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Original Article

Standardized Management Protocol in Severe Postpartum Hemorrhage: A Single-Center Study

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Abstract

Severe postpartum hemorrhage (sPPH) is an obstetric emergency that needs prompt and effective therapy to reduce the risk of complications. In this study, women who developed sPPH (study cohort, n = 27) were treated according to a standardized management protocol prescribing sequential administration of uterotonic drugs, crystalloids, tranexamic acid, labile blood products, low-dose fibrinogen, and recombinant activated factor VII (rFVIIa). This group was compared to patients treated with different strategies during 2 preceding periods: an in-house guideline regulating the administration of rFVIIa (historical cohort 1, n = 20) and no specific guideline (historical cohort 2, n = 27). The management protocol was used over 33 months. The study cohort had a lower estimated blood loss ($P = .004$) and required less red blood cell concentrates ($P = .007$), fresh frozen plasma units ($P = .004$), and platelet concentrates ($P = .020$) compared to historical cohort 1 and historical cohort 2, respectively. The necessity of emergency postpartum hysterectomy was lower in the study group ($P = .012$). In conclusion, in patients with sPPH treated with this standardized management protocol, we observed a decreased requirement of labile blood products and lower need to proceed to emergency postpartum hysterectomy.

Keywords

blood coagulation disorders, hemostatics, hysterectomy, postpartum hemorrhage, pregnancy complications

Introduction

Severe postpartum hemorrhage (sPPH) remains an obstetric emergency and a leading cause of maternal death.[1,2] Uterus-conserving strategies to stop bleeding, for example, hemostatic drugs, interventional radiology, and surgical measures including compression sutures, should be coordinated and implemented according to standard operating procedures.[3-5] Emergency postpartum hysterectomy (EPH) is performed when all conservative lifesaving treatments have failed to achieve hemostasis[6] but might end the bleeding only in 50% of the cases.[7] So far, there is no gold standard treatment for sPPH.[8] Evidence supports administration of uterotonics after delivery in order to prevent and control postpartum hemorrhage (PPH).[9-11] However, pharmacological uterotonic agents and new surgical techniques to control sPPH have limited impact on the reduction in EPH,[12,13] which remains associated with a high rate of morbidity and mortality.[14] The role of hemostatic drugs in sPPH is not fully clarified. Prophylactic application of tranexamic acid for prevention of PPH decreases postpartum blood loss after vaginal and cesarean delivery.[15-18] Its therapeutic use is effective in PPH,[19,20] and therefore, tranexamic acid is recommended for obstetric bleeding by the 2013 and 2016 guidelines

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of the European Society of Anaesthesiology.[21,22] Early administration of tranexamic acid reduces death due to bleeding in women with PPH.[23] More controversial is the role of recombinant activated factor VII (rFVIIa) in obstetric hemorrhage because its usefulness, safety, optimal dose, and timing for administration have not been determined so far.[24,25] Recombinant activated factor VII can be considered as second-line hemostatic therapy,[22] but other guidelines limit its use.[8] The new WHO recommendations on prevention and treatment of PPH do not even mention rFVIIa but recommend the implementation of a standardized institutional approach for the management of PPH, without defining the place of hemostatic drugs.[26]

In 2009, the institutional Transfusion Committee of the University Hospital, Inselspital, Bern, together with a multidisciplinary working group including obstetricians, anesthesiologists, hematologists, blood transfusion specialists, and midwives developed a standardized management protocol for PPH after vaginal and cesarean delivery, respectively. This protocol, based on the literature review and personal clinical experience,[5,27] was designed to achieve early recognition and coordinated treatment of PPH with a predefined sequence of surgical and medical interventions. The objective of the present study was to evaluate this standardized management protocol in patients with sPPH compared to 2 different cohorts treated before adoption of this strategy.

Materials and Methods

This single-center study was conducted at the tertiary care University Hospital, Inselspital, of Bern, Switzerland, in accordance with the guidelines for human participant research. Approval was obtained from the local ethics committee (decision number 197/08). Patients with sPPH treated with a standardized management protocol—study cohort—were compared to patients previously treated with an in-house guideline for rFVIIa in massive bleeding (historical cohort 1) and to patients treated without specific guideline (historical cohort 2, Figure 1).

Study Cohort

All patients aged 18 years or older who developed sPPH after vaginal delivery or cesarean section between April 1, 2010, and December 31, 2012, were prospectively included. Severe PPH was defined as continuous bleeding of more than 1500 mL within 24 hours after birth.[28,29] In order to reduce inaccuracies, estimation of blood loss during the study was verified in a standard manner by weighing all gauzes, sponges, and blood obtained in collection systems.

From April 1, 2010, to December 31, 2012, all patients were treated according to the standardized management protocol depicted on Figures 2 and 3. Specifically, in the event of severe blood loss during or after birth, the medical team treating the parturient released a "PPH code," which is an emergency call allowing clear and precise communication between

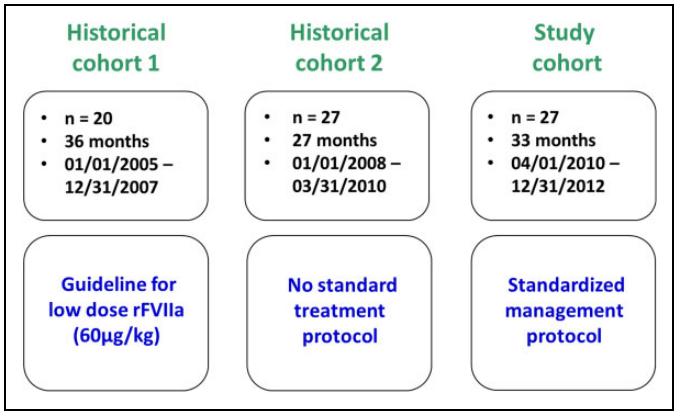

Figure 1. Study design.

