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Coagulopathy in surgical management of placenta accreta spectrum

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ABSTRACT

Background: One of the major complications of the placenta accreta spectrum (PAS) is the development of coagulopathy. The detection, prevention and prompt treatment of coagulopathy may be lifesaving.
Objective: Our objective was to study selected factors associated with coagulopathy in the management of PAS by a well-established multidisciplinary team.
Study design: This is a retrospective review of all patients with pathologically proven PAS (including placenta accreta, increta or percreta) who underwent surgery by our multidisciplinary team between January 2011 and February 2017. Coagulopathy in this setting was defined as a platelet count of <100,000/mm^3, international normalized ratio >1.5, and/or fibrinogen <300 mg/dL based on institutional protocols developed by our Division of Transfusion Medicine & Coagulation. The outcomes of those patients with and without coagulopathy were compared with appropriate adjustments. Receiver operating characteristics curves (ROCs) were constructed to assess the ability of select variables to discriminate between women with and without coagulopathy, and the area under the curves (AUCs) were calculated.
Results: Of 123 singleton patients with PAS, 37 (30.1%; 95%CI 22.1–39.0) developed coagulopathy and 86 (69.9%; 95%CI 61.0–77.9) did not. Baseline patient demographic characteristics did not differ significantly between these groups. Estimated blood loss (median and Inter-quartile range) was 2100cc (1800, 400) and 1400 (1000, 2500) in the presence and absence of coagulopathy, respectively ($P < 0.01$). The overall number of units of red blood cells (RBC) transfused was greatest in the coagulopathy group [3 (2, 9) vs. 1 (0, 4); $P < 0.01$]. Univariate regression analysis confirmed the association between coagulopathy and (i) the number of units of RBC's transfused, and (ii) the estimated blood loss. ROC curves showed that an estimated blood loss $\geq$ 1500 mL had the best discriminating power. Depth and/or severity of placental invasion were not associated with coagulopathy in patients with PAS.
Conclusions: Coagulopathy in patients with PAS undergoing hysterectomy is strongly associated with blood loss and replacement. It may be prudent to establish protocols that aggressively monitor for, and treat, coagulopathy when EBL exceeds 1500 mL in such surgeries, prior to the development of clinical coagulopathy which if uncorrected may lead to massive blood loss.

Introduction

Three degrees of morbidly adherent placentation have traditionally been defined: placenta accreta (adherence of the placenta directly to the superficial myometrium); placenta increta (deep trophoblastic invasion into the myometrium but not through to the serosa); and placenta percreta (trophoblastic invasion through the myometrium into the uterine serosa and potentially beyond) [1–4]. Recently, International Federation of Gynecology and Obstetrics (FIGO) has suggested a change in nomenclature to placenta accreta spectrum (PAS) [5]. Due to its causal link to prior cesarean delivery, the incidence of PAS in the United States is on the rise [5–7].

Multiple morbidities are associated with PAS including hemorrhage, the need for massive blood transfusion, acute kidney injury, the need for extended post-operative ventilation, and iatrogenic surgical injury to ureter/s, bowel, bladder and major pelvic blood vessels.

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Overt coagulopathy (usually preceded by varying degrees of occult coagulopathy) is one of the most serious complications of PAS, and has been reported in up to 30% of cases [8]. Coagulopathy may be dilutional, consumptive or a combination of the two and may involve both decreased clot formation, i.e., hypocoagulable state and increased clot destruction, i.e., hyperfibrinolysis.

In 2011, we established a multidisciplinary program with the goals of standardizing the clinical and surgical management of PAS and improving maternal outcomes [9]. Over time, we have noted that both maternal and neonatal morbidity have declined in our multidisciplinary program. Nevertheless, the rate of coagulopathy remains high [10,11]. Anticipation of coagulopathy and prompt treatment are unlikely without appropriate testing in a timely manner. Frequently during a post-partum hemorrhage the main focus is on the management of hypovolemia and on red blood cell replacement. Testing for, and treatment of, coagulopathy is often delayed and only instituted once clinical signs suggestive of its presence appear.

We studied our cohort for factors associated with coagulopathy that occurred during the management of PAS by a well-established and experienced multidisciplinary team.

