Towards better prognostic and diagnostic strategies for major obstetric haemorrhage

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4 ASSOCIATION BETWEEN FLUID MANAGEMENT AND DILUTIONAL COAGULOPATHY IN SEVERE POSTPARTUM HAEMORRHAGE: A NATIONWIDE RETROSPECTIVE COHORT STUDY

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Abstract

Background: The view that 2 litres of crystalloid and 1.5 litres of colloid can be infused while awaiting compatible blood for patients with major postpartum haemorrhage is based on expert opinion documents. We describe real-world changes in levels of coagulation parameters after the administration of different volumes of clear fluids to women suffering from major postpartum haemorrhage.

Methods: We performed a nationwide retrospective cohort study in the Netherlands among 1038 women experiencing severe postpartum haemorrhage who had received at least four units of red cells or fresh frozen plasma or platelets in addition to red cells. The volume of clear fluids administered before the time of blood sampling was classified into three fluid administration strategies, based on the RCOG guideline: < 2L, 2-3.5L and > 3.5L. Outcomes included haemoglobin, haematocrit, platelet count, fibrinogen, aPTT and PT levels.

Results: Haemoglobin, haematocrit, platelet count, fibrinogen and aPTT were associated with volumes of clear fluids, which was most pronounced early during the course of postpartum haemorrhage. During the earliest phases of postpartum haemorrhage median haemoglobin level was 10.1 g/dl (IQR 8.5-11.6) among the women who received < 2 L clear fluids and 8.1 g/dl (IQR 7.1-8.4) among women who received > 3.5 L of clear fluids; similarly median platelet counts were 181 x10^9/litre (IQR 131-239) and 89 x10^9/litre (IQR 84-135), aPTT 29s (IQR 27-33) and 38s (IQR 35-55) and fibrinogen 3.9 g/L (IQR 2.5-5.2) and 1.6 g/L (IQR 1.3-2.1).

Conclusions: In this large cohort of women with severe postpartum haemorrhage, administration of larger volumes of clear fluids was associated with more severe deterioration of coagulation parameters corresponding to dilution. Our findings provide thus far the best available evidence to support expert opinion-based guidelines recommending restrictive fluid resuscitation in women experiencing postpartum haemorrhage.

Background

Postpartum haemorrhage continues to be a leading cause of maternal health problems worldwide[1]. Depending on the primary cause of haemorrhage, acquired coagulopathy may develop during the course of postpartum haemorrhage and aggravate bleeding[2]. Rapid intravenous infusion of clear (crystalloid and colloid) fluids is generally applied during on-going haemorrhage to establish haemodynamic stability, restore adequate intravascular volume and improve oxygen carrying capacity and oxygen tissue delivery[3]. When given in large volumes, clear fluids initiate dilution of clotting factors resulting in impairment of coagulation and coagulopathy[4-6]. On top of that, rapid consumption of fibrinogen, clotting factors and platelets as a result of persistent blood loss, aggravates coagulopathy[5]. The use of colloid fluids has proven to negatively influence coagulation capacity and endothelial function[7,8]. These findings have led to less aggressive fluid management in patients with traumatic haemorrhagic shock[9].

International guidelines on management of women with severe postpartum haemorrhage elucidate the lack of quantitative evidence on the effect of different fluid management strategies on parameters of coagulopathy. For instance, the RCOG green-top guideline advises to follow the expert opinion-based recommendation to administer up to 3.5 litres of warmed clear fluids, starting with 2 litres of warmed isotonic crystalloids until blood products are available in case of persistent postpartum blood loss exceeding 1000 ml[10]. The experts formed their opinions based on experiments in laboratories, animals, healthy volunteers, and observations from trauma patients. However, findings from these studies may not apply to pregnant women, since pregnancy induces haemodynamic and haematologic changes that protect them against haemorrhage during birth. Maternal blood volume increases between 1.2 and 1.6 litres above non-pregnant values, creating a hypervolemic state during pregnancy[4]. To enable evidence-based recommendations on fluid management strategies in women with major postpartum haemorrhage, more insight is needed on the changes of coagulation parameters after administration of different volumes of fluids[4]. To the best of our knowledge no previous studies have been conducted into different fluid management strategies and their possible effect on coagulation parameters in women experiencing postpartum haemorrhage.

The aim of this study was to describe the association between administration of different volumes of clear fluids and levels of coagulation parameters in women experiencing postpartum haemorrhage.

Methods

Design and study population

We studied volumes of clear fluids and results of coagulation parameter measurements during postpartum haemorrhage in a cohort of women who had been included in a nationwide retrospective cohort study in 61 hospitals in the Netherlands, the TeMpOH-1 (Transfusion strategies in women during Major Obstetric Haemorrhage) study. Included in the TeMpOH-1 study were women who received at least four units of red cells or any transfusion of fresh frozen plasma (FFP) and/or platelets in addition to red cells because of *obstetric haemorrhage* defined as ≥1000 mL blood loss during pregnancy, childbirth or puerperium between January 1st, 2011 and January 1st, 2013. For the present analyses, we selected women from the TeMpOH-1 cohort who met criteria for *primary postpartum haemorrhage*: any amount of blood loss exceeding 1000mL within the first 24 hours after childbirth. Women with no coagulation parameters measured during active postpartum haemorrhage and women with missing data on volumes and timing of clear fluids were excluded. In case transfusion of blood products occurred before onset of clear fluid administration, patients were also excluded. The Ethical Committee of Leiden University Medical Centre (P12.273) and the institutional review boards of all participating hospitals approved of the study. The study was registered in the Netherlands Trial Register (NTR4079). Details regarding study design have been reported elsewhere[11]. The need to obtain informed consent was waived by the ethics committee because of the retrospective design. Women 18 years of age and older who met the inclusion criteria were selected.

