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ORIGINAL RESEARCH ARTICLE

Association of peripartum management and high maternal blood loss at cesarean delivery for placenta accreta spectrum (PAS): A multinational database study

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Abstract

Introduction: Placenta accreta spectrum (PAS) carries a high burden of adverse maternal outcomes, especially significant blood loss, which can be life-threatening. Different management strategies have been proposed but the association of clinical risk factors and surgical management options during cesarean delivery with high blood loss is not clear.

Material and methods: In this international multicenter study, 338 women with PAS undergoing cesarean delivery were included. Fourteen European and one non-European

Abbreviations: aOR, adjusted odds ratio; CD, cesarean delivery; CI, confidence interval; cOR, crude odds ratio; FIGO, International Federation of Gynecology and Obstetrics; IQR, interquartile range; IS-PAS, International Society for Placenta Accreta Spectrum; PAS, placenta accreta spectrum; TXA, tranexamic acid.

*See Appendix 1.

center (USA) provided cases treated retrospectively between 2008 and 2014 and prospectively from 2014 to 2019. Peripartum blood loss was estimated visually and/or by weighing and measuring of volume. Participants were grouped based on blood loss above or below the 75th percentile (>3500 ml) and the 90th percentile (>5500 ml).

Results: Placenta percreta was found in 58% of cases. Median blood loss was 2000 ml (range: 150-20 000 ml). Unplanned hysterectomy was associated with an increased risk of blood loss >3500 ml when compared with planned hysterectomy (adjusted OR [aOR] 3.7 [1.5-9.4], $p = 0.01$). Focal resection was associated with blood loss comparable to that of planned hysterectomy (crude OR 0.7 [0.2–2.1], $p = 0.49$). Blood loss >3500 ml was less common in patients undergoing successful conservative management (placenta left in situ, aOR 0.1 [0.0–0.6], $p = 0.02$) but was more common in patients who required delayed hysterectomy (aOR 6.5 [1.7–24.4], $p = 0.001$). Arterial occlusion methods (uterine or iliac artery ligation, embolization or intravascular balloons), application of uterotonic medication or tranexamic acid showed no significant effect on blood loss >3500 ml. Patients delivered by surgeons without experience in PAS were more likely to experience blood loss >3500 ml (aOR 3.0 [1.4–6.4], $p = 0.01$).

Conclusions: In pregnant women with PAS, the likelihood of blood loss >3500 ml was reduced in planned vs unplanned cesarean delivery, and when the surgery was performed by a specialist experienced in the management of PAS. This reinforces the necessity of delivery by an expert team. Conservative management was also associated with less blood loss, but only if successful. Therefore, careful patient selection is of great importance. Our study showed no consistent benefit of other adjunct measures such as arterial occlusion techniques, uterotonics or tranexamic acid.

KEYWORDS
abnormally invasive placenta, cesarean, high-risk pregnancy, hysterectomy, placenta, postpartum hemorrhage, uterine scar

1 | INTRODUCTION

Although maternal mortality rates are declining, the increasing incidence of cesarean delivery (CD) has resulted in an increase in placenta accreta spectrum (PAS), or abnormally invasive placenta, adversely impacting maternal outcomes globally.[1,2] PAS describes the clinical disease spectrum in which a placenta does not separate spontaneously at delivery and cannot be removed without causing abnormal and potentially life-threatening bleeding due to varying degrees of placental invasion into or through the myometrium.[3,4] Although still relatively rare, PAS carries a disproportionate risk of severe maternal morbidity and mortality, and contributes considerably to the proportion of postpartum hemorrhage with hysterectomy.[5] Not only is PAS a heterogeneous disease spectrum, but management of pregnancies with PAS varies widely across centers. Management strategies include delivery by planned cesarean hysterectomy, focal myometrial resection and conservative management leaving the placenta in situ after delivery, with or without adjunctive measures such as arterial embolization or planned delayed hysterectomy.[6]

Various efforts have been made to identify associations between clinical management and maternal blood loss, morbidity and mortality in PAS. Most studies are conducted by single centers, with limited data and generalizability to guide the optimal management of this condition. In an attempt to address these problems, international groups, including the International Society for PAS (IS-PAS) and the International Federation of Gynaecology and Obstetrics (FIGO), have published proposals for standardization of imaging[7,8] IS-PAS has joined together specifically to pool international multi-center data to identify outcomes across various centers and identify research gaps.

We aimed to determine which epidemiologic factors and which management factors were associated with high and extraordinarily high peripartum blood loss in CD complicated by PAS.

Key message

Planned procedures, including hysterectomy and focal resection for placenta accreta spectrum (PAS), are associated with lower blood loss than unplanned hysterectomies. Peripartum blood loss is less when cesarean delivery is managed by a surgeon or surgical team specialized in PAS.

