Hemorrhagic Morbidity in Invasive Placentation With and Without Placenta Previa

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Scholarly Report Title: Hemorrhagic Morbidity in Invasive Placentation with and without Placenta Previa

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Abstract

TITLE: Hemorrhagic morbidity in invasive placentation with and without placenta previa

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Purpose: To compare hemorrhagic morbidity associated with invasive placentation with and without placenta previa

Methods: A retrospective cohort was assembled of all deliveries with histologically confirmed invasive placentation that delivered at a tertiary care referral center from 1997 to 2017. Risk ratios and 95% confidence intervals were calculated and adjusted for depth of placental invasion

Results: 105 pregnancies with invasive placentation were identified. Pregnancies with co-morbid placenta previa were more likely to require blood transfusion than those without (RR: 2.0; 95% CI: 1.3-3.1). Women with previa had larger median estimated blood loss and more units of packed red blood cells transfused (both $p<0.03$). Women with previa were more likely to have a hysterectomy (crude RR: 2.7; 95% CI: 1.8-3.8) and be admitted to the intensive care unit (aRR: 3.3; 95% CI: 1.1-9.6).

Conclusions: Among women with invasive placentation, those with a co-existing previa experienced greater hemorrhagic morbidity compared to those without. Pregnancies complicated by both invasive placentation and previa warrant multi-disciplinary planning and assurance of resource availability.

Glossary of Abbreviations

BIDMC: Beth Israel Deaconess Medical Center

CD: cesarean delivery

CDSD: cesarean delivery scar defect

IRB: institutional review board

MFM: Maternal-Fetal Medicine

PA: placenta accreta

PGY: post-graduate year

REDCap: Research Electronic Data Capture

SICU: surgical intensive care unit

SMFM: Society for Maternal-Fetal Medicine

Summary of Scholarly Project Question and Description of My Contribution to the Work

Detailed Introduction, Rationale, and Background for the Project

Placental disorders are well-described pregnancy complications commonly requiring the management of high-risk obstetricians. One such disorder, placenta previa, occurs when the placenta grows in the lower uterine segment and covers a portion of or the entirety of the internal cervical os, increasing the risk of antepartum bleeding in the second and third trimesters and guaranteeing hemorrhage with vaginal delivery, which is contraindicated in these pregnancies.[1] Another such disorder, globally termed invasive placentation (or specifically named placenta accreta (PA), increta, or percreta according to the depth of invasion; here invasive placentation and PA are used synonymously for the entire spectrum of disorders) occurs when the placenta morbidly adheres to the myometrial layer of the uterus rather than the normally interposed decidual layer. Similar to placenta previa, the increased risks of hemorrhage in pregnancies complicated by PA are well-described, and disorders of invasive placentation are one of the leading causes of life-threatening obstetric hemorrhage.[2]

The question that our research sought to address in the context of these two placental pathologies was the difference in hemorrhagic morbidity between women with PA alone compared to women with PA co-occurring with placenta previa. Both placenta previa and invasive placentation disorders share the common risk factor of prior cesarean delivery (CD) as the strongest predictor of their development.[3] Though the pathoetiology of PA has yet to be fully elucidated, some evidence suggests that defects in the uterine decidua in the location of a uterine scar promote both the invasive growth and abnormally low implantation that give rise to PA and placenta previa, respectively.[4] This theory explains the high co-occurrence of these two placental disorders and meaningfully differentiates them as one of our population subgroups compared to women with PA without placenta previa in whom the pathoetiology of their disorder does not involve a lower segment uterine scar.

Because placenta previa is an independent risk factor for post-partum hemorrhage, we hypothesized prior to conducting our study that women with both

placental disorders—previa and accreta—would sustain greater blood loss than women with invasive placentation alone. We used the binary outcome of need for transfusion as our primary outcome. Our secondary outcomes sought to understand the specifics of maternal hemorrhagic morbidity, namely the need for admission to the ICU, the volume and type of blood products transfused, and the need for hysterectomy.

