unclear whether all patients undergoing a third or more Cesarean are at increased risk for blood loss requiring transfusion or if this risk is limited to a select few.

Silver and coworkers[13] found that the likelihood of transfusion increased from 2.3% in women undergoing a third Cesarean to 15.7% in women undergoing a sixth or more Cesarean; the risk was only 1.5% in women undergoing their second Cesarean. They did not report transfusion rates in women without a placenta previa. They did, however, exclude women with labor. In our study, 3.8% of

patients undergoing third or more Cesarean section required a blood transfusion. We found that placenta previa, prophylactic anticoagulation during pregnancy, and having labored are associated with transfusion. Without placenta previa, the risk for transfusion was only 1.4% and without any of these three risk factors, the risk of transfusion was only 0.7%. Given the low risk of transfusion in patients without the above risk factors, preparing blood in advance for all higher-order Cesareans may not be cost-effective. It is possible that for women undergoing third or more CD, as long as the patient does not have a placenta previa, there is no need to prepare blood in advance of the operation. Widening the criteria to women without placenta previa, labor, or anticoagulation use during pregnancy might be a more conservative approach, based on our findings. One study concluded that even collecting an admission type and screen for all patients undergoing Cesarean was not cost-effective; in the absence of a set of significant risk factors, which included history of Cesarean section, chorioamnionitis, and placenta previa, sending a routine type and screen on admission did not enhance patient care.[14]

Placenta previa was the most common risk factor for transfusion in this study; patients with a placenta previa had a 68.8% likelihood of requiring blood transfusion. Placenta previa is a well-known risk factor for PPH, and many studies have shown that it is the most significant risk factor for transfusion and peripartum hysterectomy.[15,16] The high likelihood of transfusion in patients with a placenta previa should prompt providers to counsel patients with placenta previa and two or more prior CDs that there is a high likelihood of transfusion and to plan for this eventuality.

Patients who were given prophylactic anticoagulation during pregnancy also had a significantly higher risk of transfusion. In our practice, prophylactic anticoagulation is routinely held for 24 to 48 hours before scheduled CD, so the patients were not anticoagulated at the time of their operation. It is unclear whether this increased risk is caused by some long-term effect of anticoagulation, by the resumption of anticoagulation postpartum, or by some confounding factor, such as the underlying reason these patients required anticoagulation. It is also possible that this risk factor is simply a result of overlap with other risk factors such as labor and placenta previa in this study. Due to the low incidence of transfusion, we were not able to perform a regression analysis to better address this question. This finding is consistent with those of previous studies that showed that the rate of hemorrhage is higher in women on peripartum anticoagulation, even those receiving prophylactic doses; however, there are several studies that show no increase in hemorrhage rate for women who are anticoagulated.[17-19]

As expected, operative time and estimated blood loss were associated with transfusion, but none of the preoperative risk factors examined were associated with transfusion. We examined traditional risk factors for transfusion (obesity, fibroids, maternal age) as well as other potential risk factors such as maternal race and IVF. IVF is a potential risk factor given its association with other adverse outcomes in pregnancy, including poor placental function.[20]

Strengths of our study include a large sample size, with all patients operated on and managed by the same group of physicians in one maternal-fetal medicine practice. All medical records and operative reports were available for review. Weaknesses of the study include its retrospective nature, with no standardized criteria for transfusion defined in advance, as well as a homogenous study population. The low incidence of transfusion limits our ability to identify independent risk factors for transfusion. Further studies could be used to analyze the true cost-effectiveness of routine crossmatch for patients without these preset risk factors for transfusion.

In conclusion, for patients undergoing a third or more CD, placenta previa is the risk factor most significantly associated with transfusion. Patients with placenta previa should be advised that they have a high chance of transfusion. Patients without placenta previa have a very low chance for transfusion and it may be unnecessary to prepare blood in advance of the operation. Labor and the use of anticoagulation during pregnancy may also be predictors of transfusion but more research is needed to determine their true association with transfusion in this population.

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