2 | MATERIAL AND METHODS

2.1 | Patient recruitment

The IS-PAS database contains both retrospectively and prospectively collected obstetric and surgical data of pregnant patients >14 gestational weeks with suspected and/or pathologically proven PAS. Cases from April 2008 to December 2013 were registered retrospectively in the database. Cases from 2014 to 2019 were collected prospectively. In total, 442 cases were included in the database.[9]

2.2 | Exclusion criteria

Of the 442 cases in the IS-PAS database, 32 cases of women with normal placentation (antenatally suspected PAS with normal placental separation, ie "false positive cases") were excluded from this analysis. A further 26 cases not delivered by CD (vaginal delivery [*n* = 17] and termination of pregnancy [*n* = 9]) were excluded. Thirty-one cases were excluded due to missing information on operative management and 15 cases due to missing data on blood loss. In total, 338 cases were included and analyzed (Figure 1, Table S1).

2.3 | Measurement of blood loss and clinical classification of PAS

Each center recorded blood loss using their own standardized local protocol, whether by quantified measurement or visual estimation. The degree of invasion was classified based on the IS-PAS Grading system[7] originally proposed in 2015 and upon which the more recently published FIGO Clinical Classification system was based.[8,10] The publication by Braun et al includes further details.[9]

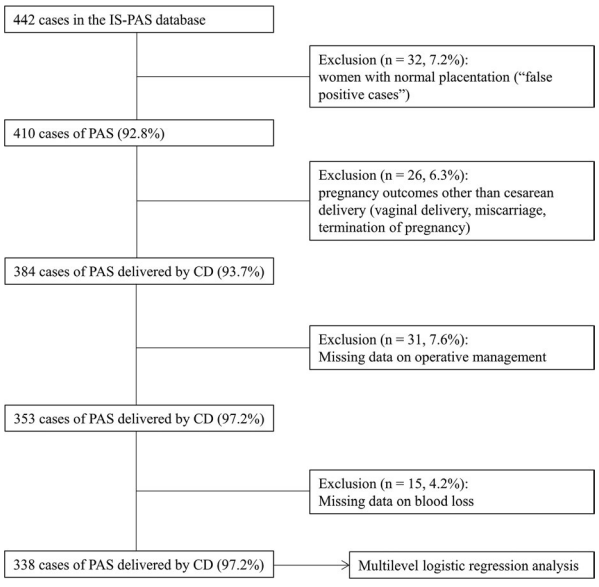

FIGURE 1 Selection of cases. CD, cesarean delivery; PAS, placenta accreta spectrum

2.4 | Data collection

Data were collected both retrospectively (cases managed from 2008 to 2014) and prospectively (2014–2019) via chart review using a standardized, secured and password-protected online data collection platform (FetView, Zeitgeist Health SE).[9] Participants were grouped based on blood loss in this study above the 75th percentile of our cohort (>3500 ml) and blood loss above the 90th percentile (>5500 ml) (Appendix S1).

The following factors were investigated with regard to their association with peripartum blood loss:

- Number of previous CD
- Presence of placenta previa
- Antenatal PAS diagnosis (antenatally suspected vs unsuspected PAS)
- IS-PAS grades of invasion 2–6[8]
- Degree of urgency of delivery
- Experience of the surgeon: specialist in PAS vs gynecologist/obstetrician with no particular training in PAS (definition: an expert is a person with significant experience in PAS and a high level of knowledge and/or skills relating to the condition)[11]
- Operative management
  - Type of management (planned hysterectomy, unplanned hysterectomy, focal resection, placenta left in situ with uncomplicated resorption, placenta in situ followed by planned or unplanned delayed hysterectomy)
  - Position of the uterine incision (fundal, lower transverse, transverse above placenta)
- Measures to support uterine contraction/aid blood clotting
  - Oxytocin (prophylactic administration – before increased blood loss occurred; therapeutic administration – after increased blood loss occurred)
  - Tranexamic acid (TXA; prophylactic administration – before increased blood loss occurred; therapeutic administration – after increased blood loss occurred)
  - Prostaglandin F2α/E2/E1 (prophylactic administration – before increased blood loss occurred; therapeutic administration – after increased blood loss occurred)
  - Intrauterine balloon (prophylactic administration – before increased blood loss occurred; therapeutic administration – after increased blood loss occurred)
- Perioperative occlusion of uterine blood supply (no other types of occlusion reported):
  - Pelvic arterial embolization
  - Intravascular balloon (femoral or iliac)
  - Uterine artery ligation
  - Internal iliac artery ligation

2.5 | Statistical analyses

Univariate and multivariate analyses were used to test associations with blood loss >3500 and >5500 ml. A multilevel logistic regression model served to control for possible variation between participating centers (Appendix S1). The 15 centers were defined as a second level variable. As a first step, the influence on peripartum blood loss was calculated for each first level variable separately (univariate analysis). In analyses comparing planned management approaches, planned hysterectomy was the reference category for operative management, as this is the most commonly used, definitive immediate treatment of placenta accreta spectrum.[12] Crude odds ratios (cOR) with 95% confidence interval (95% CI) were calculated for all results. Next, a multivariate regression analysis was carried out, including variables that had been identified as having a significant effect in univariate analysis ($p \leq 0.05$). Multivariate analyses yielded adjusted odds ratios (aOR) with 95% CI.