multidisciplinary team members (senior obstetrician, anesthesiologist, midwives, hematology consultant, blood transfusion specialist, laboratory staff, and transport service for medicaments and blood products) that a PPH is in process. Once PPH has been identified, monitoring, mechanical, and physiological measures to stimulate the uterine contraction were promptly started. They included uterine massage, bimanual uterine compression, and external aortic compression. Pharmacological measures included early administration of uterotonic drugs, fluids, tranexamic acid, and—if indicated—calcium. The maximum amount of warmed volume replacement was limited for colloids (ie, hydroxyethyl starch) to a total of 20 mL/kg body weight. Simultaneously, a package containing a predefined number of blood and hemostatic product units was sent by emergency transport from the central laboratory to the obstetric surgical suite. The "emergency package" contained 4 units of packed red blood cells (RBCs), 4 units of fresh frozen plasma (FFP), 1 platelet (PLT) concentrate, 2 g of fibrinogen concentrate, and rFVIIa at a dose of 60 µg/kg body weight.[30] Labile blood products were given in fixed ratios of 1:1, as this combination had been shown to improve survival in trauma.[31,32] Recombinant activated factor VII was administered additionally, if bleeding persisted after transfusion of 4 RBCs, 4 FFP units, and 2 g of fibrinogen. Surgical interventions included the identification and repair of lower genital tract lesions, the manual and instrumental uterine revision and curettage, uterine tamponade by a balloon catheter or by surgical towels, laparotomy and uterine compression sutures (B-Lynch or Pereira sutures, Hayman suture technique, square sutures), and uterine artery embolization. More blood products could be ordered by code if all products on site were being administered and bleeding still persisted. In this case, a second identical package was sent. A third demand of products was possible in case of persistent bleeding and included 2 g of fibrinogen and 1250 IU FXIII. After consulting the hematologist, eventually a third dose of rFVIIa was sent. If bleeding still persisted, hysterectomy was performed (Figures 2 and 3). In the event that bleeding stopped and supplemental products were judged to be unnecessary, the remaining components of the "emergency package" were sent back to the central laboratory.

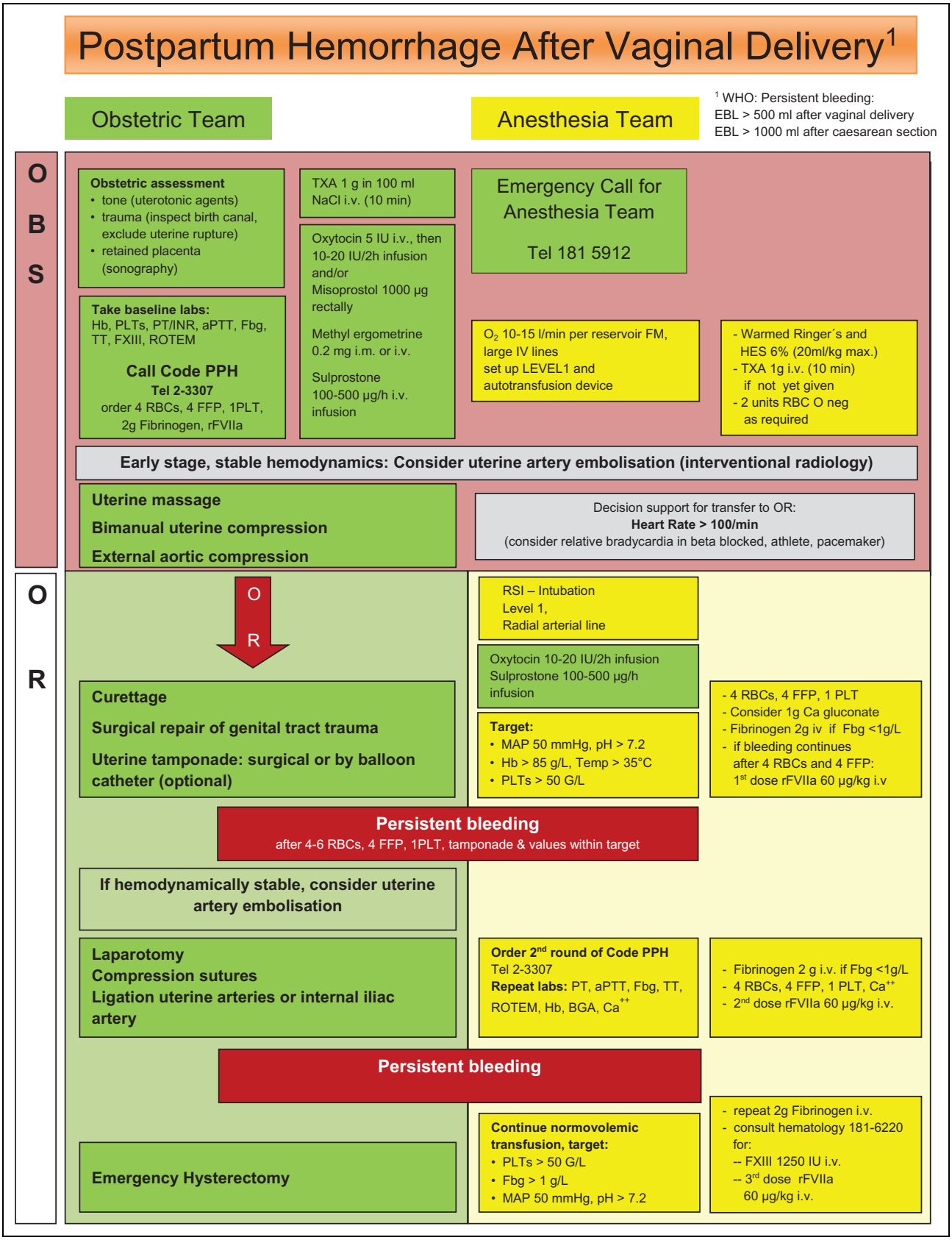

Figure 2. Protocol for the treatment of PPH after vaginal delivery. PPH indicates postpartum hemorrhage.

