Transfusion requirements with hybrid management of placenta accreta spectrum incorporating delayed hysterectomy: a retrospective study

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Abstract

Objective: To compare the number of units of red blood cells (RBCs) transfused in patients with placenta accreta spectrum (PAS) treated with or without a multidisciplinary algorithm including placental uterine arterial embolisation (P-UAE) and a selective use of delayed hysterectomy. Design: Retrospective review Setting: Tertiary care hospital, United States, 2001-2018 Population: Women with histologically-confirmed PAS delivered after 24 weeks gestation Methods: Comparison of transfusion outcomes among PAS cases managed with versus without a multidisciplinary algorithm. To improve the equity of comparison, analyses were made separately among scheduled and unscheduled cases. Subjects were assigned to one of four cohorts: scheduled/per-algorithm, scheduled/off-algorithm, unscheduled/per-algorithm, or unscheduled/off-algorithm. P values were adjusted for multiple testing. Main outcome measures: RBCs transfused and estimated blood loss (EBL). Secondary outcomes included peri-operative complications and intensive-care unit admissions. Results: 87 subjects were identified: 36 treated per-algorithm (30 scheduled, 6 unscheduled), 51 off-algorithm (24 scheduled, 27 unscheduled). Among scheduled deliveries, 9 (30.0%) subjects treated per-algorithm received RBCs, compared to 20 (83.3%) subjects treated off-algorithm ($p<0.01$), with a median (interquartile range[IQR]) of 3.0 (2.0, 4.0) and 6.0 (2.5, 7.5) units transfused ($p=0.13$), respectively. Among unscheduled deliveries, 5 (83.3%) subjects treated per-algorithm were transfused RBCs compared to 25 (92.6%) off-algorithm ($p=0.47$), with a median (IQR) of 4.0 (2.0, 6.0) and 8.0 (3.0, 10.0) units transfused ($p=0.47$), respectively. Peri-operative complications were similar between cohorts. Conclusions: A multidisciplinary algorithm including P-UAE and selective use of delayed hysterectomy is associated with a lower rate of blood transfusion in scheduled but not unscheduled cases.

Introduction

Placenta accreta spectrum (PAS) includes the extension of trophoblast into or through the uterine myometrium, typically along a dehisced uterine scar[1]. Ongoing research is contemporising the PAS classification (accreta, increta, and percreta), although placenta percreta differs from the other two subtypes as placentation extends beyond the uterine serosa to potentially involve adjacent organs such as the bladder. The most important complication is blood loss, which can quickly deteriorate into coagulopathy and multiorgan failure. Observational data support improved outcomes with sonographic antenatal diagnosis, scheduled preterm caesarean delivery, and management within centres of excellence[2-6]. Beyond these data, optimal management strategies are largely guided by expert opinion, and in the United States, the generally accepted approach is a planned, preterm caesarean hysterectomy[5]. With recent data from other countries, there is renewed interest in conservative management strategies in which hysterectomy is avoided, typically

with expectant management of placental resorption[7, 8]. A delayed or interval hysterectomy is considered a hybrid approach in women not desiring future fertility, with the intention to minimise severe blood loss and operative complications associated with immediate hysterectomy, while mitigating the long-term risks of leaving the placenta in-situ such as delayed haemorrhage or endomyometritis[9].

In 2005, our institution implemented a multidisciplinary algorithm to manage PAS, which has previously been described[10, 11] and continues to undergo periodic revisions based on our experience and review of the literature. Our current algorithm (Supplemental Figure 1) includes two critical elements: (1) prophylactic placental uterine artery embolisation (P-UAE); (2) individualised timing of hysterectomy based on the intraoperative assessment of placentation. P-UAE is an adjunct to decrease vascularity within the puerperal uterus by selectively targeting the uterine arteries and collateral cervicovaginal branches[12, 13]. P-UAE is performed in all cases, immediately after caesarean delivery. Delayed hysterectomy is reserved for certain cases of placenta percreta with extensive extrauterine placentation, such as significant parametrial or bladder involvement, in order to allow physiologic regression of pregnancy-induced collateral vasculature prior to performing completion hysterectomy.

