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Expert panel recommendation

Diagnosis and treatment of peripartum bleeding

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Abstract

Severe peripartum hemorrhage (PPH) contributes to maternal morbidity and mortality and is one of the most frequent emergencies in obstetrics, occurring at a prevalence of 0.5–5.0%. Detection of antepartum risk factors is essential in order to implement preventive measures. Proper training of obstetric staff and publication of recommendations and guidelines can effectively reduce the frequency of PPH and its resulting morbidity and mortality. Therefore, an interdisciplinary expert committee was formed, with members from Germany, Austria, and Switzerland, to summarize recent scientific findings. An up-to-date presentation of the importance of embolization and of the diagnosis of coagulopathy in PPH is provided. Furthermore, the committee recommends changes in the management of PPH including new surgical options and the off-label use of recombinant factor VIIa.

Keywords: Disseminated intravascular coagulation; peripartum hemorrhage; ultrasonography; uterotonic.

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Background

Severe peripartum hemorrhage (PPH) is one of the most life-threatening emergencies in obstetrics. In conjunction with thromboembolism, PPH is one of the main causes of maternal death and is observed in 25% of pregnancy-related complications [9]. PPH contributes to the death of approximately 140,000 women worldwide, notwithstanding the considerable number of unreported cases. Worldwide, a woman dies from postpartum hemorrhage every four minutes [2]. In the USA and Europe, 1–2 maternal deaths per 100,000 live-births due to hemorrhage are expected; with life-threatening peripartum hemorrhage affecting every 1:1000 births [9]. According to perinatal statistics, a blood loss of >1000 mL is expected in 0.5–5% of vaginal deliveries [4, 39, 55]. This prevalence has been markedly reduced by recommendations and guideline publications and the training of obstetric staff.

Peripartum blood loss following vaginal birth or cesarean section is often not measured and therefore may be significantly underestimated [14, 16]. The blood volume of a pregnant woman is approximately 9% of her total body weight. The WHO defines PPH as blood loss >500 mL following vaginal birth or blood loss >1000 mL following delivery by cesarean section. Severe bleeding is defined as follows [39, 64]:

- Blood loss >150 mL/min over 20 min; or
- Loss of 50% of circulating blood volume within 3 h; or
- Acute blood loss >1500–2000 mL.

Distinction of the time of bleeding is made between early postpartum bleeding (within 24 h following birth) and late postpartum bleeding (24 h to 6 weeks following birth). From a clinical perspective, blood loss of 500–1500 mL is generally tolerated without symptoms of shock [9].

Symptoms of hemorrhagic shock in cases of large volumes of blood loss are agitation, clouding of conscious-

ness, cold sweat, paleness, tachycardia, hypotension, hyperventilation and oligoanuria. Pathophysiologically, severe bleeding can lead to hemorrhagic shock and consumption coagulopathy and/or dilution coagulopathy. Specifically, severe bleeding (e.g., placental abruption) and chorioamnionitis, puerperal sepsis, septic abortion, amniotic fluid embolism can lead to an increased activation of the coagulation system resulting in disseminated intravascular coagulation (DIC) and subsequent consumption coagulopathy [50].

The objective of the recommendations presented in this report is to facilitate the prevention and early treatment of PPH in order to reduce maternal morbidity and mortality.

Risk factors of PPH

Pre-, intra- and postpartum risk factors

In order to identify risk factors for PPH, the patient's medical history should be taken early during pregnancy. The placental location should be documented during ultrasonography screening in the 2nd trimester. Implantation disorders should be taken into consideration, particularly if the patient had previous uterine operations or a placenta previa in the current pregnancy. Table 1 summarizes the antepartum as well as intra- and postpartum risk factors.

Preventive measures for patients at risk for PPH

Every patient with risk factors should be seen antenatally at the obstetric department where the delivery is planned. The following guidelines and procedures should be followed at the clinic:

1. Adequate venous access during delivery for each patient, large-caliber venous access if bleeding complications occur.
2. Ensure availability of uterotonic agents (oxytocin, e.g., Syntocinon®, prostaglandins (e.g., sulprostone: Nalador® and, if available, misoprostol: Cytotec® [off-label use]).
3. Check logistics:
   – Availability of an "emergency laboratory" (blood count, blood gas analyses (BGA), aPTT, PT or INR, antithrombin (AT), fibrinogen, possibly platelet function analyzer.

Table 1 Risk factors of PPH.

