

Epidemiology, prevention and management of early postpartum hemorrhage — a systematic review

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ABSTRACT

Early Postpartum Hemorrhage (EPH) is one of the leading causes of postpartum mortality. It is defined as blood loss of at least 500 mL after vaginal or 1000 mL following cesarean delivery within 24 hours postpartum. The following paper includes literature review aimed to estimate the incidence and predictors of early postpartum hemorrhage (EPH). Available prevention and treatment methods were also assessed. The inclusion criteria for the study were met by 52 studies.

The exact frequency of EPH in different populations varies from 1.2% to 12.5%. Maternal, pregnancy-associated, labor-correlated and sociodemographic risk factors seem to be important predictors of EPH. In these cases appropriate prophylaxis should be considered. However, EPH may occur without previous risk factors. The main reason for EPH is uterine atony which contributes to up to 80% of cases of postpartum hemorrhage (PPH). Other common reasons for PPH include genital tract injuries, placenta accreta or coagulopathies. Interestingly, the majority of uterotonics seem to have a similar effect. However, carbetocin seems to be the most effective in certain situations.

Appropriate diagnosis of EPH is the most important issue. The treatment should be causative. The first-line treatment should include uterotonics. Surgical interventions, if required, should be performed without delay, although preoperative uterine tamponade should be considered due to its high effectiveness.

Medical staff training in medical simulation centers is an important factor that improves the outcomes of EPH treatment. It provides adaptation to hospital protocols, team work improvement, self-confidence building, more accurate blood loss evaluation and reduced perception of stress. The implementation of systematic trainings provides better outcomes in the future.

Key words: postpartum hemorrhage; delivery; perinatology; medical simulation

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INTRODUCTION

Early postpartum hemorrhage (EPH) is usually defined as blood loss of at least 500 mL following vaginal delivery (VD) or 1000 mL following a cesarean section (CS) within 24 hours postpartum [1–3]. Late postpartum hemorrhage (LPH) occurs after 24 hours following labor and complicates 0.23% of deliveries. According to the American College of Obstetricians and Gynecologists, EPH may be recognized with the presence of signs of hypovolemia within 24 hours after delivery [4]. EPH may be divided into minor (500–1000 mL), moderate (1001–2000 mL) and severe (> 2000 mL) [3]. This complication significantly impacts global women's health as the most frequent reason for perinatal deaths all over the world [2].

The volume of blood loss is usually estimated visually. However, this method is connected with a high possibility

of error. The underestimation occurs in 30 to 50% if it is only visual [1]. To make the assessment more objective it is highly advisable to count utilized medical materials, such as surgical towels and drapes. Estimating weight difference of dry unused materials and those soaked with blood seems to be another effective method. Using a calibrated collector bag is also recommended for a more accurate blood loss estimation. Gravimetric blood loss measurement includes weighing bags after delivery [5]. Modified Brecher's formula consists in hemoglobin measurement after delivery which makes the evaluation more accurate.

Undiagnosed abnormal postpartum blood loss (UP-PBL) is defined as decrease in hemoglobin level of at least 2 g/dL without any symptoms or signs of EPH [6]. Apart from an increased risk of maternal mortality (12 to 17.2%) EPH may lead to further serious complications related to severe

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anemia, such as acute kidney injury (29.3%), hepatic failure, Sheehan Syndrome, adult respiratory distress syndrome (24.6%) and disseminated intravascular coagulopathy (DIC) (11.7%) [2].

The following paper includes a literature review of recent studies regarding PPH. The main aim of the study was to estimate the incidence and predictors of EPH. Available prevention and treatment methods of EPH were also assessed.

MATERIAL AND METHODS

The authors searched PubMed database for articles concerning postpartum hemorrhage published from June 2014 to April 2019. Searching with 'postpartum hemorrhage' query revealed 186 original studies. The inclusion criteria for the study were: a uniform definition of EPH (blood loss of at least 500 mL after VD or 1000 mL following CS within 24 hours postpartum), a study group ≥ 250 patients and the English language of the manuscripts. 52 studies met the inclusion criteria (Fig. 1).

RESULTS

According to the WHO postpartum hemorrhage is one of the leading reasons for postpartum mortality, especially in developing countries of Asia (30.8%) and Africa (33.9%). Conversely, in developed countries the average mortality

rate was estimated to 13.4% of all PPHs (1.2–49.6%). The exact frequency of EPH in different populations is shown in Table 1 [6–10] and varies from 0.4% to 33%.