The objective of this study was to compare the number of units of red blood cells (RBCs) transfused and the estimated blood loss (EBL) in patients with PAS treated with versus without the algorithm. To improve the equity of comparison, analyses were made separately among scheduled and unscheduled cases.

Methods

This is a retrospective cohort study of subjects with histologically-confirmed PAS managed at Duke University Hospital between 2001 and 2018. Outcomes for subjects treated in accordance with the multidisciplinary algorithm (*per-algorithm*) were compared to those whose treatment did not follow the algorithm (*off-algorithm*). The *per-algorithm* criteria was defined as (1) P-UAE at the time of caesarean, and (2) documented decision-making within the operative report to pursue immediate versus delayed hysterectomy. A subject not meeting the two aforementioned criteria was considered *off-algorithm* . Given that an urgent delivery has previously been demonstrated as a critical factor in the outcomes of PAS[14], the two cohorts were further divided into scheduled and unscheduled cases, depending whether delivery itself occurred on its planned date (*scheduled*), or performed on an emergent or add-on basis (*unscheduled*). Reasons for unscheduled deliveries are noted. Thus, baseline characteristics and clinical outcomes from four cohorts were studied: scheduled/per-algorithm, scheduled/off-algorithm, unscheduled/per-algorithm, and unscheduled/off-algorithm.

Primary outcomes included surrogate markers for blood loss, including the number of units of red blood cells transfused (RBCs), and the estimated blood loss (EBL). We assessed RBCs given intraoperatively, postoperatively, and in total. For subjects who underwent hysterectomy at the time of delivery, the total number of RBCs transfused was determined for caesarean hysterectomy plus any associated hospitalisation. For subjects who underwent a delayed hysterectomy, the total RBCs was the sum of RBCs transfused for both caesarean delivery plus delayed hysterectomy, and any associated hospitalisations. When comparing the volume transfused, only subjects who received any RBCs were used for analysis. The total EBL was the combined EBL from the caesarean delivery plus delayed hysterectomy if performed. If there was a discrepancy noted in documentation between the surgeon's EBL and anaesthesia's record for EBL, anaesthesia's documentation was used.

Secondary outcomes included other blood products received (fresh frosen plasma [FFP], cryoprecipitate, and platelets), postoperative disposition (intensive care unit [ICU] or routine nursing care), intraoperative complications (unintentional bladder injury, any ureter injury, any bowel injury), composite interventional radiology complications (paresthesia, postembolisation syndrome, ischemic complications), postoperative complications (venous thromboembolism, surgical site infection, wound breakdown, sepsis, pulmonary edema, or death). For any subject that had both a caesarean and delayed hysterectomy, the above complications were assessed and combined from both surgeries. Length of stay was additionally noted. For subjects who underwent hysterectomy at the time of delivery, the length of stay was measured from surgery to discharge.

For subjects who underwent a delayed hysterectomy, the length of stay was combined from the inpatient stays after caesarean delivery plus postoperative stay after delayed hysterectomy.

Subjects were identified by retrospective review of cases between 2001 (the earliest available data) through 2018. To increase the number of subjects available for comparison, we retrieved cases prior to the initiation of the protocol (between 2001 and 2005). Final pathology reports were queried using the search terms "accreta", "increta", and "percreta", as well as corresponding ICD-9 and ICD-10 codes. Subjects with pre-viable deliveries (under 24 weeks) were excluded, as were those with microinvasive accreta on final pathology. We excluded any subject that desired fertility and pursued total conservative management.

Medical records (both paper and electronic) were extracted for demographic data, clinical course, prognostic factors by the primary author (L.A.G.) and a colleague listed in the acknowledgments (I.V.R). In cases with complex management and intraoperative surgical decision-making, appropriate data entry was independently and blindly adjudicated by four members of the core PAS team and co-authors (J.B.G., C.A.G., A.A.S., and J.R.), and another from radiology (M.B.), listed in the acknowledgments. Data were combined into a REDCap (Research Electronic Data Capture 8.10.9) database for analysis. The primary outcomes were compared between per-algorithm versus off-algorithm separately for the scheduled and unscheduled cohorts. Continuous variables between the two respective cohorts were compared using Wilcoxon rank sum tests, and categorical variables were compared using either Pearson's chi-square test or Fisher's exact test, depending on the number of events in each cohort. Secondary outcomes were examined with descriptive statistics. Data were de-identified and analyses were done in SAS 9.4 (SAS Institute Inc., Cary, NC), at a significance level of 0.05 two-tailed. P values were adjusted for multiple testing using the Holm step-down procedure to control the familywise error rate at 5%. The study was approved by the Duke Health Institutional Review Board (IRB).