Data collection

To identify all consecutive women who had been transfused with the aforementioned amount of blood products because of postpartum haemorrhage in the participating hospitals, data from the hospitals' blood transfusion services were merged with data from birth registers of contributing hospitals. Qualified medical students and research nurses collected routine data from the medical records with regard to (obstetric) history and course of the current pregnancy, as well as data pertaining to characteristics of participating women, mode of birth, primary cause of haemorrhage, placentation, characteristics of shock (defined as systolic blood pressure < 90 mmHg or heartrate > 120 bpm), surgical and haemostatic interventions to stop bleeding and coagulation parameters. Results of all measurements of haemoglobin level (Hb, g/dl), haematocrit (Ht, fraction), platelet count (x10^9/litre), activated partial thromboplastin time (aPTT, seconds), prothrombin time (PT, seconds) and fibrinogen (g/L) levels from the first measurement of blood loss onwards were documented; this included parameters drawn from cases before they had bled a total volume of 1000mL. Outliers of levels of coagulation parameters were verified in the medical records. In addition, detailed information on crystalloid and colloid fluids administered during the course of postpartum haemorrhage was collected: total volume

and type of clear fluids given, as well as timing information with regard to onset and end of infusion. Information on timing and volume of repetitive blood loss measurements was also retrieved from the medical files. In most cases blood loss was measured by weighing soaked gauzes during and after birth and by use of a collector bag and suction system in the operating theatre.

Severe acute maternal morbidity and maternal mortality

The composite endpoint severe acute maternal morbidity and mortality comprised emergency peripartum hysterectomy, ligation of the uterine arteries, B-Lynch suture (in the Netherlands only used as emergency procedure), arterial embolization or admission into an intensive care unit.

Statistical analyses

The aim was to describe values of measured laboratory parameters according to increasing "volume of blood loss" and "volume of clear fluids administered" during the course of severe postpartum haemorrhage. In order to have an estimate of the "volume of blood loss" and of "volume of clear fluids administered" for all blood samples (and their respective laboratory results) we used linear interpolation of the actual measurement of "volume of blood loss" and "volume of clear fluids administered" before and after each blood sample. The volume of blood loss at the time of blood sampling was categorised in 8 groups: 0-1.0L, 1.0-1.5L, 1.5-2.0L, 2.0-2.5L, 2.5-3.0L, 3.0-3.5L, 3.5-4.0L and >4.0L. Coagulation parameters were allocated to the category representing the volume of blood loss at sampling. In case of multiple laboratory measurements per patient within one blood loss category, the mean of the values was used in the analyses, calculating a patient just once per category. Subsequently, within these blood loss categories, the volume of clear fluids administered at the time of blood sampling was calculated and classified into three fluid administration strategies: < 2.0L, 2.0-3.5L and > 3.5L. These three administration strategies were based on the RCOG green-top guideline, which recommends to administer up to 3.5 litres of warmed clear fluids, starting with 2 litres of warmed isotonic crystalloids if blood is not available[10] . Since blood sampling during postpartum haemorrhage was not performed at predefined time points and samples were obtained on request of the physician on call during postpartum haemorrhage, patients could have different frequencies and panels of coagulation parameters. Reference ranges of aPTT varied somewhat for the 61 participating hospitals as a result of use of different types of reagents. Therefore, an aPTT ratio was calculated by dividing the aPTT level of cases by the mean of the hospital specific reference range.

Results

Patient characteristics

A total of 1038 women with severe postpartum haemorrhage had at least one valid measurement of coagulation parameters sampled during active bleeding in addition to data on volume and timing of clear fluids administered *(Figure 1)*. Baseline characteristics are reported in *Table 1*. Women were on average 31 years of age, gave birth at a median gestational age of 39.7 weeks and 25% delivered by caesarean section. Uterine atony was the primary cause of bleeding in 66% of the cases and 34% of women developed a composite endpoint of severe acute maternal morbidity or mortality. The median total volume of blood loss among all 1038 women with postpartum haemorrhage was 3.0 L (interquartile range 2.5-4.0). In our cohort, women in the lowest fluid categories showed fewer signs of shock and were administered fewer blood products when compared to women in the other fluid categories for all coagulation parameters (*data presented in table adjacent to Figure 3*).

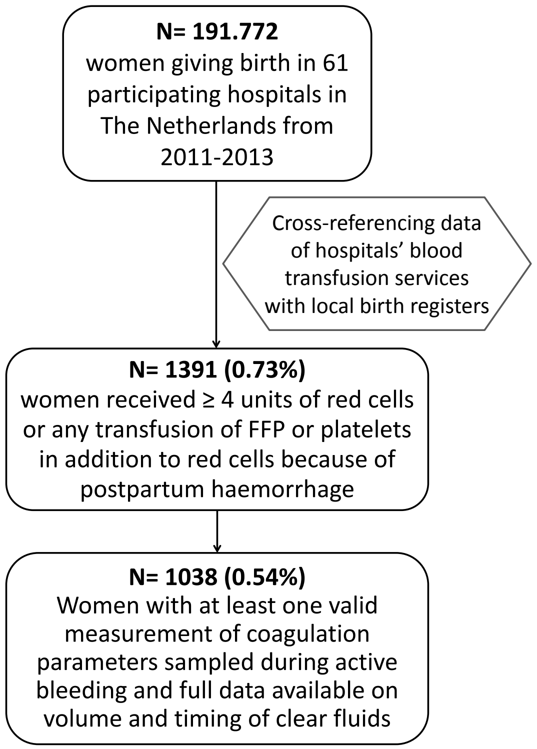

Figure 1. **Inclusion flowchart for 'fluid management and dilutional coagulopathy in severe postpartum haemorrhage: a nationwide retrospective cohort study'**

Table 1. **Clinical characteristics of the cohort of 1038 women with ongoing postpartum haemorrhage included in this analysis**

