Review

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Placenta Accreta Spectrum Part II: hemostatic considerations based on an extended review of the literature

https://doi.org/10.1515/jpm-2022-0233
Received May 13, 2022; accepted September 5, 2022;
published online October 3, 2022

Abstract: "Placenta Accreta Spectrum" (PAS) is a rare but serious pregnancy condition where the placenta abnormally adheres to the uterine wall and fails to spontaneously release after delivery. When it occurs, PAS is associated with high maternal morbidity and mortality — as PAS management can be particularly challenging. This two-part review summarizes current evidence in PAS management, identifies its most challenging aspects, and offers evidence-based recommendations to improve management strategies and PAS outcomes. The first part of this two-part review highlighted the general anesthetic approach, surgical and interventional management strategies, specialized "centers of excellence," and multidisciplinary PAS treatment teams. The high rates of PAS morbidity and mortality are often provoked by PAS-associated coagulopathies and peripartal hemorrhage (PPH). Anesthesiologists need to be prepared for massive blood loss, transfusion, and to manage potential coagulopathies. In this second part of this two-part review, we specifically reviewed the current literature pertaining to hemostatic changes, blood loss, transfusion management, and postpartum venous thromboembolism prophylaxis in PAS patients. Taken together, the two parts of this review provide a comprehensive survey of challenging aspects in PAS management for anesthesiologists.

Keywords: abnormally invasive placenta; anesthesia; coagulopathy; placenta accreta spectrum; placenta percreta; transfusion management.

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Introduction

In "Placenta Accreta Spectrum Part I: anesthesia considerations based on an extended review of the literature," we discussed "Placenta Accreta Spectrum" (PAS) as being a rare but serious condition during pregnancy where part of the placenta abnormally attaches to the uterine wall and fails to spontaneously release after delivery [1].

The term PAS includes both adherent and invasive forms of accreta placentation and refers either to clinical symptoms, pathological findings or ultrasound imaging. The term itself has been redefined several times over the last decades — for example, "Abnormally Invasive Placenta" (AIP) — for which PAS prevalence estimation is found to be challenging [2]. Nevertheless, rates are increasing and are now between 0.8 and 3.1 per 1,000 births after C-section [2]. Depending on the extent of invasive growth, PAS can be subclassified — namely, placenta accreta, increta, and percreta. Irrespective of the surgical approach or the degree of invasive placental

penetration, PAS is often accompanied with severe peripartum hemorrhage (PPH) — in comparison to placenta previa without accreta, placenta accreta shows an odds ratio (OR) of 89.5% for an estimated blood loss (EBL)>2 L, an OR of 29.6% for transfusion and an OR of 8.5% for a hospital stay > 4 days [3]. Therefore, PAS is a serious medical condition associated with high maternal morbidity and mortality and presents anesthesiologists with several challenging management aspects. In the first part of this two-part literature survey, we addressed the general anesthetic and therapeutic approaches, as well as organizational and structural demands in PAS treatment.

Moreover, PAS is frequently accompanied by hemostatic changes, coagulopathies, and high blood loss. The knowledge of these possible conditions, diagnostic options, and sufficient management strategies is essential for anesthesiologists treating women with PAS and is presented here in the second part of this review series.

Literature findings – Placenta Accreta Spectrum Part I & II: anesthesia and hemostatic considerations based on an extended review of the literature

A detailed description of the literature review and screening process is presented in part one of this review series. Briefly, to identify relevant PAS literature, we performed a computerized Medline database search and screened 7,723 publication between 1973 and February 28 2021. Of those, we identified and included 55 anesthesiology relevant trials (n=3459 PAS patients) providing the basis of this review [4–58]. Another 37 trials were included in an interventional radiology analysis (n=4507 PAS patients), which was only included in part one of this review.

From the 55 trials we extracted data regarding blood loss, transfusion, hemostatic diagnostic and therapy hysterectomy rates, intensive care unit (ICU) admission rates, operative and anesthetic approaches used, PAS type, and postoperative care. The trials included in this review are shown in Supplementary Table 1.

This part of the review summarizes the current literature in regard to the special hemostatic conditions in women with PAS, preoperative and intraoperative hemostatic diagnostics and treatment, preoperative anemia, blood loss, transfusion management, cell salvage, and postpartum venous thromboembolism (VTE) prophylaxis.

Coagulopathy in PAS

It is currently unknown exactly how coagulation is affected by PAS, but more than 30% of women with PAS undergoing hysterectomy developed coagulopathy — associated for example with changes in platelet count, international normalized ratio, and fibrinogen levels — and had an increased estimated blood loss [24].