2.6 | Ethical approval

Local Ethical Committee/IRB approval and Data Use Agreements were obtained according to local policies. Details of these can be found in the online Supporting Information contained in the Commentary of this supplement.[9]

3 | RESULTS

3.1 | Demographic, clinical and outcome characteristics of enrolled women

Table 1 shows the demographic data of the analyzed cases. Placenta percreta (PAS grade 4–6) was present in 58% of cases. Overall, median blood loss was 2000 ml (range 150–20 000 ml, Figure 2A). Perioperative occlusion of uterine blood supply was used in 28% (95/338) of cases. Among these cases, it was used therapeutically in 46% (44/95) of cases, that is, after occurrence of high blood loss. The most commonly used prophylactic intervention was intravascular balloon placement (48/338; 14%). Overall, a reduction in total blood loss was seen over time (Figure 2B).

3.2 | Factors not significantly associated with high peripartum blood loss

Tables 2 and 3 show the results of the multilevel logistic regression analyses. Blood loss >3500 ml or >5500 ml did not differ between centers (inter-center variance 1.3 [0.3–4.9], $p = 0.15$). The number of previous CD, the presence of placenta previa and antenatal diagnosis of PAS showed no association with perioperative blood loss. No difference in blood loss was noted between focal resection and planned hysterectomy. Focal resection was performed in 26 cases: three times in PAS grade 2, two times in PAS grade 3, 18 times in PAS grade 4, one time in PAS grade 5, two times in PAS grade 6. Univariate analyses did not yield significant correlations between measures to promote uterine contraction (administration of uterotonics, intrauterine balloon) or blood loss >3500 ml. No difference in blood loss was seen with *prophylactic* use of TXA (univariate analyses: >3500 ml: cOR 0.5 [0.2–1.2], $p = 0.12$; >5500 ml: cOR 0.3 [0.1–1.5], $p = 0.14$; prophylactic TXA] n = 53, [no TXA] n = 182. Blood loss >5500 ml was not significantly associated with type or timing of surgical intervention (aOR 2.4 [0.9–6.6], $p = 0.08$ for unplanned hysterectomy; aOR 0.9 [0.1–6.5], $p = 0.92$ for delayed hysterectomy). Univariate analyses showed increased association between cases with blood loss >3500 and blood loss >5500 ml in emergent CD vs scheduled CD (cOR 3.5 [1.2–10.2], $p = 0.02$ and cOR 2.6 [1.0–6.8], $p = 0.04$, respectively), but not after multivariate analysis. Univariate analyses did not yield significant correlations between perioperative occlusion of uterine blood supply available in our dataset (uterine artery embolization, femoral balloon, uterine artery ligation, internal iliac artery ligation) and blood loss >3500 or >5500 ml.

3.3 | Factors associated with significantly increased risk for high peripartum blood loss

Compared with planned hysterectomy, unplanned hysterectomy was associated with significantly higher odds of blood loss >3500 ml (aOR 3.7 [1.5–9.4], $p = 0.01$). The association with blood loss >5500 ml did not hold in multivariate analysis (aOR 2.4 [0.9–6.6], $p = 0.08$). Delayed hysterectomy was associated with a significantly higher likelihood of total blood loss >3500 ml (aOR 6.5 [1.7–24.4], $p = 0.001$). Placenta percreta with parametrial invasion (Grade 6) showed a trend to a higher proportion of cases with blood loss >3500 ml (aOR 3.4 [0.9–12.3], $p = 0.06$), with insignificant results in terms of blood loss >5500 ml (aOR 1.9 [0.6–7.0], $p = 0.32$). There was a positive correlation between *therapeutic* internal iliac artery ligation and blood loss >3500 ml (cOR 4.4 [1.2–16.2], $p = 0.03$). Manual removal of placenta was attempted significantly less frequently in the blood loss >3500 ml group and only performed in lower PAS grades of invasion (grades 2 and 3; aOR 0.2 [0.1–0.6], $p = 0.01$).