Patients	**n=1038**
Maternal characteristics	
Age (years)	31.0 (28.0-35.0) *
BMI (kg/m^2)	23.2 (21.0-26.3)
Ethnicity Caucasian	747 (72%)†
Nulliparity	534 (51%)
Gestational age	39.7 (38.1-40.7)
Mode of birth	
Caesarean section	254 (24%)
Vaginal	780 (75%)
Comorbidity	
Pre-eclampsia/ HELLP	104 (10%)
Anti-coagulant use	6 (0.6%)
Transfer to hospital	
No transfer (birth in hospital)	753 (73%)
Transfer to hospital during labour	157 (15%)
Postpartum transfer (birth at home)	128 (12%)
Primary cause of bleeding	
Uterine atony	684 (66%)
Retained placenta	168 (16%)
Pathological ingrowth of placenta	89 (9%)
Surgical bleeding and abruption/coagulopathy	97(9%)
Placentation	
Abnormal localisation placenta	65 (6%)
Pathological ingrowth placenta	97 (9%)
Composite endpoint severe maternal morbidity and mortality	**355 (34%)**
Embolisation	124 (12%)
Hysterectomy	57 (5%)
Emergency B-Lynch	27 (3%)
Ligation arteries	7 (0.7%)
ICU admission	295 (28%)
Maternal mortality	6 (0.6%)
Haemostatic interventions	
Fibrinogen administered	98 (9%)
Tranexamic acid administered	473 (46%)
Recombinant FVIIa administered	29(3%)

Continuing Table 1. Clinical characteristics of the cohort of 1038 women with ongoing postpartum haemorrhage included in this analysis

Patients	**n=1038**
Bleeding characteristics	
Bleeding rate (ml/min) ‡	2.4 (1.3-4.8)
Shock	927 (89%)
Total volume blood loss (L)	3.0 (2.5-4.0)
Total volume of clear fluids (L)	3.0 (2.0-4.0)
Total units of blood products (n)	6.0 (4.0-8.0)

* Values are presented as median with (interquartile range), † percentage, ‡ maximum

Volume expansion and volume of blood loss

Figure 2 presents volumes of blood loss and volumes of infused fluids. Among women who had one or more laboratory parameters measured during the first phases of postpartum haemorrhage (n=245 for 0 to 1L; n=306 for 1 to 1.5L; and n=351 for 1.5 to 2L) the mean volume of replacement therapy (clear fluids and blood products) administered was less or equal the total volume of blood loss. During the next phases of postpartum haemorrhage (blood loss between 2-2.5L) the mean volume of replacement therapy (clear fluids and blood products) was higher than the volume of blood loss. This "overload" enlarged with increasing blood loss volumes, reaching 32% more volume replacement compared to blood loss in the phase in which the women had lost 3.5-4L (5.3L infused /4 L lost). For all categories of blood loss, mean volume of clear fluids administered did not exceed and in most cases was similar to the maximum blood loss. With increasing blood loss, the proportion of blood products (versus clear fluids) administered showed a gradual increase, from 118/1178mL (10%) at 1000-1500mL blood loss to 1605/5279mL (30%) after blood loss up to 4000mL.

Laboratory parameters after different volumes of clear fluids in the course of postpartum haemorrhage

Figure 3 presents results of laboratory tests according to received volumes of clear fluids (0 to 2 L, 2 to 3.5 L or more than 3.5 L) during the first two litres of postpartum haemorrhage. From 1031 women a total of 2714 haemoglobin measurements were available. Administration of higher volumes of clear fluids was associated with lower haemoglobin and haematocrit levels and this was most pronounced in the earlier phases of postpartum haemorrhage (Figure 3 and supplemental table S1 and figure S2). For example, when the women had lost less than 1.0 L of blood, the median haemoglobin level was 10.1 g/dl (IQR 8.5-11.6) if they had received < 2.0 L of clear fluids, whereas after receiving 2.0 – 3.5 L clear fluids median haemoglobin was 8.4g/dl (IQR 6.4-9.7).