Results

There were 95 cases of histologically-confirmed PAS between 2001 and 2018, of which 8 subjects were ineligible due to previability (n=1) or microinvasive accreta on final placental pathology (n=7). Due to inconsistent documentation, is unclear how many patients pursued total conservative management during this time period. Subject recruitment is demonstrated in Figure 1. Of the 36 cases managed per-algorithm, 30 subjects underwent a scheduled delivery at a median (interquartile range [IQR]) of 35.4 (34.3, 36.0) weeks gestation. The remaining 6 delivered unscheduled at a median (IQR) of 32.1 (29.9, 34.1) weeks gestation, with the components of the multidisciplinary algorithm able to be mobilised in time for delivery. Of the 51 subjects not delivered in accordance with the current multidisciplinary algorithm, 24 subjects were scheduled at a median (IQR) of 37.0 (36.5, 37.6) weeks gestation, and 27 subjects delivered unscheduled at a median (IQR) of 34.0 (31.1, 37.4) weeks gestation. Baseline and delivery characteristics for the four cohorts are presented in Table 1. Eight cases were managed prior to the introduction of the protocol (2001-2005).

All subjects (n=87) underwent a hysterectomy. In total there were 24 delayed hysterectomies completed (22 per-algorithm, and 2 off-algorithm because no P-UAE was used after caesarean). In subjects managed per-algorithm, 14 hysterectomies were performed at the time of caesarean (13 scheduled, 1 unscheduled), and 22 delayed hysterectomies were performed (17 scheduled, 5 unscheduled). For subjects not managed with the multidisciplinary algorithm, there were 49 hysterectomies at the time of caesarean (22 scheduled and 27 unscheduled), and 2 delayed hysterectomies (both in the scheduled cohort).

Primary outcomes are demonstrated in Table 2. Among scheduled cases, 9 (30.0%) subjects managed per-algorithm were transfused RBCs compared to 20 (83.3%) subjects managed off-algorithm ($p<0.01$). Subjects who were managed per-algorithm received a median (IQR) of 3.0 (2.0, 4.0) RBC units, while subjects managed off-algorithm received 6.0 (2.5, 7.5) ($p=0.13$). In contrast to the scheduled deliveries, there was no significant difference in the rate of transfusion among unscheduled deliveries: five (83.3%) subjects managed per-algorithm were transfused RBCs, compared to 25 (92.6%) subjects managed off-algorithm ($p=0.47$). Unscheduled/per-algorithm subjects received a median (IQR) of 4.0 (2.0, 6.0) RBC units compared to 8.0 (3.0, 10.0) in unscheduled/off-algorithm subjects ($p=0.47$).

EBL (mL) followed a similar pattern to RBCs transfused. The median (IQR) of the combined EBL (the sum of the EBL from caesarean and the EBL from delayed hysterectomy, where appropriate) for scheduled subjects managed per algorithm was 1275 (1000, 2000), compared to 3000 (2125, 3750) for scheduled, off-algorithm cases ($p<0.01$). There was no significant difference among unscheduled cases for total blood loss: median (IQR) for the combined EBL for unscheduled cases managed per-algorithm was 2150 (1350, 2900), compared to 3000 (2000, 4300) for unscheduled cases managed off-algorithm ($p=0.47$).

