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Hemostasis restoring in postpartum hemorrhage — algorithm 2023

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Summary

Postpartum hemorrhage (PPH) is still the leading cause of perinatal death in women of reproductive age. It is characterized by high dynamics, and most women die within the first day of puerperium and as many as 88% of them within the first 4 hours from the onset of hemorrhage. Management of each massive obstetric hemorrhage requires interdisciplinary, team-based and multidirectional action. The need for simultaneous application of uterotonic agents, surgical and/or endovascular methods as well as procedures aimed at restoring volume and hemostasis should be emphasized. The protocol for the management of severe PPH should be individualized and take into account hemorrhage etiology. Each time the volume of circulating blood as well as the degree of blood loss have to be determined, and the adequate procedures, the starting points for implementing aggressive treatment and the satisfactory end points must be defined. The most common cause of severe, life-threatening PPH is uterine atony. Restoration of hemostasis in massive PPH consists in transfusion of blood components, administration of antifibrinolytic drugs and coagulation factor concentrates, rFVIIa included. Patient survival is often determined by the very risk assessment for hemorrhage, early diagnosis and rapid implementation of PPH management algorithms.

Key words: hemorrhage, massive life-threatening PPH, severe postpartum hemorrhage, massive transfusion, hemostasis, rFVIIa

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Postpartum hemorrhage (PPH) is still the most common cause of perinatal death in women of reproductive age [1, 2]. It is characterized by high dynamics, and its occurrence may surprise the obstetrician team. Most women die within the first day of the postpartum period, and as many as 88% during the first 4 hours of the onset of hemorrhage [3]. Most likely, even up to 90% of these deaths could have been avoided if standardized medical procedures were implemented [4]. Management of each massive obstetric hemorrhage should be interdisciplinary, team-based and multidirectional. The management strategy emphasizes the need for administration of uterotonic agents, surgical and/or endovascular procedures aimed at restoring hemostasis [5]. Patient survival is often determined by

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the physician's awareness of the risk for hemorrhage, early diagnosis and rapid implementation of PPH management algorithms.

It is not easy to precisely define PPH; there is currently no single satisfactory definition as reflected by several terms referring to this emergency the use of which depends on the accepted criterion [6]. The multitude of definitions is most likely one of the reasons for delayed implementation of proper management. PPH is most commonly defined as the loss of 2000 ml of circulating blood. This term however is too general and not sufficiently precise. From the point of view of hemodynamic changes, systemic effects/consequences and necessity of timely therapeutic decisions, more functional seem definitions referring to the rate of blood loss at a definite time interval in relation to the patient's circulating blood volume. The most reliable definition of massive PPH refers to the loss of 20% of circulating blood which corresponds to a loss of 150 ml/minute [7]. The current algorithms for the management of severe postpartum hemorrhage (sPPH), severe) are based on the physiology of the womant's homeostasis and hemostasis in pregnancy and puerperium as well as on the cellular model of thrombus/clot formation and dissolution [8–10].

The maternal organism adapts itself to the developing pregnancy and the process of adaptation induces changes in numerous systems and organs. The adjusted mechanisms regulate the pregnant woman's homeostatic system at the molecular, immunological, hormonal and neurogenic levels, and together with the function and role of the uteroplacental unit they determine her response to nociceptive stimuli. In response to peripartum haemorrhage, the adaptative ability of the circulatory and coagulation systems is of crucial importance as is the disturbed equilibrium between thrombus formation and fibrinolysis within the placenta [11].

At the term of delivery, the serum platelet count of pregnant women is lower than in the population of non-pregnant women as caused by subliminal disseminated intravascular coagulation (DIC) only in placental capillaries. A pregnant woman synthesizes 200–500% of all coagulation factors, with the exception of factor XIII (FXIII), which is a fibrin stabilizing factor [12]. FXIII activity cannot be assessed with such routine tests as: activated partial thromboplastin time (APTT), prothrombin time (PT) and thrombin time (TT) [13].

In response to vascular injury, the body in labor or postpartum rapidly forms a clot which is unstable. "Point of care" testing ([POC]: TEG — thromboelastography, ROTEM — thromboelastometry) used to assess the overall physiological response of the system of clot formation and dissolution, display a hypercoagulable profile for pregnancy. Hypercoagulability is primarily determined by an increased concentration of coagulation factors, fibrinogen included [14–16].

Fibrinogen plays a key role at all stages of hemostasis, including platelet hemostasis, clot formation and fibrinolysis. Recent research emphasizes the correlation between fibrinogen concentration at delivery and the risk of PPH; this refers to 20–25% of patients with a fibrinogen level > 4 g/l. Hemorrhage might be expected in 50% of pregnant women with normal fibrinogen level at term, while all pregnant women with a fibrinogen level < 2 g/l are likely to develop PPH [17].

Placental hemostasis is characterized by a disturbed equilibrium/balance between TF (tissue factor) and TFPI (tissue factor inhibitor) and impaired fibrinolysis which occurs as result of adaptive changes [18, 19]. Activation of the coagulation system and increased TF expression are the main mechanisms that protect the parturient against excessive blood loss following placental abruption, while impaired fibrinolysis facilitates fibrin deposition and clot formation. Physiological placenta abruption is associated with a simultaneous reduction in platelet count and lower concentration of coagulation factors involved in the process of clot formation [20, 21]. Fibrinogen level is reduced not only as result of clot formation, but also due to deposition of fibrinogen in the extraplacental hematoma. Fibrinolysis impairment facilitates clot formation, while the relative deficiency of factor XIII in pregnant women is responsible for lower cohesion, stability and durability. In the physiological bleeding at normal delivery, fibrinolysis is significantly impaired and clot-formation activity predominates [22, 23].

Any hemorrhage in the perinatal period activates fibrinolysis within the endometrium and induces a mechanism of a vicious circle that intensifies blood loss [24]. Fibrinolysis in PPH results from endothelial ischemia and increased activity of tissue plasminogen activator (tPA) [25]. A major problem in controlling PPH is fibrinolysis in capillaries [26]. Activation of fibrinolysis at the onset of hemorrhage may be confined merely to the extraplacental site and often goes undetected with POC methods such as thromboelastography or thromboelastometry (TEG, ROTEM). Due to fibrinogen consumption and deposit following physiological placenta separation, the lowest fibrinogen concentration is observed on the first

postpartum day and in such cases PPH correlates with severe coagulopathy, afibrinogenemia and life-threatening hemorrhage which is difficult to control with conventional methods [27]. Fibrinogen is an acute-phase protein and its concentration increases systematically from the 72nd postpartum hour. Additionally, in the first 3 postpartum days, platelet adhesion and aggregation is impaired [28].