	Antepartum	Intra- and postpartum
Placenta	– History of placental abruption – Placenta previa and its risks as well as history of cesarean section – Placenta accreta, increta, percreta [55, 62]	– Retained placenta [4, 62]
Uterus	– Uterine atony in previous pregnancy (risk of recurrence is up to 25%) – Previous uterine operations (e.g., c-section, curettage) – Leiomyoma of uterus – Excessive distension of uterus (e.g., multiple pregnancy, polyhydramnios, transverse fetal lie)	– Uterine atony [31, 33, 56] – Uterine rupture, inversion of uterus [62]
Coagulation	– Acquired coagulation disorder (e.g., drug-induced or organ-related thrombopathy, Werlhof's disease) – Congenital coagulation disorder (e.g., von Willebrand's disease, deficiency of individual coagulation factors, congenital thrombopathy)	– Co-morbidity with disseminated intravascular coagulation (DIC) (e.g., in the case of severe pre-eclampsia/HELLP syndrome, placental abruption, chorioamnionitis, sepsis and amniotic fluid embolism) – Other hemostatic disorders (dilution coagulopathy, hyperfibrinolysis etc.)
Other	– Risks of premature placental abruption (pathologic uterine blood flow with high resistance diagnosed by PW Doppler, thrombophilia) – Antepartum bleeding – Multiparity (>5 births) [55] – Gestational hypertension [62] (e.g., HELLP syndrome with risk of DIC) – Chorioamnionitis – Nicotine and Cocaine abuse	– Prolonged labor [4, 62] – Labor induction and long-lasting oxytocin administration [62] – Macrosomia (>4000 g [4] or large-for-date baby [62]) – Operative vaginal delivery (in some cases isolated atony of the lower uterine segment) [4, 62] – Laceration of the birth canal [62] – Cesarean section (especially emergency section after prolonged birth) [55]

- Anesthesiologist on call (in-house).
- Experienced obstetrician on call (in-house).
- Blood bank availability with timely provision of packed red cells and fresh frozen plasma.
- Check availability of coagulation factors (fibrinogen, recombinant factor VIIa (rFVIIa, NovoSeven®), antifibrinolytics).

To prevent harm to the patient, such conditions must be checked at each obstetric unit, in particular the timely availability (preferably within 30 min) of blood components (e.g., fresh frozen plasma, packed red cells, platelets as well as coagulation factors).

Strategy for the management of severe PPH

1. Measure blood loss (Note: blood loss in clots etc.).
2. Rapidly evaluate the cause of bleeding: palpate uterine tone, check for incomplete placenta (ultrasonographic control, manual or instrumental exploration), exclude trauma of birth canal by speculum.
3. Initiate pharmacotherapy and/or surgical therapy depending on etiology.
4. Control vital parameters, possibly invasive monitoring.
5. Initial volume replacement in order to maintain normovolemia: crystalloid and colloid solutions.
6. Matching of blood, emergency laboratory (blood count, coagulation, etc.).
7. Order packed red cells and fresh frozen plasma, prepare as applicable (delivery room or operating room).
8. If blood loss is critical (see Table 2), administer packed red cells and fresh frozen plasma, coagulation factors as necessary, e.g., fibrinogen, rFVIIa and other hemostatic agents (tranexamic acid, desmopressin).
9. Consider admission to ICU with possibly invasive monitoring.
10. Timely operative intervention if conservative measures fail.

Table 2 Threshold values for replacement of red cells, platelets and coagulation factors in patients with acute or persistent bleeding (modified and updated from Pötzsch et al. 2007 [53]).

Parameter	Limits
Hemoglobin	7–8 g/dL
Platelet count	$<$50,000/μL
INR value	$>$1.5*
aPTT	$>$1.5-fold prolongation of normal value
Fibrinogen	$<$1.5 g/L [67]

*Corresponds, e.g., to a PT of $<$40% with Roche, Dade-Behring reagent.

Etiology of bleeding

The causes of bleeding fall into four categories (“4T’s”):

- Tone (postpartum uterine atony).
- Trauma (laceration of the birth canal).
- Tissue (retained placenta and impaired separation).
- Thrombin (decompensation of coagulation, coagulopathy).

Postpartum atony

The most common cause of PPH is uterine atony (67–80% of all PPH, 2–8% of all births) [31, 33, 56]. Recommendations for physicians include:

- Anticipate risk factors (see Table 1).
- Obtain diagnosis: uterine fundus abnormally high and soft, and primarily intermittent and projectile bleeding. Note: 500–1000 mL blood may accumulate in the uterine cavity; discrepancy between visually estimated blood loss and clinically profound volume deficiency.
- Empty the bladder.
- Mechanical procedures: Massaging the uterus (endogenous synthesis of prostaglandins), expression and holding of the uterus in order to improve contractility, bimanual uterine compression (e.g., Hamilton’s maneuver).
- Exclude retained products of conception (ultrasonography) and birth injuries (speculum). In the case of uterine rupture, a marked mobility of the uterus may be palpable and a hematoma or free fluid/clots may be visible by ultrasonography (often no heavy vaginal bleeding).