Materials and methods

We performed an IRB approved (H-28609) retrospective cohort analysis of the records of all women diagnosed with pathology-proven PAS at our institution between January 1, 2011 and February 30, 2017. Ongoing clinical rosters of these women are maintained by the Division of Maternal Fetal Medicine at our institution. Only women diagnosed with a singleton pregnancy were included in this study. The details of our multidisciplinary approach to the preparation and surgical management of these women has previously been described in detail [9]. All subjects are histology-confirmed had antenatal diagnosis and underwent cesarean hysterectomy or modified radical cesarean hysterectomy including those who required urgent delivery. Depth of invasion was determined based on pathologic findings after the surgery. Coagulopathy was defined as a platelet count of <100,000/mm^3, international normalized ratio >1.5, and/or fibrinogen <300 mg/dL based on institutional protocols developed by our Division of Transfusion Medicine & Coagulation. Overt disseminated intravascular coagulation (DIC) was defined based on the International Society of Thrombosis and Haemostasis (ISTH) Scoring System (Table 1) [12].

Table 1
ISTH Scoring for Overt-DIC.

Coagulation Test		Score
Platelet count,/μL		
	>100,000	0
	50,000–100,000	1
	<50,000	2
Prolongation of PT, s		
	<3	0
	3–6	1
	>6	2
Fibrinogen, mg/dL		
	≥100	0
	<100	1
D-dimer, μg/mL FEU		
	No increase	0
	Moderate increase	2
	Strong increase	3
Interpretation		
	Overt DIC	≥5

ISTH, International Society on Thrombosis and Haemostasis;
DIC = disseminated intravascular coagulation;
PT = prothrombin time; FEU = fibrinogen equivalent unit.

The laboratory coagulation assays for PT, fibrinogen, and D-dimer were performed on a STA-R analyzer (Diagnostica Stago, Parsippany, NJ) using commercially available reagents, and platelet count was measured on a Sysmex XE-2100 analyzer (Sysmex America, Lincolnshire, IL).

All continuous variables were tested for normality using descriptive statistics for skewness and kurtosis, visual evaluation of histograms, and the Kolmogorov Smirnov test. Continuous data are reported as mean with standard deviation or as median [interquartile range IQR] as appropriate. Categorical data are reported as proportions and percentages. Comparisons between those with and without coagulopathy were made using Student's t-test, Mann Whitney U test and Chi Square test, as appropriate. To assess the ability of estimated blood loss (EBL) and number of units of red blood cell (RBC) transfused to discriminate between women with and without coagulopathy, receiver operating characteristics curves (ROCs) were constructed and the area under the curves (AUCs) was calculated. Using coordinates for drawing the ROC curves, the cut-off points with the most optimal values of sensitivity and specificity were calculated for EBL and the number of units of RBC transfused. These optimal values were regarded as those maintained (1-sensitivity) 2 + (1- specificity) 2 at the minimum. SPSS software (version 23.0; SPSS Inc, Chicago, IL) was used, and a P value of <0.05 was considered statistically significant.

Results

One hundred and twenty-three patients were studied, 37 of whom (30.1%; 95% CI 22.1–39.0) had coagulopathy and 86 (69.9%; 95%CI 61.0–77.9) did not. Baseline patient demographic characteristics did not differ significantly between these groups (Table 2).

Twenty-four of the 37 patients (cases) in the coagulopathy group (64.9%; 95% CI 47.5–79.8) and 34 of the 86 patients in the control group (39.5%; 95% CI 29.2–50.7) had undergone urgent rather than planned delivery because of labor or bleeding (P = 0.01), but still were managed through the multidisciplinary management protocol.

Per the ISTH scoring system for DIC 22/37 cases with coagulopathy (59.5%; 95%CI 42.1–75.2) met criteria for DIC versus 0/86 controls (P < 0.01). (Fig. 1) EBL was 2100 mL (1800, 4000) and 1400 (1000, 2500) in the cases and controls, respectively (P < 0.01). (Table 3) The overall number of units of RBC's transfused was significantly higher in the cases vs. controls [3 (2, 9) vs. 1 (0, 4); P < 0.01] (Table 3). Univariate regression analysis confirmed the association between coagulopathy and (i) EBL and (ii) the number of units of transfused RBC's. There was no association between

Table 2
Demographics and baseline characteristics of study participants.