Etiology

The leading cause of EPH is uterine atony which contributes 60 to 80% of those complications and 20–30% of mothers' deaths [10]. Childbirth via CS may also lead to PPH. There are only few papers concerning PPH occurrence after CS in which PPH ratio amounted to 0.3–6% [11]. The prevalence of PPH has increased over the past few years, which may be caused by an increased incidence of uterine atony and CS. The number of emergency hysterectomies (5.8–6.3/10,000 births), blood transfusions, performing B-Lynch sutures (10.7/10,000 births) and uterine artery embolizations are the most correlated with uterine atony. Other common causes of EPH are genital tract injuries or episiotomy (16.7%), placental abnormalities (4 to 36% of retained placenta, abnormal placental implantation or placental abruption) or coagulopathies (e.g. anticoagulant treatment or DIC) (7.4%) [10].

Risk factors

Unmodifiable risk factors of EPH include a history of EPH (OR = 2.3–10.5) and a delivery of a large for gestational age

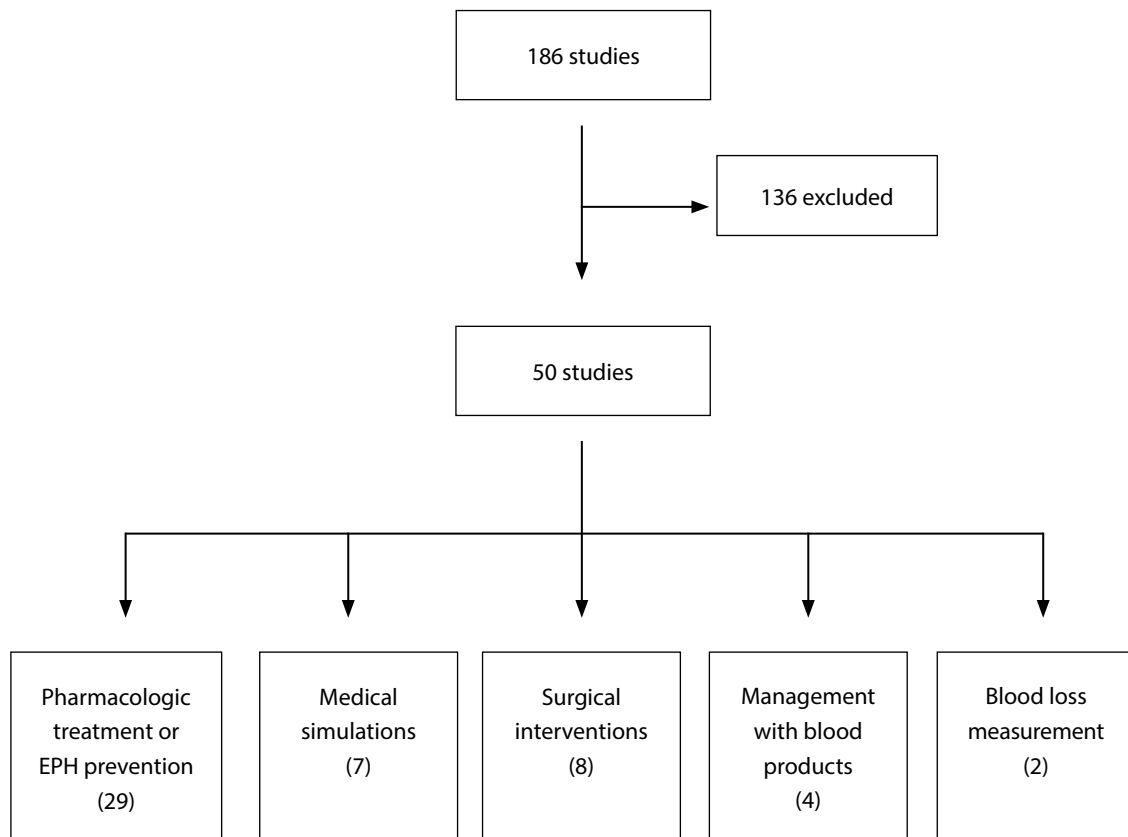


Figure 1. Study flow diagram

Table 1. Frequency of PPH [3, 10, 13, 15, 17–35] identified using a multivariable analysis, were: retained placenta (OR 3.5, 95% CI 2.1–5.8