Pharmacological therapy Uterotonic agents should be administered in accordance with the following guidelines. All midwifes and obstetricians should be acquainted with the following, and these guidelines should be included in the delivery room manual.

a) Intravenous oxytocin (intramuscularly if indicated): Do not inject more than 6 I.U. slowly undiluted, 3 I.U. as a bolus, perhaps an additional 3 I.U. fractionated +10–40 I.U. oxytocin in 500–1000 mL lactated Ringer’s solution by an intravenous drip (the dose will depend on the uterine effect [2]). Onset of action is usually within one minute following i.v. administration, and within 3–5 min following i.m. administration (10 I.U. max.). Note: dose-dependent hemodynamic effect of oxytocin is more pronounced with bolus administration than with short infusion (e.g., 5 I.U. over 5 min) as a consequence of vasodilatory effect: reflex tachycardia, increased cardiac output, temporary decrease in arterial blood pressure [71]. Myocardial ischemia and deaths have been described [51, 70]. Other side effects include: increase in blood

pressure, cardiac arrhythmias, flushing, head and thoracic pain, nausea and vomiting (especially when a bolus is administered). Minimal effective dose of oxytocin i.v. (ED_{90}): 0.35 I.U. [10].

b) Methylergometrine (Methergin®): One ampoule (= 1 mL) contains 0.2 mg methylergometrine. According to Jacobs (2006) [31], Methergin® should not be administered as an intravenous bolus, and due to its side effect profile, the intravenous route of administration is no longer used. In Germany, it is authorized as a slow intravenous administration up to 0.1 mg (half an ampoule) in patients with postpartum hemorrhage. Major contraindications: hypertension, preeclampsia/eclampsia, uterine fibroma, ischemic vascular disease, severe impairment of liver and kidney function, sepsis. Note: an increasing number of severe maternal complications, e.g., coronary spasms, cardiac arrhythmias, myocardial infarction resulting in death, cerebral angiopathy have been reported [21, 24, 38, 60, 75].

c) If oxytocin fails, immediate intravenous administration of sulprostone (Nalador® 500): 1 ampoule = 500 μg in 500 mL solution for infusion via droplet infusion pump, initial dose: 1.7 mL/min, up to 8.3 mL/min max as necessary, maintenance dose: 1.7 mL/min. Maximum daily dose: 1500 μg: In Germany, prostaglandin $F_{2\alpha}$ (Dinoprost, Minprostin® $F_{2\alpha}$) is no longer authorized for the treatment of uterine atony or postpartum hemorrhage. Misoprostol (Cytotec®) has been taken off the German market for economic reasons but is still available in other countries (e.g., Switzerland) (Note: off-label use). Dosage: 1000 μg misoprostol rectally [30, 36, 37, 68]. According to a Cochrane analysis [42], there remains insufficient data providing evidence of an advantage of misoprostol compared with other first-line uterotonic agents.

d) Intrauterine use of prostaglandins: If intravenous prostaglandin application fails, uterine tamponades can be successful (e.g., abdominal packs soaked in sulprostone). In cases of uterine atony, the effect of such an action is questionable since contractility of the uterus is impeded and the risk of infection is increased. In the case of diffuse bleeding from placental abruption areas, a tamponade can be helpful, especially as an effective stopgap measure prior to surgical intervention [2]. Relatively scant data exist on intracavitary application of sulprostone, and it is not approved for this application (off-label use). Intramyometrial application of sulprostone (e.g., into the uterine fundus in patients undergoing cesarean section) does not comply with marketing authorization.

Another mechanical method to achieve intracavitary hemostasis is the Bakri balloon (also Sengstaken-Blakemore tube or similar balloon catheter, content approximately 300 mL), however, limited data are available on its use for postpartum uterine atony. This application system enables an additional intracavitary application of uterotonics following intrauterine filling of the balloon; the balloon can remain *in utero* for up to 24 h. Use of a balloon catheter in the case of a "tamponade test": If effective, leave in place for 24 h. If not sufficiently effective: surgical treatment is required (commonly laparotomy) [13, 61].

Surgical measures Surgical measures to preserve the uterus should be performed if manual treatment and pharmacotherapy (including tamponade test) fail to treat PPH. Surgical measures are described below:

a) Uterine compression sutures: The purpose of this measure is to reduce the placental adhesion surface and to tamponade the source of bleeding. This measure is recommended for patients with diffuse uterine bleeding following spontaneous birth as well as following a cesarean section. Methods:
   - Traditional B-Lynch suture ("brace suture", see Figure 1a), details and modifications of the method are described in [7, 43]. Haymen et al. published a modification with four vertical compression sutures to prevent the risk of a displacement of the sutures [20, 25].
   - Compression sutures according to Pereira et al. (2005) [49]: combination of transversal and vertical sutures (Figure 1B).
   - Method according to Cho et al. (2000) [11]: entails square suturing of the entire uterine wall, including the uterine cavity, around the bleeding area. The sutures are passed twice transmurally from the anterior to the posterior wall, with stitches posterior to anterior, which produces squares of 3–4 cm with local compression of the uterine walls – a procedure known as "multiple square suturing". This procedure is also suitable for hemorrhage from the lower uterine segment (Figure 1C).
   - Further methods of suturing e.g.: Z-suture according to Kainer et al. (2003) [34].