We do know, however, that both (1) systemic coagulation changes during normal pregnancy and (2) the endothelium-like functions of placental-trophoblasts in the third stage of labor lead to increased coagulation and decreased fibrinolytic activity before birth [59–61]. On the one hand, coagulation activation increases in PAS due to abnormal trophoblast invasion and maternal endothelium dysfunction in the placenta or the surrounding organs infiltrated by the placenta [1, 62, 63]. On the other hand, especially in extensive PAS (FIGO grade 3), prolonged prothrombin time and increased d-dimer and fibrin degradation products were detectable [64].

Prolonged prothrombin time might be indicate hypocoagulopathy [64]: In normal gestation, trophoblasts provide laminar maternal blood flow and prevent bleeding at the maternal-fetal interface [59, 60, 65]. Placental trophoblasts express tissue factor (TF) and initialize coagulation via activation of blood-coagulation factor VII (FVII) and thrombin (blood-coagulation factor II; FII). In abnormal gestation, the invasive growth, the increased angiogenesis and proliferation — which might be induced by hypoxia inducible factor-1α (HIF-1α), one of the regulators of the signaling pathway in trophoblasts invasion — leads to increased TF and coagulation with consecutive consumption of coagulation factors during endothelial expression [66].

Increased d-dimer and fibrin degradation products in extended PAS are a result of increased fibrinolysis: Angiogenesis and lacunar deletions cause in in increased blood velocity and shear forces with excessive fibrinoid deposition at the uteroplacental interface and consumption of fibrinogen and increased fibrinolysis via reduced Plasminogen Activator Inhibitor (PAI I) level [67].

Thus, the abnormal trophoblast invasion and enhanced trophoblast activity, raises the suspicion that both local and systemic coagulation activities can switch from an increased coagulation state in the third stage of labor to a decreased state in extensive PAS. This may result in disseminated intravascular coagulation (DIC) with subsequent uncontrolled systemic coagulation activation and consumption, consecutive bleeding, and microvascular thrombosis as a dreaded complication in PPH in PAS patients [59, 60, 65]. When massive bleeding in PAS occurs, an inflammation-

induced release of proinflammatory cytokines, like tumor necrosis factor-α (TNF) and interleukins (IL-1, IL-6), lead to massive expression of TF activating coagulation at the endothelium-like trophoblastic surface and normal endothelium [59, 60, 65]. On the one hand, decreased fibrinolysis, enhanced expression of PAI 1 + 2 and TAFI, and reduced coagulation inhibitors antithrombin (AT III) and protein C + S [12, 31, 59, 60, 65] may intensify coagulation in PPH related DIC. On the other hand, the changes in extensive PAS can cause consumption of utero-placental and systemic coagulation factors with enhanced bleeding during local resection or hysterectomy.

In conservative/expectant PAS management, leaving the placenta untouched minimizes the initial blood loss and the odds of a possible transition to a DIC-like hemostatic state. However, if the placenta is not removed, trophoblast-induced local coagulation activity can lead to massive consumption over a three month period, marked by decreased fibrinogen, increased D-dimers as a marker of local fibrinolysis, and increased risk of secondary PPH [11, 20, 68, 69].

Preoperative-prepartum anemia

International guidelines currently recommend both the (1) preoperative diagnosis and treatment of anemia and (2) patient blood management (PBM) concepts to maintain adequate hemoglobin levels and thereby reduce the need for allogenic blood transfusion intraoperatively [70–74]. Prepartum anemia is associated with impaired peripartum outcome (e.g. morbidity), transfusion, and has been shown to be associated with postpartum depression, fatigue, and altered maternal-infant bonding [75]. Nevertheless, we only identified one case report where a PAS patient (who was a Jehovah`s Witness with a Hb 12.5 g/dL) was administered a single dose of erythropoietin and intravenous iron before undergoing a caesarean section and delayed hysterectomy [76].

Because of the high risk of PPH in PAS, women should be preoperative screened for anemia and, if diagnosed, treated before childbirth [73, 74]. Hemodilution effects by increased red blood cells and plasma volume leads to a kind of physiological anemia in pregnancy [73]. According to the UK National Institute for Health Care and Excellence (NICE), anemia is defined in hemoglobin-(Hb-)levels below 11 g/dL in the first trimester of pregnancy and below 10.5 g/dL from the second trimester until birth [77]. Apart from PAS, the main cause of anemia in pregnancy is iron deficiency anemia, which should be diagnosed in the early pregnancy stage and at 28 weeks gestation in every woman [70, 77–79]. Most guidelines recommend oral iron therapy when ferritin levels are below 30 µg/L [75]. In PAS, anemia treatment might be indicated as early as possible to maintain Hb-levels above 11 g/dL during pregnancy. Particularly in advanced pregnancy, late PAS diagnoses, severe iron-deficiency, and oral iron intolerance, intravenous iron should be considered as a quick and effective method to increase preoperative Hb-levels [75, 78]. The Society of Obstetricians and Gynaecologists of Canada (SOGC) guidelines recently recommended the optimization of preoperative hemoglobin levels with intravenous iron [80].