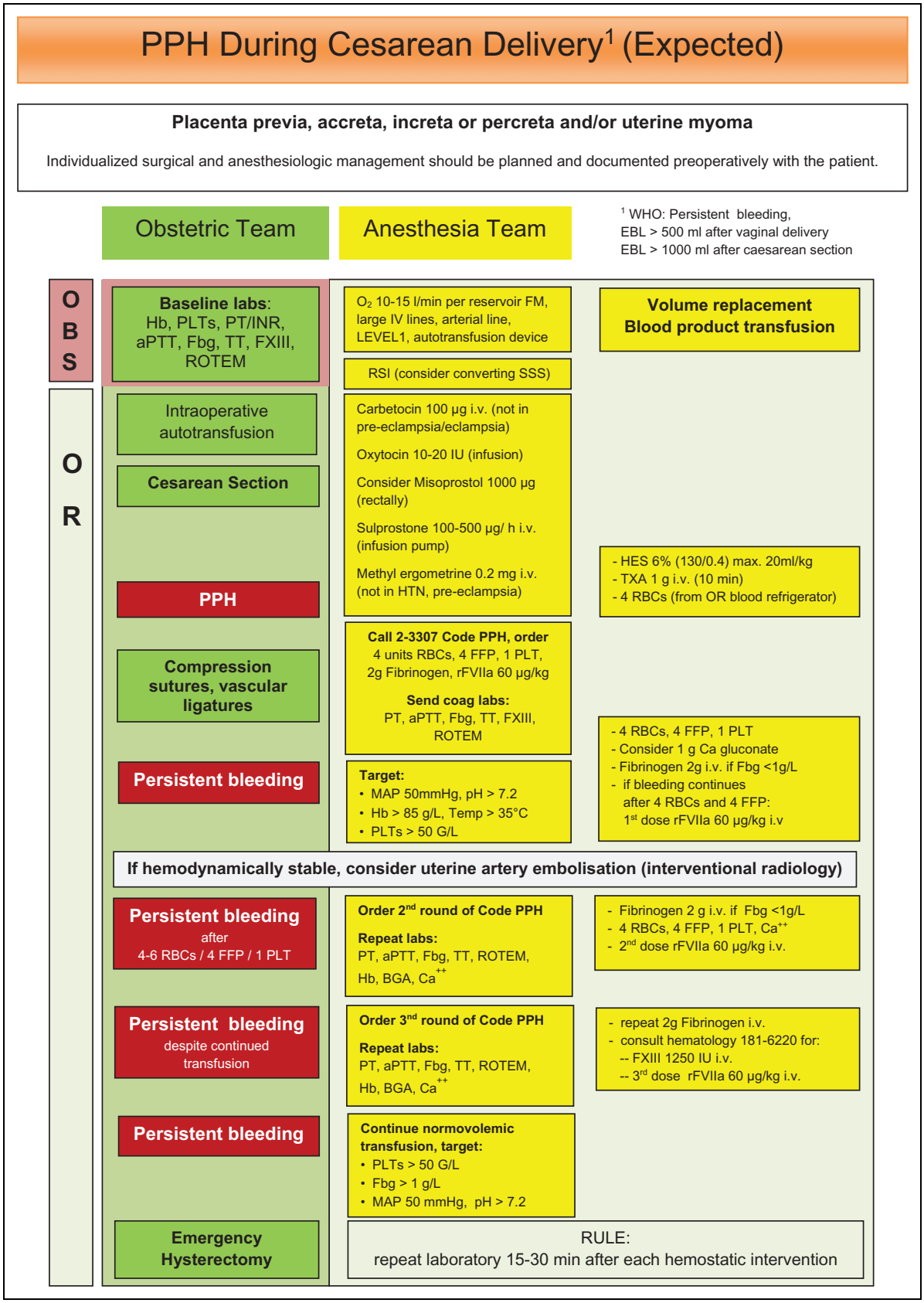

Figure 3. Protocol for the treatment of PPH during cesarean delivery. PPH indicates postpartum hemorrhage.

Table 1. Demographic Data of Total Cohort With Severe Postpartum Hemorrhage (sPPH).

	Historical Cohort 1 n = 20	Historical Cohort 2 n = 27	Study Cohort n = 27	*P* Value
Maternal age (years), median (IQR)	32 (28-36)	36 (32-37)	31 (27-33)	.025
<20 years	0	0	1	
20-34 years	14	12	20	
≥35 years	6	15	6	
Parity				.491
Primiparous	10	9	10	
Multiparous	10	18	17	
Gestation				.067
Singleton	18	27	22	
Multiples	2	0	5	
Gestational age (weeks)				.385
<28 weeks	0	1	2	
28-36 weeks	5	12	11	
37-41 weeks	15	14	14	
Maternal weight (kg)				.788
Median (IQR)	70 (57-80)	70 (62-82)	70 (64-83)	
Cause of PPH (n)				.023
Uterus or parametria lesion	0	7	1	
Uterine atony	15	14	16	
Placenta retention	5	6	10	
Preexisting coagulation defect	0	0	0	

Abbreviations: IQR, interquartile range; PPH, postpartum hemorrhage.