3.4 | Factors associated with significantly reduced risk for high peripartum blood loss

Interestingly, fewer cases with blood loss >3500 ml occurred for placenta percreta grade 4 in multivariate analysis (aOR 0.4 [0.1–0.9]; $p = 0.04$, reference category: PAS grade of invasion 2). This was more pronounced for blood loss >5500 ml (aOR 0.2 [0.1–0.8], $p = 0.01$). Leaving the placenta in situ was associated with fewer cases of blood loss >3500 ml but only if it was successful without further interventions (aOR 0.1 [0.0–0.6], $p = 0.02$). Delivery by a surgeon experienced in PAS was strongly related to blood loss >3500

TABLE 1 Demographic, clinical and outcome characteristics of enrolled women (*n* = 338)

Variable	*n* = 338	% of cases
Characteristics at enrolment		
Maternal age, years[a]	34.6 (34.1–35.2)	
Gravidity[b]	3 (2–5)	
Parity[b]	2 (1–3)	
Number of prior cesarean deliveries[c]	338	100
0 (no prior cesareans)	56	17
1 prior cesarean	135	40
≥2 prior cesareans	147	43
Placenta previa[c]	298	88
Outcome characteristics		
Gestational age at delivery in weeks[b]	36 (34–37)	
Cesarean delivery[c]	338	100
PAS diagnosed antenatally[c]	306	91
Operative management[c]		
Planned cesarean hysterectomy	182	54
Unplanned cesarean hysterectomy	40	12
Focal resection	26	8
Leaving placenta in situ	24	7
Leaving placenta in situ + delayed HE	15	4
Manual removal of placenta	51	15
PAS Grading[c]		
Grade of invasion 2	79	23
Grade of invasion 3	62	18
Grade of invasion 4	123	37
Grade of invasion 5	48	14
Grade of invasion 6	26	8
Blood loss in ml (range)[b,c]	2000 (150–20 000)	
Blood loss >3500 ml	92	27
Blood loss <3500 ml	246	73
Blood loss >5500 ml	33	10
Blood loss <5500 ml	305	90
Transfused red packed cells (range)[b,c]	2 (0–108)	
0–1 red packed cells	153	45
2–4 red packed cells	86	26
More than four red packed cells	99	29
Oxytocin[c]	321[d]	**95**
No oxytocin (reference)	156	49
Prophylactic oxytocin	113	35
Therapeutic oxytocin	52	16
Prostaglandin[c]	**336**[d]	**98**
No prostaglandin (reference)	275	81
Prophylactic prostaglandin	13	4
Therapeutic prostaglandin	48	14
Tranexamic acid[c]	**330**[d]	**98**
No tranexamic acid (reference)	182	54
Prophylactic tranexamic acid	53	16
Therapeutic tranexamic acid	95	28
Urgency of cesarean delivery[c]	**337**[d]	**100**
At a time to suit the woman and maternity team (elective)	228	68
Needing early delivery but no maternal or fetal compromise	44	13
Maternal or fetal compromise which is not immediately life-threatening	50	15
Immediate threat to life of woman or fetus (crash)	15	5
Grade of surgeon[c]	**325**[d]	**96**
Specialist in PAS (reference)	249	77
No specialist	76	23
Position of uterine incision[c]	**323**[d]	**96**
Lower transverse (reference)	98	30
Fundal	157	49
Transverse above placenta	68	21
Intravascular balloon[c]	**337**[d]	**100**
No balloon (reference)	285	84
Prophylactic	48	14
Therapeutic	4	1
Embolization[c]	**335**[d]	**99**
No embolization (reference)	319	94
Prophylactic	2	1
Therapeutic	14	4
Uterine artery ligation[c]	**338**	**100**
No ligation (reference)	321	95
Prophylactic	1	0
Therapeutic	16	5
Internal iliac artery ligation[c]	**338**	**100**
No ligation (reference)	328	97
Prophylactic	0	0
Therapeutic	10	3
Intrauterine balloon[c]	**334**[d]	**99**
No balloon (reference)	289	86
Prophylactic	9	3
Therapeutic	36	11
Maternal death	0	0

Abbreviations: PAS, placenta accreta spectrum.

[a]Data presented as mean (95% CI).

[b]Data presented as median (IQR).

[c]Data presented as *n* (%).

[d]Case numbers that do not add up to 338 cases (100%) denote missing data.