Gaps that Our Research Helps to Fill

To our knowledge, no prior research specifically differentiated women with invasive placentation into two groups, one with co-occurring placenta previa and one without, and compared morbidity and mortality between the two. As explained above, it is likely that these two groups represent different etiologies for their invasive placentation and thus are likely meaningfully distinct subsets of the PA population. Because placenta previa can be diagnosed with near 100% certainty prenatally thanks to the precision of transvaginal ultrasound, understanding the increased morbidity associated with co-occurring PA and previa may have important management implications as discussed below.

Clinical, Research, and Policy Implications of Our Research

Our work has concrete clinical implications. Because our research established statistically significant differences between pregnancies with invasive placentation with co-morbid placenta previa compared to those without, these two subgroups may be distinguished clinically for risk stratification with regards to the primary and secondary outcomes we measured, all of which are meaningful to patients (e.g. preparing for a possible postpartum ICU admission). Our results suggest that patients with PA may be counseled with greater specificity regarding risks since our research shows that not all PA cases are similar, as those with comorbid placenta previa had significantly worse outcomes. Our research suggests that those with co-occurring placenta previa warrant various precautionary steps: multidisciplinary planning prior to delivery to assure the appropriate level of care is given (frequently involving gynecologic oncologists for cesarean hysterectomy, urologists for prophylactic ureteral stenting, and so forth); the involvement of transfusion specialists ahead of time to guarantee adequate blood bank

supplies; and perhaps involvement of the SICU in pre-operative planning given that greater than 1/3 of patients with both conditions required time in the SICU in our study.

The potential research implications of our work are broad. Research is currently being done to elucidate the aspects of the cesarean delivery scar defect (CDSD) that increase the risk for invasive placentation. Given the increased morbidity associated with PA when it occurs in the CDSD as demonstrated by our study, the importance of this type of research to clarify why the uterine scar permits this low implantation and abnormal invasion of the placenta is even further emphasized. Our study may spur more basic research in fields like pathology to clarify the histologic pathways that lead to invasive placentation. It may also help to generate clinical research to see if outcomes can be improved for women with comorbid PA and previa when greater prophylactic measures are taken prior to their deliveries as our research suggests is warranted in these dual-diagnosis cases.

The policy implications of our work are more speculative. Given that cesarean delivery is the chief risk factor for PA, policies that encourage the monitoring and evaluation of the CD rate to make sure each CD is an indicated and judicious one will slow the rate of rise of both invasive placentation and placenta previa. Hospital-level policies triggering multidisciplinary team planning for women with known PA may also decrease morbidity and mortality and are a natural extension of our research and that of others who have demonstrated improved outcomes with this type of foresight and planning.[5]

My Role in the Design, Execution, Analysis, and Writing

In the fall of 2017, Dr. Scott Shainker contacted me to aid him in a project of his design analyzing outcomes of pregnancies complicated by invasive placentation. I completed the required trainings to be added to the IRB and to gain access to BIDMC's medical records. Then, together with Dr. Bethany Mulla (a PGY-7 in her final year of MFM fellowship at BIDMC), I abstracted roughly 50% of the data needed for our analysis from the online medical record system of BIDMC in October and November of 2017. This process involved identifying all prenatal visits to assess for antepartum hemorrhage, reading through operative delivery notes for details on surgical

approaches and blood loss, and identifying peaks and valleys of various laboratory values through the course of the index pregnancy. I entered these data into a REDCap database designed for our project. When Dr. Mulla and I had collected all of the data for the assembled cohort, these were handed over to Dr. Michele Hacker and Dr. Anna Merport, doctorate-level statisticians who work within the Department of Obstetrics and Gynecology at BIDMC. They processed our data and produced statistical tables necessary for our analysis, identifying statistically significant differences in both our primary and secondary outcomes between the two subpopulations of our cohort.