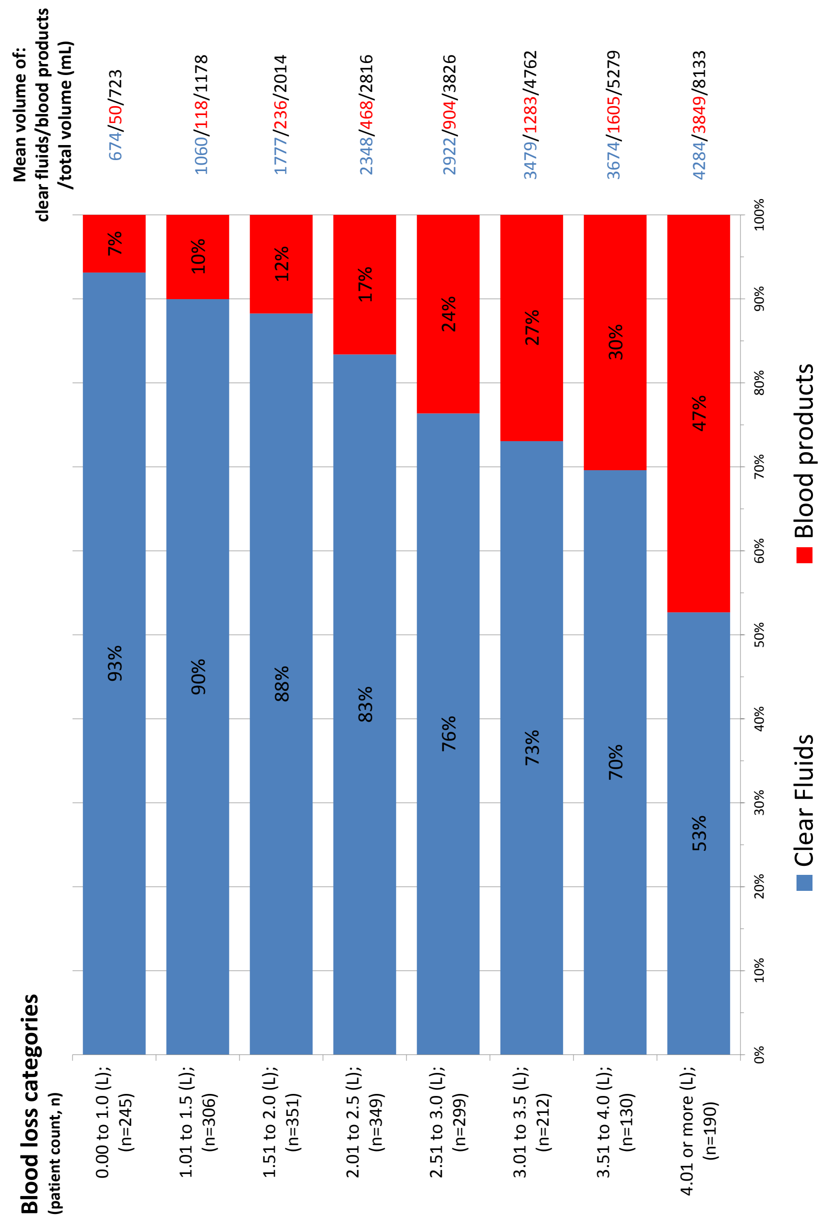

Figure 2. Volume of clear fluids and blood products administered per blood loss category.
For example: in the blood loss category 0.0 to 1.0 L 245 women had one or more laboratory parameter tested, and at the time of blood sampling for the laboratory parameters these women had received 674 ml clear fluids, 50 ml blood products, yielding a total volume administered of 723 mL.

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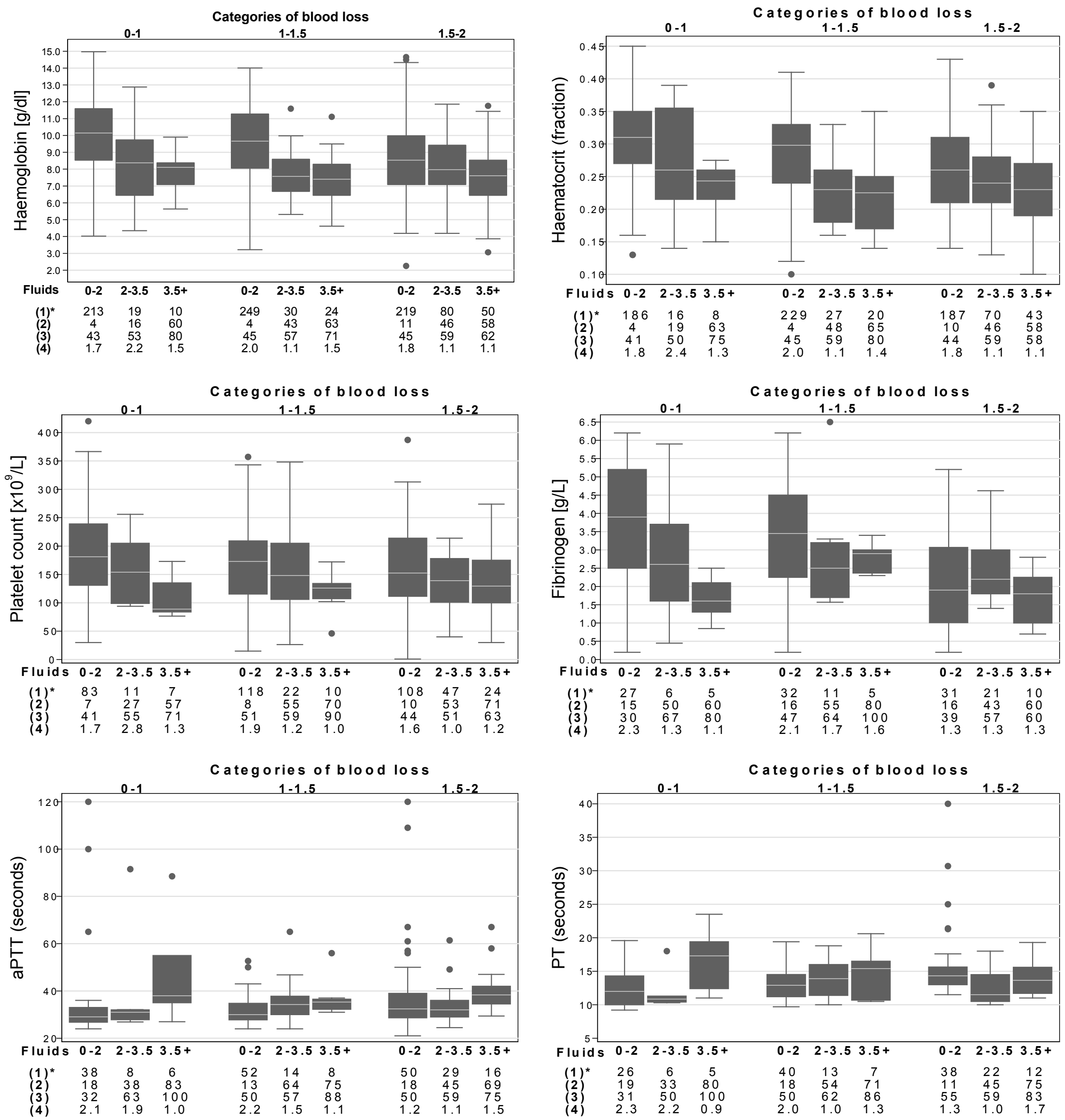

Figure 3. Coagulation parameters according to clear fluid administration (0-2L, 2L-3.5L, >3.5L) and increasing volume of blood loss (0-1.0, 1.0-1.5, 1.5-2.0 L).