Anesthetic considerations:
- PAS is associated with a high incidence of peripartal coagulopathy and accompanying PPH

Prepartum and intrapartum hematology laboratory tests, point-of-care (POC) diagnostics

Neither the recent SOGC guidelines [80] nor the studies included here offered any recommendations regarding preoperative coagulation tests. Other than Hb-levels, only 13 studies/case reports listed pre- and/or intraoperative blood tests including partial thromboplastin time (PTT) and/or prothrombin time (PT), platelets, D-dimers, and/or fibrinogen levels (Supplementary Table 1). We observed that the time of blood draw, coagulation studies/lab tests performed, and hemostatic therapies reported in the literature prior to transfusion varied considerably and were inconsistent. Five studies/case reports, for instance, measured D-dimer levels. Of those five, four studies reported a strong increase in D-dimers as a marker for the activation of the coagulation and fibrinolytic system during conservative management of PAS [10, 11, 20, 23]. We recommend assessing pre- and intrapartum coagulation, performing serial blood gas analyses and POC coagulation testing. Though prepartum fibrinogen levels and standard coagulation parameters in combination with viscoelastic tests (like rotational thrombelastometry-derived parameters; ROTEM®) are not able to "predict"

Anesthetic considerations
- Prepartum anemia is associated with impaired peripartum outcome
- Prepartum anemia should be diagnosed and treated (related to the cause of anemia)
- Consider administering intravenous iron to PAS patients with advanced pregnancy, late diagnoses of PAS, severe iron-deficiency, or oral iron intolerance

PPH, if PPH occurs, reduced fibrinogen levels and viscoelastic tests have been shown to correlate with the severity of bleeding [81–85]. The following blood tests should be performed mandatory prepartum: complete blood count (CBC) (specifically including platelets), fibrinogen levels, standard coagulation parameters, and D-dimers. Additionally, due to hemostatic changes in PAS, FVII, FVIII, von Willebrand factor (VWF), blood-coagulation factor XIII (FXIII), protein C + S, antithrombin, and/or viscoelastic tests may help determine the physiological pro-coagulant state before birth or to identify pre-, intra-, and postpartum changes during PAS treatment. A questionnaire may help identify patients at risk for potential secondary PPH due to personal and family history of bleeding (e.g. unusual bleeding after minor trauma, surgery or tooth extraction, known coagulation disorders, heavy or prolonged menstrual periods, and bleeding after delivery) [86].

Blood loss and transfusion

Measurement of blood loss

Blood loss was reported in 47 of the included case repots/studies. These included data from 2,982 women, reporting an average blood loss of approximately 1854 mL. 22 publications reported losses greater than 2 L (Figure 1, Supplementary Table 1).

In a recently published international multicenter study of 338 women with PAS, the median of visually estimated and/or measured and/or weighted blood loss was 2 L [17]. Unplanned hysterectomy or delivery by surgeons without experience in PAS was associated with an increased risk of blood loss > 3.5 L compared to planned hysterectomy, focal resection, or conservative management when delayed hysterectomy was not required [17].

We recommend a multimodal approach to assessing intraoperative blood loss during PAS-surgery—namely, (1) using blood collection drapes, (2) weighing wringed surgical sponges, (3) assessing fluid levels in surgical suction canisters, and finally (4) verifying non-transfused cell salvage blood canister levels [87–89]. Moreover, verification via calculation using the formula *Volume of Blood Loss (mL) = Estimated Blood Volume (mL) x* ln *(hemoglobin [g/L]/0.33 before delivery/postpartum hemoglobin [g/L]/0.33)* might be helpful to estimate blood loss [90].

Anesthetic considerations:

- PAS patients should undergo (at least) the following prepartum blood tests: Prepartum CBC (Hb, platelets), fibrinogen, and standard coagulation parameters.
- Intrapartum coagulation tests, blood gas analysis, and point-of-care coagulation testing should be considered when PPH occurs
- In conservative PAS management, fibrinogen and D-dimer levels should be continuously monitored
- If prior history of bleeding is noted, extended hemostatic blood tests are required

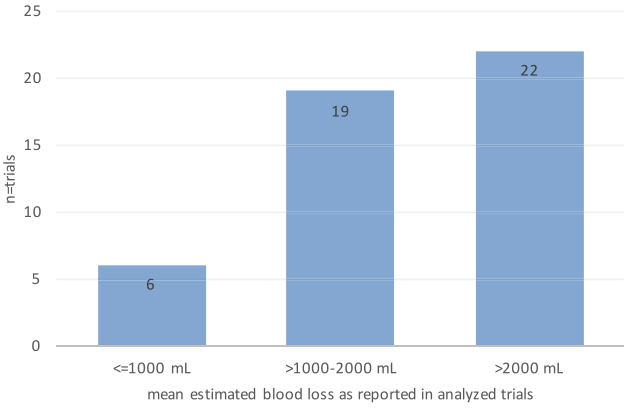

Figure 1: Estimated blood loss. Mean estimated blood loss (EBL) as reported in trials.