Management of sPPH requires defining the parturient's circulating blood volume, the degree of blood loss, the starting points for aggressive management and the satisfactory end points as well as timely implementation of adequate procedures [29–31].

The most common cause of severe, life-threatening PPH is uterine atony (70% PPH) [32]. In the setting of the maternity/obstetric ward, the key problem is to define the volume of circulating blood [33, 34].

The presented algorithm (Tables 1 and 2) estimates the volume and percentage of blood loss in relation to body weight and body mass index (BMI) [35]. In normal weight pregnant women the circulating blood volume is about 100/ml/kg [36], while in women with BMI > 35–73 ml/kg; similar to the estimated volume for non-pregnant women with normal body weight (70 ml/kg on body weight) [37]. In the clinical setting, the estimation of the circulating blood loss in PPH may be difficult and is usually underestimated [38]. In pregnant women with low body weight or obese women the risk of underestimation is high.

The loss of blood is estimated mainly by the number of surgical drapes used during a procedure; in everyday clinical practice however not all surgical dressing material is routinely weighed. Depending on the degree of saturation, a standard surgical drape (45 × 45 cm) corresponds to the loss of 100–300 ml of blood but this may be subjective. For example, a 5 × 5 cm wet swab corresponds to 30 ml of blood loss and a 10 × 10 cm swab to as much as 60 ml. The difference is usually overlooked [39].

Depending on the degree of blood loss and the accompanying clinical symptoms, four categories of hypovolemic shock have been determined (Table 3) [40, 41].

The intensity of hemorrhagic shock can currently be estimated in a minute with an analyzer for rapid assessment of acid-base balance and the reading is based only on the base excess (BE) parameter. Successive assessment of this BE parameter (approx. every 20 minutes) enables hemorrhage follow-up. It also has prognostic value because — as result of the adaptation of the circulatory system to pregnancy — the maternal general condition parameters remain normal for long despite significant blood loss [42].

Noninvasive measurement of systolic and diastolic arterial blood pressure displays normal value in 20–30% of pregnant women who lose more than 1500–2000 ml of blood [43]. The critical point is the loss of 40% of circulating blood because it is then that the transition from hypovolemic shock to decompensated shock occurs [44].

Disturbed microvascular flow in vital organs brings about impaired oxygen delivery to tissues, which results in hypoxia. Hypoxia enhances metabolic acidosis, as well as neutrophil adhesion to endothelial cells, blood stasis, intravascular coagulation, ischemia and multiple organ failure, associated with poor prognosis and poor quality of life (if the patient survives). Therefore, the last moment to implement aggressive PPH management is the loss of 30% of circulating blood. Obstetricians call it the "Rule of 30" (Table 4) [45].

In every case of PPH, it is necessary to consider the response of the coagulation system to hemorrhage of different etiology. In uterine atony and trauma to the genital tract, coagulopathy is equally dependent on the consumption of coagulation factors and hemodilution [46], while premature separation of a correctly positioned placenta is a clear example of fibrinogen consumption up to afibrinogenemia [47]. Amniotic fluid embolism is a coagulopathy resulting from the loss and biodegradation of coagulation factors and the intravascular coagulation syndrome. Uterine atony during caesarean section may also be an atypical form of amniotic fluid embolism that requires implementing the AOK algorithm (ATROPINE-ONDANSETRON-KETONAL) to inhibit the transition from the pulmonary phase to the next phases (cardiac, coagulopathy) [48]. It has been determined that each PPH episode is primarily related to fibrinogen consumption [49]. There is a linear correlation between the circulating blood loss and fibrinogen concentration that has not been observed for hemoglobin levels and routine coagulation tests [50, 51].

The management of severe PPH is a multidisciplinary approach that is conducted simultaneously. The treatment of a patient with severe PPH is not based on the knowledge and skills of a single physician but that of a team of professionals who cooperate with each other. Severe PPH always implies massive transfusion and volume and hemostatic resuscitation. Implementation of the

Table 1. Volume of circulating blood and % of blood loss related to body mass and body mass index (BMI) < 35

	Body mass [kg]																				
	50	**55**	**60**	**65**	**70**	**75**	**80**	**85**	**90**	**95**	**100**	**105**	**110**	**115**	**120**	**125**	**130**	**135**	**140**	**145**	**150**
BMI < 35: blood volume 100 ml/kg [ml]	**5000**	**5500**	**6000**	**6500**	**7000**	**7500**	**8000**	**8500**	**9000**	**9500**	**10 000**										
20% loss [ml]	1000	1100	1200	1300	1400	1500	1600	1700	1800	1900	2000										
30% loss [ml]	**1500**	**1650**	**1800**	**1950**	**2100**	**2250**	**2400**	2550	2700	2850	3000										
40% loss [ml]	**2000**	**2200**	**2400**	2600	2800	3000	3200	3400	3600	3800	4000										

Table 2. Volume of circulating blood and % of blood loss related to body mass and body mass index (BMI) > 35

	Body mass [kg]																				
	50	**55**	**60**	**65**	**70**	**75**	**80**	**85**	**90**	**95**	**100**	**105**	**110**	**115**	**120**	**125**	**130**	**135**	**140**	**145**	**150**
BMI > 35: Blood volume 73 ml/kg [ml]							**5840**	**6205**	**6570**	**6935**	**7300**	**7665**	**8030**	**8395**	**8760**	**9125**	**9490**	**9855**	**10 220**	**10 585**	**10 950**
20% loss [ml]							1168	1241	1314	1387	1460	1533	1606	1679	1752	1825	1898	1971	2044	2117	2190
30% loss [ml]							**1753**	**1861**	**1971**	**2080**	**2190**	**2299**	**2409**	2518	2628	2737	2847	2956	3066	3176	3285
40% loss [ml]							**2336**	**2482**	2628	2774	2920	3066	3212	3358	3504	3650	3796	3942	4088	4234	4380

Table 3. Four categories of hypovolemic shock intensity related to the degree of blood loss and clinical symptoms

Category/ /shock intensity	**% loss**	**Blood volume [ml]**	**Tachycardia [μ/min]**	**SBP/DPB**	**SI=HR/ /SBP**	**Sodium deficiency**	**Symptoms**	**Prohemostatic management**	
I/Compensated	10–15	500–1000	100/min	Normal	0.9–1.0	≤ 2		Tranexamic acid	
II/ Mild	15–20	1200–1500	< 120/min	SBP — normal DBP ↓	1.0	–2 do –6	Peripheral vasoconstriction CRT > 2 s Weak pulse Lower urine output	Tranexamic acid	RBCs
III/Moderate	25–35	1600–2200	> 120/min	SBP ↓ 70–80 mmHg	1.0–1.4	–6 do –10	Pale skin Agitation Pulse filamentation Tachypnoea Oliguria	Tranexamic acid Fibrinogen Calcium Noradrenalin	RBCs/FFP/ /CRYO/ /rFVIIa PCC
IV/Severe	35–45	> 2500	> 140/min	SBP ↓ ↓ 50–70 mmHg	> 1.5	≥ 10	Drowsiness Gray skin No CRT Anuria	Tranexamic acid Fibrinogen Calcium Noradrenalin	RBCs/FFP/ /CRYO/ /rFVIIa PCC