Historical Cohort 1

From January 1, 2005, to December 31, 2007, all patients with sPPH were treated with uterotonic drugs, such as oxytocin, methylergometrine, misoprostol, sulprostone, fluid management, RBCs, FFP, and/or fibrinogen and PLT transfusion according to current practice. If conservative and surgical measures failed and massive bleeding persisted after transfusion of 8 RBCs and 4 units of FFP, all patients received rFVIIa at a dose of 60 μg/kg body weight, according to an in-house guideline for treatment of massive bleeding.[30] If blood loss was still ongoing, a second rFVIIa dose was given. If uncontrollable bleeding persisted after this second rFVIIa application, hysterectomy was performed. The protocol is detailed in the Supplemental Table 1.[30]

Historical Cohort 2

From January 1, 2008, to March 31, 2010, no specific treatment guidelines were followed. The obstetrical and medical care teams performed the same procedures as listed above for the preceding period. However, the decision whether and when to administer blood products, hemostatic agents, such as tranexamic acid, fibrinogen, and rFVIIa, was left to the discretion of individual team leaders, according to their best clinical and personal experience. During this period, the approach and management of a single patient were not standardized. Therefore, the sequence of the same procedures may have been different between the patients. Data from all patients with sPPH as previously defined were obtained from medical records. To avoid bias in the inclusion, all patients were searched with a hospital computer code for PPH. Furthermore, all patients transfused after birth during this time period were checked for the inclusion criteria of sPPH.

All clinical data were documented by the treating physician(s) or nurse(s)/midwife(s). Missing clinical data were searched in the original documentation and in the transfusion medicine record system. The amount of blood obtained through recovery techniques and reinfused was computed. Patients were followed until their hospital discharge. The following data were obtained from each woman: age, weight, parity, gravidity, gestational age (weeks), estimated total blood loss, risk factors predisposing to PPH, mode of delivery, cause of PPH, complete or incomplete placenta and membranes, infused fluids, blood product replacement, medical and surgical treatment, duration of bleeding prior to administration of hemostatic agents including rFVIIa administration, necessity of EPH, thromboembolic complications, death, and cause of death.

Statistical Analysis

All quantitative data are presented as number, percentage (%), median and interquartile range (IQR), minimum–maximum (min–max), mean, and standard deviation (SD), as appropriate. Nonparametric statistics were applied and all analyses were performed with SigmaPlot 12.3 (Systat Software, Inc. Chicago, Illinois). Comparisons between various groups were performed with the Kruskal-Wallis test or χ^2 test for categorical data. A Mann-Whitney *U* test was used for independent samples. Size effect was determined between groups of similar size according

Table 2. Treatment of sPPH: Results Expressed as Medians and Interquartile Ranges (IQR) and Numbers and Percentages (%) of Patients Receiving Defined Amounts of Blood Products.

	Historical Cohort 1 n = 20	Historical Cohort 2 n = 27	Study Cohort n = 27	*P* Value
Allogeneic Transfusion				
RBCs median (IQR)	12 (8-16)	12 (6-16)	6 (3-9)	.007
≤4, n (%)	2 (10)	5 (18.5)	13 (48)	
5-8, n (%)	5 (25)	5 (18.5)	8 (30)	
>8, n (%)	13 (65)	17 (63)	6 (22)	
FFP median (IQR)	10 (7-13)	10 (4-12)	5 (2-8)	.004
≤4, n (%)	2 (10)	8 (30)	13 (48)	
5-8, n (%)	6 (30)	5 (18)	10 (37)	
>8, n (%)	12 (60)	14 (52)	4 (15)	
PLT median (IQR)	2 (1-3)	1 (0-2)	1 (0-1)	.020
≤2, n (%)	14 (70)	25 (93)	23 (85)	
>2, n (%)	6 (30)	2 (7)	4 (15)	
Hemostatic agents				
Tranexamic acid	5 (25%)	17 (63%)	27 (100%)	<.001
Fibrinogen	1 (5%)	2 (7%)	20 (74%)	<.001
rFVIIa	20 (100%)	15 (55%)	14 (52%)	.018
FXIII	0	0	0	
Surgical procedures				
Ligation of pelvic vessel	0	1 (3.7%)	1 (3.7%)	.687
Embolization of pelvic vessel	1 (5%)	0	4 (15%)	.092
Hysterectomy	5 (25%)	10 (37%)	1 (3.7%)	.012

Abbreviations: FFP, fresh frozen plasma; PLT, platelet concentrates; RBC, red blood cell concentrates; rFVIIa, recombinant activated factor VII; sPPH, severe postpartum hemorrhage.

to Cohen *d* by calculating the mean difference between 2 groups and then dividing the result by the pooled SD. Between groups of different size Hedges' *g* was calculated, which provides a measure of effect size weighted according to the relative size of each sample. A 2-tailed *P* value of <.05 was considered significant.

Results

During the study period, data from 74 patients who had sPPH were collected: 20 in the historical cohort 1 and 27 in both the historical cohort 2 and the study group. The patients' characteristics are presented in Table 1. Median age was 32 years (IQR 28-36 years) for the cohort 1, 36 years (IQR 32-37 years) for the cohort 2, and 31 years (IQR 27-33 years) for patients of the study group ($P = .025$). Uterine atony was the most frequent cause of sPPH (Table 1).

