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Risk Factors for Severe Postpartum Hemorrhage after Cesarean Delivery: Case-Control Studies

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Abstract

Background—Women who undergo intrapartum caesarean delivery (CD) are at increased risk of postpartum hemorrhage (PPH) compared to those undergoing prelabor CD. To determine whether the presence and strength of the associations between individual risk factors and severe PPH vary among women undergoing prelabor CD or intrapartum CD, stratified analyses are needed according to CD subtype.

Methods—To identify risk factors for severe PPH within two distinct CD populations: prelabor CD and intrapartum CD, we performed two case-control studies. Women in each study cohort delivered at a tertiary obstetric center in the United States between 2002 and 2012. For each study,

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cases were women who had a blood loss ≥ 1500 ml or who received an intraoperative or postoperative transfusion up to 48 hr after delivery. Risk factors for severe PPH among women undergoing prelabor CD or intrapartum CD were examined in separate logistic regression models.

Results—For prelabor CD, we identified 269 cases and 550 controls. Clinical factors with the highest adjusted odds for severe PPH during prelabor CD were: general anesthesia (adjusted odds ratio (aOR) = 22.3; 95% confidence intervals (CI) = 4.9 – 99.9; reference group = spinal anesthesia), multiple pregnancy (aOR = 8.0; 95% CI = 4.2 – 15.0; reference group = singleton pregnancy), and placenta previa (aOR = 6.3; 95% CI = 3.4 – 11.8). For intrapartum CD, we identified 278 cases and 572 controls. Clinical factors with the highest adjusted odds for severe PPH during intrapartum CD were: general anesthesia (aOR = 5.4; 95% CI = 1.7 – 17.1); multiple pregnancy (aOR = 3.2; 95% CI = 1.7 – 6.3); and a predelivery hemoglobin ≥ 9.9 g/dl (aOR = 3.0; 95% CI = 1.3 – 6.9; reference group = predelivery hemoglobin < 11 g/dl).

Conclusion—Women who undergo prelabor CD and intrapartum CD have several shared risk factors for severe PPH (general anesthesia and multiple pregnancy). However, the risk factor profiles for severe PPH differed between these CD cohorts. Recognizing these differences may be important when planning resources and interventions for high-risk patients undergoing either prelabor or intrapartum CD.

Keywords

Postpartum Hemorrhage; Cesarean Section; Risk Factors

INTRODUCTION

Severe postpartum hemorrhage (PPH) is an important cause of maternal death and severe maternal morbidity.^{1–3} Compared to vaginal delivery, women undergoing cesarean delivery (CD) incur the highest risk of PPH and hemorrhage-related morbidity.^{4,5} Furthermore, evidence suggests that PPH during CD is occurring more frequently. In the United States, between 1994 and 2006, the rate of atonic PPH increased 160% among women undergoing CD after induction and 130% among women undergoing non-induced CD.⁶

The International PPH Collaborative group, which comprises an international panel of clinical epidemiologists, has called for more studies using clinically-rich data to better understand relevant, and potentially preventable, risk factors associated with PPH.⁷ Once risk factors for PPH are identified, clinical predictive rules could be developed. Implementation of predictive rules into clinical practice could optimize patient outcomes^{8,9} by improving the planning and timely mobilization of staffing and resources before bleeding onset. For example, when an ‘at-risk’ pregnant patient is identified before delivery, providers would have the opportunity to order and prepare blood products, obtain additional venous access, and prepare additional equipment for PPH management. High-risk pregnant patients could also receive enhanced postpartum surveillance for excessive blood loss. Lastly, for high-risk patients awaiting prelabor CD, arrangements could be made for delivery in an obstetric center with the necessary staff and resources for providing effective PPH management.

Identifying risk factors for PPH during CD has been challenging as key differences exist in patient, obstetric, and intrapartum characteristics for women who undergo prelabor CD versus CD after onset of labor or induction of labor (hereafter referred to as intrapartum CD). Based on data from two population-wide studies in Norway, the risk of PPH is reported to be higher for women undergoing intrapartum CD compared to prelabor CD (3.1% vs. 2% respectively).^{4,10} Although intrapartum factors, such as chorioamnionitis and oxytocin exposure,^{11–13} may explain why the risk of atonic PPH is higher after labor induction, to the best of our knowledge, only three studies have investigated risk factors for PPH for women who underwent elective CD and non-elective or emergency CD.^{14–16} Only one study differentiated women by the presence or absence of labor prior to CD.¹⁶ To determine whether the presence and strength of the associations between individual risk factors and severe PPH vary among women undergoing prelabor CD or intrapartum CD, stratified analyses are needed according to CD subtype.

The primary objectives of this observational study were to perform two case-control studies to identify independent predictors for severe PPH within each of the following CD subpopulations: prelabor CD and intrapartum CD.

METHODS

This study was approved by the Stanford University IRB (Protocol ID=25236). We performed two case-control studies to identify clinical risk factors for severe PPH after prelabor CD and intrapartum CD. Our study cohorts were identified from a population who delivered by CD at Lucile Packard Children's Hospital (LPCH), a tertiary care obstetric center, between January 2002 and December 2012.