	Coagulopathy Present (n = 37)	Coagulopathy Absent (n = 86)	*P* Value
Maternal age, mean ± SD	32.8 ± 4.8	32.8 ± 5.2	0.99
BMI, mean ± SD	30.6 ± 6.3	31.2 ± 7.3	0.66
Gestational age at delivery (weeks), median(IQR)	33 (31, 34)	34 (32, 35)	0.08
Gravidity, median(IQR)	5 (4, 6)	4 (3, 6)	0.16
Number of previous cesarean deliveries, median(IQR)	2 (2, 3)	2 (2, 3)	0.53
Depth of invasion, n (%)			
Accreta	9 (24.3)	20 (23.3)	0.89
Increta/ Percreta	28 (75.7)	66 (76.7)	
Placenta Previa, n (%)	31 (83.8)	72 (83.7)	0.99
Urgent Multidisciplinary Delivery, n (%)	24 (64.9)	34 (39.5)	**0.01**

BMI = body mass index.
Values are presented as mean ± SD (independent t-test), median (IQR) (Mann-Whitney U test) and n (%) (Chi-square test).

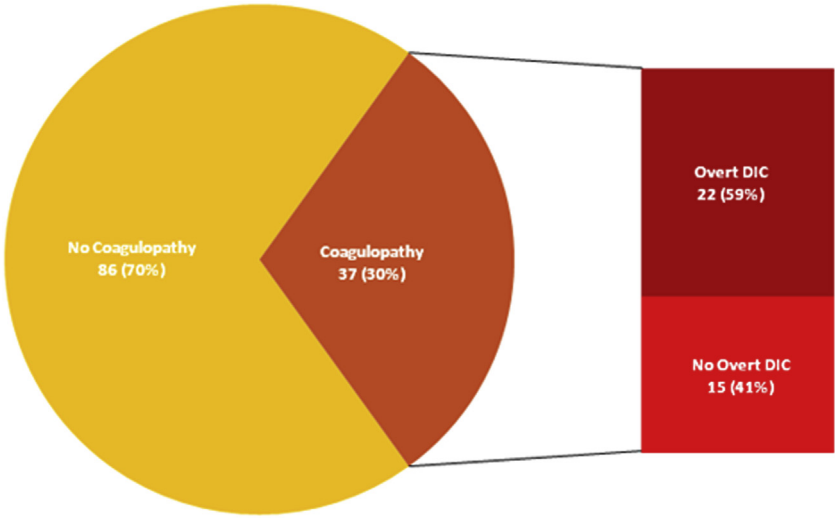

Fig. 1. Distribution of coagulopathy and disseminated intravascular coagulation in study subjects.

Table 3
Maternal and neonatal outcomes in the presence and absence of coagulopathy.

	Coagulopathy Present (n = 37)	Coagulopathy Absent (n = 86)	*P* Value
Estimated blood loss (cc), median (IQR)	2100 (1800, 4000)	1400 (1000, 2500)	< **0.01**
RBC transfusion units, median (IQR)	3 (2, 9)	1 (0, 4)	< **0.01**
Platelet transfusion units, median(IQR)	0 (0, 1)	0 (0, 0)	0.06
FFP transfusion units, median(IQR)	2 (0, 4)	0 (0, 2)	< **0.01**
Nadir Fibrinogen (mg/dL), median (IQR)	246 (212, 277)	382 (337, 451)	< **0.01**
RBC transfusion, n (%)	29 (80.6)	46 (54.1)	< **0.01**
RBC transfusion unit ≥ 4, n (%)	18 (50.0)	23 (27.1)	**0.01**
RBC transfusion unit ≥ 8, n (%)	13 (36.1)	10 (11.8)	< **0.01**
RBC transfusion unit ≥ 10, n (%)	8 (22.2)	2 (2.4)	< **0.01**
Crystalloid Transfusion (cc), median (IQR)	4000 (3300, 5000)	3500 (2900, 4500)	**0.01**
Hospital stay after surgery (day), median (IQR)	5 (4, 7)	4 (4, 6)	0.21
Overt DIC, n (%)	22 (59.5)	0	< **0.01**