b) Abdominal ligation of the uterine artery, rarely results in complications (fistula between uterine artery and vein, intraligamentary hematoma, ureteral lesion) [45] (Figure 1D). There are also individual reports about transvaginal ligation of the uterine artery [26]. Note: ureteral lesion.

c) Stepwise uterine devascularisation: ligation of the ascending and descending branches of the uterine artery as well as the collaterals from the ovarian artery [1].

d) Ligation of the internal iliac artery: this measure is technically demanding, since exposure of the internal iliac artery over 3–4 cm is necessary and the artery has to be ligated twice distal to the dorsal main stem – approximately 2.5 cm after the bifurcation – without separation. Prior to ligation, the ureter, the external

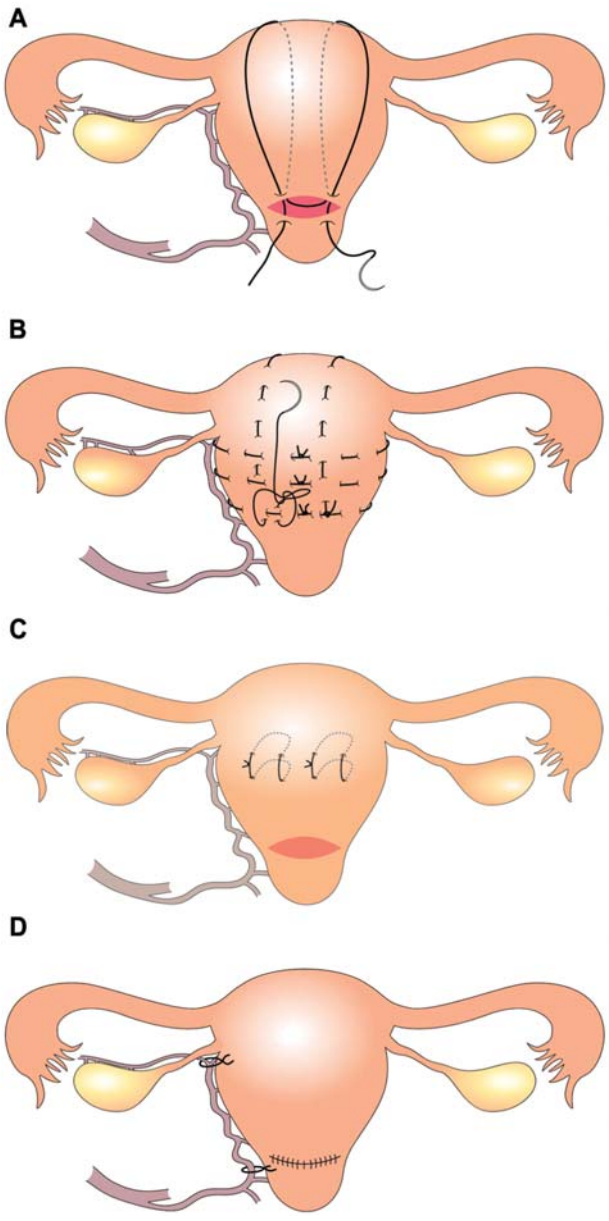

Figure 1 (A) Traditional B-lynch suture according to B-Lynch [7]. (B) Compression sutures according to Pereira et al. (2005) [49]. (C) Method according to Cho et al. (2000) [11]. (D) Abdominal ligation of the uterine artery according to O'Leary (1995) [45].

iliac artery and the common iliac artery as well as the internal iliac veins must be identified (Note: injury to these veins when undermining the arteries).

e) Laparoscopic bilateral application of transitional uterine clips (Yasargil clips), which will be removed via laparoscopy during the postpartum period (personal communication A. Schneider, Berlin).

Arterial embolization Embolization of the uterine arteries (reviewed in Royal College of Radiologists and ROC of Obstetricians and Gynecologists 2001 [57]) has been used in severe obstetric lacerations, as well as in the case of abnormalities of placental implantation, uterine atony, cervical and abdominal pregnancy with an 80–100% success [15, 46, 47, 65, 73, 74, 77]. Embolization may also be performed as a last resort in women with persistent diffuse bleeding in the pelvis following postpartum hysterectomy [6]. Any department of obstetrics should clarify whether and within which timeframe this method is available. Complications include perforation of the internal iliac artery [47], uterine and bladder necrosis [54], temporary ischemia of the gluteus muscle, ischialgiform neuropathy and postembolization syndrome.

Relative contraindications for uterus-preserving measures Uterus-preserving measures have a relative contraindication in:

- Patients with extended abnormality of placental implantation (placenta increta/percreta), in which the implantation bed of the placenta is opened, with treatment-resistant bleeding or one that involves large portions of the uterine wall.
- Non-reconstructable uterine injury.
- Septic uterus.