To identify women who underwent CD between January 2002 and December 2006, we used the Stanford Translational Research Integrated Database Environment (STRIDE) through a combined search of International Classification of Diseases (ICD-9) procedure codes (74.x) and Current Procedural Terminology (CPT) codes (01961, 01963, 01968, 59510, 59515, 59618, 59620, 59622, 1008991, 1014218, and 1014220). Based on a standards-based informatics platform, STRIDE is a clinical data warehouse that contains linked demographic, administrative, and clinical data (from electronic or scanned medical records) from LPCH and Stanford University Medical Center. The clinical data warehouse can be searched using search queries inputted by programmers based in the Stanford Center for Clinical Informatics, Stanford University. We identified women with severe PPH through a combined search for ICD-9 codes for postpartum hemorrhage (666.x). Because an electronic medical record system was implemented at LPCH in 2007, we searched a computerized clinical database (LPCH Information and Knowledge System) to identify CDs between January 2007 and December 2012 through a search of Medicare Severity Diagnosis Related Group (DRG) codes 765 and 766. EBL and transfusion data for CDs between 2007 and 2012 were available in the clinical database. Between 2002–2006 and 2007–2012, there were a total of 6997 CDs and 8192 CDs respectively.

Trained research assistants (PH, BR) reviewed medical charts to determine whether patients met inclusion criteria for prelabor CD or intrapartum CD. Inclusion criteria for prelabor CD

were: scheduled CD without labor; CD following unsuccessful external cephalic version; and CD for obstetric or fetal indications, such as pre-eclampsia, non-reassuring fetal trace without labor or induction. Inclusion criteria for intrapartum CD were: women with documented evidence of painful regular contractions or induction of labor prior to CD. We excluded women with known hematologic or coagulation disorders (apart from those with HELLP syndrome) or who were anticoagulated prior to CD. Based on literature review,^{4,5,10,17–19} the criteria for severe PPH were: an estimated blood loss (EBL) 1500 mL after CD or RBC transfusion during or within 48 hr after CD. We selected severe PPH as our primary outcome for several reasons. Firstly, average EBL values during CD can approach EBL thresholds for defining PPH. Secondly, an EBL of 1500 ml may reflect the point where physiological compensation starts to fail resulting in greater obstetric morbidity.²⁰ Thirdly, EBL may often be underestimated. Therefore, to account for subjects in whom EBL may have been underestimated, we incorporated RBC transfusion within 48 hr of CD as a classifier for severe PPH. In each CD cohort, two controls were randomly selected with same year of delivery as each case using incidence density sampling. Each control had an EBL<1500 ml and no transfusion. EBL and transfusion data were reviewed in the medical records to confirm correct classification of each case and control.

Based on literature review^{5,10,14–16,21–23} and clinical plausibility, potential risk factors for severe PPH in each CD cohort were considered. For both CD cohorts, we abstracted data from the medical records for the following candidate variables: maternal age, self-reported race/ethnicity, weight, parity, gestational age at delivery, number of prior CDs, chronic hypertension, gestational diabetes, singleton/multiple pregnancy, gestational hypertension, pre-eclampsia, HELLP syndrome, hemoglobin (Hb) most proximate to delivery, time of CD (classified as weekday daytime [between 7am and 4.59 pm], weekday nighttime [between 5pm and 6.59 am], and weekend) and mode of anesthesia (spinal, epidural, combined spinal-epidural (CSE), or general anesthesia). We designated the final mode of anesthesia prior to surgical incision as the mode of anesthesia in our analysis (data on final anesthesia mode are presented in Supplemental Digital Content). For example, if, prior to surgery, a patient received a spinal as the primary anesthetic which ‘failed’, and then received a second block – a CSE – which provided adequate surgical anesthesia, the designated anesthesia mode was CSE. To account for temporality of the potential relationship between the pre-incision mode of anesthesia with severe PPH, we did not include information for patients who required *intraoperative* conversion from neuraxial to general anesthesia in our analyses. For prelabor CD, we abstracted additional data for the following characteristics: prior history of dilatation and curettage (D&C) or dilatation and evacuation (D&E), and prior myomectomy. For CD after labor, we abstracted additional data for the following characteristics: spontaneous vs. induced labor, labor augmentation with oxytocin, chorioamnionitis, and cervical dilatation prior to CD. In light of American College of Obstetricians and Gynecologists (ACOG) guidelines to avoid non-medically indicated deliveries before 39 weeks’ gestation,²⁴ we presumed that some women with a history of prior CD were admitted with spontaneous labor and underwent intrapartum CD before 39 weeks. Therefore, we accounted for number of prior CDs in our regression model for intrapartum CD. Because curettage of the uterus during a D&E or D&C may significantly damage the endometrium and uterine cavity to influence placental adherence, we only considered this variable in the prelabor CD cohort.

Primary indications for prelabor and intrapartum CD were also examined (data presented in Supplemental Digital Content) and were stratified by mode of anesthesia. The most common indications for prelabor CD were prior CD (56%) and macrosomia (23%). The most common indications for intrapartum CD were non reassuring fetal trace (76%) and labor arrest (32%). (Frequencies total more than 100% as some patients had more than one indication for intrapartum CD).

Among intrapartum CDs, we performed subanalyses to assess rates of severe PPH among women with cervical dilatation <10 cm who did and did not experience arrest of the first stage, and women with a cervical dilatation of 10 cm who did and did not experience a prolonged second stage of labor. Women were classified with arrest of the first stage of labor and prolonged second stage using criteria described by the American College of Obstetricians and Gynecologists²⁵ (see Appendix for full descriptions). These guidelines were in place during the study period.