BMI = body mass index; RBC = red blood cell; FFP = fresh frozen plasma; DIC = disseminated intravascular coagulation.
Values are presented as mean ± SD (independent t-test), median (IQR) (Mann-Whitney U test) and n (%) (Chi-square test).
Adjusted *P* values are calculated (for parameters age, BMI and gestational age) using analysis of covariance and regression analysis, when needed.

coagulopathy and placenta previa, occurrence of antepartum bleeding, or degree of placental invasion (using the previously accepted classification for accreta, increta and percreta). ROC curve analysis showed that an estimated blood loss ≥1500 mL was the best discriminator of coagulopathy [sensitivity of 80% (95%CI 66–90) and specificity of 60% (95%CI 50–70)] followed by the transfusion of more than 2 units of RBC [sensitivity of 78% (95% CI 63–87) and specificity of 55% (95%CI 44–65)] (Table 4, Fig. 2).

Discussion

The finding that, despite the known thromboplastic effects of placental tissue entering the maternal circulation, the degree of placental invasion was not associated with coagulopathy during surgery in patients with PAS was surprising.

A major unexpected finding of this study was that even a relatively small blood loss (1500 mL) may be associated with coagulopathy in as many as 30% of patients undergoing surgery for PAS, and that in this group the rate of serious coagulation abnormality was extremely high (as evidenced by a 60% rate of DIC). This suggests that PAS patients undergoing hysterectomy are at increased risk for coagulopathy well before massive blood loss is appreciated. As shown in Fig. 3, as EBL increases and more units of RBC are transfused, subjects are more likely to develop coagulopathy. Our data also further support the previously observed finding that women with a fibrinogen level <300 mg/dL are at risk

Table 4
Diagnostic indices of EBL and RBC transfusion units in cases of coagulopathy.

	AUC	SN (%)	SP (%)	PPV (%)	NPV (%)	LR+	LR-
Estimated Blood Loss (>1500 ml)	0.74 (0.6-0.8)	80 (66-90)	60 (50-70)	47 (35-59)	88 (77-94)	2.1 (1.5-2.8)	0.3 (0.2-0.6)
RBC Transfusion Units (>2)	0.70 (0.6- 0.8)	78 (63-87)	55 (44-65)	43 (32-54)	85 (74-92)	1.7 (1.3-2.3)	0.4 (0.2-0.7)

AUC = area under curve; SN = sensitivity; SP = specificity; PPV = positive predictive value; NPV = negative predictive value; LR = likelihood ratio; EBL = estimated blood loss; RBC = red blood cell.
Indices are calculated based on the prevalence and optimal cut-off values (Receiver Operating Characteristics).
Values are presented with 95% confidence interval.

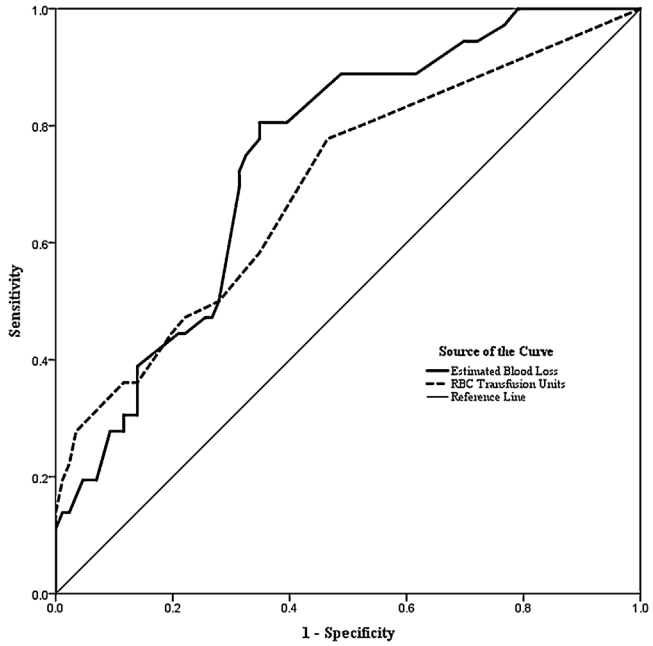

Fig. 2. ROC curves for estimated blood loss and units of RBC transfusion as discriminators of subjects with and without coagulopathy.