There were 7 vaginal deliveries each in both historical cohorts and 9 in the study group ($P = .762$), resulting in a total of 23 vaginal and 51 cesarean deliveries. No differences in the incidence of embolization or ligation of pelvic vessels were observed between the 3 groups (both interventions together $P = .133$). Five (25%) women in the historical cohort 1, 10 (37%) in the cohort 2, but only 1 (3.7%) in the study group underwent hysterectomy, showing a reduced necessity for this procedure after introduction of the standardized protocol ($P = .012$, Table 2).

The estimated total blood loss was significantly lower in the study cohort (study cohort: median 3000 mL [IQR 2000-4000 mL] vs historical cohort 1: 4500 mL [IQR 3000-5500 mL] and historical cohort 2: 6000 mL [IQR 3000-6500 mL], respectively, $P = .004$). The total amount of infused crystalloids was similar in the 3 groups, whereas the amount of colloids administered was lower in the study cohort ($P < .001$, Table 3).

The number of transfused labile blood product units was lower in the study group compared to both historical cohorts (Table 2). Median RBC units transfused decreased from 12 (IQR 8-16) in cohort 1 and 12 (IQR 6-16) in cohort 2 to 6 (IQR 3-9) in the study cohort ($P = .007$). A similar trend was observed for FFP units (historical cohort 1: median 10 [IQR 7-13], historical cohort 2: median 10 [IQR 4-12], study group: median 5 [IQR 2-8], $P = .004$) and for PLT concentrates (median 2 [IQR 1-3], median 1 [IQR 0-2], and median 1 [IQR 0-1], respectively, $P = .020$). Analysis of study cohort omitting patients undergoing ligation (n=1) or embolization of pelvic vessels (n=4) leaving 22 patients in the study cohort (Table 2) showed unchanged results regarding estimated blood loss (median 3000 mL, IQR 2000-4000 mL) and number of transfused labile blood products (total RBC units: median 5 [IQR 3-8], FFP: median 5 [IQR 2-8] and PLT concentrates: median 0 [IQR 0-1]). According to the protocol, a significant increase in tranexamic acid and fibrinogen administration was observed in the study group ($P < .001$, Table 2). The proportion of patients receiving rFVIIa decreased from 100% (historical cohort 1) to 55% (historical cohort 2) and 52% (study cohort), respectively

Table 3. Estimated Blood Loss and Fluid Replacement in the 3 Periods (Results Expressed as Medians and Interquartile Ranges, IQR).

	Historical Cohort 1 n = 20	Historical Cohort 2 n = 27	Study Cohort n = 27	*P* Value
Estimated blood loss (mL), median (IQR)	4500 (3000-5500)	6000 (3000-6500)	3000 (2000-4000)	.004
Normal saline–glucose (mL), median (IQR)	0 (0-900)	500 (400-1000)	500 (0-500)	.072
Ringer's solution (mL), median (IQR)	1800 (1000-3000)	2000 (1200-3000)	2000 (1000-3000)	.558
Colloids (mL), median (IQR)	1850 (1000-2375)	1500 (1000-2000)	1000 (500-1500)	<.001

Table 4. Units of Allogeneic Blood Products Transfused Before Application of Hemostatic Drugs (Fibrinogen and/or rFVIIa if Necessary), After rFVIIa Exposure and Bleeding Duration Before rFVIIa in the 3 Periods.[a]

Transfused Allogeneic Blood Products				
Before Hemostatic Drugs (Fibrinogen and/or rFVIIa)	Historical Cohort 1 n = 20	Historical Cohort 2 n = 27	Study Cohort n = 27	*P* Value
RBCs, median (IQR)	9 (6.5-15)	8 (6-12)	4 (3-7)	.002
FFP, median (IQR)	8.5 (5-11.5)	6 (4-10)	4 (2-6)	.002
PLT, median (IQR)	1 (1-2)	0 (0-1)	0 (0-1)	.010
After rFVIIa	Historical Cohort 1 n = 20	Historical Cohort 2 n = 15	Study Cohort n = 14	*P* Value
RBCs, median (IQR)	1 (0-2.75)	4 (2-8)	2 (0-5.25)	.071
FFP, median (IQR)	0.5 (0-2)	2 (0-4)	1 (0-4)	.482
PLT, median (IQR)	0 (0-1)	0 (0-1)	0 (0-1)	.698
Bleeding duration before rFVIIa (minutes), median (IQR)	n = 20 328 (151-640)	n = 15 190 (150-240)	n = 14 135 (108-173)	.021

Abbreviations: FFP, fresh frozen plasma; PLT, platelet concentrates; RBC, red blood cell concentrates; rFVIIa, recombinant activated factor VII.
[a]Results expressed as medians and interquartile ranges (IQRs).

($P = .018$). The dose of administered rFVIIa calculated in μg/kg body weight was similar in all 3 groups (historical cohort 1: median 63.4 μg/kg [IQR: 57.3-68.0, min–max: 24.0-92.3], historical cohort 2: median 60.0 μg/kg [IQR: 57.1-69.5, min–max: 50.0-114.2], and study cohort: median 59.5 μg/kg [IQR: 54.2-66.6, min–max 31.2-70.4]; $P = .586$). The dose of administered fibrinogen increased in the study cohort (study cohort: median 2 g [IQR: 0-2, min–max: 0-4] and historical cohorts 1 and 2: median 0 g [IQR: 0-0, min–max: 0-1], $P < .001$).