STATISTICAL ANALYSIS

We performed two analyses to assess characteristics and risk factors for (i) women undergoing prelabor CD, and (ii) women undergoing intrapartum CD. Within each CD population, patient and obstetric characteristics for women with and without severe PPH were compared using ANOVA, Mann-Whitney U tests for continuous variables and χ^2 test and Fisher's exact test for categorical variables. For each analysis, the primary outcome was severe PPH. For each continuous variable associated with PPH we used restricted cubic spline functions to test whether the associations met the assumptions of a linear relationship. Continuous variables were categorized if they were not linearly related to the outcome using cubic spline function plots (maternal age and gestational age at delivery) or clinically relevant cut points (predelivery Hb). Multivariable analysis was performed using multivariable logistic regression, which included all variables with a P value <0.10 in the univariable analyses. We used variance inflation factor testing to assess collinearity between candidate variables. Collinearity was determined to be insignificant as variance inflation factor (VIF) scores for the prelabor CD ranged from 1.03 and 1.27 (mean VIF score=1.14) and for CD after labor ranged from 1.01 to 1.6 (mean VIF score=1.21). To account for the increased probability of making a type 1 error when making multiple comparisons, we adjusted the confidence intervals and P values for each comparison in our multivariable models using a Bonferroni correction.²⁶ Goodness of fit was evaluated using the Hosmer-Lemeshow statistic. We calculated the area under the receiver-operating characteristic curve (AUROC) using standard methods.²⁷ We recalculated the c-index for each model using 500 iterations of Efron's enhanced bootstrap method.²⁸ With approximately 270 cases in each CD cohort, a 1:2 ratio of cases:controls, a 10% prevalence for characteristics among controls, and an alpha of 0.05, we calculated that the smallest odds greater than one that could be detected with 80% power is an odds ratio of 1.85.

All analyses were conducted using STATA version 12 (StataCorp, College Station, TX). Data are presented as mean (SD), median [interquartile range] or n (%).

RESULTS

Prelabor Cesarean Delivery

In this cohort, we identified 269 women with severe PPH and 550 matched controls. Women with severe PPH had a significantly higher median EBL compared to controls (1600 [1500–2000] ml vs. 800 [600–900] ml; $P<0.001$). Among severe PPH cases, 223 (82.9%) women had at least 1500 ml EBL, and 148 (55%) women received RBC intraoperatively or within 48 hr post-CD. Among all women who received RBC, 91 women received RBC intraoperatively, and 90 women received RBC within 48 hr post-CD, of whom 33 (36.7%) had an EBL <1500 ml and did not receive intraoperative RBC. Twenty-four women (19 cases; 5 controls) experienced primary anesthetic block failure prior to surgery (Supplemental Digital Content).

Maternal, obstetric, intrapartum, and perioperative characteristics of women with and without severe PPH are presented in Table 1. Unadjusted and adjusted odds ratios for clinical factors selected for multivariable analysis are presented in Table 2. In the multivariable model, factors independently associated with severe PPH were: general anesthesia (adjusted odds ratio (aOR)=22.3; 95% confidence intervals (CI)=4.9 – 99.9; reference group = spinal anesthesia), multiple pregnancy (aOR=8.0; 95% CI=4.2 – 15.0; reference group = singleton pregnancy), placenta previa (aOR=6.3; 95% CI=3.4 – 11.8), pre-delivery Hb 9.9 g/dl (aOR=2.8; 95% CI=1.0 – 7.5 [reference group=pre-delivery Hb 11 g/dl]), Hispanic race (aOR=2.4; 95% CI = 1.0 – 5.8 [reference group=Non-Hispanic White]), and a history of prior D&C or D&E (aOR=1.9; 95% CI=1.2 – 3.0). Model calibration (Hosmer-Lemeshow test, $P=0.3$) and model discrimination (AUROC=0.86; 95% CI=0.83 – 0.89) were good. After 500 cycles of bootstrapping, the c index remained unchanged.

Intrapartum Cesarean Delivery

In this cohort, we identified 278 women with severe PPH and 572 matched controls. The mean EBL values were significantly higher among cases compared to controls (1685 (665) ml vs. 781 (202) ml; $P<0.001$). Among severe PPH cases, 209 (75.4%) women had at least 1500 ml EBL, and 157 (56.5%) women received RBC intraoperatively or within 48 hr post-CD. Among all women who received RBC, 51 women received RBC intraoperatively, and 122 women received RBC within 48 hr post-CD, of whom 59 (48.4%) had an EBL <1500 ml and did not receive intraoperative RBC. Maternal, obstetric, intrapartum, and perioperative characteristics are presented in Table 3. Because prior clinical studies have observed an association between labor augmentation with PPH,^{11,23,29,30} we forced labor augmentation with oxytocin into the final multivariable model. Sixteen patients (10 cases; 6 controls) experienced primary neuraxial block failure prior to surgery (Supplemental Digital Content). Severe PPH was more common among women who underwent CSE anesthesia and general anesthesia. Clinical factors independently associated with severe PPH are presented in Table 4. In the multivariable model, factors independently associated with severe PPH were: general anesthesia (aOR=5.4; 95% CI=1.7 – 17.1), multiple pregnancy (aOR=3.2; 95% CI=1.7 – 6.3), predelivery Hb 9.9 g/dl (aOR=3.0; 95% CI=1.3 – 6.9), predelivery Hb: 10–10.9 g/dl (aOR=2.6; 95% CI=1.4–4.9) [reference group = predelivery Hb 11 g/dl]), multiple pregnancy (aOR=1.8; 95% CI=1.1–2.9), and government-assisted insurance (aOR=1.6; 95%