Secondary outcomes are demonstrated in Table 3. Among scheduled deliveries, no (0.0%) subject managed per-algorithm was admitted to the intensive care unit (ICU), compared to 6 (25.0%) subjects off-algorithm. Among unscheduled deliveries, 3 (50.0%) subjects managed per-algorithm were sent to the ICU compared to 12 (44.4%) managed off-algorithm. Median (IQR) days for the total length of stay was higher for per-algorithm cases (median [IQR] 6.0 [3.0, 7.0] if scheduled, and 7.5 [7.0, 9.0] if unscheduled). The rate and amount of transfusion of additional blood products was lowest for subjects managed per-algorithm with a scheduled delivery (fresh frosen plasma [FFP]: n=3 [10.0%]; cryoprecipitate: n=1 [3.3%]; and platelets: n=0 [0.0%]). The rate of transfusion for cryoprecipitate was highest among unscheduled cases, as 2 (33.3%) subjects managed per-algorithm and 11 (40.7%) subjects managed off-algorithm were transfused. No subject managed per-algorithm was given platelets, compared to 9 (37.5%) scheduled/off-algorithm subjects and 9 (33.3%) unscheduled/off-algorithm subjects. Tranexamic acid was given most frequently in subjects managed per-algorithm after its adoption following the WOMAN trial in 2017[15].

Intraoperative complications were similar across cohorts. Two (6.7%) subjects managed per-algorithm with a scheduled delivery had an unintentional cystotomy or ureteral injury, compared to 3 (12.5%) among the scheduled/off-algorithm cases. There was one IR complication noted, with the subject (per-algorithm/scheduled) having a self-limited paresthesia in the femoral nerve distribution, due to iatrogenic nerve injury rather than target embolisation The rates of postoperative complications were otherwise similar among cohorts, including venous thromboembolism, surgical site complications. There were no maternal deaths.

Discussion

Main Findings

Using EBL and the rate of RBC transfusion as a proxy for blood loss, this retrospective study assesses a multidisciplinary algorithm for PAS including the routine use of P-UAE and individualised use of immediate or delayed hysterectomy, stratified by scheduled and unscheduled deliveries. Among scheduled deliveries, fewer RBCs were transfused when the multidisciplinary algorithm was used. The rate of transfusion, EBL, and ICU admission rates were highest among unscheduled cases, and the use of the multidisciplinary algorithm was not associated with a reduced rate of transfusion or estimated blood loss in these cases.

Interpretation

We initially developed our multidisciplinary algorithm in 2005 incorporating delayed hysterectomy in order to avoid extensive blood loss, transfusion, and bladder resection commonly experienced with caesarean hysterectomy[23]. Concerns regarding the risk of infection or secondary postpartum haemorrhage with a retained placenta were balanced with the known risk of surgical morbidity with placenta percreta[8]. The algorithm's bifurcation in decision making allows for individualised risk-benefit assessment, taking into consideration the extent of extrauterine involvement of adjacent anatomic structures. This risk-benefit discussion for the management of women with PAS begins antenatally, and includes thorough counseling with the patient preoperatively about the investigative approaches.

At the onset of our multidisciplinary algorithm to the present, however, observational data on the safety of caesarean hysterectomy have evolved. The present study echoes previous data suggesting that an experienced and multidisciplinary team, as well as scheduled (i.e. non-urgent) deliveries are associated with less blood loss. Our study supports the findings of Erfani *et al* [6], in which transfusion outcomes were improved with an algorithmic approach when delivery was scheduled. Although our results agree with the latter study,

the institutional algorithms have markedly different approaches to management. Regardless of the specific components within the algorithm, the improved outcomes from both studies underscore that antenatal diagnosis of PAS is critical as it provides an opportunity for referral to subspecialty care and allows for multidisciplinary delivery planning. Over the past two decades, the development of regional, high-volume centres has been associated with reduced blood loss, transfusion, and perioperative complications for patients with PAS. As the safety of institutional multidisciplinary algorithms using caesarean hysterectomy has improved, particularly in specialised centres[3, 4], the risks of delayed hysterectomy may outweigh the benefits for the majority of PAS cases. A randomised trial to answer this question is unlikely. Furthermore, recent data suggest significant patient-reported anxiety, grief, and depression in the setting of PAS[16]. While not studied in the present manuscript, delayed hysterectomy may prolong the risk of a patient's psychological experience with PAS and must be considered.