After data analysis, I drafted an abstract of our presentation that I submitted to the other co-authors for edits and review. This required familiarizing myself with the existing literature on a range of topics relevant to our presentation. After submitting our final version of the abstract to the New England Perinatal Society, we were granted an oral presentation at the 2018 Scientific Meeting held in Newport, Rhode Island on March 2 – 4, 2018. As the presenting author, I created a PowerPoint presentation of our study and met with the statisticians to deepen my understanding of our analysis and outcomes. I presented our study during a 15-minute presentation on March 4, 2018. In August 2018, I drafted another abstract of our study for submission to the SMFM Annual Pregnancy Meeting. I sent it to the co-authors for edits and review and submitted the final version to the SMFM which was granted a poster presentation. I drafted the mock-up of our poster which I sent to the co-authors for comments and review. We finished the final product on January 31, 2019 in advance of the Annual Pregnancy Meeting. I will present our poster at the SMFM Annual Pregnancy meeting in Las Vegas on February 14, 2019. The abstract of our poster has been published in the January 2019 edition of the *American Journal of Obstetrics and Gynecology*, volume 220, number 1 on page S254.

Our manuscript was drafted exclusively by Dr. Bethany Mulla who sent it to the co-authors, including myself, for our edits and suggestions, which I gave her. I was not responsible for drafting any part of the manuscript. She submitted it to *Archives of Gynecology and Obstetrics* for publication. We are awaiting their decision.

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Appendix: Complete Manuscript

Hemorrhagic morbidity in invasive placentation with and without placenta previa

Running Title: Hemorrhagic morbidity and invasive placentation

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Abstract

Objective: To compare hemorrhagic morbidity associated with invasive placentation with and without placenta previa.

Study Design: Retrospective cohort of 105 deliveries from 1997-2017 with histologically-confirmed invasive placentation. We calculated risk ratios adjusted for depth of invasion and 95% confidence intervals.

Result: We identified 105 pregnancies with invasive placentation. Pregnancies with previa were more likely to require blood transfusion than those without (RR: 2.0; 95% CI: 1.3-3.1). Women with previa had larger median estimated blood loss and more units of packed red blood cells transfused (both $p \leq 0.03$). Women with previa were more likely to have a hysterectomy (crude RR: 2.7; 95% CI: 1.8-3.8) and be admitted to the intensive care unit (aRR: 3.3; 95% CI: 1.1-9.6).

Conclusion: Among women with invasive placentation, those with a co-existing previa experienced greater hemorrhagic morbidity compared to those without. Pregnancies complicated by both invasive placentation and previa warrant multi-disciplinary planning and assurance of resource availability.

Introduction

Invasive placentation (placenta accreta, increta or percreta) is a leading cause of life-threatening obstetric hemorrhage [1]. As such, it is a significant contributor to maternal morbidity, including blood transfusion and intensive care unit admission. Up to 90% of women with invasive placentation require blood transfusion, and 40% require more than 10 units of packed red blood cells. Invasive placentation has been associated with a maternal mortality risk of up to 7% [2]. Subsequent to the increased incidence of cesarean delivery, the incidence of invasive placentation has increased, particularly in the setting of placenta previa (previa) [3-6]. In the United States, the incidence of invasive placentation increased 30% from 2000-2011 among women with repeat cesarean delivery [3].

While women with invasive placentation are known to have significant morbidity and mortality risk, little is known about the role of a co-existing previa in term of hemorrhagic risk. Given that previa is an independent risk factor for postpartum hemorrhage, pregnancies complicated by invasive placentation and previa may be at increased risk of hemorrhagic complications beyond what would be expected with invasive placentation alone. Therefore, we evaluated pregnancies with histologically-confirmed invasive placentation and compared the perinatal hemorrhagic morbidity among pregnancies complicated by previa to those without. We hypothesized that invasive placentation with previa is associated with increased hemorrhagic morbidity compared to invasive placentation without previa.