Postpartum hysterectomy Hysterectomy should be performed only when all other available measures have been exhausted (frequency: approx. 1:2500 births) [33, 63]. The following should be taken into consideration:

- Due to the strong vascularization of the uterus (uterine artery perfusion at term of delivery approx. 500 mL/min) and the difficulty in delimiting the uterus from the cervix, this operation is demanding.
- The mean blood loss is 2–3 L.
- Supracervical hysterectomy is preferred, the adnexa should be preserved.
- Placenta previa commonly requires total hysterectomy.
- Morbidity and mortality are high (1% maternal mortality).
- The decision of whether conservative approaches are no longer promising and surgical intervention is indispensable, requires consideration about the hemodynamics and coagulation status. The decision to perform hysterectomy must not be taken too late.
- In order to avoid fatal bleeding, the administration of packed red cells, fresh frozen plasma, and platelets as necessary is mandatory prior to surgical intervention (Table 2).
- To avoid hysterectomy, physicians should consider administration of rFVIIa (off-label use) [3]. However,

administration of rFVIIa must not delay intervention in critical situations (Appendix).

Retained products of conception or failure of separation

Retained product of conception Retained products of conception occur with a frequency of 1:300 births. Clinical signs are increased bleeding following delivery of the placenta and poor uterine contraction (possibly).

Management:

- Immediate postpartum inspection of the placenta (possibly second opinion: midwife/obstetrician): defects of placental surface, bleeding from placental defects, aberrant vessels into the fetal membranes (to exclude accessory placental lobe).
- Ultrasonography.
- Therapy: early manual exploration and possibly curettage in order to prevent further blood loss, intravenous administration of high-dose uterotonic agents.

Failure of placental separation Failures of separation are the consequence of partial or complete lack of the maternal decidua, leading to direct contact between villous chorion and myometrium. Depending on the depth of invasion, distinction is made between placenta accreta, increta or percreta (up to the serosa or even exceeding the uterine wall; Figure 2). The frequency of this disorder is between 1:540 and 1:7000 births [44] (increasing prevalence due to increasing rates of cesarean sections). Twenty percent of cases are associated with placenta previa.

Antepartum management:

- Anticipate predisposing factors: e.g., previous cesarean section, previous curettage, in patients with submucous myomas, previous endometritis, myomectomy and retained placenta in a previous pregnancy.
- Ultrasonography: sonographic features suggestive for placenta accreta/increta are irregular shapes, placental lacunae (vascular spaces) within the placenta, thinning of the myometrium overlying the placenta, loss of retroplacental "clear space", protrusion of the placenta into the bladder, increased vascularity of the uterine serosa – bladder interface, and, on Doppler ultrasonography, turbulent blood flow through the lacunae [12, 48]. Vaginal sonography enables a more precise assessment of infiltration depth under the bladder and allows an assessment to be made as to whether invasion into the cervical stroma is present in patients with placenta previa. To date, the diagnostic value of MRI in these cases has not been clarified and is currently being investigated [12].

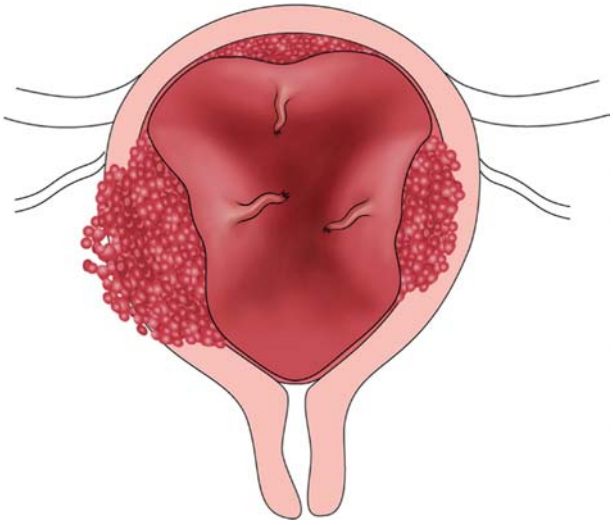

Figure 2 Scheme of deep placental invasion (placenta acreta, increta, percreta).

Failure of placental separation after vaginal birth Placenta adherens, accreta, increta or percreta are causes of failure of separation following vaginal delivery.

Management:

If there is no placental separation within 30 min following birth and/or blood loss is >500 mL:

- Ultrasonography, particularly if predisposing factors are present (see above).
- Exclude placenta incarcerata: empty bladder.
- General or regional anesthesia.
- Manual placental separation and possibly secondary curettage (ultrasound monitoring may be helpful) [35]. Concomitantly: high dose administration of i.v. uterotonic agents, single intraoperative i.v. administration of antibiotics.
- If the placenta is incompletely removed without increased bleeding, retained products of conception may be left *in utero* to be removed at a later date (even after several weeks) during a second operation or expelled spontaneously after several weeks with regular outpatient monitoring [72].

Avoid inadequate traction of the umbilical cord (abruption of the umbilical cord).