CI=1.0–2.4). Compared to women who underwent primary CD, women with one prior CD had a reduced odds of severe PPH (aOR=0.4; 95% CI=0.2 – 0.9). Women aged ≥ 30 yr had a reduced odds of PPH compared to women aged less than 30 yr (aOR=0.7; 95% CI=0.5–1.0). The model had good calibration (Hosmer-Lemeshow test, P=0.47) and modest discrimination (AUROC=0.75; 95% CI=0.71–0.78). After bootstrapping, the c index was unaltered. In separate models, the interactions between magnesium with pre-eclampsia and gestational age at delivery were not statistically significant (data not presented).

Sensitivity and Subgroup Analyses

To determine whether point estimates for modes of anesthesia were influenced by women who experienced primary neuraxial block failure prior to surgery, we performed sensitivity analyses examining women in each CD cohort whose primary mode of anesthesia was successful. For each CD cohort, point estimates for mode of anesthesia did not appreciably change from those in the original multivariable models (data not presented).

Because general anesthesia may be considered more often for women with placental disorders, for the prelabor CD cohort, we performed an additional sensitivity analysis to assess point estimates for anesthetic techniques excluding women with abnormal placentation (n=51) or placenta previa (n=121). Based on chart review, we identified women with abnormal placentation based on information in the obstetrician's operative note or from a placental pathology report (if available). Among those without these placental disorders, we observed similar point estimates for anesthetic techniques to those in our original multivariable model (CSE aOR=3.87; 95% CI=1.93 – 7.73; epidural: aOR=1.7; 95% CI=0.3 – 9.5; general anesthesia: aOR=47.6; 95% CI=7.26 – 311.9).

For women undergoing intrapartum CD, we compared PPH frequencies among those with vs. without labor arrest before full cervical dilatation. Severe PPH was more common among women with vs. without labor arrest (132/203 (65%) vs. 214/382 (56%) respectively; P=0.04). Similarly, we compared PPH rates between those with vs. without a prolonged second stage of labor; rates were similar in both groups (36/61 (59%) vs. 99/151 (66%) respectively; P=0.37).

In both CD cohorts, we assessed the frequency of women who experienced an EBL ≥ 1500 ml, intraoperative and postoperative RBC transfusion stratified by predelivery Hb categories (Supplemental Digital Content). Among cases identified in each CD cohort, rates of intraoperative and postoperative transfusion were highest among women with a predelivery Hb level less than 10 g/dl. Lastly, to determine whether predelivery Hb influences the magnitude of blood loss, we performed sensitivity analyses with the outcome based solely on the criteria of an EBL ≥ 1500 ml. On multivariable analyses, we observed that predelivery Hb category was not independently associated with an EBL ≥ 1500 ml in each CD cohort (data not presented).

DISCUSSION

Using detailed clinical data abstracted from 1669 medical records, we performed two case-control studies to identify risk factors for severe PPH during prelabor CD and intrapartum

CD. Risk factors common to each CD cohort included: general anesthesia, predelivery anemia, and multiple pregnancy. Other risk factors identified in our analyses were also well-recognized: placenta previa (prelabor CD) and chorioamnionitis (intrapartum CD). We identified several risk factors that were less established, such as: CSE anesthesia, non-transverse uterine incision, prior D&C, and Hispanic race (prelabor CD); and GDM, young maternal age, government-assisted insurance, and primary cesarean delivery (intrapartum CD). Future studies are needed to determine whether confounding by indication explains the associations between CSE and general anesthesia with severe PPH.

Although a number of studies have sought to identify risk factors for PPH during CD,^{15,16,21,31} the majority have not accounted for key differences in the maternal characteristics and delivery indications between prelabor and intrapartum CDs.³² Only two studies examined risk factors across distinct CD populations; elective/non-elective CD¹⁶ and planned/emergency CD¹⁵. Consistent with our findings, these studies identified placenta previa and general anesthesia as key risk factors across all CD cohorts. However, neither study stratified cohorts according to the presence vs. absence of labor or induction before CD.

We believe that our approach to construct separate logistic models according to CD subtype is clinically justified for several reasons. It is not clinically intuitive to consider labor or other intrapartum characteristics as potential predictors in a single multivariable model for severe PPH during prelabor CD. Similarly, women with placenta previa are unlikely to be considered for induction or trial of labor, therefore it would be intuitive to consider placenta previa as a candidate variable only for women who undergo prelabor CD. However, from an epidemiological standpoint, we acknowledge that future cohort studies using nuanced clinical data are needed to investigate whether interactions truly exist between relevant predictors and the presence vs. absence of labor or induction prior to CD. Large study populations would also be needed to construct adequately sized derivation and validation study cohorts.