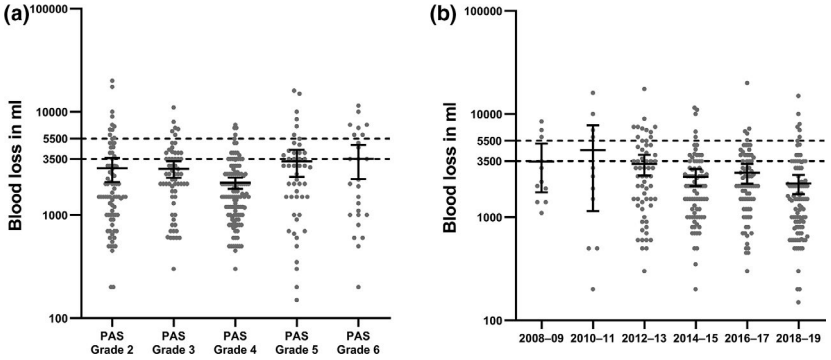

FIGURE 2 Scatter plots showing blood loss according to PAS grade of invasion (A) and the year of delivery (B). Mean blood loss in ml (± 95% CI) per grade: Grade 2: 2834 (2085–3583), Grade 3: 2808 (2289–3327), Grade 4: 2048 (1792–2304), Grade 5: 3311 (2342–4279), Grade 6: 3508 (2230–4785). Non-significant tendency toward lower blood loss in PAS Grade 4 (p = 0.05, Kruskal-Wallis test). PAS Grade 1 is not shown as it denotes normal placentation. 3500 ml (75th percentile) and 5500 ml (90th percentile) are marked to illustrate the thresholds used to compare cases with high peripartum blood loss

and >5500 ml (multivariate analyses: >3500 ml: aOR 3.0 [1.4–6.4], p = 0.01; >5500 ml: aOR 4.0 [1.6–9.9], p = 0.003, respectively).

4 | DISCUSSION

As reported elsewhere, planned cesarean hysterectomy remains the most common treatment method used within our multi-center international cohort.[12,13] Conservative management, whether by leaving the placenta in situ or via partial myometrial resection has been shown to be feasible, with favorable short-term maternal outcomes and subsequent fertility.[14-16] To date, it is unclear whether conservative approaches confer a significant reduction in peripartum blood loss. Within this cohort, leaving the placenta in situ was associated with lower odds of blood loss >3500 ml compared with planned cesarean hysterectomy *when successful* (62% of cases, n = 24). When hysterectomy was performed as a delayed procedure (38% of cases, n = 15, including planned and unplanned), it was associated with *higher* odds of total blood loss >3500 ml or >5500 ml. Additionally, leaving the placenta in situ confers risks of secondary postpartum hemorrhage, sepsis or disseminated intravascular coagulation.[15-17] A multicenter retrospective case series by Palacios-Jaraquemada et al on outcomes after resective-reconstructive techniques has compared the blood loss of 326 patients with different topographic forms of PAS.[14] The median blood loss of the 338 cases in our study was 2000 ml (interquartile range [IQR] 1000–3500 ml). This is similar to, but with a wider range, compared with the results of Palacios-Jaraquemada et al.[14] Although this was not the subject of this study, it seems possible that specific hemostasis over pedicles that irrigate the placenta and the invaded area can help to reduce blood loss >3500 ml.

Interestingly, the odds for blood loss >3500 ml were similar between focal resection and planned hysterectomy. This suggests that focal resection is a feasible option for women who want to keep their uterus, when the location and size of placental invasion permits this procedure.

There was no significant association of blood loss >3500 and >5500 ml and the use of adjunctive measures to reduce blood loss, including use of the anti-fibrinolytic medication (TXA). Therapeutic use of TXA positively correlated with blood loss >3500 ml (OR 2.4 [1.4–4.2; p = 0.001). This positive correlation likely reflects the indication of ongoing bleeding rather than a failure of efficacy. Overall, the prophylactic use of adjunctive measures was relatively infrequent within the cohort. In the TRAAP study, a large multicenter study from France published in 2018, no difference in the rate of blood loss <500 ml was seen between women receiving oxytocin alone or oxytocin plus prophylactic TXA.[18] One recently published double-blinded randomized controlled study (46 patients) demonstrated that TXA during surgery for PAS (without specification of the grade of invasiveness) was effective in significantly reducing the intraoperative blood loss compared with the placebo group.[19] Well-designed and appropriately powered studies to address the safety and efficacy of adjunctive measures are essential to understand their utility. Newer studies suggest that arterial occlusion of the aorta reduces blood loss in PAS patients.[20,21] In a recent randomized controlled trial that included 100 women with placenta previa and different grades of PAS, the use of intraoperative bilateral internal iliac artery balloon occlusion did not reduce the number of units of packed red blood cells transfused or otherwise improve outcomes.[22]

Even placenta accreta or increta (lower grades) can be associated with blood loss >3500 and >5500 ml. Conversely, in placenta percreta (higher grades), blood loss >3500 ml occurred more frequently in cases involving placental invasion into other organs, whereas placenta percreta without invasion of other organs was associated with lower blood loss. One reason might be that PAS Grade 4 can be easily detected both on antenatal ultrasound as well as intraoperatively, so that manual removal of the placenta was not attempted, yet compared with PAS infiltrating urinary bladder or other organs (PAS Grade 5 or 6), the surgical complexity in PAS Grade 4 is manageable. Lesser degrees of invasion may permit partial placental separation and bleeding from the placental bed or greater willingness on the part of the provider to attempt manual placental extirpation,

TABLE 2 Multilevel logistic regression analysis of maternal peripartum blood loss >3500 ml