Country	Years	Population	PPH frequency
Israel	1988–2002	154 311	0.4%
Africa Asia Europe	2008	505 379	Severe EPH: 0.3–3.8% 2.7% 5.5%
Asia, Africa, Middle East, Latin America (data from 28 countries)	2010–2011	274 985	VD: 1.2%
WHO	2012		2%
USA	1995–2004	870 000	2.93%
USA	1999–2008	8 500 000	3%
USA	2006–2012	1 339 397	CS: 2%
Canada	2003–2010	2 200 000	6.2%
Norway	1999–2004	307 415	Severe EPH: 1.1%
Norway	2008–2011	43 105	Severe EPH: 2.5%
United Kingdom	2003–2013	24 230	CS: 12.4%
France	2004–2006	146 781	6.4%
France	2016	3 917	VD UPPBL: 11% VD EPH: 11.2%
Nederland	2000–2008	1 599 867	4.5%
Denmark	2008	147 132	CS: 2.24% VD: 1.75%
Ireland	1999–2009	649 019	2.6%
Spain	2017	1 352 691	3%
Brazil	2010	9 555	12.5%
RPA	2012	15 725	2.5%
Nigeria	2014	4 889	3.4%
India	2010–2012	96	CS: 1.8% VD: 1.3% Instrumental: 5.3%
Tunisia	2010–2013	39	Severe PPH included to the study
Japan	2011	1 294	VD: 33%
German	2010–2013	1 550	8.4%

fetus (> 4000 g) (OR = 1.7–1.9). Uterine abnormalities such as uterine fibroids (OR = 2.0–2.7) also played an important role in the incidence of EPH [6]. Pregnancy complications, such as maternal anemia (hemoglobin level below 9 [g/dL]) (OR = 4.1), hypertensive disorders (OR = 1.6–3.6), gestational diabetes mellitus (OR = 1.6), a multiple gestation (OR = 1.5–3.7), polyhydramnios (OR = 2.6) and preterm delivery (OR = 2.6) were significantly correlated with EPH [12].

Maternal fever (OR = 1.7–2.5), labor induction (OR = 1.5–1.7) and instrumental (OR = 1.2–2.9) or operative delivery (OR = 1.4–5.7) increase the risk of EPH. Retained placenta

increase the risk of hemorrhage immediately after delivery (OR = 3.5–4.1) as well as after subsequent pregnancy [12].

Sociodemographic factors, such as obesity [BMI > 35 (kg/m²)] (OR = 2.3), mother's age over 35 years (OR = 1.5–1.7) and Middle Eastern ethnicity (OR = 1.8) increase the risk of EPH [13]. Conversely, smoking (OR = 0.8) during pregnancy seems to reduce the risk of EPH [6, 13]. All the mentioned risk factors of PPH are shown in Table 2 [6, 10, 14].

Risk factors of UPPBL are similar to those in EPH and include Asian ethnicity (aOR = 2.3), previous cesarean section (aOR = 3.4), episiotomy (aOR = 2.6), primiparity, prolonged labor, instrumental delivery and retained placenta [6].

Prevention

WHO guidelines for the prevention of EPH include a thorough assessment of possible risk factors as the primary prophylaxis of this complication. Moreover, pharmacological prophylaxis includes 10 IU of oxytocin in bolus (intravenously or intramuscularly), 100 µg of carbetocin (intravenously or intramuscularly), misoprostol (400 µg or 600 µg, per os), ergometrine/methyletergometrine (200 µg, intramuscularly or intravenously) or oxytocin and ergometrine together (5 IU and 500 µg, intramuscularly) [15]. According to German guidelines 3–5 IU of intravenous oxytocin or 100 µg of intravenous carbetocin should be recommended (Tab. 3.) [1]. Conversely, RCOG suggested 0.5–1 g of intravenous injection of tranexamic acid, carboprost or misoprostol to be superior to oxytocin prophylaxis. However oxytocin and/or ergometrine or 100 µg of intravenous carbetocin is highly advised, similarly to the guidelines of the Society of Obstetricians and Gynaecologists of Canada [3]. RCOG guidelines suggest that the prevention of minor EPH with 5 IU and 10 IU of oxytocin has comparable results [3]. ACOG recommends to prevent EPH by using 10 IU of oxytocin intramuscularly or intravenously as the most effective [4]. An intravenous bolus of tranexamic acid at a dose of 0.5–2 g (15–30 mg/kg BW) should also be considered [2, 3]. Moreover, it could be used as prophylaxis of EPH after VD.