In both CD cohorts, general anesthesia had the highest adjusted odds of severe PPH compared with spinal anesthesia. Because some anesthesiologists may prefer to use general anesthesia for patients with placenta previa or abnormal placentation,³³ we excluded these conditions in our sensitivity analyses for the prelabor cohort, and observed that the association between general anesthesia and severe PPH persisted, albeit with wider confidence intervals. This association has been reported in other observational and randomized studies, with varying degrees of magnitude.^{15,16,21,31,34–36} General anesthesia may itself directly influence the likelihood of severe blood loss. Volatile agents have a concentration-dependent inhibitory effect *in-vitro* on uterine smooth muscle contractility,^{37,38} thereby increasing the likelihood of uterine atony. Volatile agents (halothane, sevoflurane) and induction agents (propofol) can also inhibit platelet function in a dose-dependent manner.³⁹ However, we cannot exclude the possibility of confounding by indication because patients with anticipated risk factors for PPH may be more likely to receive general anesthesia. For example, in the prelabor CD cohort, general anesthesia was used for 21% of women with placenta previa, 46% of women with abnormal placentation, and 22% of women with antenatal vaginal bleeding (Supplemental Digital Content). In the

prelabor CD cohort, women who underwent CSE anesthesia had a 3-fold increased odds of severe PPH compared to those receiving a single-shot spinal. The reason for this finding is unclear. Because equivalent doses of intrathecal local anesthetic drugs are commonly used for spinal and CSE anesthesia, it is doubtful that a drug effect explains this finding. Therefore, confounding by indication is also likely, as patients with anticipated risk factors for PPH may require longer durations of surgery and receive a CSE technique. To assess the potential for bias from confounding by indication for CSE and general anesthesia, context-specific studies are needed to examine the relations between these modes of anesthesia with severe PPH.

Predelivery anemia was associated with our primary outcome, which included a composite of major blood loss or postpartum transfusion; this association was not confirmed in our sensitivity analysis that focused on major blood loss only. These findings are consistent with those by Butwick et al. who reported that predelivery anemia is an independent risk factor for severe postpartum anemia after CD, classified by a postpartum Hb 8 g/dl.⁴⁰ Furthermore, several obstetric societies, including The Royal College of Obstetricians and Gynecologists (UK) and the French College of Gynecologists and Obstetricians, have published PPH guidelines recommending that a Hb level above 8 g/dl is a therapeutic goal.⁴¹ These observations, coupled with our findings, have important clinical relevance for several reasons. Firstly, antenatal anemia is a modifiable risk factor for transfusion. Secondly, in the non-obstetric literature, limiting anemia before surgery is a key component of patient blood management.⁴² With antenatal anemia affecting up to 25% pregnant women,⁴³ similar initiatives may be necessary to promote anemia correction before delivery. Future studies are needed to examine whether optimization of maternal Hb levels prior to delivery limits the likelihood of postpartum RBC transfusion. Thirdly, RBC transfusion may be used during acute episodes of blood loss as well as for treating symptomatic postpartum anemia in a non-bleeding patient. Studies are also needed to determine best approaches for anemia management during and after an episode of severe PPH.

We identified a number of other well-established risk factors, including: multiple gestation (both cohorts), placenta previa (prelabor CD) and chorioamnionitis (intrapartum CD).^{5,15,31,44} Other risk factors are less recognized. Hispanic women had a 2-fold increased odds of severe PPH compared to Caucasians, after prelabor CD, but not intrapartum CD. Disparities in PPH have been described by others.⁴⁵ These may due to differences in the provision of medical care as well as underlying social, biological, and genetic factors. Only one study has investigated whether type of uterine incision influences PPH risk. Coombs et al. reported that a classical uterine incision was an independent risk factor.²¹ Compared to a low transverse incision, a greater degree of blood loss may occur with non-transverse incisions because thicker and more vascular myometrial tissue may be surgically incised. The risk of PPH among women with prior D&E or D&C may be related to altered placentation.⁴⁶ Future studies are needed to determine whether this association is observed among women undergoing intrapartum CD. The relationship between GDM and severe PPH may be explained by fetal macrosomia, a recognized risk factor for PPH.⁴⁷ In the intrapartum CD cohort, women with a history of one prior CD had a lower adjusted odds of severe PPH compared to women with no prior CDs. Because of concern of uterine rupture, it is possible that obstetric providers are less likely to consider long periods of labor or

augmentation for women undergoing trial of labor after prior CD. This may partly explain why these women were at lower risk of severe PPH compared to those without a history of prior CD.

Our study had a number of limitations. Although we considered a large number of candidate variables, unmeasured factors may have influenced PPH risk, such as obstetric or anesthesia provider experience. In a systematic review, Bauer et al. previously reported that the risk of failed conversion of labor epidural analgesia to cesarean delivery anesthesia is higher if care is provided by a non-obstetric anesthesiologist compared with care given by an obstetric anesthesiologist.⁴⁸ Studies are needed to evaluate whether specific anesthetic practices that may influence the magnitude of blood loss, such as the use of high concentrations of volatile anesthetic and blood product use, vary according to anesthesia provider experience. Due to the low frequency of several factors, such as fibroids and prolonged second stage labor, we could not accurately examine associations between these variables with severe PPH. We did not collect data for the frequency, timing or indications for patients who underwent intraoperative conversion from neuraxial to general anesthesia. Given that combined rates of pre- and intraoperative conversion from neuraxial to general anesthesia are low (1.7%–5.8%),^{49–51} any influence of intraoperative conversion on the point estimates for severe PPH among those undergoing neuraxial anesthesia is likely to be small.