Transfusion and fluid management

Forty-four case reports/studies reported blood product transfusion data, including red blood cell concentrates (RBC), platelet concentrates (PLT), or fresh frozen plasma (FFP) (Supplementary Table 1). Up to two units of RBC were given in eight studies/case reports, two to four units in 12 studies/case reports, and greater than 4 units of RBCs were transfused in 20 studies/case reports. Four studies/case reports reported no RBC transfusion (Figure 2). The analysis contained data from 2,660 women with an average transfusion of 4.5 units of RBC per woman.

Thirty studies/case-reports reported having transfused 1 to 5 units of FFPs and 14 studies/case reports reported PLT transfusion (Supplementary Table 1). Taken together, this data indicates that though not every PAS patient undergoing C-section suffered from PPH, the patients with PAS who did have PPH were frequently transfused due to massive blood loss and accompanying coagulopathy.

Postpartum anemia due to bleeding may be associated with an increased risk of infection, enhanced cardiovascular stress, symptoms of anemia (including reduced capability for postpartum care of the baby, headache, fatigue, reduced lactation), postpartum depression, and prolonged hospital stay [91, 92]. That said, a prospective randomized non-inferiority trial in 521 women found that patients with severe postpartum anemia (Hb-level 4.8–7.9 g/dL, without severe anemic symptoms or comorbidities) who received RBC transfusion were significantly

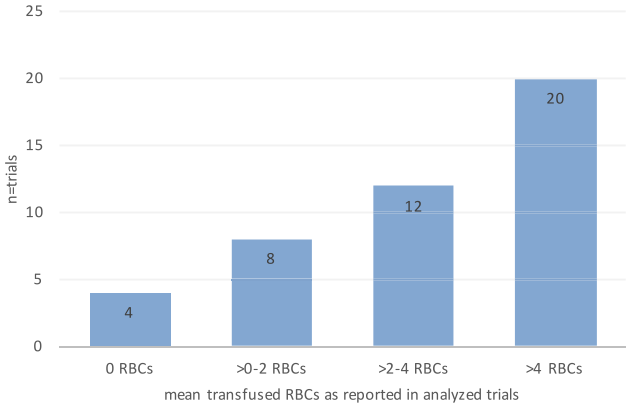

Figure 2: Transfused units of packed red blood cells mean units of packed red blood cells (RBCs) transfused, as reported in included trials.

less likely to have physical fatigue three days respectively one week postpartum than patients who were not transfused [93]. However, the observed effect was only little. Moreover, there was no difference in health-related quality of life six weeks postpartum between the transfusion and control groups. Therefore, restrictive transfusion management is justifiable [93]. According to NATA guidelines (Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis), women should undergo crossmatching for blood type and red cell antibodies at 28 weeks gestation [92]. In non-bleeding patients whose Hb-levels are < 6 g/dL, we consider transfusing a single RBC and then continue Hb-monitoring post-transfusion [92].

To generate balanced hemostasis and avoid dilutional coagulopathy (note: dilutional coagulopathy generally occurs when RBCs are exclusively transfused—i.e. without FFP or PLT) fixed RBC:FFP:PLT transfusion ratios in massive bleeding are currently being debated. In theory, a fixed-ratio transfusion approach is useful to mimic the replacement of whole blood specifically in emergency settings where diagnostic coagulation test results are not available. Currently, however, fixed transfusion ratios vary across PPH guidelines [94, 95]. For PAS patients with PPH in particular there are no fixed ratio transfusions recommended in current guidelines. This may be for several reasons. First, when bleeding occurs in PAS, massive blood loss is likely to be limited to specific timepoints, e.g. during local placental resection, in contrast to the unlimited continuous bleeding seen in uterine atony. In our opinion, because PAS patients have an increased risk of coagulopathy, transfusion treatment should focus on hemostatic requirements, meaning that peripartum permissive anemia can be tolerated if Hb-levels are > 6 g/dL. Secondly, massive blood loss in PAS can usually be anticipated, which allows for preoperative diagnostics (e.g. point-of-care testing, hemostatic state), hemostatic agent treatment, and the preparation and organization of transfusion-related systems prior to surgery, namely, setting up rapid transfusion systems (Level 1®), fast-thawing FFP microwaves, and cell salvage systems (Cell Saver®). Finally, because bleeding is generally anticipated in PAS patients, cell salvage systems are frequently used intraoperatively. Therefore, it is understandable that none of the studies that we identified in this review reported using fixed transfusion ratios. A multimodal approach combining classical institutional fluid, transfusion, and hemostatic/PPH protocols seems more useful than fixed transfusion ratios [96]. Patient comorbidity, wishes, clinical anemia, and risk of intraoperative bleeding prior to surgery should be considered. If massive bleeding is encountered, rapid transfusion systems and ready-to-use blood products should already be in the operating room.