In twin pregnancies carbetocin prophylaxis of EPH after CS seems to be more effective than oxytocin in the prevention of EPH [16]. The authors found several publications concerning a higher efficacy of carbetocin than oxytocin in the 3rd stage of labor. Moreover, in another study carbetocin was a better alternative to traditional oxytocin in the prevention of PPH after vaginal delivery. The most significant adverse effect after drug administration was hypotension with no difference between those two drugs. Pruritus was the only symptom which was more often experienced in carbetocin-treated group. By contrast, the authors of another study reported that carbetocin had the same effectiveness as oxytocin at lower doses and needed less time to be effective. Conversely, misoprostol needed the longest period to reach sufficient uterine contractility [17]. No differences in effectiveness were

Table 2. Risk factors of PPH [10, 15, 17, 21, 22, 25, 27, 30, 36, 41–44] the incidence of severe postpartum hemorrhage (PPH)

Risk factors of PPH	OR	95% CI
Mother diseases and pregnancy-associated conditions		
Past history of PPH	2.3–10.5	1.3–10.6
Uterine anomaly in the past	2.4	1.2–5.0
Uterine surgery in the past	3.4	1.6–7.1
Multiple pregnancy	1.5–3.7	1.3–5.3
IVF/ICSI	1.8–2.9	2.2–3.9
Preeclampsia or HELLP syndrome	1.8–3.6	1.6–5.7
Hypertension disorder	1.6–2.0	1.1–3.9
Chorioamnionitis	2.9	2.5–3.4
Delivery < 37 weeks of gestation	2.6	2.3–3.0
Delivery > 41 weeks of gestation	1.6–1.9	1.0–2.8
Fibroids	2.0–2.7	1.8–4.2
Lacerations	2.4	2.0–2.8
Nulliparity	1.1–2.0	1.0–2.6
Third pregnancy	1.3	1.1–1.6
Anemia (Hb ≤ 9.0 g/dL)	4.1	2.8–6.1
GDM	1.6	1.1–2.3
Polyhydramnios	2.6	1.2–5.5
Anticoagulant medication	4.7	2.8–7.7
Placenta previa	3.0–7.0	2.9–7.3
Labour related factors		
Retained placenta	3.5–4.1	2.1–5.8
Placenta accrete	3.3	1.7–6.4
Instrumental delivery	1.2–2.9	0.9–3.5
CS	1.4–5.7	1.2–6.5
CS in the second stage of labor	2.1–3.4	1.2–4.7
Uterine rupture	11.6	9.7–13.8
Labour induction	1.5–1.7	1.1–2.0
PROM	1.4–1.5	1.0–1.9
Body temperature in labour > 38°C	1.7–2.5	1.1–3.6
Labour induction or augmentation	1.4–2.0	1.1–2.4
LGA	1.7–1.9	1.2–2.6
Sociodemographic		
BMI > 35kg/m ²	2.3	1.3–3.6
Age > 35 years	1.5–5.7	1.1–7.1
Middle Eastern descent	1.8	1.2–2.7
African descent	1.5	1.1–2.2
Smoking	0.8	0.6–1.0

reported for an intravenous administration of 100 µg of carbetocin and 5 IU of oxytocin [18]. Furthermore, no differences in efficacy were found between 10 IU and 30 IU of oxytocin administered intravenously, but the higher dose was effective for a longer period (8–12 vs 2–4 hours) [19].

Table 3. Carbetocin usage

Multiple pregnancy
≥ 4 deliveries in past
≥ 2 cesarean sections in past
Other uterine scare
Large uterine fibroids
PPH or uterine atony in the past
Suspected fetal macrosomia
Polyhydramnios
Placenta previa
Placenta accreta
BMI > 35 kg/m ²
HCT < 35%
Fibrinogen concentration < 4 g/L
PLT < 100 000

BMI – body mass index; HCT – hematocrit; PLT – platelets

The authors found the advantages of 5 IU of oxytocin administered intramuscularly over 200 µg of sublingual misoprostol. However, misoprostol is more cost-effective, may be stored at room temperature and is easier to use. Therefore, it may be a good alternative to oxytocin. Heat-stable carbetocin compared to oxytocin and 800 µg of rectal misoprostol had a similar effectiveness compared to 10 IU of intramuscular oxytocin in the 3rd stage of labor [20].