Subjects and Methods

This was a retrospective cohort study of women with histologically-confirmed invasive placentation who delivered at a single tertiary referral medical center from January 1, 1997 to July 18, 2017. We identified cases by querying the Department of Pathology's clinical database

for the term ‘creta’ and reviewing pathology reports to confirm the diagnosis of invasive placentation. We confirmed the presence or absence of previa by either pathology report or the prenatal ultrasound report preceding delivery. If the diagnosis of invasive placentation was unclear from the pathology report, slides from the case were examined by a perinatal pathologist (JLH) to determine inclusion. We abstracted demographic information, medical history, and characteristics and outcomes of the index pregnancy from the medical record. Antenatal suspicion of invasive placentation was based on prenatal ultrasound records. The prenatal ultrasound diagnosis of suspected invasive placentation was based on the presence of at least one of the following previously published ultrasound markers: absence of hypoechoic retroplacental zone, multiple placental lacunae (vascular spaces), presence of bridging vessels, and retroplacental myometrial thickness less than 1mm [7].

Our primary outcome was blood product transfusion, which was defined as receiving one or more of the following within 48 hours of delivery: packed red blood cells, fresh frozen plasma, platelets, cryoprecipitate, and cell salvage. Our secondary outcomes included the transfusion of individual products within 48 hours of delivery, number of units transfused, estimated perinatal blood loss, hysterectomy, and admission to the intensive care unit. We obtained the type and volume of blood products from blood bank records and estimated blood loss from operative reports and delivery notes.

Data are presented as median (interquartile range) or proportion. We used the Wilcoxon-rank sum test to compare continuous data and the Chi-square or Fisher’s exact test for categorical data. We also performed log-binomial regression to calculate risk ratios (RR) and 95% confidence intervals (CI). We considered depth of invasion and number of prior cesarean deliveries as potential confounders; however, the low incidence of some outcomes restricted our ability to adjust for both. Thus, models are adjusted only for depth of invasion. Data were

analyzed with SAS 9.4 (SAS Institute Inc., Cary, NC). All tests were two-sided and p-values <0.05 denoted statistical significance. The protocol was approved by our institutional review board.

Results

We identified 334 potential cases of invasive placentation through our database query, of which 115 were histologically confirmed. Of the 219 potential cases that were excluded, 3 were hysterectomy specimens from non-pregnant patients, 1 was missing delivery outcome data, and 215 were identified in the query for 'creta' because the pathology report included comments such as "no evidence of accreta" or "rule out accreta". Of the 115 cases of histologically-confirmed invasive placentation, 10 were excluded due to pregnancy termination, leaving 47 (40.9%) pregnancies with co-existing previa and 58 (50.4%) without. Women with and without previa were similar with regard to baseline characteristics such as age, race/ethnicity and body mass index. However, women with previa were more likely to report current smoking, less likely to be nulliparous and more likely to have had a prior cesarean delivery as compared to women without previa. Among women with a prior cesarean delivery, 71.4% of those with previa and 66.7% of those without previa had a history of low transverse cesarean incision. Demographic characteristics and relevant obstetric and surgical history are shown in Table 1.

Antenatal suspicion of invasive placentation occurred more often for women with previa (72.3%) compared to those without (6.9%); those with previa also were more likely to experience antepartum bleeding (both p<0.001). Nearly all women with invasive placentation and a co-existing previa underwent cesarean delivery (97.9%). Median gestational age at delivery was earlier among pregnancies with previa. Prenatal and intrapartum characteristics are shown in Table 2.