DBP — diastolic blood pressure; FFP — fresh frozen plasma; HR — heart rate; RBC — red blood cells; CRYO — cryoprecipitate; PCC — prothrombin complex concentrates; rFVIIa — recombinant activated factor VII; SBP — systolic blood pressure; SI — shock index = HR/SBP

Table 4. Rule of „thirty" estimates approximate 30% blood loss. Estimation is based on changes of selected parameters by 30 (in corresponding units)

Rule of „30"
Fall of systolic blood pressure by 30%
Increase of heart rate (HR) by 30%
A 30% increase in respiratory rate
Fall in hemoglobin level (HGB) and hematokryt (HT) by 30%
Urine output of less than 30 ml/h

Holocomb algorithm (the RBC:FFP ratio of 1:1) is successfully used in obstetrics and has contributed to significant improvement of prognosis in severe, life-threatening PPH [52].

The recommended initial procedure is the quickest possible order of 4 units of RBC, 4 units of FFP and 4 units of cryoprecipitate (Cryo). If bleeding continues or becomes more intensive, the next step is to order another 4 units of RBCs, 4 units of FFP, 4 units of Cryo and 1 therapeutic dose of PC (platelet concentrate), either pooled or from apheresis. If more than 5 units of RBC are ordered from the start, it is recommended to order PC in a stoichiometric ratio [53]. When ordering blood components, even in centers with their own Blood Bank, one should include the time necessary for FFP and cryoprecipitate thawing which delays transfusion by about 30–40 minutes [54]. Immediate access to RBCs for rapid transfusion which requires no compatibility test, is also possible but the delivery of erythrocytes does not restore hemostasis.

At least two large peripheral accesses ports should be secured and intravenous fluid therapy with balanced crystalloids should be started according to the ROSE algorithm (resuscitation-optimization-stabilization-elimination), taking into account the strong ion difference (SID) [55] to restore the circulating blood volume [56]. In hypovolemic shock the infused crystalloids act like colloids in the blood vessel. After infusion, 60–70% leave the vascular bed. Stabilization of the vascular bed with intravenous catecholamines (norepinephrine) should be considered to maintain permissive hypotension with mean arterial pressure (MAP) not exceeding 65 mmHg until the surgical cause of bleeding is controlled [57]. Aggressive efforts to restore circulating volume often result in iatrogenic hemodilution [58]. Moreover, acidosis and hypothermia exacerbate coagulopathy and impair clot formation. Maternal death is usually caused by hemostatic disorders and hypovolemia rather than by abnormal hemoglobin levels [59].

One of the pillars of the operating team is the "fourteenth" factor — a skilled and experienced obstetrician (perinatologist) familiar with procedural techniques of postpartum hemorrhage control [60].

Simultaneously, the team of anesthesiologists strives/struggles to maintain normal body temperature (normothermia) and to prevent acidosis [61]. It is of crucial importance to inhibit fibrinolysis by prompt intravenous administration of tranexamic acid (TXA) at a dose of 20 mg/kg body weight, usually 1 g [62–64]. The next step is fibrinogen substitution with fibrinogen concentrate at a dose of 2–4 g or with cryoprecipitate (2 U/10 kg b.w.) [65]. Centers with no Blood Bank of their own can use prothrombin complex concentrates (PCC) at a dose of 500–1000 U as emergency bridging therapy until blood components are delivered. [66].

In April 2022, the European Medicines Agency (EMA) registered recombinant activated factor VII (rFVIIa) for the management severe postpartum hemorrhage [67, 68]. The drug is for intravenous use if uterotonic drugs are ineffective, intensive bleeding cannot be controlled by conventional means, and surgical measures to save the patient's life must be escalated [69]. The procedure of rFVIIa (1 rFVIIa) administration is presented as the first step in the algorithm for restoring hemostasis in obstetric hemorrhage (Fig. 1) [70].

Given the high physiological levels of fibrinogen and other coagulation factors in pregnancy even despite the rapid loss of 20–30% of the circulating blood, prompt/early administration of the recommended dose of rFVIIa ensures conditions for the drug to act so there is no time for acidosis or hypothermia to develop. A routine dose of 60––90 μg/kg b.w. is recommended and can be repeated after 30 minutes [71]. The body mass dependent rFVIIa dosage is presented in Table 5.

Clot formation profiles based on TEG, ROTEM thromboelastometry confirmed high safety of a single infusion of up to 4 g of TXA in PPH. Tranexamic acid reduces blood loss and the need for transfusions by 50% [72].

Every case of PPH requires fibrinogen supplementation; 1 g of fibrinogen concentrate increases the level of the patient's fibrinogen in plasma by 0.3 g/dl [73–76]. In Poland, the main source of fibrinogen is cryoprecipitate. Apart from F I it also contains FXIII, FVIII and VWF factor.

Transfusion of cryoprecipitate is called for because pregnant women are deficient in factor XIII, indispensable for clot stabilization and prevention