Colloid solutions enhance dilutional coagulopathy (and may impair long-term renal function) and should therefore be avoided or strictly limited to emergency use during PAS bleedings [97–99]. Balanced gelatin polypeptide solutions also have been shown to integrate into clots and may alter fibrin-polymerization and clot-firmness [100]. Therefore, to avoid coagulopathy and interstitial and tissue edema, extracellular fluids should be replaced in a protocol-based manner [101]. During (emergency) massive bleeding in PAS, high volume resuscitation with balanced crystalloid and colloid solutions should specifically be used only to “bridge” the time until FFP transfusion and advanced hemodynamic monitoring is available.

Autologous blood transfusion: Cell salvage systems (e.g. Cell Saver®) collect and process maternal blood for re-/autotransfusion during surgery. This process has been shown to be well tolerated in obstetric patients with a high risk of bleeding [92, 101]. Thirteen of the studies included here reported the use of cell salvage in PAS management and re-transfused roughly 300–500 mL of blood (Supplementary Table 1). In a recent trial, 3,038 women at risk of PPH were randomly assigned to cell salvage vs. routine care [102]. Allogenic donor blood transfusion was similar in both groups, but increased in the routine care group if emergency C-section was performed [102]. During massive bleeds, cell salvage may reduce the need for additional allogenic transfusion without increasing the risk of amniotic fluid embolism due to high quality filtering techniques [92, 94, 101, 102]. In PAS, cell salvage systems can be prepared prior to surgery and should be used according to multimodal fluid, transfusion, and hemostatic/PPH protocols [94]. Autologous blood transfusion seems especially useful in non-massive continuous bleeding. In this setting, transfusing roughly 300 mL of autologous blood may circumvent allogenic RBC transfusion altogether.

Importantly, rhesus testing and appropriate treatment (anti-D isoimmunization) is necessary before transfusion of autologous blood to avoid maternal immunization by rhesus positive child [92, 94, 101, 102]. As a side note, cell salvage systems have white blood cell (WBC) filters that additionally remove remaining components of the amniotic fluid, WBCs, and squamous cells. These filters additionally reduce bacterial contamination of the autologous blood during re-transfusion [103], but can induce hypotension by inducing bradykinin release from platelets as they pass through the negatively charged filter membrane [104, 105].

Tranexamic acid (TXA) and hemostatic agent requirements

Both decreased and increased fibrinolysis can occur as part of PAS coagulopathy [1, 62, 63, 67]. Therefore, prophylactic antifibrinolytic agents like TXA should be handled with care and might be considered in PAS patients with high risk of bleeding, e.g. immediately before starting caesarean section (due to high risk on hyperfibrinolysis during massive bleeding in PAS) [24]. All data on the prophylactic use of TXA are mainly based on all-cause PPH: A metanalysis of eight RCTs found reduced postpartum bleeding (mean difference −160 mL blood; −224 mL to −95 mL) after prophylactic administration of 1–2 *g* TXA prior to elective C-sections [106]. A multicenter RCT of prophylactic TXA vs. placebo after planned cesarean delivery at ≥34 weeks gestation in 4,431 women showed that TXA significantly reduced the incidence of PPH (26.7 vs. 31.6%), though secondary outcomes (EBL and transfusion rate) did not differ across groups [107]. For vaginal delivery, a multicenter double-blind randomized trial in 4,079 women found that patients who received 1 *g* of TXA prophylactically were significantly less likely to have clinically relevant PPH, though no difference in RBC transfusion was observed [107]. None of the studies reported an increased risk of adverse events, but history of thromboembolic events and contraindications for the use of TXA as well as potentially decreased fibrinolysis should be considered if TXA is administered prophylactically in PAS patients.