If the attempt to separate the placenta and curettage fails and prostaglandin-resistant bleeding persists: timely surgical intervention (compression sutures or hysterectomy) might be necessary. If circulation is stable and radiological intervention is available, a bilateral uterine embolization may be considered [46].

Impairment of placental separation in patients undergoing cesarean section In the case of extended transmural implantation abnormalities, especially in the area

of the anterior uterine wall (e.g., placenta percreta), large areas or small foci of placental tissue may show through under the uterine serosa; large-diameter subserous vessels and lacunae are visible. The following procedure is possible in the case of extended placental implantation abnormalities:

1. Cesarean section hysterectomy, particularly in the case of uncontrolled and severe bleeding from the placental site (e.g., following focal "iatrogenic" separation of the placenta).
2. Delivery of the infant without touching the placenta (e.g., transverse incision of the fundus in the case of deep placenta percreta located at the anterior wall) and keeping the placenta *in utero*.
3. If the intraoperative diagnosis (see above) is confirmed, hysterectomy can be performed following delivery of the baby without trying to detach the placenta.
4. Focal resection of the affected uterine wall and preservation of the uterus in cases of local placental implantation abnormalities [32].
5. Focal intracavitary Z-sutures to achieve hemostasis in small bleeding areas.

If the conservative procedure without hysterectomy is used and the placenta is left in place, the usual uterotonic agents should be administered. Following delivery of the baby, the placenta must not be separated manually, but should be left in place and the uterotomy should be closed in two layers using interrupted sutures [44, 48]. Basically, expectant management for several weeks is possible if the placenta is left *in situ* as the placenta may be spontaneously expelled at a later date [27, 44, 72]. In the case of severe postoperative bleeding resulting from deliberately leaving the placenta in place and a concomitant significant fall in hemoglobin level, a vascular occlusion (transient if necessary) can also be achieved by embolization or using a balloon catheter in the internal iliac artery. It remains debatable as to whether this procedure may help to reduce perioperative blood loss [8, 46]. A two-stage hysterectomy following a previous cesarean section with partial uterine involution may be more predictable and reduce surgical morbidity [44, 46].

Peripartum injuries

Peripartum injury is the third most common cause of postpartum bleeding, accounting for approximately 10% of cases [56]. In addition to uterine rupture, causes include extended vaginal laceration, cervical injuries, parametrial bleeding or profuse bleeding from large episiotomies (e.g., in patients with varicose veins).

Management:

- Anticipation of risks (e.g., operative vaginal delivery, macrosomia, shoulder dystocia).
- Exclusion of other causes of bleeding (e.g., atony).
- Timely availability of anesthesiologist (in-house).
- Optimal view with additional assistance and exact location of the source of bleeding.
- Early anesthesia in cases of non-compliance or poor visualization.
- Rapid surgical treatment by an experienced obstetrician in order to minimize blood loss:

  Note: incorrect suture technique, omission of the upper wound angle may lead to formation of hematoma with "occult blood loss " (diagnosis: palpation and ultrasound).

Coagulopathy

Coagulopathy due to blood loss Coagulopathy due to blood loss is one of the most common causes of peripartum disorders of hemostasis. This is expected when the blood loss is 1.5 L or more. Replacement of major blood loss with crystalloid and colloidal solutions as well as packed red cells leads to dilution with a decline of the concentration of all coagulation factors and their activity. Therefore, coagulopathy due to blood loss is almost always associated with dilution coagulopathy, the extent of which depends on the type and volume of the replacement fluid, the original concentration of the coagulation factors and the dynamics of blood loss. If the entire blood volume is replaced only by red cells, crystalloid and colloidal solutions, the residual activity of the coagulation factors is between 30 and 40% and sufficient for hemostasis [17].

After an approximately 2.5-fold replacement of blood volume, a clinically relevant thrombocytopenia can be expected ($<$50,000/μL) [28]. Fibrin polymerization is disturbed by the interaction with artificial colloids. Moreover, coagulopathy is favored by hypothermia (e.g., after infusion of volume replacement agents that have not been pre-warmed prior to application) and acidosis [22].

DIC and consumption coagulopathy Frequently, disseminated intravascular coagulation (DIC) with subsequent consumption coagulopathy in obstetrics results from:

- Premature placental abruption (possibly combined with blood loss coagulopathy).
- Serious hypertensive complications of pregnancy: pre-eclampsia/eclampsia/HELLP syndrome.
- Septic complications (chorioamnionitis).
- Amniotic fluid embolism (rare: 1:13,000 births).
- Extensive tissue laceration.

It is unlikely that a "dead-fetus syndrome" results in a maternal coagulation disorder.