		Blood loss >3500 ml (75. P.)			
		Univariate analysis		Multivariate analysis	
Variable	*N* (total *n* = 338)	Crude odds ratio (95% CI)	*p* value	Adjusted odds ratio (95% CI)	*p* value
Number of previous cesarean deliveries	338	1.1 (0.9–1.3)	0.53		n/i
Placenta previa	338	1.3 (0.6–2.9)	0.48		n/i
PAS diagnosed antenatally	338	0.7 (0.3–1.5)	0.36		n/i
Operative management			**<0.001**		**<0.001**
Planned caesarean hysterectomy (reference)	182				
Unplanned caesarean hysterectomy	40	3.9 (1.8–8.7)	**0.001**	3.7 (1.5–9.4)	**0.01**
Focal resection	26	0.7 (0.2–2.1)	0.49		n/s
Leaving placenta in situ	24	0.1 (0.0–0.9)	**0.04**	0.1 (0.0–0.6)	**0.02**
Leaving placenta in situ + delayed HE	15	4.6 (1.4–14.6)	**0.01**	6.5 (1.7–24.4)	**0.001**
Manual removal of placenta	51	0.4 (0.2–0.9)	**0.04**	0.2 (0.1–0.6)	**0.01**
PAS Grading			**0.005**		**0.001**
Grade of invasion 2 (reference)	79				
Grade of invasion 3	62	1.5 (0.7–3.2)	0.31	0.6 (0.2–1.6)	0.28
Grade of invasion 4	123	0.6 (0.3–1.3)	0.17	0.4 (0.1–0.9)	**0.04**
Grade of invasion 5	48	1.8 (0.8–4.1)	0.14	1.1 (0.4–3.1)	0.91
Grade of invasion 6	26	2.7 (1.0–7.3)	**0.04**	3.4 (0.9–12.3)	0.06
Oxytocin			0.25		
No oxytocin (reference)	156				
Prophylactic oxytocin	113	0.8 (0.4–1.3)	0.32		n/i
Therapeutic oxytocin	52	1.4 (0.7–2.7)	0.34		n/i
Prostaglandin			0.16		
No prostaglandin (reference)	275				
Prophylactic prostaglandin	13	2.7 (0.8–9.4)	0.11		n/i
Therapeutic prostaglandin	48	1.9 (0.9–3.8)	0.08		n/i
Tranexamic acid			**0.001**		
No tranexamic acid (reference)	182				
Prophylactic tranexamic acid	53	0.5 (0.2–1.2)	0.12		n/i
Therapeutic tranexamic acid	95	2.4 (1.4–4.2)	**0.001**		n/i
Urgency of cesarean delivery			**0.05**		0.82
At a time to suit the woman and maternity team (elective, reference)	228				
Needing early delivery but no maternal or fetal compromise	44	0.8 (0.4–1.9)	0.64	0.8 (0.3–2.0)	0.63
Maternal or fetal compromise which is not immediately life-threatening	50	1.8 (0.9–3.9)	0.11	1.1 (0.4–3.1)	0.78
Immediate threat to life of woman or fetus (crash)	15	3.5 (1.2–10.2)	**0.02**	1.6 (0.4–6.3)	0.48
Grade of surgeon			**0.001**		**0.01**
Specialist in PAS (reference)	249				
No specialist	76	2.6 (1.5–4.4)	**0.001**	3.0 (1.4–6.4)	**0.01**
Position of uterine incision			0.83		
Lower transverse (reference)	98				n/i
Fundal	157	1.0 (0.6–1.8)	0.07		n/i
Transverse above placenta	68	1.2 (0.6–2.5)	0.62		n/i

(Continues)

TABLE 2 (Continued)

Variable	*N* (total *n* = 338)	Blood loss >3500 ml (75. P.) Univariate analysis Crude odds ratio (95% CI)	*p* value	Multivariate analysis Adjusted odds ratio (95% CI)	*p* value
Intravascular balloon			0.70		
No balloon (reference)	285				
Prophylactic	48	0.7 (0.3–1.6)	0.40		n/i
Therapeutic	4	n/a	0.97		n/i
Pelvic arterial embolization			0.68		
No embolization (reference)	319				
Prophylactic	2	0.8 (0.2–3.1)	0.83		n/i
Therapeutic	14	0.8 (0.1–7.6)	0.78		n/i
Uterine artery ligation			0.25		
No ligation (reference)	321				
Prophylactic	1	0 (n/a)	0.94		n/i
Therapeutic	16	2.4 (0.9–6.9)	0.10		n/i
Internal iliac artery ligation			**0.03**		
No ligation (reference)	328				
Prophylactic	0		n/a		n/i
Therapeutic	10	4.4 (1.2–16.7)	**0.03**		n/i
Intrauterine balloon			**0.04**		
No balloon (reference)	289				
Prophylactic	9	0.4 (0.0–3.0)	0.35		n/i
Therapeutic	36	2.7 (1.3–5.6)	**0.01**		n/i

Note: Data presented as odds ratio (95% CI). Statistically significant *p* values (< 0.05) are written in bold.