We did not assess risk factors among women who underwent elective or non-elective CD because we chose to differentiate our cohorts by the presence vs. absence of spontaneous labor or induction of labor. We chose this approach because patient characteristics and CD indications are known to markedly differ across these cohorts.³² Furthermore, determining the ‘electiveness’ of CD may have been more challenging, resulting in misclassification bias.

We identified women with abnormal placentation based on information in the medical record documented after the time of delivery. We elected not to include abnormal placentation as an *a priori* risk factor because we could not ascertain, from chart review, whether all cases of abnormal placentation were suspected during the antenatal period. We acknowledge this is an important limitation as abnormal placentation is strongly associated with major postpartum hemorrhage and massive transfusion.⁵² However, placenta previa and number of prior CDs are well known risk factors for abnormal placentation,⁵³ and both variables were considered as candidate variables in our regression model for the prelabor cesarean cohort.

The findings from our analyses cannot be used to determine individual patient prediction of severe PPH. Such analyses would require large population-wide cohort studies using nuanced clinical data. However, our data could be used to guide investigators in the selection of relevant candidate variables in studies investigating prediction models of PPH during CD. Relevant prediction models require external validation in independent cohorts.

In conclusion, our findings suggest that the risk factor profile for severe PPH differs according to whether CD is performed before or after the onset of labor or induction. To confirm these findings, population-wide studies are needed to determine whether data should be partitioned according to CD subtype.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Criteria for Arrest of First Stage of Labor and Prolonged Second Stage of Labor

We defined arrest of active phase of the first stage of labor if latent phase was completed and no documented evidence of cervical change for >2 hrs. These criteria were also used to define prolonged second stage for nulliparous women (second stage exceeding 2 hr and 3 hrs with and without regional anesthesia respectively) and for multiparous women (second stage exceeding 1 hr and 2 hr with and without regional anesthesia respectively).

These definitions were based on guidelines published by the American College of Obstetricians and Gynecologists in 2003 (ACOG Practice Bulletin Number 49, December 2003: Dystocia and augmentation of labor. *Obstet Gynecol* 2003;102:1445-54).

Table 1

Characteristics of Women with and without Severe Postpartum Hemorrhage undergoing Prelabor Cesarean Delivery.

	No Severe PPH (n=550)	Severe PPH (n=269)	P value
Maternal age (y)	35 (6)	34 (6)	0.07
Weight at delivery (kg) ^a	84 (22)	84 (22)	0.94
Insurance			0.09
Private	392 (71.3%)	176 (65.4%)	
Government-assisted/Other	158 (28.7%)	93 (34.6%)	
Race/Ethnicity			0.001
Non-Hispanic White	241 (43.8%)	77 (28.6%)	
Hispanic	130 (23.6%)	82 (30.5%)	
Non-Hispanic Black	28 (5.1%)	14 (5.2%)	
Asian	123 (22.4%)	76 (28.3%)	
Other	28 (5.1%)	20 (7.4%)	
Chronic hypertension	19 (3.4%)	23 (8.6%)	0.002
Gestational age at delivery (wks)	39 [37 – 39]	37 [34 – 38]	<0.001
Parity	1 [0–2]	1 [0–2]	0.78
Number of prior CDs			<0.001
0	204 (37.1%)	139 (51.7%)	
1	239 (43.4%)	68 (25.3%)	
2	88 (16%)	42 (15.6%)	
3	19 (3.4%)	20 (7.4%)	
Type of pregnancy			<0.001
Singleton	516 (93.8%)	210 (78.1%)	
Multiple pregnancy	34 (6.2%)	59 (21.9%)	
Placenta previa	29 (5.3%)	92 (34.2%)	<0.001
GDM	80 (14.6%)	59 (21.9%)	0.008
Pre-eclampsia	32 (5.8%)	37 (13.7%)	<0.001
Prior history of D&C or D&E	98 (17.8%)	66 (24.5%)	0.02
Prior history of myomectomy	27 (4.9%)	13 (4.8%)	0.96
Predelivery hemoglobin (g/dl) ^b	12.2 (1.1)	11.6 (1.4)	<0.001
Time of delivery			0.01
Weekday daytime	448 (81.5%)	195 (72.5%)	
Weekday nighttime	41 (7.5%)	32 (11.9%)	
Weekend	61 (11.1%)	42 (15.6%)	
Mode of anesthesia			<0.001
Spinal	379 (68.9%)	103 (38.3%)	
CSE	156 (28.4%)	117 (43.5%)	

	No Severe PPH (n=550)	Severe PPH (n=269)	P value
Epidural	11 (2%)	19 (7.1%)	
General anesthesia	4 (0.7%)	30 (11.1%)	
Type of uterine incision			<0.001
Transverse	531 (96.6%)	211 (78.4%)	
Other	19 (3.4%)	58 (21.6%)	

Data presented as n (%); mean (SD); median [IQR]

CD = cesarean delivery; D&C = dilatation and curettage; D&E = dilatation and evacuation; GDM = gestational diabetes

^aData missing for 1 case and 1 control

^bData missing for 6 cases and 10 controls

Table 2

Unadjusted and Adjusted Odds Ratios for Variables associated with Severe Postpartum Hemorrhage during Prelabor Cesarean Delivery