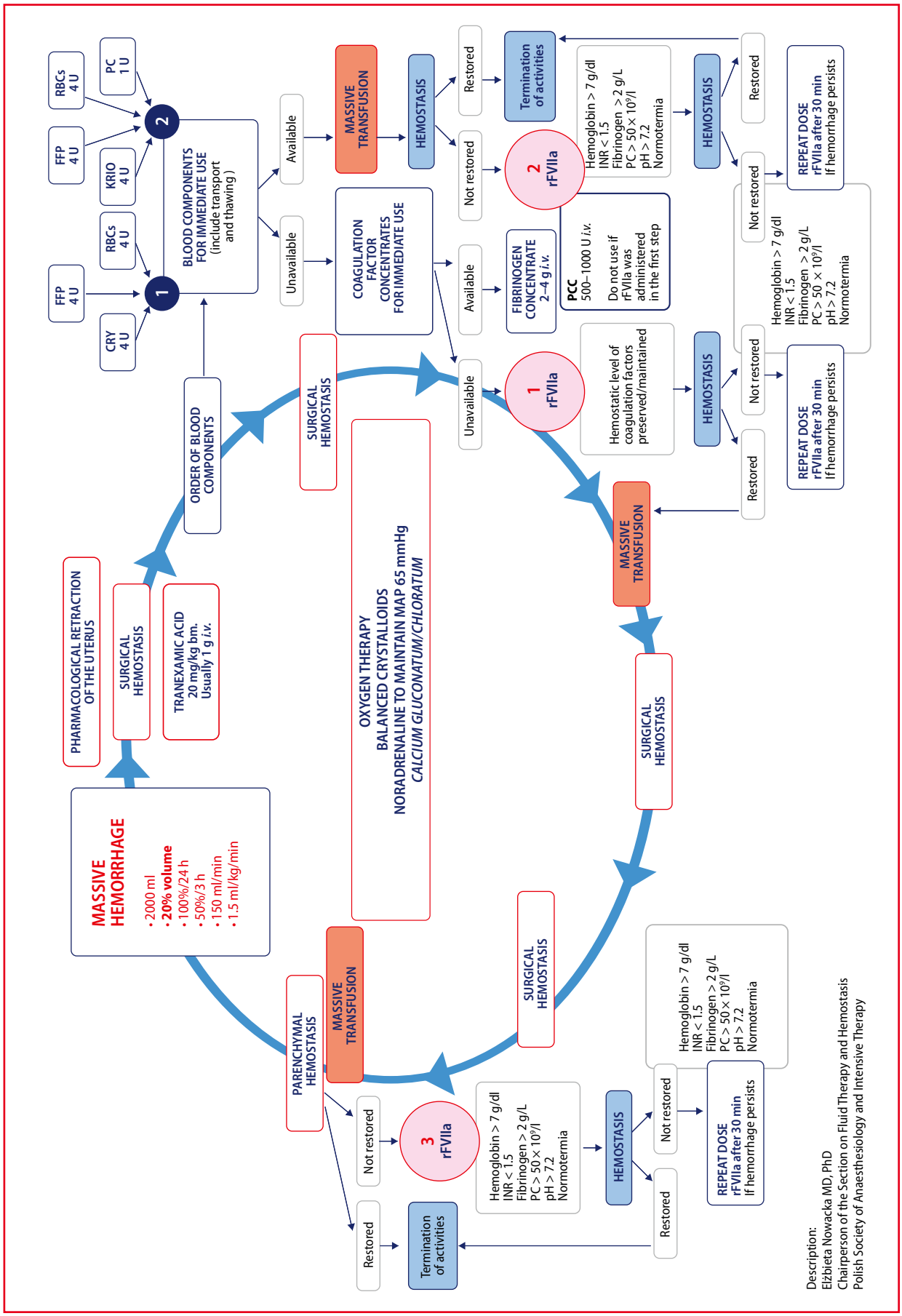

Figure 1. Anesthetic and obstetric management in severe PPH — algorithm for restoring hemostasis in obstetric hemorrhage 2023

FFP — fresh frozen plasma; INR — international normalized ratio; RBC — red blood cell concentrate; PC — platelet concentrate; CRYO — cryoprecipitate; MAP — mean arterial pressure; PCC — prothrombin complex concentrates; rFVIIa — recombinant activated factor VII

Table 5. Dosage of recombinant activated factor VII (rFVIIa) in severe PPH related to body mass and available vials/ampoules

Body mass [kg]	**50**	**55**	**60**	**65**	**70**	**75**	**80**	**85**	**90**	**95**	**100**	**105**	**110**	**115**	**120**	**125**	**130**	**135**	**140**	**145**	**150**
Dosage of rFVIIa related to body mass and available vials/ ampoules																					
Number of mg per dose of 60 µg/kg bm.	**3**	**3.3**	**3.6**	**3.9**	**4.2**	**4.5**	**4.8**	**5.1**	**5.4**	**5.7**	**6**	**6.3**	**6.6**	**6.9**	**7.2**	**7.5**	**7.8**	**8.1**	**8.4**	**8.7**	**9**
Number of vials p er one dose	1 × 1 mg + 1 × 2 mg	2 × 2 mg	2 × 2 mg	2 × 2 mg	1 × 5 mg	1 × 5 mg	1 × 5 mg	1 × 5 mg + 1 × 1 mg	1 × 5 mg + 1 × 1 mg	1 × 5 mg + 1 × 1 mg	1 × 5 mg + 1 × 1 mg	1 × 5 mg + 1 × 2 mg	1 × 5 mg + 1 × 2 mg	1 × 5 mg + 1 × 2 mg	1 × 8 mg	1 × 8 mg	1 × 8 mg	1 × 8 mg + 1 × 1 mg	1 × 8 mg + 1 × 1 mg	1 × 8 mg + 1 × 1 mg	1 × 8 mg + 1 × 1 mg
Number of mg per dose of 90 µg/kg bm.	**4.5**	**4.95**	**5.4**	**5.85**	**6.3**	**6.75**	**7.2**	**7.65**	**8.1**	**8.55**	**9**	**9.45**	**9.9**	**10.35**	**10.8**	**11.25**	**11.7**	**12.15**	**12.6**	**13.05**	**13.5**
Number of vials per one dose	1 × 5 mg	1 × 5 mg	1 × 5 mg + 1 × 1 mg	1 × 5 mg + 1 × 1 mg	1 × 5 mg + 1 × 2 mg	1 × 5 mg + 1 × 2 mg	1 × 8 mg	1 × 8 mg	1 × 8 mg + 1 × 1 mg	1 × 8 mg + 1 × 1 mg	1 × 8 mg + 1 × 1 mg	1 × 8 mg + 1 × 2 mg	1 × 8 mg + 1 × 2 mg	1 × 8 mg + 1 × 2 mg + 1 × 1 mg	1 × 8 mg + 1 × 2 mg + 1 × 1 mg	1 × 8 mg + 2 × 2 mg	1 × 8 mg + 2 × 2 mg	1 × 8 mg + 1 × 5 mg	1 × 8 mg + 1 × 5 mg	1 × 8 mg + 1 × 5 mg + 1 × 1 mg	1 × 8 mg + 1 × 5 mg + 1 × 1 mg
Average dose (rounded)	**4**	**4**	**5**	**5**	**5**	**6**	**6**	**6**	**7**	**7**	**8**	**8**	**8**	**9**	**9**	**9**	**10**	**10**	**11**	**11**	**11**
Number of vials per one average dose	**2 × 2 mg lub 1 × 5 mg**	**2 × 2 mg lub 1 × 5 mg**	**1 × 5 mg**	**1 × 5 mg**	**1 × 5 mg**	**1 × 5 mg + 1 × 2 mg***	**1 × 5 mg + 1 × 2 mg***	**1 × 5 mg + 1 × 2 mg***	**1 × 5 mg + 1 × 2 mg**	**1 × 5 mg + 1 × 2 mg**	**1 × 8 mg**	**1 × 8 mg**	**1 × 8 mg**	**1 × 8 mg + 1 × 2 mg***	**1 × 8 mg + 1 × 2 mg***	**1 × 8 mg + 1 × 2 mg***	**1 × 8 mg + 1 × 2 mg**	**1 × 8 mg + 1 × 2 mg**	**1 × 8 mg + 2 × 2 mg****	**1 × 8 mg + 2 × 2 mg****	**1 × 8 mg + 2 × 2 mg****
Optimal number of vials to secure the ward with 2 doses per patient of 50–150 kg bm	**2 × 2 mg + 2 × 5 mg** *1 mg may be administered just after reconstitution while the rest may be kept in the vial for 6 h at up to 25°C then used for the repeat dose with the second 5 mg vial										**+ 2 × 8 mg** **3 mg may be administered just after reconstitution while the rest may be kept in the vial for 6 h at up to 25° C then used for a repeat dose with the second 8 mg vial to reach the minimum dose										
	The 10 ml volume of a pre-filled syringe with a solvent for 5 mg and 8 mg doses allows to combine reconstituted doses for patients of 60–135 kg																				