Among women with invasive placentation, 85.1% with previa required a blood product transfusion as compared to 37.9% without previa ($p<0.001$). After adjusting for depth of invasion, women with previa were twice (95% CI: 1.3-3.1) as likely to receive a transfusion of any blood product compared to women without previa. When evaluating individual blood products, women with previa were more likely to received packed red blood cells, platelets, and cryoprecipitate; however, the groups were similar with regard to the incidence of transfusion of fresh frozen plasma and use of cell salvage. The incidences and risk ratios for blood product transfusion are shown in Table 3. Among those who received packed red blood cells, the median number of units received was significantly higher for those with previa [6.0 (3.0-12.0)] than those without [3.5 (2.0-6.0); $p=0.03$]. The median number of units of fresh frozen plasma received was similar for women with previa [4.0 (2.0-10.5)] and those without [3.0 (2.0-6.0); $p=0.53$)]. Similarly, there was no difference in the median units of cryoprecipitate received by those with previa [2.0 (2.0-5.0)] and those without [3.0 (1.0-6.0); $p=1.0$].

Median estimated perinatal blood loss in women with and without previa was 3500 (2000-6500) mL and 1200 (800-2100) mL, respectively ($p<0.001$). Compared to those without previa, those with previa experienced a significantly higher incidence of hysterectomy and intensive care unit admission (Table 3).

Discussion

Our findings support the hypothesis that women with invasive placentation and a co-existing previa have greater hemorrhagic morbidity than those without previa. Pregnancies complicated by both invasive placentation and previa were twice as likely to require a transfusion of at least one blood product compared to pregnancies without previa. Specifically, those with previa were more likely to receive packed red blood cells, platelets and

cryoprecipitate. Women with invasive placentation and previa also had a higher risk of hysterectomy and intensive care unit admission.

One prior study evaluated the presence of "massive blood loss," defined as receiving ≥10 units of red blood cells, for women with and without previa and reported a significant difference between those with previa as compared to those without in regard to requiring large volume blood transfusion.[8] In a secondary analysis of national data on hemorrhagic morbidity associated with primary cesarean delivery, women with previa were more likely to receive a transfusion of packed red blood cells and to have a hysterectomy [9], though none of the women had invasive placentation. Both of these studies suggest that among pregnancies without invasive placentation, previa is an independent risk factor for hemorrhagic morbidity. Though all the pregnancies in our study were complicated by invasive placentation, our findings are consistent with these studies.

Prenatal diagnosis of invasive placentation is associated with decreased maternal morbidity compared to intrapartum diagnosis and allows for pre-operative planning and care. [10-11] One intervention that has been shown to improve outcomes and reduce hemorrhagic morbidity in the setting of invasive placentation is a multidisciplinary team approach [12]. In our cohort, only four women without previa (6.9%) had a prenatal diagnosis of invasive placentation, which highlights the difficulty of diagnosing invasive placentation in the absence of previa. If we could enhance our ability to improve diagnose of invasive placentation in the absence of previa, thus allowing for multi-disciplinary care, we suspected hemorrhagic morbidity for these women could be even further reduced.

Our study has several limitations. First, some of our outcomes are subjective; specifically, the need for transfusion and estimated blood loss are physician-dependent. Due to the retrospective study design we could not assess adherence to standard guidelines for

transfusion, which may have changed over the course of the study period. Given that previa is a known risk factor for peripartum hemorrhage, regardless of invasive placentation, those with previa may have been more likely to be transfused due to heightened physician awareness and concern. In addition, the generalizability of our findings may be limited as our study was performed at a single institution which serves as a regional referral center for invasive placentation.

Importantly, our study also has several strengths. All cases of invasive placentation and previa were histologically confirmed. Our samples were collected over two decades, which lessened the likelihood of uniform treatment of the diagnosis and increased the likelihood of management variation, which may better approximate clinical care. To our knowledge, this is the first study to attempt to assess the individual risk of a previa with invasive placentation as it pertains to maternal hemorrhagic morbidity.

Though women with invasive placentation and co-existing previa had a higher risk of hemorrhagic morbidity compared to women with invasive placentation alone, both groups had a rather high absolute risk of hemorrhage, as measured by blood product transfusion, and intensive care unit admission. This highlights the importance of prenatal diagnosis and *preparation for delivery involving a multi-disciplinary team. Future work is needed to improve antenatal diagnosis to ensure multidisciplinary delivery planning and reduction in hemorrhagic morbidity.*

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