	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI) *	P value †
Maternal age (y) ^a			
< 34	Reference	Reference	
34–37	1.21 (0.85 – 1.74)	1.16 (0.63 – 2.14)	1.0
38	1.24 (0.88 – 1.76)	1.17 (0.64 – 2.14)	1.0
Insurance			
Private	Reference	Reference	
Government-assisted/Other	1.31 (0.96 – 1.79)	0.62 (0.35 – 1.07)	0.09
Race/Ethnicity			
Non-Hispanic White	Reference	Reference	
Hispanic	1.97 (1.35 – 2.88)	2.43 (1.02 – 5.78)	0.04
Non-Hispanic Black	1.56 (0.78 – 3.12)	2.42 (0.69 – 8.52)	0.49
Asian	1.93 (1.31 – 2.83)	1.9 (0.91 – 3.94)	0.14
Other	2.24 (1.19 – 4.19)	2.35 (0.73 – 7.58)	0.4
Chronic hypertension	2.61 (1.4 – 4.89)	1.59 (0.7 – 3.61)	0.27
Gestational age (wks) ^a			
38	Reference	Reference	
34 – 37	3.41 (2.43 – 4.78)	1.03 (0.56 – 1.87)	1.0
33	12.57 (7.18 – 22.0)	2.39 (0.93 – 6.18)	0.08
Number of prior CDs			
0	Reference	Reference	
1	0.42 (0.29 – 0.59)	0.65 (0.34 – 1.22)	0.44
2	0.70 (0.46 – 1.07)	0.67 (0.29 – 1.54)	1.0
3	1.54 (0.8 – 3.0)	0.66 (0.17 – 2.55)	1.0
Type of pregnancy:			
Singleton	Reference	Reference	
Multiple pregnancy	4.26 (2.71 – 6.7)	8.0 (4.25 – 15.04)	<0.001
GDM	1.65 (1.14 – 2.4)	1.52 (0.92 – 2.5)	0.1
Placenta Previa	9.34 (5.95 – 14.66)	6.33 (3.4 – 11.76)	<0.001
Prior D&C or D&E	1.5 (1.05 – 2.14)	1.88 (1.17 – 3.0)	0.009
Pre-delivery hemoglobin (g/dl)			
11	Reference	Reference	
10 – 10.9	1.58 (1.04 – 2.4)	1.11 (0.55 – 2.24)	1.0
9.9	2.95 (1.58 – 5.52)	2.80 (1.05 – 7.5)	0.04
Time of CD			
Weekday daytime	Reference	Reference	

	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI) *	P value [†]
Weekday nighttime	1.79 (1.1 – 2.93)	0.98 (0.4 – 2.39)	1.0
Weekend	1.58 (1.03 – 2.43)	1.64 (0.83 – 3.24)	0.25
Mode of anesthesia			
Spinal	Reference	Reference	
CSE	2.76 (1.98 – 3.84)	3.13 (1.71 – 5.71)	<0.001
Epidural	4.52 (2.02 – 10.09)	2.54 (0.56 – 11.44)	0.61
General anesthesia	30.36 (12.61 – 73.1)	22.25 (4.95 – 99.89)	<0.001
Uterine incision			
Transverse	Reference	Reference	
Other	7.68 (4.47 – 13.21)	4.12 (2.05 – 8.26)	<0.001

CD = cesarean delivery; CSE=combined spinal-epidural; D&C = dilatation and curettage; D&E = dilatation and evacuation; GDM = gestational diabetes

^aCategories created according to the relationship between log odds of the variable with the outcome, based on cubic spline function models.

^{*} The confidence intervals and P values for all pairwise comparisons presented in the multivariable model adjusted using a Bonferroni correction to account for multiple comparisons.

[†]Statistically significant associations in the multivariable model are denoted by bold text

Table 3

Antepartum and Intrapartum Characteristics of Women with and without Severe Postpartum Hemorrhage undergoing Intrapartum Cesarean Delivery

Characteristic	No Severe PPH (n=572)	Severe PPH (n=278)	P value
Maternal age (y)	32 (6)	30 (7)	<0.001
Weight at delivery (kg)	80 (16) ^a	81 (18)	0.44
Insurance ^b			<0.001
Private	362 (63.3%)	141 (50.7%)	
Government-assisted/Other	210 (36.7%)	137 (49.3%)	
Race/Ethnicity			0.01
Non-Hispanic White	203 (35.5%)	69 (24.8%)	
Hispanic	180 (31.5%)	116 (41.7%)	
Non-Hispanic Black	35 (6.1%)	13 (4.7%)	
Asian	126 (22%)	64 (23%)	
Other	28 (4.9%)	16 (5.8%)	
Chronic hypertension	15 (2.6%)	11 (4%)	0.29
Gestational age at delivery (wks)	39 [38–40]	39 [36–40]	0.002
Parity	0 [0–1]	0 [0–1]	0.72
Number of prior CDs			0.004
0	455 (79.6%)	243 (87.4%)	
1	90 (15.7%)	21 (7.6%)	
2	27 (4.7%)	14 (5%)	
Type of pregnancy			<0.001
Singleton	547 (95.6%)	242 (87%)	
Multiple pregnancy	25 (4.4%)	36 (13%)	
GDM	60 (10.5%)	51 (18.4%)	0.001
Pre-eclampsia	34 (5.9%)	32 (11.5%)	0.004
Predelivery hemoglobin (g/dl) ^c	12.3 (1.1)	11.8 (1.5)	<0.001
Type of labour:			0.49
Spontaneous	368 (64.3%)	172 (61.9%)	
Induction	204 (35.7%)	106 (38.1%)	
Oxytocin augmentation	387 (67.7%)	189 (68%)	0.92
Chorioamnionitis	68 (11.9%)	56 (20.1%)	0.001
Magnesium infusion	41 (7.2%)	38 (13.7%)	0.002
Cervical dilatation before CD			0.17
1–9 cm	384 (67.1%)	204 (73.4%)	
10 cm	152 (25.6%)	61 (21.9%)	
Missing	36 (6.3%)	13 (4.7%)	
Time of CD			0.05