rFVIIa — recombinant activated factor VII; sPPH — severe postpartum hemorrhage

of bleeding [77, 78]. Supplementation of fibrinogen concentrate and/or cryoprecipitate is the only way to increase fibrinogen content in plasma to a target fibrinogen level for hemostasis (2.5–3 d/l for a bleeding patient) [65] whereas transfusion of FFP often results in dilution of endogenous fibrinogen. To achieve hemostasis, it is necessary to administer FFP at a dose of 30 ml/kg b.w., because the routine dose of 10–15 ml/kg b.w. is insufficient [79]. Intravenous PCC at a dose of 500–1000 units is more effective than equivalent doses of FFP [80, 81]. If rFVIIa was used in the first step as defined by the EMA, PCC cannot be administered for higher risk of thromboembolic complications.

If PPH management proceeds according to the hemostasis restoration algorithm (administration of TXA, fibrinogen concentrate/cryoprecipitate, PCC) followed by massive transfusion (RBC:FFP — 1:1, cryoprecipitate 2 U/10 kg/b.w., PC — platelet concentrate), maintenance of normal plasma ionized calcium level, in the absence of satisfactory hemostasis and/or uncontrollable parenchymal bleeding and/or "ongoing" phenomenon, it is recommended to administer rFVIIa according to the second point of the hemostasis restoration algorithm (2 rFVIIa) [82] provided no acidosis or hypothermia is reported and hemoglobin concentration is above 7 g/dl, fibrinogen > 2 g/l, platelet count > 50×10^9/l.

During ongoing surgery and persistent bleeding, another dose of rFVIIa may be administered 30 minutes after the first one, if the drug is effective. In exceptional situations, if parenchymal hemostasis has not been restored despite surgical procedures, administration of two doses of rFVIIa at 30-minute intervals may be considered under conditions that ensure drug effectiveness (fibrinogen concentration > 2 g/l, platelet count over 50×10^9/l, pH > 7.2) according to the third point of the hemostasis restoration algorithm (3 rFVIIa) [83, 84].

Medical procedures in severe, life-threatening PPH, performed according to the presented hemostasis restoring algorithm, contribute to significant reduction of the risk of maternal death in the perinatal period, improve prognosis and fertility preservation. Crucial for effective performance of all professional teams involved in PPH management are constant knowledge update and upgrading of qualifications and skills. Optimization of management, preparation of background, rational use of resources and recording of activities add to better outcome of treatment and prognosis in patients with postpartum hemorrhage.

Conflict of interest: none declared

References

1. Say L, Chou D, Gemmill A, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014; 2(6): e323–e333, doi: 10.1016/S2214-109X(14)70227-X, indexed in Pubmed: 25103301.
2. World Health Organization. Trends in maternal mortality 2000 to 2017: estimates by WHO, UNICEF, UNFPA, World Bank Group and the United Nations Population Division 2019, Available from: https://apps.who.int/iris/handle/10665/327596.
3. WHO. Maternal mortality: key facts. 2018. http://www.who.int/en/news-room/factsheets/detail/maternal-mortality (accessed Dec 12, 2022).
4. Diguisto C, Saucedo M, Kallianidis A, et al. BÃdker B, Buoncristiano M. Maternal mortality in eight European countries with enhanced surveillance systems: descriptive population based study. BMJ 2022: 379.
5. Bohren MA, Lorencatto F, Coomarasamy A, et al. Formative research to design an implementation strategy for a postpartum hemorrhage initial response treatment bundle (E-MOTIVE): study protocol. Reprod Health. 2021; 18(1): 149, doi: 10.1186/s12978-021-01162-3, indexed in Pubmed: 34261508.
6. Bienstock JL, Eke AC, Hueppchen NA, et al. Postpartum hemorrhage. N Engl J Med. 2021; 384(17): 1635–1645, doi: 10.1056/NEJMra1513247, indexed in Pubmed: 33913640.
7. Shah A, Kerner V, Stanworth SJ, et al. Major haemorrhage: past, present and future. Anaesthesia. 2023; 78(1): 93–104, doi: 10.1111/anae.15866, indexed in Pubmed: 36089857.
8. Llau JV, Acosta FJ, Escolar G, et al. Multidisciplinary consensus document on the management of massive haemorrhage (HEMOMAS document). Med Intensiva. 2015; 39(8): 483–504, doi: 10.1016/j.medin.2015.05.002, indexed in Pubmed: 26233588.
9. Kogutt BK, Vaught AJ. Postpartum hemorrhage: Blood product management and massive transfusion. Semin Perinatol. 2019; 43(1): 44–50, doi: 10.1053/j.semperi.2018.11.008, indexed in Pubmed: 30527516.
10. Collis RE, Collins PW. Haemostatic management of obstetric haemorrhage. Anaesthesia. 2015; 70: 78–86, doi: 10.1111/anae.12913, indexed in Pubmed: 25440400.
11. Greer O, Shah N, Johnson M. Maternal sepsis update: current management and controversies. Obstet Gynaecol. 2019; 22(1): 45–55, doi: 10.1111/tog.12623.
12. Coopland A, Alkjaersig N, Fletcher AP. Reduction in plasma factor 13 (fibrin stabilizing factor) concentration during pregnancy. J Lab Clin Med. 1969; 73(1): 144–153, indexed in Pubmed: 5762158.
13. Bedson R, Riccoboni A. Physiology of pregnancy: clinical anaesthetic implications. Continuing Education in Anaesthesia Critical Care & Pain. 2014; 14(2): 69–72, doi: 10.1093/bjaceaccp/mkt036.
14. Ramler P, Gillissen A, Henriquez D, et al. Clinical value of early viscoelastometric point-of-care testing during postpartum hemorrhage for the prediction of severity of bleeding: A multicenter prospective cohort study in the Netherlands. Acta Obstet Gynecol Scand. 2021; 100(9): 1656–1664, doi: 10.1111/aogs.14172, indexed in Pubmed: 33999407.
15. Gillissen A, van den Akker T, Caram-Deelder C, et al. Comparison of thromboelastometry by ROTEM Delta and ROTEM Sigma in women with postpartum haemorrhage. Scand J Clin Lab