A DIC with consumption coagulopathy develops as follows:

- Phase I: activation of the coagulation system (hypercoagulability) by entrance of thromboplastic material (Tissue Factor) into the maternal circulation.
- Phase II: disseminated intravascular coagulation with consumption of coagulation factors and inhibitors, reactive hyperfibrinolysis.
- Phase III: consumption coagulopathy with bleeding and/or micro- and macrothrombogenesis.
- Phase IV: recovery phase, with an initial increase of fibrinogen concentration followed by an increase of other coagulation factors (details in Barthels and von Depka 2003 [5]).

Diagnosis of DIC In addition to the diagnostic parameters and threshold values presented in Table 2, the following parameters are of importance:

- Thromboelastography in whole blood: enables rapid measurement of fibrin formation and clot assessment in whole blood as well as polymerization disorders by fibrin split products or colloids.
- Clot observation test: observation of clot formation in whole blood, following its transfer into an uncoated glass vessel/tube or into a syringe (e.g., normal 5-mL-syringe). A clot will usually form in approximately 8–10 min (shake carefully every 30 s). Dissolution of the clot after 30–60 min indicates hyperfibrinolysis [52].
- D-dimers: As D-dimers are always increased in the post partum period, serial measurements are required and the low specificity of this test should be kept in mind.

A patient suffering from DIC requires intensive care. Repeated measurements of coagulation parameters (INR, aPTT, fibrinogen levels, antithrombin concentrations, D-dimers, possible thromboelastrography [TEG], blood count) should be performed.

Treatment of hemostatic disorder When treating patients with coagulopathy timely elimination of the underlying cause should be the main aim (e.g., immediate delivery in the case of placental abruption). At the same time symptomatic treatment of DIC is required. The critical limits in the case of acute bleeding are summarized in Table 2. If bleeding persists, the following should be performed:

1. Adequate volume replacement with warmed crystalloid and colloid solutions.
2. Correction of metabolic acidosis, maintenance of ionized calcium within the normal range, avoidance of hypothermia.
3. If blood loss is $>20\%$ of blood volume, or if the limits given in Table 2 are reached: administration of packed red cells and fresh frozen plasma (FFP, initially 15–20 mL per kg body weight) (Strategy for the management of severe PPH). In emergency cases without cross-matching: packed red cells of blood group 0 rhesus negative and fresh frozen plasma of the blood group AB.
4. If fresh frozen plasma is not sufficiently effective/not available:
   - Fibrinogen concentrates: replacement with 2–4 g is generally sufficient. The fibrinogen concentration should be at least 1.5 g/L following fibrinogen administration. Administration of 3 g fibrinogen with a plasma volume of 3 L increases the fibrinogen concentration by approximately 1 g/L. Note: fibrinogen should be applied only if a pathologically increased coagulation activity (mostly with hyperfibrinolysis) no longer persists (difficult to assess in the acute obstetric situation). An antifibrinolytic agent, e.g., 1000 mg tranexamic acid i.v., should be administered [58, 67].
   - If INR cannot be corrected with fresh frozen plasma, a prothrombin complex concentrate (PCC) preparation can be administered, e.g., 20 IU/kg body weight when INR is >1.5. Note: potential thrombogenic risk by high prothrombin concentration (long half-life) and other factors.
5. Consider timely application of rFVIIa (Figure 3), if bleeding does not stop or there is a bleeding reaction in spite of adequate surgical treatment. Note: previous administration of prothrombin complex concentrates (PCCs) due to increased prothrombin concentration (see above).
6. Thrombocytopenia ($<50{,}000/\mu L$), in patients with persistent blood loss requiring replacement of red blood cells, constitutes a compelling indication of platelet transfusion [23, 53, 58, 66].
7. If there is evidence of hyperfibrinolysis (clot observation test, TEG analysis), antifibrinolytics should be administered (e.g., tranexamic acid at least 1000 mg i.v.) or considered if hyperfibrinolysis is expected.
8. No heparin should be administered during bleeding or in the case of increased risk of bleeding (Note: bleeding increases!). Instead, antithrombin activity should be adjusted to $\geq 70\%$, and 1000–2000 I.U. antithrombin administered (e.g., 2000 I.U. in the case of replacement of the entire blood volume).
9. Hemostatic parameters should be analyzed at least every 4 h, and more frequently in acute situations (approximately every 30 min).

Appendix: The use of recombinant factor VIIa (rFVIIa, NovoSeven®)

Mode of action

rFVIIa acts by binding to tissue factor, eliciting subsequent activation of coagulation. However, in pharmaco-