Legend: Laboratory parameters are presented in box plots. Circles are outliers. The box represents the 25th and 75th percentiles and the whiskers are the upper and lower adjacent values.
*Statistics: (1) Patient count; (2) Percentage of women who received blood products; (3) Percentage of women who experienced shock surrounding blood sampling; (4) mean bleeding rate in ml/min surrounding blood sampling.

Platelet counts of 804 women decreased over the three increasing fluid administration categories. In samples drawn in the earliest phase of postpartum haemorrhage (0-1L blood loss), median platelet counts were 181 (IQR 131-239), 154 (IQR 99-205) and 89 x10^9/litre (IQR 84-135) in the three categories of increasing volumes of fluids administered. A similar pattern was observed in consecutive blood loss categories.

Fibrinogen measurements of 438 women were available for analyses. Administering higher volumes of clear fluids was associated with a decreasing level of fibrinogen in measurements in the early phases of postpartum haemorrhage (up to 2L of blood loss). The largest change was displayed for measurements performed in the earliest phase of postpartum haemorrhage (blood loss 0-1000mL): 3.9 g/L (IQR 2.5-5.2), 2.6 g/L (IQR 1.6-3.7), 1.6 g/L (IQR 1.3-2.1) over the three fluid management categories.

PT and aPTT were longer after administration of larger volumes of clear fluids. For both, the largest difference was observed between measurements in the most restrictive fluids category (<2L) and the most liberal category (>3.5L). In samples drawn between 0-1L blood loss, PT was 13 (IQR 11-15) and 17 seconds (IQR 12-19) and aPTT 29 (IQR 27-33) and 38 seconds (IQR 35-55) in lowest and highest fluid administration categories respectively. Levels of PT and aPTT of women administered 2-3.5L of fluids were similar to blood samples of women who were administered less than 2L of fluids. Results of the aPTT ratio showed similar results (S3).

Discussion

This nationwide retrospective multicentre cohort study describes coagulation parameters after administering different volumes of resuscitation fluids in 1038 women with ongoing severe postpartum haemorrhage. The administration of larger volumes of clear fluids was associated with deterioration of levels of haemoglobin, haematocrit, platelet count, fibrinogen, aPTT and PT which was most pronounced during the earlier phases of postpartum haemorrhage.

Strengths and limitations of our study

A strength of the study is that we included a large cohort of women who had suffered severe postpartum haemorrhage and who had been treated with different volume replacement strategies. Women in our study were categorised based on similar volumes of blood loss at time of blood sampling, thereby making them comparable on a clinical level during the course of haemorrhage. Volume replacement had been carefully documented in the medical files in all the participating hospitals ensuring correct classification of women according to the different replacement strategies. Both these strengths allow for reliable description of abnormalities in coagulation in relation to volume replacement therapy.

We stratified our findings according to volume of blood loss. Volume of blood loss was measured in most cases by weighing soaked gauzes during and after birth and by use of a collector bag and suction system in the operating theatre, in addition to visual estimation. Thus, there may be misclassification of volume of blood loss in both directions, over- and underestimation and it is therefore difficult to know whether and how our findings are affected by this misclassification. Our findings are also affected by the fact that inherently more blood samples are drawn from women with more severe bleeding. This may have led to overestimation of the number of women with abnormal laboratory test results. Because of the design of the study we did not have influence on the number and specific panels of coagulation samples requested. Therefore, our results show different selections of women in all blood loss categories that we present. Although it is tempting to infer that high volumes of clear fluids are causally related to the observed dilution our study does not allow such inference. There are many other factors that may have influenced coagulation parameters such as the primary cause of haemorrhage, bleeding and treatment characteristics and the presence of comorbidities. This descriptive study does not allow for disentanglement of the separate effects of these joint risk factors. We excluded 353 women because they had no valid lab measurement available during active bleeding or data were missing on volume or timing of clear fluids administered. To be certain their exclusion did not induce a systemic error to our data resulting from selection bias, we compared these women on the most relevant table 1 items: mode of birth, nulliparity, primary cause of haemorrhage, the composite endpoint of severe maternal morbidity and mortality, bleeding rate at sampling, presence of shock and total volume of blood loss. No differences were observed compared to the women that were included in the study, ruling out the presence of a systemic error influencing the results.

Comparison with other studies

To the best of our knowledge no previous studies have described the association between different fluid management strategies and coagulation parameters during the various phases of severe postpartum haemorrhage. Yet, our findings corroborate results of previous studies into the effect of dilution on coagulation parameters. An in vitro study evaluating the effect of haemodilution on coagulation factors found that PT and aPTT were significantly prolonged after 60% and 80% dilution[12]. Another in vitro study investigated the effect of haemodilution on the course of global coagulation tests and clotting factors. Levels of dilution-dependent coagulation factors and aPTT were found to decrease in an almost linear manner. Critically low activities for coagulation factors and a critically low level of fibrinogen were measured at dilutions of between 60% and 75%[13]. An in vivo study reported coagulation parameters in hypotensive patients with penetrating torso injuries who were treated with immediate versus delayed fluid resuscitation. Patients in the immediate fluid administration group showed worse levels of haemoglobin, platelet count, PT and APTT compared to patients in the delayed fluid administration group[14]. No previous studies were found that examined the change in coagulation parameters as a result of different fluid management strategies in women experiencing postpartum haemorrhage.

Clinical implications

In our cohort of women experiencing postpartum haemorrhage, we displayed changes occurring on coagulation parameter level after administering different volumes of fluids. Administration of larger volumes of clear fluids was associated with more severe worsening of levels of haemoglobin, haematocrit, platelet count, fibrinogen, aPTT and PT which was most pronounced during the earlier phases of postpartum haemorrhage. Our findings provide quantitative evidence to reinforce expert opinion-based guidelines recommending restrictive fluid resuscitation strategies in case of postpartum haemorrhage;

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Conclusions

In this nationwide retrospective cohort study in 1038 women on the change in coagulation parameters with increasing volumes administered during the course of postpartum haemorrhage necessitating blood transfusion, the administration of large volumes of clear fluids was associated with changes in coagulation parameters corresponding to dilutional coagulopathy. Our findings provide thus far the best available evidence to support expert opinion-based guidelines recommending restrictive fluid resuscitation in women experiencing postpartum haemorrhage.