Invest. 2019; 79(1-2): 32–38, doi: 10.1080/00365513.2019.1571220, indexed in Pubmed: 30727759.
16. Liew-Spilger AE, Sorg NR, Brenner TJ, et al. Viscoelastic hemostatic assays for postpartum hemorrhage. J Clin Med. 2021; 10(17), doi: 10.3390/jcm10173946, indexed in Pubmed: 34501395.
17. Charbit B, Mandelbrot L, Samain E, et al. PPH Study Group. The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. J Thromb Haemost. 2007; 5(2): 266–273, doi: 10.1111/j.1538-7836.2007.02297.x, indexed in Pubmed: 17087729.
18. Aharon A, et al. Tissue factor and tissue factor pathway inhibitor levels in trophoblast cells: implications for placental hemostasis. Thromb Haemost. 2004; 92(4): 776–786, doi: 10.1160/TH04-01-0033, indexed in Pubmed: 15467908.
19. Dusse LM, Carvalho Md, Cooper AJ, et al. Tissue factor and tissue factor pathway inhibitor: a potential role in pregnancy and obstetric vascular complications? Clin Chim Acta. 2006; 372(1-2): 43–46, doi: 10.1016/j.cca.2006.03.025, indexed in Pubmed: 16713593.
20. Bremme KA. Haemostatic changes in pregnancy. Best Pract Res Clin Haematol. 2003; 16(2): 153–168, doi: 10.1016/s1521-6926(03)00021-5, indexed in Pubmed: 12763484.
21. Anderson CA, Avery MD. Anatomy and physiology during labor and birth. In: King TL, Brucker MC, Osborne K, Jevitt CM, eds. Varney's Midwifery. 6th ed. Burlington, MA: Jones & Bartlett Learning, LLC; 2019: 861–880.
22. Fu M, Liu J, Xing J, et al. Reference intervals for coagulation parameters in non-pregnant and pregnant women. Sci Rep. 2022; 12(1): 1519, doi: 10.1038/s41598-022-05429-y, indexed in Pubmed: 35087162.
23. Chapin JC, Hajjar KA. Fibrinolysis and the control of blood coagulation. Blood Rev. 2015; 29(1): 17–24, doi: 10.1016/j.blre.2014.09.003, indexed in Pubmed: 25294122.
24. Collins PW, Lilley G, Bruynseels D, et al. Fibrin-based clot formation as an early and rapid biomarker for progression of postpartum hemorrhage: a prospective study. Blood. 2014; 124(11): 1727–1736, doi: 10.1182/blood-2014-04-567891, indexed in Pubmed: 25024304.
25. Huissoud C, Carrabin N, Benchaib M, et al. Coagulation assessment by rotation thrombelastometry in normal pregnancy. Thromb Haemost. 2009; 101(4): 755–761, indexed in Pubmed: 19350122.
26. Moore HB, Moore EE, Morton AP, et al. Shock-induced systemic hyperfibrinolysis is attenuated by plasma-first resuscitation. J Trauma Acute Care Surg. 2015; 79(6): 897–903; discussion 903, doi: 10.1097/TA.0000000000000792, indexed in Pubmed: 26680132.
27. Erez O. Disseminated intravascular coagulation in pregnancy - Clinical phenotypes and diagnostic scores. Thromb Res. 2017; 151 Suppl 1: S56–S60, doi: 10.1016/S0049-3848(17)30069-5, indexed in Pubmed: 28262236.
28. Valera MC, Parant O, Vayssiere C, et al. Physiologic and pathologic changes of platelets in pregnancy. Platelets. 2010; 21(8): 587–595, doi: 10.3109/09537104.2010.509828, indexed in Pubmed: 20873962.
29. Bose P, Regan F, Paterson-Brown S. Improving the accuracy of estimated blood loss at obstetric haemorrhage using clinical reconstructions. BJOG. 2006; 113(8): 919–924, doi: 10.1111/j.1471-0528.2006.01018.x, indexed in Pubmed: 16907938.
30. Dildy GA, Paine AR, George NC, et al. Estimating blood loss: can teaching significantly improve visual estimation? Obstet Gynecol. 2004; 104(3): 601–606, doi: 10.1097/01.AOG.0000137873.07820.34, indexed in Pubmed: 15339775.
31. Lertbunnaphong T, Lapthanapat N, Leetheeragul J, et al. Postpartum blood loss: visual estimation versus objective quantification with a novel birthing drape. Singapore Med J. 2016; 57(6): 325–328, doi: 10.11622/smedj.2016107, indexed in Pubmed: 27353510.
32. Nyfløt L, Sandven I, Stray-Pedersen B, et al. Risk factors for severe postpartum hemorrhage: a case-control study. BMC Pregnancy and Childbirth. 2017; 17(1), doi: 10.1186/s12884-016-1217-0, indexed in Pubmed: 28068990.
33. Langlois C. Post-partum transfusion: The view of the anaesthetist in a delivery room. Transfus Clin Biol. 2019; 26(3): 150–151, doi: 10.1016/j.tracli.2019.06.233, indexed in Pubmed: 31400931.
34. Kogutt BK, Vaught AJ. Postpartum hemorrhage: Blood product management and massive transfusion. Semin Perinatol. 2019; 43(1): 44–50, doi: 10.1053/j.semperi.2018.11.008, indexed in Pubmed: 30527516.
35. Hernandez JS, Alexander JM, Sarode R, et al. Calculated blood loss in severe obstetric hemorrhage and its relation to body mass index. Am J Perinatol. 2012; 29(7): 557–560, doi: 10.1055/s-0032-1310528, indexed in Pubmed: 22495893.
36. Hytten F. Blood volume changes in normal pregnancy. Clin Haematol. 1985; 14(3): 601–612, indexed in Pubmed: 4075604.
37. Vricella LK, Louis JM, Chien E, et al. Blood volume determination in obese and normal-weight gravidas: the hydroxyethyl starch method. Am J Obstet Gynecol. 2015; 213(3): 408.e1–408.e6, doi: 10.1016/j.ajog.2015.05.021, indexed in Pubmed: 25981844.
38. Kennedy H, Haynes SL, Shelton CL. Maternal body weight and estimated circulating blood volume: a review and practical nonlinear approach. Br J Anaesth. 2022; 129(5): 716–725, doi: 10.1016/j.bja.2022.08.011, indexed in Pubmed: 36167682.
39. Patel A, Goudar SS, Geller SE, et al. Drape estimation vs. visual assessment for estimating postpartum hemorrhage. Int J Gynaecol Obstet. 2006; 93(3): 220–224, doi: 10.1016/j.ijgo.2006.02.014, indexed in Pubmed: 16626718.
40. Gaddipati S, Vercauteren M. Shock. In Velde M, Scholefield H, Plante L (Eds.). Maternal critical care: a multidisciplinary approach. Cambridge University Press, Cambridge 2013: 160–173.
41. Chauhan M, Gray K, Foley M. Bleeding During Pregnancy. Obstetric Catastrophes. 2021: 587–606, doi: 10.1007/978-3-030-70034-8_46.
42. Rixen D, Raum M, Bouillon B, et al. Arbeitsgemeinschaft. Base deficit development and its prognostic significance in posttrauma critical illness: an analysis by the trauma registry of the Deutsche Gesellschaft für unfallchirurgie. Shock. 2001; 15(2): 83–89, doi: 10.1097/00024382-200115020-00001, indexed in Pubmed: 11220646.
43. Vousden N, Nathan HL, Shennan AH. Innovations in vital signs measurement for the detection of hypertension and shock in pregnancy. Reprod Health. 2018; 15(Suppl 1): 92, doi: 10.1186/s12978-018-0533-4, indexed in Pubmed: 29945641.
44. Pacagnella RC, Borovac-Pinheiro A. Assessing and managing hypovolemic shock in puerperal women. Best Pract Res Clin Obstet Gynaecol. 2019; 61: 89–105, doi: 10.1016/j.bpobgyn.2019.05.012, indexed in Pubmed: 31345740.
45. Carillo AP, Chandraharan E. Postpartum haemorrhage and haematological management. Obstetrics, Gynaecology & Re-