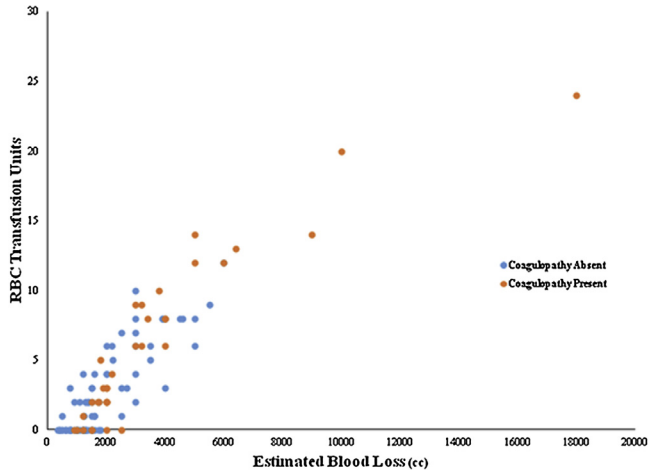

Fig. 3. Scatter plot of estimated blood loss and RBC transfusion unit by presence or absence of coagulopathy.

for DIC and hemorrhage [13,14]. Currently, most institutional protocols do not routinely include coagulation testing until severe and prolonged bleeding has already begun. Our data support early, repetitive use of such testing, even if massive bleeding is not appreciated. If blood product replacement is delayed, or insufficiently robust, due to late or absent monitoring of coagulation markers and platelet count, tissue hypoperfusion and shock could potentially lead to the development of coagulopathy and overt DIC. Although we utilized a home-made definition for coagulopathy for the first time, our analysis shows that this definition has zero false negative rate for prediction of overt-DIC. Therefore, our data suggest that in cases of PAS where cesarean hysterectomy is being performed, early and repeated monitoring for coagulopathy along with appropriate product replacement is essential and can prevent deteriorating to overt-DIC. It is not yet clear whether the use of protocols that include intra-operative thromboelastography result in significant improvements in clinical outcomes in the setting of PAS, however the thought of assessing clotting function in this way and intervening in cases with abnormal results using targeted therapy (i.e. tranexamic acid, cryoprecipitate or platelets) is intriguing and worthy of further research.

We also observed that the incidence of coagulopathy was significantly higher in women who underwent urgent surgery versus those who had a planned delivery. Our study demonstrated that disturbingly high rates of coagulopathy (30%–37/123) and DIC (18%–22/123) may be present in patients with PAS undergoing cesarean-hysterectomy following as little as 1500 mL of EBL, and as few as 2 units of transfused RBC. Currently, mostly institutional post-partum protocols do not routinely include coagulation testing until much later in the process at which severe and prolonged bleeding has already begun. However, because of this predisposition we now recommend the early initiation of serial laboratory evaluation to detect and monitor evolving coagulopathy in such patients with the potential to allow for targeted transfusion therapy.

Our study has a number of strengths. These include a robust, contemporaneous sample of patients with pathologically confirmed PAS all of whom were managed in a single center by the same team using the same surgical methodology and pre-, intra- and postoperative management protocols. In addition, detailed clinical data were collected and captured by trained physician researchers. Limitations of this study include those inherent with retrospective analyses.

In summary, we have identified 2 clinical factors associated with the development of coagulopathy in women undergoing extirpative treatment for PAS. This information may be helpful in identifying the need for either timely initiation of a massive transfusion protocol, or, preferably, a more directed, laboratory-driven transfusion approach to prevent DIC. Either of these approaches is likely to decrease morbidity and mortality in women with PAS.

Disclosure of interests

The authors did not report any potential conflicts of interest.

Contribution to authorship

AlAS and KAF designed the study, analysed the data and corrected the final version of the manuscript. HE participated in the study design, statistical analysis and writing the manuscript draft. SLC, SKH, AmAS, AAN, YNL, BWB and JT contributed to the analysis of the data and collaborated in the editing of the manuscript. MAB contributed to the analysis of the data and corrected the final version of the manuscript of the study. AlAS, KAF and MAB were members of the surgical team. Each author has indicated that he or she has met the journal's requirements for authorship.

Details of ethics approval

Approved by Institutional Review Board at Baylor College of Medicine (H-28609; 01/16/2018).

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