References

1. Say L, Chou D, Gemmill A, Tuncalp O, Moller AB, Daniels J, Gulmezoglu AM, Temmerman M, Alkema L: Global causes of maternal death: a WHO systematic analysis. The Lancet Global health 2014, 2(6):e323-333.
2. Collis RE, Collins PW: Haemostatic management of obstetric haemorrhage. Anaesthesia 2015, 70 Suppl 1:78-86, e27-78.
3. Ruth D, Kennedy BB: Acute volume resuscitation following obstetric hemorrhage. The Journal of perinatal & neonatal nursing 2011, 25(3):253-260.
4. Bonnet MP, Basso O: Prohemostatic interventions in obstetric hemorrhage. Seminars in thrombosis and hemostasis 2012, 38(3):259-264.
5. Schorn MN, Phillippi JC: Volume replacement following severe postpartum hemorrhage. Journal of midwifery & women's health 2014, 59(3):336-343.
6. Cotton BA, Guy JS, Morris JA, Jr., Abumrad NN: The cellular, metabolic, and systemic consequences of aggressive fluid resuscitation strategies. Shock (Augusta, Ga) 2006, 26(2):115-121.
7. Fenger-Eriksen C: Acquired fibrinogen deficiency caused by artificial colloid plasma expanders. Wiener klinische Wochenschrift 2010, 122 Suppl 5:S21-22.
8. Fenger-Eriksen C, Moore GW, Rangarajan S, Ingerslev J, Sorensen B: Fibrinogen estimates are influenced by methods of measurement and hemodilution with colloid plasma expanders. Transfusion 2010, 50(12):2571-2576.
9. Chang R, Holcomb JB: Optimal Fluid Therapy for Traumatic Hemorrhagic Shock. Critical care clinics 2017, 33(1):15-36.
10. Mavrides E AS, Chandraharan E, Collins P, Green L, Hunt BJ, Riris S, Thomson AJ on behalf of the Royal College of Obstetricians and Gynaecologists.: Prevention and Management of Postpartum Haemorrhage: Green-top Guideline No. 52. BJOG : an international journal of obstetrics and gynaecology 2017, 124(5):e106-e149.
11. Gillissen A, Henriquez D, van den Akker T, Caram-Deelder C, Wind M, Zwart JJ, van Roosmalen J, Eikenboom J, Bloemenkamp KWM, van der Bom JG: The effect of tranexamic acid on blood loss and maternal outcome in the treatment of persistent postpartum hemorrhage: A nationwide retrospective cohort study. PloS one 2017, 12(11):e0187555.
12. Darlington DN, Delgado AV, Kheirabadi BS, Fedyk CG, Scherer MR, Pusateri AE, Wade CE, Cap AP, Holcomb JB, Dubick MA: Effect of hemodilution on coagulation and recombinant factor VIIa efficacy in human blood in vitro. The Journal of trauma 2011, 71(5):1152-1163.
13. Weiss G, Lison S, Spannagl M, Heindl B: Expressiveness of global coagulation parameters in dilutional coagulopathy. British journal of anaesthesia 2010, 105(4):429-436.
14. Bickell WH, Wall MJ, Jr., Pepe PE, Martin RR, Ginger VF, Allen MK, Mattox KL: Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. The New England journal of medicine 1994, 331(17):1105-1109.

Supplemental material

S1 Patient count, mean, sd, median and IQR for coagulation parameters in addition to Figure 3

S2 Coagulation parameters according to clear fluid administration (0-2L, 2L-3.5L, >3.5L) and increasing volume of blood loss (0-1.0, 1.0-1.5, 1.5-2.0 L, 2.0-2.5L, 2.5-3.0L, 3.0-3.5L, 3.5-4.0L and >4L).

S3 aPTT ratio according to clear fluid administration (0-2000mL, 2000mL-3500mL, >3500mL) and increasing blood loss (0-1.0, 1.0-1.5, 1.5-2.0, 2.0-2.5 l)

S1 Patient count, mean, sd, median and IQR for coagulation parameters in addition to Figure 3