The therapeutic use of TXA is targeting potential enhanced clot destruction and deficient clot strength during PPH. However, only six of the studies included in this review reported TXA treatment, the majority of which did not perform prophylactic administration before bleeding (Supplementary Table 1). Again, there is no evidence on differential approaches of TXA administration depending on the grade of PAS or the prepartum coagulation state in PAS and recommendations are mainly based on PPH data of all causes: The results of the international double-blind placebo-controlled multicenter World Maternal Antifibrinolytic (WOMAN) trial (20,060 patients with PPH) suggest that early administration of TXA (within 3 h of childbirth) reduces the risk of exsanguination without an increased risk for adverse events [108]. However, several issues in trial performance should be considered. The trial was mainly performed in low-income countries (with 20-30-fold higher mortality rates than European countries) without using a nationwide-adjusted PPH algorithm. Initial primary outcome (prevention of hysterectomy) was modified after patient recruitment due to high hysterectomy rates and lack of alternatives in PPH treatment [108]. No differences in transfusion or volume of blood lost were observed. Thromboembolic events (like deep vein thrombosis) were detected via patient reporting with a lower incidence than in obstetric patients without PPH in European countries [108]. Therefore, it is unclear if these results are universally applicable. Nevertheless, the therapeutic use of TXA is highly recommended in PPH- and PAS guidelines [80, 92, 96, 107, 109–111].

Of the studies included in this review, 14 reported the administration of additional hemostatic agents during in PAS treatment. Fibrinogen was required in only two of the reported cases/studies. Cryoprecipitate (not universally licensed throughout Europe), a plasma-derived frozen blood product containing mainly fibrinogen, factor VIII, factor XIII and von Willebrand factor, was administrated in ten of the reported cases/studies (Supplementary Table 1). Activated recombinant factor VII and prothrombin complex concentrate (PPC/PPSB: factor II, VII, IX, X and protein C + S) was administered during massive bleeding in one case report (Supplementary Table 1).

International PPH guidelines currently recommended fibrinogen administration following TXA administration and cryoprecipitate/PPSB/FFP if persistent bleeding is observed and >1.5 L of blood has been lost [96, 109, 111, 112].

Anesthetic considerations:

- Blood loss should be estimated or calculated and communicated continuously during the operation
- Prepare for massive bleeding: 6 type-compatible cross-matched RBC and 6 type-compatible FFP should be placed nearby (3 thawed FFPs and 2 RBCs should be in the operating room before surgical incision), 2 apheresis units of ABO-compatible platelets should be provided
- 14–16 G peripheral venous catheters should be placed and a rapid transfusion system and microwave for fast FFP-thawing and massive transfusion should be prepared
- Autologous blood transfusion systems including WBC filter should be ready for use in the operating room

Additionally, both (1) FXIII (to improved clot stability) and (2) desmopressin (to increased endothelial VWF release and prevention of FVIII reduction) may be indicated as supportive coagulation treatments in persistent bleeding [96, 109, 111, 112]. To minimize dilutional coagulopathy and DIC in PAS, hemostatic agents might be administered in the early stages of PPH, especially if extensive invasive placenta percreta is observed or intraoperative bleeding risk is high.

Initial coagulopathy is likely less pronounced in patients undergoing conservative PAS management. However, local and secondary systemic hemostatic consumption may lead to time-delayed coagulopathy. Therefore, coagulation should be closely monitored and TXA, fibrinogen, and FXIII administration may be indicated [10]. There is no data concerning the time frame or periodical of coagulation monitoring in conservative PAS management. The placental period may be drawn out for months [10]. During this time a continuous consumptions factors may occur—indicating a close meshed monitoring of coagulation factors. With lack of evidence, an interval of 4 weeks appears to be appropriate, in absence of clinical symptoms.

Postpartum venous thromboembolism (VTE) prophylaxis

None of the trials/case reports included in this review reported increased postoperative VTE incidence in PAS. Moreover, specifics regarding postoperative anticoagulant VTE prophylaxis were generally not reported. However, pregnancy-associated VTE is a leading cause of maternal morbidity and mortality [113]. In pregnancy the hypercoagulable state and the inferior vena cava compression by the gravid uterus increases the risk for VTE. The adjusted odds ratio (OR) for VTE after any cesarean section is 3.5. Therefore, all women undergoing cesarean sections should be considered for thromboprophylaxis with low-molecular-weight heparin (LMWH) for ten days after delivery apart from those having an elective cesarean section without any additional risk factors. Persistence of three or more risk factors should warrant extended VTE prophylaxis up to six weeks [116]. Beside VTE history prior to pregnancy and/or the presence of thrombophilia (e.g. Factor-V-Leiden mutation) most of the VTE-risk factors such as age > 35 years, parity ≥ 3, preterm delivery < 37 weeks, PPH and surgery, transfusion are common in women with PAS [113, 117].