Characteristic	No Severe PPH (n=572)	Severe PPH (n=278)	P value
Weekday daytime	168 (29.4%)	87 (31.3%)	
Weekday nighttime	237 (41.4%)	92 (33.1%)	
Weekend	167 (29.2%)	99 (35.6%)	
Mode of anesthesia			<0.001
Spinal	137 (24%)	40 (14.4%)	
CSE	44 (7.7%)	32 (11.5%)	
Epidural	376 (65.7%)	181 (65.1%)	
General anesthesia	15 (2.6%)	25 (9%)	
Type of uterine incision			0.05
Transverse	562 (98.2%)	267 (96%)	
Other	10 (1.8%)	11 (4%)	

Data presented as n (%); mean (SD); median [IQR]

CD = cesarean delivery; CSE=combined spinal-epidural; D&C = dilatation and curettage; D&E = dilatation and evacuation; GDM = gestational diabetes; PPH = postpartum hemorrhage

^aData missing for 1 patient

^bData missing for 1 case and 7 controls

^cData missing for 21 cases and 7 controls

Table 4

Unadjusted and Adjusted Odds Ratios for Variables associated with Severe Postpartum Hemorrhage during Intrapartum Cesarean Delivery

	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI) *	P value †
Maternal age (y) ^a			
< 30	Reference	Reference	
30	0.63 (0.47 – 0.84)	0.69 (0.48 – 1.0)	0.05
Insurance			
Private	Reference	Reference	
Government-assisted/Other	0.39 (0.32 – 0.47)	1.56 (1.0 – 2.44)	0.05
Race/Ethnicity			
Non-Hispanic White	Reference	Reference	
Hispanic	1.9 (1.32 – 2.71)	1.23 (0.6 – 2.51)	1.0
Non-Hispanic Black	1.09 (0.55 – 2.18)	0.58 (0.17 – 1.95)	1.0
Asian	1.49 (1.0 – 2.24)	1.47 (0.77 – 2.79)	0.93
Other	1.68 (0.86 – 3.29)	0.94 (0.31 – 2.87)	1.0
Gestational age (wks) ^a			
40	Reference	Reference	
39	1.06 (0.72 – 1.58)	1.23 (0.68 – 2.22)	1.0
35–38	1.32 (0.92 – 1.89)	1.25 (0.69 – 2.28)	1.0
<35	2.29 (1.42 – 3.71)	1.24 (0.45 – 3.43)	1.0
Number of prior CDs			
0	Reference	Reference	
1	0.44 (0.27 – 0.72)	0.43 (0.21 – 0.91)	0.02
2	0.97 (0.5 – 1.89)	0.49 (0.16 – 1.49)	0.37
Type of pregnancy:			
Singleton	Reference	Reference	
Multiple pregnancy	3.25 (1.91 – 5.54)	3.25 (1.67 – 6.31)	<0.001
GDM	1.92 (1.28 – 2.87)	1.83 (1.15 – 2.93)	0.01
Pre-eclampsia	2.06 (1.24 – 3.41)	1.53 (0.74 – 3.21)	0.25
Pre-delivery hemoglobin (g/dl)			
11	Reference	Reference	
10 – 10.9	2.64 (1.66 – 4.18)	2.6 (1.38 – 4.9)	0.001
9.9	3.44 (1.89 – 6.24)	2.99 (1.29 – 6.92)	0.005
Oxytocin augmentation	1.02 (0.75 – 1.38)	0.78 (0.47 – 1.31)	0.35
Chorioamnionitis	1.87 (1.27 – 2.75)	1.76 (1.13 – 2.75)	0.01
Magnesium infusion	2.05 (1.29 – 3.27)	1.26 (0.6 – 2.64)	0.54
Time of CD			
Weekday daytime	Reference	Reference	

	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI) *	P value [†]
Weekday nighttime	0.75 (0.53 – 1.07)	0.64 (0.39 – 1.03)	0.08
Weekend	1.14 (0.8 – 1.63)	1.05 (0.63 – 1.73)	1.0
Mode of anesthesia			
Spinal	Reference	Reference	
CSE	2.59 (1.45 – 4.62)	2.31 (0.91 – 5.85)	0.11
Epidural	1.65 (1.11 – 2.44)	2.06 (0.99 – 4.31)	0.06
General anesthesia	5.95 (2.69 – 13.14)	5.44 (1.73 – 17.12)	0.006
Uterine incision			
Transverse	Reference	Reference	
Other	2.32 (0.97 – 5.52)	2.75 (0.95 – 8.01)	0.06

CD = cesarean delivery; CSE = combined spinal-epidural

^a Categories created according to the relationship between log odds of the variable with the outcome, based on cubic spline function models.

^{*} The confidence intervals and P values for all pairwise comparisons presented in the multivariable model adjusted using a Bonferroni correction to account for multiple comparisons.

[†] Statistically significant associations in the multivariable model are denoted by bold text