Several studies compared the effectiveness of 10 IU of bolus of oxytocin with 600 µg of intramuscular misoprostol in the prevention of EPH, with no significant differences between groups. Furthermore, other authors found that 800 µg of misoprostol seemed to be more effective than the standard dose of oxytocin [21].

A combination of methylergonovine and oxytocin infusion during CS successfully decreased severity of EPH [22]. On the other hand a combination of misoprostol and oxytocin seemed to increase the risk of side effects related to pharmacotherapy, such as fever, nausea and shivering.

Tranexamic acid was effective in reducing the rate of EPH, especially if administered within 3 hours after labor (RR 0.69, 95% CI: 0.5–0.9; p = 0.008) [23]. Another study demonstrated that tranexamic acid did not enhance the anti-hemorrhagic effect in a group of women after oxytocin administration [24]. The supplementation of fibrinogen after EPH in women with normal fibrinogen level also did not improve those results. In contrast to those findings some researchers recommended a routine administration of 3 g of fibrinogen in case of EPH.

Delayed umbilical cord clamping and cord drainage presented a protective effect against EPH.

Treatment

It is important to estimate the occurrence of probable reversible reasons for EPH. An injury of the uterus or the genital tract seems to be the most recognizable factor and requires primary surgical treatment.

The management of retained placenta includes controlled cord traction, Credé maneuver and manual placenta removal [2].

External uterine massage or bimanual uterine compression should be considered as the first-line treatment of uterine atony. The second-line treatment might involve intrauterine tamponade with Foley catheter, or other dedicated intrauterine balloon catheters, which effectiveness reached up to 80–90% [25]. The availability, easy usage and safety are important issues of this method when uterine subatony or undiagnosed focal placenta accreta is present. However, no papers have been found to compare those methods. Early balloon tamponade is effective when used before coagulopathy occurrence.

Another tools utilized in the treatment of uterine subatony are uterine compression sutures (B-Lynch, Cho and Hayman) with effectiveness estimated to 60–75% [26]. However there is insufficient data concerning comparison of different techniques. On the other hand endovascular balloon techniques seem to be more effective (uterine preservation, less blood loss and higher postoperative hemoglobin levels). Several previous studies showed similar effectiveness of compression sutures, intrauterine tamponade and uterine artery ligation. However, intrauterine tamponade should be preferred option because of lower costs and invasiveness as well as faster therapeutic effect. In severe cases combination of aforementioned methods should be considered to preserve female fertility [26].

Obviously, pharmacologic treatment should be introduced simultaneously — intravenous 10–30 IU of oxytocin or 100 µg of intravenous bolus of carbetocin, with similar clinical effectiveness (blood loss, severe postpartum hemorrhage, blood products transfusions). On the other hand few studies has shown higher effectiveness (amount of blood loss and the need for other uterotonics) of 100 µg carbetocin vs 5 IU oxytocin in EPH management [17].

Other vasoconstrictors, such as methylergometrine 0.2–0.4 mg intramuscularly, PGF_{2α} (enzaprost) 1 mg into the uterine muscle, PGE₁ (misoprostol) 600–1000 µg per rectum are also used [2].

Total hysterectomy is the last-ditch intervention in case of uterine atony. The incidence of such intervention constitutes 1.1–2.3% of EPH [27] and 0.63 per 1000 childbirths. Over 30 minutes desmopressin infusion 0.3 µg/kg BW should be considered in women with hypovolemic shock [28].

The administration of crystalloids and colloids should be obligatory apart from drugs increasing the contractility of the uterus. In case of massive perinatal bleeding, blood product transfusion (4 or more units of packed red blood cells (RBC), fresh frozen plasma (12–15 mL/kg BW), (25 IU/kg BW) prothrombin complex concentrate and platelets, when platelet count is below $75 \times 10^9/l$) should be considered [2, 3]. One study suggested cell salvage but this procedure is very expensive and not easily available.

1 g of calcium chlorate and the substitution of fibrinogen (30–60 mg/kg BW), rFVIIa (90 µg/kg BW or 15–20 IU/kg BW) or factor XIII should be considered when severe bleeding is present [3].

Late EPH requires vaginal microbiology and subsequent antimicrobial treatment of endometritis if such a diagnosis is confirmed. Ultrasound should be performed to look for placenta retained tissue and subsequent surgical intervention should be planned.