Uterine artery embolisation is a well-accepted modality in the acute management of refractory postpartum haemorrhage. Targeted embolisation has been increasingly employed as an alternative method for surgical treatment or in association with surgery for uterine myoma, vascular malformations, and interstitial ectopic pregnancies. With placental uterine artery embolisation, there is a deliberate search for, and embolisation of collateral arterial blood supply to the uterus. Embolisation of placental arterial blood supply is carried out with large polyvinyl alcohol particles (>900 microns) which provide a more durable occlusion than temporary gelfoam material, which is known to allow for arterial recanalisation within approximately two weeks[21]. The role of targeted embolisation in the adjunctive management of PAS remains under investigation[12, 13, 17-20]. Data are published on its use in caesarean hysterectomy: one study of seven patients managed at Weill Cornell Medical Center with pathologic placenta increta, treated with a embolisation after caesarean delivery and prior to hysterectomy, demonstrated a significantly lower median estimated blood loss, transfusion requirement, and length of ICU stay compared to a control group with caesarean hysterectomy and no UAE[13].

Strengths and limitations

A strength of this study is the analysis of scheduled and unscheduled cases separately. The clinical scenario in which a patient presents with bleeding prior to surgery may confound the demand for blood transfusion. An additional strength includes the seventeen-year history of collecting data. Both paper and electronic charts were verified twice prior to data entry, and complex cases were blindly reviewed by a team including members from maternal fetal medicine, gynecologic oncology, radiology, and interventional radiology.

Study limitations include the retrospective data collection which is limited by the time periods for which data were entered. Until 2017, operative notes did not include images. Therefore, we were dependent on the surgical teams' documented assessment of placentation in the operative note, which is limited by subjectivity and, therefore, impossible to standardise for comparison aside from the fact that these cases were managed by the same four surgeons (C.A.G, J.B.G, A.A.S, P.S.L). As team learning improved with experience, the surgical team may have felt more comfortable proceeding with caesarean hysterectomy rather than pursuing a delayed approach. Subjects who underwent a delayed hysterectomy were also prone to selection bias, as they had to live within thirty minutes of the hospital and have social support that would permit an emergent presentation to the hospital if needed. Additionally, the past two decades have seen an innovation in surgical instruments, such as vessel sealing devices, which may contribute to decreased surgical blood loss. Furthermore, while this study represents the largest cohort of delayed hysterectomy to date, a small number of subjects limits our ability to adequately control for potential confounders and is underpowered to assess intraoperative or postoperative complications. Lastly, the multidisciplinary algorithm places a significant demand on institutional resources, and, therefore, may not be generalisable to other centres or patient populations.

Conclusion

Practical recommendations

A multidisciplinary algorithm including routine use of P-UAE followed by selective use of immediate or

delayed hysterectomy appears to be safe and feasible in appropriately selected patients, but in this dataset is not associated with a reduced demand for blood transfusion in unscheduled deliveries. Identification and stratification of patients at risk for emergent delivery are needed in order to optimise patient outcomes within multidisciplinary teams.

Research recommendations

While associated with a lower rate of transfusion for scheduled deliveries, it is unclear if the risks of delayed hysterectomy outweigh the benefits when compared to cesarean hysterectomy. While a randomised trial is unlikely, observational data of PAS cases managed with a delayed approach may be pooled to improve the strength of comparison to cesarean hysterectomy. Additionally, further evaluation of P-UAE is needed to assess efficacy in reducing blood loss and transfusion requirements in PAS, and whether or not the embolisation makes a clinical impact with reduced blood loss at the time of surgery. A cost-effectiveness study is also warranted as it contributes to operative time.

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Contribution to authorship:

LAG : Writing – original draft, data curation, investigation, project administration; **JMW:** formal analysis, writing – review; **JBG:** conceptualization, methodology, validation, resources, writing – review; **PSL** : conceptualization, methodology, resources; **CAG:** conceptualization, methodology, validation, resources, writing – review; **KAH:** writing – review; **CFP:** conceptualization, methodology, validation, resources, writing – review; **JEM:** resources, writing – review; **WPR** : resources, writing – review; **ASH:**resources, writing – review; **KCS** : resources, validation, writing – review; **AAS** : conceptualization, methodology, validation, writing – review; **AHJ:** methodology, validation, writing – review; supervision

Details of Ethics Approval:

This study has been approved on 6/25/2018 by the Duke Institutional Review Board (Pro00100007 and Pro00025434), and has been determined to be in compliance with all HIPAA regulations.

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