	Fluids category																	
	0-2(L)						2-3.5(L)						3.5+(L)					
Blood loss	n	mean	sd	p50	p25	p75	n	mean	sd	p50	p25	p75	n	mean	sd	p50	p25	p75
Hemoglobin																		
0.00 to 1.0 (L)	213	10.1	2.1	10.1	8.5	11.6	19	8.4	2.3	8.4	6.4	9.7	10	7.9	1.1	8.1	7.1	8.4
1.01 to 1.5 (L)	249	9.6	2.1	9.7	8.1	11.3	30	7.6	1.5	7.6	6.7	8.6	24	7.4	1.6	7.4	6.4	8.3
1.51 to 2.0 (L)	219	8.7	2.2	8.5	7.1	10.0	80	8.0	1.7	8.0	7.1	9.4	50	7.5	1.8	7.6	6.4	8.5
2.01 to 2.5 (L)	158	7.9	1.9	7.8	6.6	9.2	102	7.7	1.8	7.7	6.4	8.9	86	7.5	1.7	7.5	6.6	8.4
2.51 to 3.0 (L)	76	7.7	1.6	7.8	6.4	8.7	105	7.6	1.7	7.6	6.4	8.7	107	7.7	1.7	7.9	6.4	8.9
3.01 to 3.5 (L)	37	8.0	1.7	8.1	6.8	8.7	69	8.1	1.9	8.1	6.9	9.3	102	8.0	1.7	8.1	6.8	9.0
3.51 to 4.0 (L)	23	8.7	2.0	9.3	7.4	9.8	42	8.2	1.6	8.5	7.1	9.4	65	8.0	1.7	8.2	7.1	9.0
4.01 or more (L)	27	9.1	2.0	8.7	7.7	10.5	50	8.2	1.5	8.1	7.2	8.9	110	8.4	1.7	8.3	7.2	9.5
Total	1002	9.0	2.2	8.9	7.4	10.6	497	7.9	1.7	7.9	6.8	9.0	554	7.9	1.7	7.9	6.8	8.9
Hematocrit																		
0.00 to 1.0 (L)	186	0.31	0.06	0.31	0.27	0.35	16	0.27	0.08	0.26	0.21	0.36	8	0.23	0.04	0.24	0.21	0.26
1.01 to 1.5 (L)	229	0.29	0.06	0.30	0.24	0.33	27	0.23	0.05	0.23	0.18	0.26	20	0.22	0.06	0.23	0.17	0.25
1.51 to 2.0 (L)	187	0.26	0.06	0.26	0.21	0.31	70	0.24	0.05	0.24	0.21	0.28	43	0.23	0.05	0.23	0.19	0.27
2.01 to 2.5 (L)	132	0.24	0.06	0.24	0.20	0.28	82	0.24	0.05	0.24	0.20	0.27	73	0.23	0.05	0.23	0.20	0.26
2.51 to 3.0 (L)	62	0.24	0.05	0.23	0.20	0.26	90	0.23	0.05	0.22	0.19	0.26	98	0.23	0.05	0.23	0.19	0.27
3.01 to 3.5 (L)	33	0.24	0.05	0.24	0.21	0.26	56	0.25	0.05	0.25	0.21	0.28	84	0.24	0.05	0.24	0.21	0.27
3.51 to 4.0 (L)	21	0.27	0.06	0.28	0.25	0.30	38	0.24	0.05	0.23	0.20	0.27	53	0.23	0.05	0.24	0.20	0.26
4.01 or more (L)	25	0.28	0.07	0.26	0.22	0.34	42	0.24	0.04	0.24	0.20	0.26	101	0.25	0.05	0.25	0.21	0.28
Total	875	0.27	0.06	0.27	0.22	0.32	421	0.24	0.05	0.24	0.20	0.27	480	0.24	0.05	0.24	0.20	0.27

Continuing S1 Patient count, mean, sd, median and IQR for coagulation parameters in addition to Figure 3