Medical simulations of EPH are important for the improvement of medical staff skills. A reduction in the number of possible errors, easier and faster medical interventions, shortening the time to the preparation of blood products, more appropriate blood loss evaluation, self-confidence and comfort level, practices in surgical and pharmacological management are the main goals of medical simulations [29]. Such courses improve the recognition of EPH and shorten the duration of appropriate medical intervention — uterine massage and the administration of second-line medications. The results showed an improvement of medical skills in that publication from 27.3% to 63.6% ($p=0.01$) [30]. Another study showed a significant improvement in team cooperation [31]. Some research also showed that such simulations have a positive influence on obstetric outcomes in the future. A subsequent trial showed a higher rate of appropriate EPH evaluation and fundal massage implementation. Another publication proved that one-day simulation caused a significant improvement in medical skills and the effect persisted over the next 3 months (0.4% vs 0.03%, OR 19, 95% CI 2.5–147) [32].

DISCUSSION

An inconsistent definition of EPH, varying across countries contributes to the publication of non-comparable results and different conclusions concerning EPH. The frequency of EPH was compared in this study and an increasing trend was observed. Furthermore, EPH is the main cause of maternal mortality [32]. Apart from death it is associated with severe maternal condition after childbirth. Therefore, an interest in the subject is not surprising. Risk factors listed in the Results section are one of research areas. Prediction strategy assumes risk factor evaluation before any childbirth. EPH causes may be easier to memorize by remembering

their division in 4Ts: tone, tissue, trauma and thrombin with higher attention to uterine atony as the most frequent cause of EPH [10]. It seems that an increased rate of EPH is caused by an increased level of uterine atony secondary to a higher rate of CSs. Regrettably, EPH occurs in two-thirds of women without any risk factors [28].

It is commonly known that it is better to prevent than to treat possible complications. For that reason, the main attention is paid to preventive methods which consist of uterotonics (oxytocin, carbetocin, enzaprost/carboprost or misoprostol, ergometrine or methylegometrine) and tranexamic acid. Thus, the prophylaxis should include 3–10 IU of oxytocin intravenously or 100 µg of carbetocin intravenously in the 3rd stage of labor and 100 µg of carbetocin intravenously during CS in high risk patients. Economic issues should also be considered because of a higher carbetocin cost. Moreover, an intravenous administration of oxytocin was shown as more effective (due to severe EPH, blood transfusion and admission to a high dependency unit) than intramuscular administration in the 3rd stage of labor [33]. Another trial showed acceptable outcomes of misoprostol in comparison with oxytocin, but a high price of misoprostol was emphasized [34]. Previous studies showed also the efficacy of other uterotonics in the absence of oxytocin and carbetocin. Tranexamic acid should be also considered.

Apart from early prophylaxis, in any case of EPH pharmacological and if severe - surgical treatment should be introduced. Pharmacologic intervention seems to be superior to a surgical one. However, if surgical intervention is necessary, no delay in its performance should occur, especially when regards pelvic vessel occlusion, compression sutures (eg B-Lynch) management or emergency hysterectomy. Hamilton maneuver is the best option in preparation to the surgical procedures.

In case of hypovolemic shock, desmopressin 0.3 µg/kg of BW and other vasoconstrictors like norepinephrine should be considered.

Pelvic packing may be performed in case of the lack of selective arterial embolization, for patient transport to a tertiary care unit or in case of persistent bleeding after hysterectomy [7].

Intravenous infusions of crystalloids and colloids should be obligatory apart from previously mentioned drugs. Moreover, blood transfusion may be necessary [2, 3]. Fibrinogen substitution (30–60 mg/kg BW), which could reach ≥ 2 g/L as well as rFVIIa (90 µg/kg BW or 15–20 IU/kg BW) or factor XIII use could improve the PPH outcomes [3].

Medical simulations of EPH are important for the improvement of medical staff skills, which had an influence on EPH outcomes. Importantly, attention should be paid to becoming familiar with hospital protocols, team work

improvement, understanding one's own mistakes, building self-confidence, and reduced perception of stress. Blood loss evaluation is also improved after such trainings. It seems rational that it should be implemented as early as the beginning of medical practice and repeated every 3 months.

No research on the frequency of EPH in the Polish population is currently available. Further studies should also evaluate more accurate blood loss measurement methods and their customization.

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