In the study cohort, bleeding duration was shorter than in both historical cohorts 1 and 2. Of note, duration of bleeding before rFVIIa administration was shorter in the study cohort (n = 14, median 135 minutes, IQR 108-173 minutes) compared to historical cohort 1 (n = 20, median 328 minutes, IQR 151-640 minutes) and historical cohort 2 (n = 15, median 190 minutes, IQR 150-240 minutes), respectively ($P = .021$). As indicated in Table 4, the management protocol used in the study cohort especially impacted the number of blood products transfused before specific hemostatic therapy, shortening the time delay to the decision to administer fibrinogen and/or rFVIIa. The number of transfused blood products before administration of hemostatic agents (fibrinogen and/or rFVIIa if necessary) was significantly lower in the study cohort (RBCs, median 4 [IQR 3-7]; FFP, median 4 [IQR 2-6]; and PLT, median 0 [IQR 0-1]) compared to historical cohort 1 (RBCs, median 9 [IQR 6.5-15]; FFP, median 8.5 [IQR 5-11.5]; PLT, median 1 [IQR 1-2]) and historical cohort 2 (RBCs, median 8 [IQR 6-12]; FFP, median 6 [IQR 4-10]; PLT, median 0 [IQR 0-1]; Table 4). Obstetric and medical interventions performed in the study cohort were able to stop bleeding in the majority of patients. Administration of FXIII concentrate or of a third dose of rFVIIa had never been necessary (Table 2).

Of particular note, the amount of blood products transfused after the administration of fibrinogen and/or rFVIIa was not different between the 3 groups. For instance, looking only at the patients who received rFVIIa, the amount of blood products transfused after rFVIIa was similar in the 3 cohorts (Table 4). The introduction of this standardized management protocol reduced the need of blood products in patients with sPPH. The size effects calculated between the 3 cohorts range from medium to large (Table 5).

Of all 74 patients, only 1 (1.4%) in the historical cohort 2 experienced a clinically manifest pulmonary embolism diagnosed on day 10 after delivery. Interestingly, this patient had neither received tranexamic acid nor fibrinogen and rFVIIa; however, she had undergone emergency hysterectomy. There were no maternal deaths.

Discussion

Postpartum hemorrhage remains one of the most unpredictable emergencies in obstetrics. During sPPH, blood loss may

Table 5. Allogeneic Transfusion[a,b]

	Study Cohort n = 27	Historical Cohort 1 n = 20	Effect Size Hedges' *g*	Historical Cohort 2 n = 27	Effect Size Cohen *d*
Total					
RBCs, mean (SD)	7.6 (7.4)	13.2 (7.6)	0.75	11.1 (6.7)	0.50
FFP, mean (SD)	5.7 (5.4)	11.1 (7.7)	0.83	8.7 (5.6)	0.55
PLT, mean (SD)	0.96 (1.29)	2.05 (2.14)	0.64	0.93 (1.00)	0.03
Before hemostatic drugs (fibrinogen and/or rFVIIa)					
RBCs, mean (SD)	5.7 (3.6)	10.7 (5.6)	1.09	8.6 (4.8)	0.68
FFP, mean (SD)	4.4 (3.2)	8.2 (3.6)	1.12	7.2 (4.7)	0.70
PLT, mean (SD)	0.55 (0.75)	1.6 (1.93)	0.77	0.70 (0.95)	0.17

Abbreviations: FFP, fresh frozen plasma; PLT, platelet concentrates; RBC, red blood cell concentrates; rFVIIa, recombinant activated factor VII; sPPH, severe postpartum hemorrhage.
[a]Results expressed as means and standard deviation (SD).
[b]Size effect between groups calculated for all transfused allogeneic products (A) and for these transfused before hemostatic drugs (B).

become uncontrollable and life-threatening. A gold standard therapy is not well established, and it is suggested to implement a local protocol to avoid time loss and management errors. To evaluate a standardized management protocol at our institution, we compared patients with sPPH to 2 different cohorts treated before adoption of this strategy. After implementation of the standardized protocol providing early and sequential interventions, we noted a reduction in the bleeding duration and severity, in the total amount of transfused labile blood products and, most importantly, in the EPH rate. This standardized management protocol enabling early recognition of PPH, rapid and coordinated response with predefined therapeutic procedures improved globally the approach to the severe bleeding and finally the clinical course. Although our study shows that this protocol was associated with a reduction in the need of blood components in our cohort, we were not able to define the role of a single step and of each individual hemostatic agent. It is important to note that the protocol incorporates several procedures to maternity care and it is not simply a massive transfusion protocol. Slightly more patients in the study cohort were subjected to pelvic vessel ligation or embolization as compared to patients in the 2 historical cohorts ($P = .092$). Thus we cannot exclude a benefit of these interventional measures for the better outcome of our study cohort. The clinical benefit may be related to the standardized procedures and the sum of the individual therapeutic measures during the study period.