productive Medicine. 2014; 24(10): 291–295, doi: 10.1016/j.ogrm.2014.07.004.
46. Bolliger D, Görlinger K, Tanaka KA. Pathophysiology and treatment of coagulopathy in massive hemorrhage and hemodilution. Anesthesiology. 2010; 113(5): 1205–1219, doi: 10.1097/ALN.0b013e3181f22b5a, indexed in Pubmed: 20881594.
47. Kim JW, Lee YK, Chin JH, et al. Development of a scoring system to predict massive postpartum transfusion in placenta previa totalis. J Anesth. 2017; 31(4): 593–600, doi: 10.1007/s00540-017-2365-8, indexed in Pubmed: 28466102.
48. Long M, Martin J. Biggio, J. Atropine, ondansetron, and ketorolac: supplemental management of amniotic fluid embolism. Ochsner Journal. 2022; 22(3): 253–257, doi: 10.31486/toj.21.0107, indexed in Pubmed: 36189093.
49. Butwick AJ. Postpartum hemorrhage and low fibrinogen levels: the past, present and future. Int J Obstet Anesth. 2013; 22(2): 87–91, doi: 10.1016/j.ijoa.2013.01.002, indexed in Pubmed: 23473552.
50. Cortet M, Deneux-Tharaux C, Dupont C, et al. Association between fibrinogen level and severity of postpartum haemorrhage: secondary analysis of a prospective trial. Br J Anaesth. 2012; 108(6): 984–989, doi: 10.1093/bja/aes096, indexed in Pubmed: 22490316.
51. Huissoud C, Carrabin N, Audibert F, et al. Bedside assessment of fibrinogen level in postpartum haemorrhage by thrombelastometry. BJOG. 2009; 116(8): 1097–1102, doi: 10.1111/j.1471-0528.2009.02187.x, indexed in Pubmed: 19459866.
52. Barbieri RL. Control of massive hemorrhage: Lessons from Iraq reach the US labor and delivery suite OBG Manag. 2007 July; 19(7): 8–16.
53. Goodnough LT, Daniels K, Wong AE, et al. How we treat: transfusion medicine support of obstetric services. Transfusion. 2011; 51(12): 2540–2548, doi: 10.1111/j.1537-2995.2011.03152.x, indexed in Pubmed: 21542850.
54. Ministerstwo Zdrowia, Narodowe Centrum Krwi. Wytyczne w zakresie leczenia krwią i jej składnikami oraz produktami krwiopochodnymi w podmiotach leczniczych wydanie III. Wojskowy Instytut Medyczny, Warszawa; 2020.
55. Kilic O, Gultekin Y, Yazici S. The impact of intravenous fluid therapy on acid-base status of critically ill adults: a stewart approach-based perspective. Int J Nephrol Renovasc Dis. 2020; 13: 219–230, doi: 10.2147/IJNRD.S266864, indexed in Pubmed: 33061531.
56. Malbrain ML, Langer T, Annane D, et al. Intravenous fluid therapy in the perioperative and critical care setting: Executive summary of the International Fluid Academy (IFA). Ann Intensive Care. 2020; 10(1): 64, doi: 10.1186/s13613-020-00679-3, indexed in Pubmed: 32449147.
57. Natrella M, Di Naro E, Loverro M, et al. The more you lose the more you miss: accuracy of postpartum blood loss visual estimation. A systematic review of the literature. J Matern Fetal Neonatal Med. 2018; 31(1): 106–115, doi: 10.1080/14767058.2016.1274302, indexed in Pubmed: 28002983.
58. Getrajdman C, Sison M, Lin HM, et al. The effects of hemodilution on coagulation in term parturients: an study utilizing rotational thromboelastometry. J Matern Fetal Neonatal Med. 2022; 35(10): 1969–1977, doi: 10.1080/14767058.2020.1776250, indexed in Pubmed: 32519906.
59. Centers for Disease Control and Prevention (CDC). (2019). Pregnancy-related deaths. Retrieved,January15,2020,from https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pregnancy-relatedmortality.htm.
60. Püchel J, Sitter M, Kranke P, et al. Procedural techniques to control postpartum hemorrhage. Best Pract Res Clin Anaesthesiol. 2022; 36(3-4): 371–382, doi: 10.1016/j.bpa.2022.09.002, indexed in Pubmed: 36513432.
61. Sultan P, Habib AS, Cho Y, et al. The Effect of patient warming during Caesarean delivery on maternal and neonatal outcomes: a meta-analysis. Br J Anaesth. 2015; 115(4): 500–510, doi: 10.1093/bja/aev325, indexed in Pubmed: 26385660.
62. Shakur H, Elbourne D, Gülmezoglu M, et al. The WOMAN Trial (World Maternal Antifibrinolytic Trial): tranexamic acid for the treatment of postpartum haemorrhage: an international randomised, double blind placebo controlled trial. Trials. 2010; 11: 40, doi: 10.1186/1745-6215-11-40, indexed in Pubmed: 20398351.
63. Muñoz M, Stensballe J, Ducloy-Bouthors AS, et al. Patient blood management in obstetrics: prevention and treatment of postpartum haemorrhage. A NATA consensus statement. Blood Transfus. 2019; 17(2): 112–136, doi: 10.2450/2019.0245-18, indexed in Pubmed: 30865585.
64. Hofer S, Blaha J, Collins PW, et al. Haemostatic support in postpartum haemorrhage: A review of the literature and expert opinion. Eur J Anaesthesiol. 2023; 40(1): 29–38, doi: 10.1097/EJA.0000000000001744, indexed in Pubmed: 36131564.
65. Collins PW, Solomon C, Sutor K, et al. Theoretical modelling of fibrinogen supplementation with therapeutic plasma, cryoprecipitate, or fibrinogen concentrate. Br J Anaesth. 2014; 113(4): 585–595, doi: 10.1093/bja/aeu086, indexed in Pubmed: 25064078.
66. Ahonen J, Stefanovic V, Lassila R. Management of post-partum haemorrhage. Acta Anaesthesiol Scand. 2010; 54(10): 1164–1178, doi: 10.1111/j.1399-6576.2010.02309.x, indexed in Pubmed: 21069897.
67. Affronti G, Agostini V, Brizzi A, et al. The daily-practiced post-partum hemorrhage management: an Italian multidisciplinary attended protocol. Clin Ter. 2017; 168(5): e307–e316, doi: 10.7417/T.2017.2026, indexed in Pubmed: 29044353.
68. Abdul-Kadir R, McLintock C, Ducloy AS, et al. Evaluation and management of postpartum hemorrhage: consensus from an international expert panel. Transfusion. 2014; 54(7): 1756–1768, doi: 10.1111/trf.12550, indexed in Pubmed: 24617726.
69. Gallos ID, Papadopoulou A, Man R, et al. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis. Cochrane Database Syst Rev. 2018; 12(12): CD011689, doi: 10.1002/14651858.CD011689.pub3, indexed in Pubmed: 30569545.
70. Colucci G, Helsing K, Biasiutti FD, et al. Standardized management protocol in severe postpartum hemorrhage: a single-center study. Clin Appl Thromb Hemost. 2018; 24(6): 884–893, doi: 10.1177/1076029618758956, indexed in Pubmed: 29669438.
71. Shaylor R, Weiniger CF, Austin N, et al. National and International Guidelines for Patient Blood Management in Obstetrics: A Qualitative Review. Anesth Analg. 2017; 124(1): 216–232, doi: 10.1213/ANE.0000000000001473, indexed in Pubmed: 27557476.
72. Ducloy-Bouthors AS, Jude B, Duhamel A, et al. EXADELI Study Group. High-dose tranexamic acid reduces blood loss in postpartum haemorrhage. Crit Care. 2011; 15(2): R117, doi: 10.1186/cc10143, indexed in Pubmed: 21496253.
73. Aawar N, Alikhan R, Bruynseels D, et al. Fibrinogen concentrate versus placebo for treatment of postpartum haemorrhage: study