In addition to VTE prophylaxis with LMWH, intermittent pneumatic compression (IPC) may facilitate VTE prevention. There is no evidence regarding IPC in PAS in particular. However, several trials showed effectiveness and safety of IPC—for example in women undergoing gynecologic surgery [118–121]. Therefore, the use of IPC may be considered.

Anesthetic considerations:
- Hemostatic agents, fluid resuscitation, and transfusion should follow PPH algorithms according to national and international guidelines
- 1–2 *g* TXA bolus can be given intravenously before surgical incision in PAS patients with high risk of bleeding or should be given when PPH occurs (administer TXA continuously i.v. if needed)
- Fibrinogen and PCC (and or FXIII, rFVIIa, desmopressin) might be necessary in early stage PPH due to massive blood loss and consumption coagulopathy (use viscoelastic testing if applicable)

Anesthetic considerations:
- Consider LMWH VTE prophylaxis > 10 days postpartum based on presence of VTE risk factors

PAS-algorithm

This review highlights numerous aspects to be considered in PAS management. A PAS-algorithm optimizes interdisciplinary communication over the entire period of therapy and helps schedule (preoperative) diagnostics and therapy. Every aspect associated with PAS can and should be approached in a structured way. Part I of this review includes a PAS-Algorithm that also contains the hemostatic considerations discussed here in this second part of this review series.

Figure 3 shows a possible PAS-Algorithm, already presented in the first part of this review series.

Limitations

As reported in part one of this two-part review series, PAS is a rare and heterogeneous condition. Definitions vary and few studies were designed to specifically assess coagulopathies and transfusion management in PAS patients. As such, the information garnered herein was frequently drawn from secondary outcome measures or baseline study characteristics. Study quality varied and methods, reporting, and statistics were heterogeneous. Currently, there are few meta-analyses, systematic reviews, or randomized-controlled trials available and the majority of PAS data are

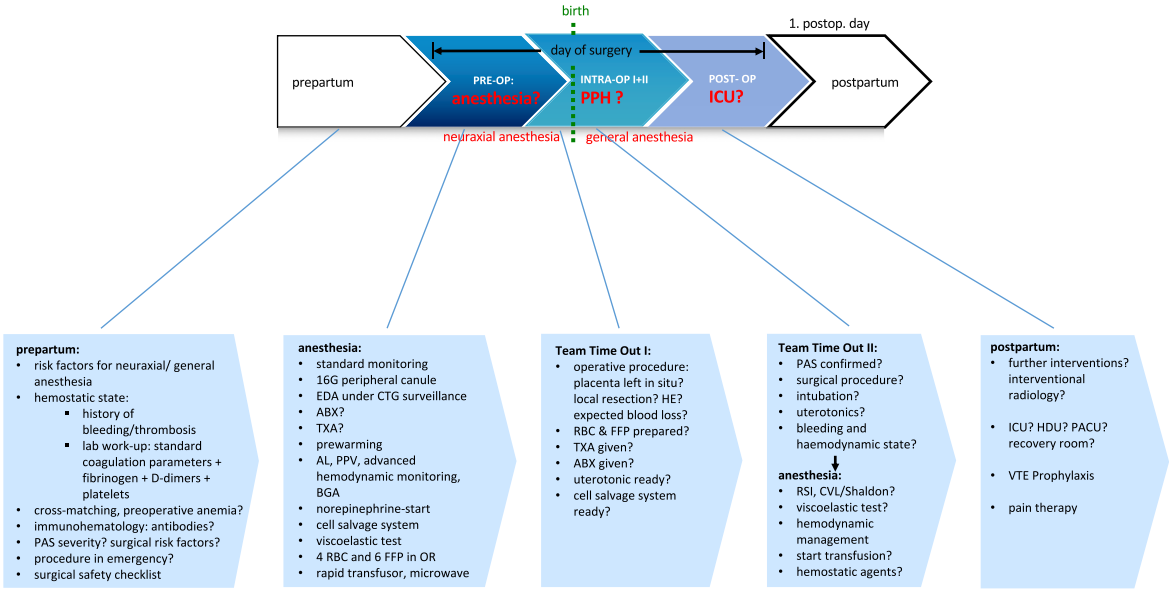

Figure 3: PAS-algorithm. AL, arterial line; ABX, antibiosis; BGA, blood gas analysis; CVL, central venous line; EDA, epidural anesthesia; FFP, fresh frozen plasma; HE, hysterectomy; ICU, intensive care unit; INTRA-OP, intraoperative; OR, operation room; PACU, post-anesthesia care unit; PAS, placenta accreta spectrum; PCEA, patient-controlled epidural anesthesia; POST-OP, postoperative; PPH, peripartum hemorrhage; PPV, pulse pressure variation; PRE-OP, preoperative; RBC, red blood cell (concentrates); RSI, rapid sequence induction; TTO, team time out; TXA, tranexamic acid.

taken from retrospective studies, case reports, or case series. Besides, due to the different terms used to describe the condition of PAS, the research may be incomplete. Furthermore, there is no database recording every PAS case. Therefore, it seems reasonable, that omplicative PAS cases were published more frequently, potentially leading to an overestimation of the severity of this condition.