Obstetric and hemostatic interventions combining limitation of hydroxyethyl starch, immediate administration of tranexamic acid, early labile blood products with a 1:1 ratio of RBCs to FFP, and—if necessary—early administration of low-dose fibrinogen reduced or stopped the bleeding in about 50% of patients (n = 13, Table 2). It is important to note that the protocol of the study cohort differs from current international guidelines regarding several points: First, the volume replacement with colloids was limited to a maximum of 20 mL/kg body weight. Second, all patients received promptly tranexamic acid. Furthermore, the "emergency package" contained rFVIIa at a dose of 60 μg/kg body weight ready to be administered after 2 g of fibrinogen concentrate, 4 units of RBCs, 4 units of FFP, and 1 PLT concentrate, if blood loss persisted. The early administration of products, particularly of rFVIIa, diverges from current guidelines that suggest that rFVIIa can be considered for ongoing PPH unresponsive to standard therapy[8] or can be considered as the second-line hemostatic therapy.[22] We believe that an early and adequate intervention to limit the blood loss may reduce the progression to uncontrollable bleeding. In patients necessitating rFVIIa (n = 14, Table 2), the bleeding duration before rFVIIa was shorter compared to historical cohorts 1 and 2 (Table 4). In future studies, we suggest to consider the time point for rFVIIa administration which represents another important difference between this protocol and international guidelines advocating the use of rFVIIa for ongoing PPH[8] or as a last resort after conventional therapies fail.[33] In this study, we can observe that administration of rFVIIa after a long-lasting and massive blood loss, as a last resort to prevent hysterectomy (as performed in the historical cohort 1) and particularly its liberal use in the absence of any guideline (as in the historical cohort 2), was less efficacious. Of particular note, the smaller amount of blood products transfused in the study cohort (Table 2) was due to less blood products transfused before—and not after—additional hemostatic intervention (Table 4). Therefore, we speculate that the timing of the therapeutic intervention is relevant for reducing the bleeding severity and controlling coagulopathy. It seems that an aggressive management at the initial stage of bleeding would limit the coagulopathy and the progression to life-threatening hemorrhage.

Of note, no patients with preexisting bleeding disorders were present in our cohort. We believe that low-dose rFVIIa should not yet be discarded as an early measure in therapeutic algorithms for patients with PPH and should not be restricted to specific hematological indications.[27] Our approach in the study cohort—offering a standardized management protocol for obstetrician, anesthesiologist, and the other treating staff with defined procedures and immediate application of tranexamic acid, RBCs, FFP, PLT, and low-dose fibrinogen—reduced the use of rFVIIa significantly to about 50% and improved outcome. Prospective clinical trials with defined PPH resuscitation

protocols are needed to confirm the beneficial effects observed in our cohort.

While this study reporting everyday clinical practice at our institution documents an improvement across 3 consecutive periods with evolving PPH management strategy, it has limitations and weaknesses as well. Its observational character, the lack of blinding and randomization, and the small sample size render our findings only hypothesis generating. A prospective randomized controlled trial will be needed to ultimately validate the usefulness of such a standardized protocol. Moreover, as mentioned above, we cannot distinguish the effect of a single hemostatic agent or specific measure of our protocol. Nevertheless, the sum of all elements of the algorithm is effective and our results are in-line with recent studies that describe reduced use of blood products and improved patient safety following comprehensive maternal hemorrhage protocols.[34,35] The beneficial effects of this standard protocol are indicated not only by the diminution of the estimated blood loss but also by the lower number of EPH.

In conclusion, the implementation of a standardized interdisciplinary approach to the management of sPPH is beneficial and therefore recommended. This study suggests that the protocol should consider in addition to uterotonic drugs immediate administration of tranexamic acid, transfusion of RBC concentrates, FFP, PLT concentrates, and sequential administration of low-dose fibrinogen concentrate and rFVIIa. Timely application of these measures appears to reduce blood product administration and EPH rates.

Authors' Note

G. Colucci was responsible for the concept and study design, collection of data, statistical analysis of data, writing of the manuscript, correction, approval, and submission of the final version. K. Helsing contributed to collection of data, discussion, and approval of the final version. F. Demarmels Biasiutti contributed to critical discussion and writing of the manuscript and approved the final version. L. Raio and B. Eberle contributed to the study design, discussion of data, critical writing of the manuscript, and approval of the final version. P. Schmid helped collecting data and approved the final version. D. Tsakiris and D. Surbek contributed to critical writing of the manuscript and approval of the final version. B. Lämmle made a substantial contribution to study concept, discussion of data, critical writing of the manuscript, and review and approval of the final version. L. Alberio was responsible for concept and study design, analysis and discussion of data, critical writing of the manuscript, and review and approval of the final version. This study was presented at the Abstract Symposium Pregnancy-related bleeding complications at the XXV Congress of the International Society on Thrombosis and Haemostasis, Toronto, Canada, June 24, 2015 [Abstract AS163]. J Thromb Haemost 13(Suppl 2):59.

Declaration of Conflicting Interests

The author(s) declared the following potential conflict of interest with respect to the research, authorship, and/or publication of this article: L. Alberio has served as a member of the Swiss Advisory Board for rFVIIa.

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References

1. Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. *Lancet*. 2006;367(9516):1066-1074.
2. Joseph KS, Rouleau J, Kramer MS, Young DC, Liston RM, Baskett TF;Maternal Health Study Group of the Canadian Perinatal Surveillance System. Investigation of an increase in postpartum haemorrhage in Canada. *BJOG*. 2007;114(6):751-759.
3. McLintock C, James AH. Obstetric hemorrhage. *J Thromb Haemost*. 2011;9(8):1441-1451.
4. Su LL, Chong YS. Massive obstetric haemorrhage with disseminated intravascular coagulopathy. *Best Pract Res Clin Obstet Gynaecol*. 2012;26(1):77-90.
5. Ghezzi F, Cromi A, Uccella S, Raio L, Bolis P, Surbek D. The Hayman technique: a simple method to treat postpartum haemorrhage. *BJOG*. 2007;114(3):362-365.
6. Pavord S, Maybury H. How I treat postpartum hemorrhage. *Blood*. 2015;125(18):2759-1770.
7. Michelet D, Ricbourg A, Gosme C, et al. Emergency hysterectomy for life-threatening postpartum haemorrhage: Risk factors and psychological impact. *Gynecol Obstet Fertil*. 2015;43(12): 773-779.
8. Collins P, Abdul-Kadir R, Thachil J. subcommittees on women's health issues in thrombosis and haemostasis and on disseminated intravascular coagulation. Management of coagulopathy associated with postpartum hemorrhage: guidance from the SSC of the ISTH. *J Thromb Haemost*. 2016;14(1):205-210.
9. Begley CM, Gyte GM, Devane D, McGuire W, Weeks A. Active versus expectant management for women in the third stage of labour. *Cochrane Database Syst Rev*. 2011;(11): CD007412.
10. Gulmezoglu AM, Lumbiganon P, Landoulsi S, et al. Active management of the third stage of labour with and without controlled cord traction: a randomised, controlled, non-inferiority trial. *Lancet*. 2012;379(9827):1721-1727.
11. Tuncalp O, Hofmeyr GJ, Gulmezoglu AM. Prostaglandins for preventing postpartum haemorrhage. *Cochrane Database Syst Rev*. 2012;(8):CD000494.