protocol for a randomised controlled trial. Trials. 2015; 16: 169, doi: 10.1186/s13063-015-0670-9, indexed in Pubmed: 25906770.

74. Wikkelsø AJ, Edwards HM, Afshari A, et al. FIB-PPH trial group. Pre-emptive treatment with fibrinogen concentrate for postpartum haemorrhage: randomized controlled trial. Br J Anaesth. 2015; 114(4): 623–633, doi: 10.1093/bja/aeu444, indexed in Pubmed: 25586727.
75. Deleu F, Deneux-Tharaux C, Chiesa-Dubruille C, et al. EPI-MOMS study Group. Fibrinogen concentrate and maternal outcomes in severe postpartum hemorrhage: A population-based cohort study with a propensity score-matched analysis. J Clin Anesth. 2022; 81: 110874, doi: 10.1016/j.jclinane.2022.110874, indexed in Pubmed: 35662057.
76. Vermeulen T, Van de Velde M. The role of fibrinogen in postpartum hemorrhage. Best Pract Res Clin Anaesthesiol. 2022; 36(3-4): 399–410, doi: 10.1016/j.bpa.2022.10.002, indexed in Pubmed: 36513434.
77. Armstrong S, Fernando R, Ashpole K, et al. Assessment of coagulation in the obstetric population using ROTEM® thromboelastometry. Int J Obstet Anesth. 2011; 20(4): 293–298, doi: 10.1016/j.ijoa.2011.05.004, indexed in Pubmed: 21835606.
78. Butwick AJ, Goodnough LT. Transfusion and coagulation management in major obstetric hemorrhage. Curr Opin Anaesthesiol. 2015; 28(3): 275–284, doi: 10.1097/ACO.0000000000000180, indexed in Pubmed: 25812005.
79. Kozek-Langenecker S, Sørensen B, Hess JR, et al. Clinical effectiveness of fresh frozen plasma compared with fibrinogen concentrate: a systematic review. Crit Care. 2011; 15(5): R239, doi: 10.1186/cc10488, indexed in Pubmed: 21999308.
80. DeLoughery E, Avery B, DeLoughery TG. Retrospective study of rFVIIa, 4-factor PCC, and a rFVIIa and 3-factor PCC combination in improving bleeding outcomes in the warfarin and non-warfarin patient. Am J Hematol. 2016; 91(7): 705–708, doi: 10.1002/ajh.24384, indexed in Pubmed: 27074566.
81. Nienaber U, Innerhofer P, Westermann I, et al. The impact of fresh frozen plasma vs coagulation factor concentrates on morbidity and mortality in trauma-associated haemorrhage and massive transfusion. Injury. 2011; 42(7): 697–701, doi: 10.1016/j.injury.2010.12.015, indexed in Pubmed: 21392760.
82. Lumbreras-Marquez M, Villela-Franyutti D, Reale S, et al. Coagulation management in obstetric anesthesia. Curr Anesthesiol Rep 2022; 12(2): 266–276, doi: 10.1007/s40140-022-00517-1.
83. de Lloyd L, Bovington R, Kaye A, et al. Standard haemostatic tests following major obstetric haemorrhage. Int J Obstet Anesth. 2011; 20(2): 135–141, doi: 10.1016/j.ijoa.2010.12.002, indexed in Pubmed: 21439811.
84. Negrier C. Optimizing on-demand treatment with NovoSeven room temperature stable. Haemophilia. 2010; 16 Suppl 3: 35–40, doi: 10.1111/j.1365-2516.2010.02258.x, indexed in Pubmed: 20586800.