Anesthetic considerations:

- An algorithm for PAS management should be developed in a multidisciplinary manner, anesthetic considerations should be accounted for and adjusted according to on-site structural conditions
- Preoperative hematology laboratory tests, POC testing, assessment of blood loss and PPH treatment strategies should be included in this algorithm

Conclusions

PAS is a rare condition with several peculiarities that lead to a high morbidity and mortality. This presents a challenge to everyone involved in PAS therapy, especially anesthesiologists. Apart from the specifics in anesthetic, surgical, and interventional approaches, as well as structural and organizational requirements—all of which were addressed in the first part of this series—PAS is frequently accompanied by coagulopathy and massive PPH. Coagulopathy often even presents as a "DIC-like" state. Anesthesiologists need to anticipate possible hemostatic changes and severe bleeding. Over the past few years, diagnostic and therapeutic options have evolved considerably. POC testing provides prompt diagnosis of hemostatic disturbances and specific hemostatic agents may, if used reasonably, help prevent or stop ongoing PPH. Therefore, the knowledge of a targeted medical diagnosis and therapy is essential. Structured preoperative interdisciplinary planning is vital to reduce morbidity and mortality. A PAS-Algorithm provides good feasibility to organize and optimize multidisciplinary care throughout entire treatment course. Though evidence is increasing, we have made the recommendations herein based on a relative paucity of literature. High-quality trials are needed to ensure the best possible treatment for PAS patients.

Research funding: None declared.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: All authors state no conflict of interest in relation to this study. R.E. states no conflict of interest. P.C. states no conflict of interest. PY.D. received honoraria for lecture and consulting for CAF-DCF an LFB company. T.B. received research funds in relation to DFG-project BR2925/11-1. C.O.L. states no conflict of

interest. P.N. states no conflict of interest. C.S. reports grants from Deutsche Forschungsgemeinschaft/German Research Society, grants from Deutsches Zentrum für Luft- und Raumfahrt e.V. (DLR)/German Aerospace Center, grants from Einstein Stiftung Berlin/Einstein Foundation Berlin, grants from Gemeinsamer Bundesausschuss/Federal Joint Committee (G-BA), grants from Inneruniversitäre Forschungsförderung/Inner University Grants, grants from Projektträger im DLR/Porject Management Agency, grants from Stifterverband/Non-Profit Society Promoting Science and Education, grants from European Society of Anaesthesiology and Intensive Care, grants from Baxter Deutschland GmbH, grants from Fresenius Medical Care, grants from Grünenthal GmbH, grants from Masimo Europe Ltd., grants from Pfizer Pharma PFE GmbH, personal fees from Georg Thieme Verlang, grants from Dr. F. Köhler Chemie GmbH, grants from Sintetica GmbH, grants from Stifterverband für die deutsche Wissenschaft e.V./Philips, grants from Stiftung Charité, grants from AGUETTANT Deutschland GmbH, grants from AbbVie Deutschland GmbH & Co. KG, grants from Amomed Pharma GmbH, grants from InTouch Health, grants from Copra System GmbH, grants from Correvio GmbH, grants from Gemeinsamer Bundesausschuss/Federal Joint Committee (G-BA) -Innovationsfond, grants from Max-Planck-Gesellschaft zur Förderung der Wissenschaft e.V., grants from Deutsche Gesellschaft für Anesthesiologie & Intensivmedizin (DGAI), grants from Stifterverband für die deutsche Wissenschaft e.V./Medtronic, grants from Philips Electronics Nederland BV, grants from BMBF/RKI, grants from BMBF, grants from Deutsche Forschungsgemeinschaft/German Research Societ, grants from Drägerwerk AG & Co. KGaA outside the submitted work. In addition C.S. has the patents 10 2014 215 211.9, 10 2018 114 364.8, 10 2018 110 275.5, 50 2015 010 534.8, 50 2015 010 347.7, 10 2014 215 212.7 licensed. W.H. states no conflict of interest. L.K. reports honoraria for lecture from Novo Nordisk, CSL Behring and HICC Deutschland GbR.

Informed consent: Not applicable.

Ethical approval: Not applicable.

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Supplementary Material: The online version of this article offers supplementary material (https://doi.org/10.1515/jpm-2022-0233).