12. Lone F, Sultan AH, Thakar R, Beggs A. Risk factors and management patterns for emergency obstetric hysterectomy over 2 decades. *Int J Gynaecol Obstet*. 2010;109(1):12-15.
13. Orbach A, Levy A, Wiznitzer A, Mazor M, Holcberg G, Sheiner E. Peripartum cesarean hysterectomy: critical analysis of risk factors and trends over the years. *J Matern Fetal Neonatal Med*. 2011;24(3):480-484.
14. Machado LS.Emergency peripartum hysterectomy: incidence, indications, risk factors and outcome. *N Am J Med Sci*. 2011; 3(8):358-361.
15. Simonazzi G, Bisulli M, Saccone G, Moro E, Marshall A, Berghella V. Tranexamic acid for preventing postpartum blood loss after cesarean delivery: a systematic review and meta-analysis of randomized controlled trials. *Acta Obstet Gynecol Scand*. 2016; 95(1):28-37.
16. Alam A, Choi S. Prophylactic use of tranexamic acid for postpartum bleeding outcomes: a systematic review and meta-analysis of randomized controlled trials. *Transfus Med Rev*. 2015;29(4):231-241.
17. Novikova N, Hofmeyr GJ. Tranexamic acid for preventing postpartum haemorrhage. *Cochrane Database Syst Rev*. 2010(7): CD007872.
18. Peitsidis P, Kadir RA. Antifibrinolytic therapy with tranexamic acid in pregnancy and postpartum. *Expert Opin Pharmacother*. 2011;12(4):503-516.
19. Ducloy-Bouthors AS, Jude B, Duhamel A, et al. High-dose tranexamic acid reduces blood loss in postpartum haemorrhage. *Crit Care*. 2011;15(2):R117.
20. Ducloy-Bouthors AS, Duhamel A, Kipnis E, et al. Postpartum haemorrhage related early increase in D-dimers is inhibited by tranexamic acid: haemostasis parameters of a randomized controlled open labelled trial. *Br J Anaesth*. 2016;116(5):641-648.
21. Kozek-Langenecker SA, Afshari A, Albaladejo P, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology. *Eur J Anaesthesiol*. 2013; 30(6):270-382.
22. Kozek-Langenecker SA, Ahmed AB, Afshari A, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology: first update 2016. *Eur J Anaesthesiol*. 2017;34(6):332-395.
23. Collaborators WT. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *Lancet*. 2017; 389(10084):2105-2116.
24. Haynes J, Laffan M, Plaat F. Use of recombinant activated factor VII in massive obstetric haemorrhage. *Int J Obstet Anesth*. 2007; 16(1):40-49.
25. Franchini M, Franchi M, Bergamini V, Salvagno GL, Montagnana M, Lippi G. A critical review on the use of recombinant factor VIIa in life-threatening obstetric postpartum hemorrhage. *Semin Thromb Hemost*. 2008;34(1):104-112.
26. Tuncalp O, Souza JP, Gulmezoglu M, World Health Organization. New WHO recommendations on prevention and treatment of postpartum hemorrhage. *Int J Gynaecol Obstet*. 2013;123(3): 254-256.
27. Huber AW, Raio L, Alberio L, Ghezzi F, Surbek DV. Recombinant human factor VIIa prevents hysterectomy in severe postpartum hemorrhage: single center study. *J Perinat Med*. 2011;40(1): 43-49.
28. Bonnar J. Massive obstetric haemorrhage. *Baillieres Best Pract Res Clin Obstet Gynaecol*. 2000;14(1):1-18.
29. Singh S, McGlennan A, England A, Simons R. A validation study of the CEMACH recommended modified early obstetric warning system (MEOWS). *Anaesthesia*. 2012;67(1):12-18.
30. Schmid P, Mordasini A, Luginbuhl M, et al. Low-dose recombinant factor VIIa for massive bleeding: a single centre observational cohort study with 73 patients. *Swiss Med Wkly*. 2011;141: w13213.
31. Borgman MA, Spinella PC, Perkins JG, et al. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. *J Trauma*. 2007;63(4): 805-813.
32. Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *JAMA*. 2015;313(5):471-482.
33. 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):216-32.
34. Shields LE, Smalarz K, Reffigee L, et al. Comprehensive maternal hemorrhage protocols improve patient safety and reduce utilization of blood products. *Am J Obstet Gynecol*. 2011;205(4):368 e1-e8.
35. Shields LE, Wiesner S, Fulton J, Pelletreau B. Comprehensive maternal hemorrhage protocols reduce the use of blood products and improve patient safety. *Am J Obstet Gynecol*. 2015;212(3): 272-280.