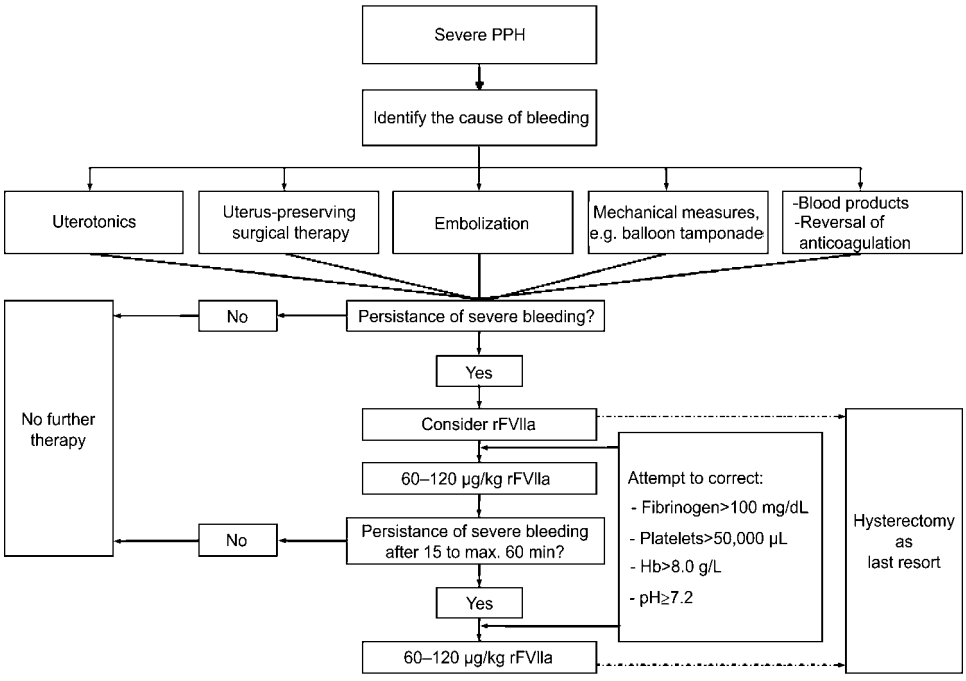

Figure 3 Algorithm for the use of rFVIIa in patients with severe PPH.
Note: The administration of rFVIIa should be considered before the clinical and hemostaseological situation escalates [17].

logical doses, rFVIIa acts onto the surface of activated platelets independently of tissue factor with formation of factor IXa, factor Xa and a thrombin burst. Thrombin leads to an activation of factor XIII, contributing to the formation of a stable fibrin clot and protects this clot from premature dissolution by plasmin. Moreover, resistance of the clots to subsequent fibrinolysis is achieved by the thrombin-mediated activation of TAFI (thrombin activable fibrinolysis inhibitor). rFVIIa does not provoke systemic activation of coagulation [29].

Registration

rFVIIa was authorized in 1996 for the treatment of hemophilia with inhibitors, and later for congenital factor VII deficiency and Glanzmann's thrombasthenia. Since then, rFVIIa has successfully been used for various indications which have not yet received official marketing authorization (off-label use). According to the expert panel, the off-label use must be seen in the context of a therapeutic attempt in life-threatening situations of women with serious treatment-resistant obstetric bleeding. The administration of rFVIIa would therefore be justified in such situations.

Off-label use of rFVIIa in obstetrics

- Serious obstetric bleeding refractory to adequate pharmacotherapy, surgery and blood component therapy (Figure 3).
- rFVIIa does not replace adequate surgical, embolizing and conventional hemostatic measures [76]; however, rFVIIa may possibly avoid postpartum hysterectomy.
- The decision to administer rFVIIa is jointly made by obstetricians, intensive care specialists/anesthesiologists and, if possible, hemostaseologists.
- The effect of rFVIIa depends on several concomitant factors. Therefore, the maintenance of the parameters mentioned in Figure 3 is paramount.
- Informed consent of patient/relatives, if possible.

Contraindications

- Allergic reactions.
- Relative contraindications: thromboembolic complications within the last six months (pulmonary embolisms, myocardial infarction, cerebrovascular accident, deep leg vein or pelvic vein thrombosis). In patients with coronary heart disease, rFVIIa should be administered only following a risk-benefit assessment.
- Familial thrombophilia without a history of thromboembolic events is not a contraindication.

These contraindications are very rare in young, healthy, pregnant women. rFVIIa may be associated with an increased risk of thromboembolic events in patients with a prior history of vascular disease. However, no thromboembolic complications due to rFVIIa were described in 140 patients treated with rFVIIa for PPH [3, 19, 69]. In

other studies published to date, no significant increase of thromboembolic events were found in the randomized and placebo-controlled studies on rFVIIa. In previously healthy patients with serious bleeding, the risk seems to be low even in patients with DIC [41]. Following administration of rFVIIa for PPH, it is recommended to monitor the patient for thromboembolic events.

Dosage

To date, no recommendations for dose and intervals of administration/repeated doses exist in obstetrics [18, 19]. Sixty to 120 μg/kg body weight rFVIIa are commonly administered as i.v. bolus. If severe bleeding persists, a second bolus of 60–120 μg/kg body weight rFVIIa may be administered following a period of 15 min to a maximum time of 60 min.

Criteria for success

Based on case reports, a 75% success rate for the administration of rFVIIa results when the following criteria are used:

- Marked reduction of bleeding/cessation of bleeding (clinically).
- No further blood transfusions.
- Uterine preservation.

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