Abbreviations: HE, hysterectomy; n/a, not available; n/i, not included in multivariate analysis; n/s, not significant; PAS, placenta accreta spectrum.

whereas deep invasion is associated with bleeding risk from extensive neovascularization. Our data clearly demonstrate the need for availability of blood products, no matter what the degree of anticipated invasion. Surgical vigilance, prompt hemorrhage control and early correction of coagulopathy are paramount in all cases.

The data clearly show that experience matters. The presence of a senior surgeon with expertise in the management of PAS showed the strongest correlation with reduced odds of blood loss >3500 and >5500 ml. The risk for blood loss >3500 and >5500 ml did not vary among centers, even though over this study period, each center followed local protocols, rather than a single, standardized treatment guideline. The importance of an experienced team is consistent with findings of others and underscores the importance of timely referral of patients to a PAS center where an experienced, multidisciplinary team is available.[23] We observed a trend toward less maternal blood loss over time during the study period, suggestive of a learning curve among participating centers.

This study provides insight into the actual treatment rendered across multiple, international referral centers within the International Society of Placenta Accreta Spectrum (IS-PAS) over a 12-year epoch. As a (partly retrospective) analysis of a contemporaneously collected cohort, it includes the limitations inherent with such an analysis. All participating centers are in high-resource settings and have established PAS treatment teams, therefore, our results may not be generalizable to centers in low-income countries or without multidisciplinary team care. There was no standardized way to measure or estimate peripartum blood loss, which we tried to account for, using multilevel regression analysis. The extent of placental invasion was graded using the system available grading system at the time,[7,8] which differs slightly compared with the FIGO grading system, specifically in the differentiation between placenta accreta and increta. As with any grading system, it is possible that different centers assigned these grades slightly differently between cases; however, we believe that the use of a standardized grading system based on clinical criteria at the time of delivery is far more accurate than the use of a system of descriptors based solely on pathologic evaluation, which inherently cannot take into consideration the appearance of tissues and structures when the placenta and uterus remain in vivo and excludes cases managed expectantly. Another way to classify placenta accreta spectrum is to categorize its topography depending on the blood supply.[14,24] Topographic placental invasion has been shown to correlate with intraoperative blood loss.[14] As topographic classifications have not been endorsed by the IS-PAS or FIGO, our case reporting form does not include topographic information, and

TABLE 3 Multilevel logistic regression analysis of maternal peripartum blood loss >5500 ml

		Blood loss >5500 ml (90. P.)			
		Univariate analysis		Multivariate analysis	
Variable	*n* (total *n* = 338)	Crude odds ratio (95% CI)	*p* value	Adjusted odds ratio (95% CI)	*p* value
Number of previous cesarean deliveries	338	0.9 (0.7–1.3)	0.60		n/i
Placenta previa	338	1.2 (0.4–3.9)	0.71		n/i
PAS diagnosed antenatally	338	1.3 (0.4–4.9)	0.67		n/i
Operative management			**0.049**		**0.01**
Planned cesarean hysterectomy (reference)	182				
Unplanned cesarean hysterectomy	40	2.9 (1.1–7.5)	**0.03**	2.4 (0.9–6.6)	0.08
Focal resection	26	0.6 (0.1–3.0)	0.52	1.3 (0.3–6.3)	0.73
Leaving placenta in situ	24	n/a	0.99	0.2 (0.0–1.7)	0.13
Leaving placenta in situ + delayed HE	15	1.6 (0.3–9.5)	0.62	0.9 (0.1–6.5)	0.92
Manual removal of placenta	51	0.1 (0.0–1.0)	0.06	0.1 (0.1–0.6)	**0.01**
PAS grading			**0.02**		**0.002**
Grade of invasion 2 (reference)	79				
Grade of invasion 3	62	0.8 (0.3–2.5)	0.71	0.3 (0.1–0.9)	**0.03**
Grade of invasion 4	123	0.2 (0.1–1.8)	**0.03**	0.2 (0.1–0.8)	**0.01**
Grade of invasion 5	48	1.0 (0.3–3.3)	0.95	0.3 (0.1–1.2)	0.09
Grade of invasion 6	26	2.5 (0.7–8.4)	0.14	1.9 (0.6–7.0)	0.32
Oxytocin			0.09		
No oxytocin (reference)	156				
Prophylactic oxytocin	113	0.9(0.4–2.5)	0.91		n/i
Therapeutic oxytocin	52	2.6 (1.0–6.8)	0.05		n/i
Prostaglandin			0.30		
No prostaglandin (reference)	275				
Prophylactic prostaglandin	13	2.6 (0.5–14.2)	0.28		n/i
Therapeutic prostaglandin	48	1.3 (0.4–3.8)	0.68		n/i
Tranexamic acid			0.45		
No tranexamic acid (reference)	182				
Prophylactic tranexamic acid	53	0.3 (0.1–1.5)	0.14		n/i
Therapeutic tranexamic acid	95	1.0 (0.4–2.4)	0.93		n/i
Urgency of cesarean delivery			0.05		0.55
At a time to suit the woman and maternity team (elective, reference)	228				
Needing early delivery but no maternal or fetal compromise	44	0.3 (0.0–2.1)	0.20	0.4 (0.1–1.8)	0.23
Maternal or fetal compromise which is not immediately life-threatening	50	2.6 (1.0–6.8)	**0.04**	1.4 (0.5–4.1)	0.53
Immediate threat to life of woman or fetus (crash)	15	2.7 (0.7–11.2)	0.16	0.9 (0.2–3.8)	0.85
Grade of surgeon			**0.001**		**0.003**
Specialist in PAS (reference)	249				
No specialist	76	4.3 (1.9–10.0)	**0.001**	4.0 (1.6–9.9)	**0.003**
Position of uterine incision			0.17		
Lower transverse (reference)	98				n/i
Fundal	157	0.4 (0.1–1.0)	0.06		n/i
Transverse above placenta	68	0.8 (0.3–2.0)	0.56		n/i

(Continues)

TABLE 3 (Continued)

Variable	*n* (total *n* = 338)	Blood loss >5500 ml (90. P.) Univariate analysis Crude odds ratio (95% CI)	*p* value	Multivariate analysis Adjusted odds ratio (95% CI)	*p* value
Intravascular balloon			0.17		
No balloon (reference)	285				
Prophylactic	48	6.7 (0.8–56.0)	0.08		n/i
Therapeutic	4	0.7 (0.2–2.4)	0.61		n/i
Pelvic arterial embolization			0.60		
No embolization (reference)	319				
Prophylactic	2	2.4 (0.2–26.5)	0.48		n/i
Therapeutic	14	2.0 (0.4–9.8)	0.41		n/i
Uterine artery ligation			0.75		
No ligation (reference)	321				
Prophylactic	1	n/a	0.98		n/i
Therapeutic	16	1.9 (0.4–9.2)	0.45		n/i
Internal iliac artery ligation			0.20		
No ligation (reference)	328				
Prophylactic	0		n/a		n/i
Therapeutic	10	3.1 (0.6–16.9)	0.20		n/i
Intrauterine balloon			**0.02**		
No balloon (reference)	289				
Prophylactic	9	n/a	0.99		n/i
Therapeutic	36	4.1 (1.7–10.0)	**0.002**		n/i

Note: Data presented as odds ratio (95% CI). Statistically significant *p* values (< 0.05) are written in bold.

Abbreviations: HE, hysterectomy; n/a, not available; n/i, not included in multivariate analysis; n/s, not significant; PAS, placenta accreta spectrum.

therefore such an analysis of the existing cases is not feasible. The analysis of perioperative arterial occlusion is limited by low case numbers, regional availability of such interventions; because these measures are frequently used in escalation and response to active bleeding, rather than prophylaxis, correlation with high blood loss is also possibly confounded by reversed causation. As the cohort included only patients with uterine or internal iliac artery ligation, the impact of ligation of other pelvic arteries was not evaluated. Due to the partly retrospective design, our data do not allow us to conclude that non-significant variables have no association with blood loss, especially for variables that may be underpowered. Such questions would ideally be answered through well-designed randomized controlled trials.

5 | CONCLUSION

Even PAS with low degrees of invasion (IS-PAS Grades 2 and 3) was associated with high peripartum blood loss. Blood loss could not be accurately predicted by the anticipated degree of placental invasion. No correlation of adjunctive measures or prior knowledge of clinical aspects such as the number of previous cesarean deliveries, the presence of placenta previa or antenatally diagnosed PAS with the incidence of high peripartum blood loss could be shown in our cohort. For PAS (IS-PAS Grades 2–6), lower blood loss was equally observed during planned hysterectomies and planned focal resections. The incidence of high blood loss was lowest when patients were treated by surgeons specialized in PAS. Well-designed and appropriately powered studies to address the safety and efficacy of adjunctive measures are essential to understand their utility.

CONFLICT OF INTEREST

Karin A Fox received funds from: an SMFM/Banner Health honorarium for participation in an annual critical care obstetrics course; Symposia Medicus – honorarium for educational lectures in high risk obstetrics; Wolters Kluwer - honorarium for UpToDate chapter authorship; and an NICHD R01 grant paid to her institution – Molecular and Vascular MRI of Placenta Accreta Spectrum. None of the other authors has any conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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APPENDIX 1

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