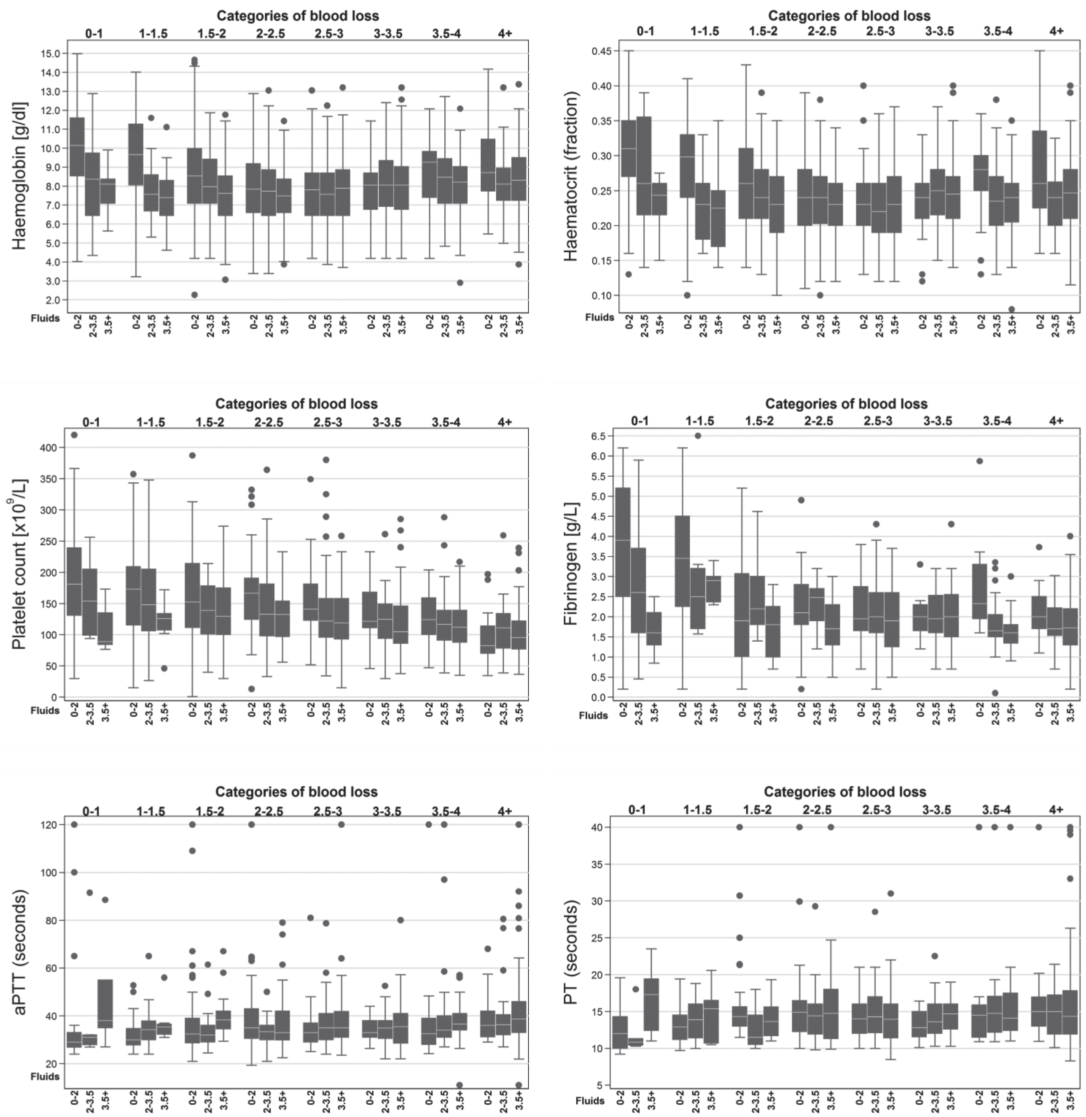
	Fluids category																	
	0-2(L)						2-3.5(L)						3.5+(L)					
Blood loss	n	mean	sd	p50	p25	p75	n	mean	sd	p50	p25	p75	n	mean	sd	p50	p25	p75
Platelet count																		
0.00 to 1.0 (L)	83	184	80	181	131	239	11	163	59	154	99	205	7	111	37	89	84	135
1.01 to 1.5 (L)	118	167	72	173	116	209	22	159	74	148	106	205	10	123	36	126	107	134
1.51 to 2.0 (L)	108	164	72	153	112	214	47	137	48	139	101	178	24	136	56	130	100	175
2.01 to 2.5 (L)	84	164	58	167	125	190	60	147	68	133	98	181	50	130	42	133	97	154
2.51 to 3.0 (L)	59	151	55	141	123	181	75	133	61	122	96	158	73	125	47	119	93	158
3.01 to 3.5 (L)	20	137	41	122	111	168	47	124	43	125	94	149	67	120	52	105	86	146
3.51 to 4.0 (L)	17	131	47	124	100	159	34	119	50	117	91	139	46	114	39	112	88	139
4.01 or more (L)	22	94	41	83	70	114	47	108	40	111	79	134	100	103	39	96	77	122
Total	511	161	69	159	112	203	343	132	57	124	94	160	377	118	46	110	88	145
Fibrinogen																		
0.00 to 1.0 (L)	27	3.5	1.8	3.9	2.5	5.2	6	2.8	1.9	2.6	1.6	3.7	5	1.7	0.6	1.6	1.3	2.1
1.01 to 1.5 (L)	32	3.4	1.4	3.5	2.3	4.5	11	2.7	1.4	2.5	1.7	3.2	5	2.8	0.5	2.9	2.4	3.0
1.51 to 2.0 (L)	31	2.2	1.4	1.9	1.0	3.1	21	2.5	0.9	2.2	1.8	3.0	10	1.7	0.7	1.8	1.0	2.3
2.01 to 2.5 (L)	35	2.2	0.9	2.1	1.8	2.8	25	2.3	0.6	2.5	1.9	2.7	22	1.8	0.6	1.7	1.3	2.3
2.51 to 3.0 (L)	24	2.2	0.8	1.9	1.7	2.8	39	2.1	0.8	2.0	1.6	2.6	40	2.0	0.9	1.9	1.3	2.6
3.01 to 3.5 (L)	8	2.1	0.6	2.0	1.7	2.3	23	2.0	0.7	2.0	1.6	2.5	40	2.1	0.7	2.0	1.5	2.6
3.51 to 4.0 (L)	11	2.7	1.2	2.3	2.0	3.3	20	1.8	0.8	1.7	1.5	2.0	25	1.6	0.5	1.6	1.3	1.8
4.01 or more (L)	18	2.1	0.7	2.0	1.7	2.5	31	1.8	0.5	1.7	1.5	2.2	62	1.8	0.7	1.7	1.3	2.2
Total	186	2.6	1.4	2.2	1.7	3.4	176	2.1	0.9	2.0	1.6	2.6	209	1.9	0.7	1.8	1.3	2.3

Continuing S1 Patient count, mean, sd, median and IQR for coagulation parameters in addition to Figure 3

	Fluids category																	
	0-2(L)						2-3.5(L)						3.5+(L)					
Blood loss	n	mean	sd	p50	p25	p75	n	mean	sd	p50	p25	p75	n	mean	sd	p50	p25	p75
PT																		
0.00 to 1.0 (L)	26	13	3	12	10	14	6	12	3	11	10	11	5	17	5	17	12	19
1.01 to 1.5 (L)	40	13	2	13	11	15	13	14	3	14	11	16	7	15	4	15	11	17
1.51 to 2.0 (L)	38	16	6	14	13	16	22	13	2	12	11	14	12	14	3	14	12	16
2.01 to 2.5 (L)	44	15	5	15	12	16	29	15	4	14	12	16	26	16	6	15	11	18
2.51 to 3.0 (L)	38	14	3	14	12	16	57	15	3	14	12	17	40	15	4	14	11	16
3.01 to 3.5 (L)	12	13	2	13	12	15	29	14	3	14	12	16	44	14	2	15	13	16
3.51 to 4.0 (L)	15	16	7	15	12	16	24	16	6	15	12	17	29	15	5	14	12	18
4.01 or more (L)	17	17	6	15	13	17	35	15	3	15	12	17	74	16	7	14	12	18
Total	230	15	5	14	12	16	215	14	4	14	12	17	237	15	5	14	12	17
APTT																		
0.00 to 1.0 (L)	38	34	19	29	27	33	8	38	22	31	28	32	6	47	22	38	35	55
1.01 to 1.5 (L)	52	32	6	30	28	35	14	36	10	34	30	38	8	37	8	35	32	37
1.51 to 2.0 (L)	50	38	19	32	29	39	29	34	8	32	29	36	16	40	10	38	35	42
2.01 to 2.5 (L)	51	39	16	35	31	43	36	33	6	33	30	36	35	38	13	33	30	42
2.51 to 3.0 (L)	43	35	9	33	29	37	59	37	10	35	30	41	59	38	14	35	31	42
3.01 to 3.5 (L)	13	34	5	33	31	38	36	35	7	35	31	38	57	37	10	36	29	41
3.51 to 4.0 (L)	14	40	24	33	28	39	27	41	21	34	31	40	34	38	9	37	34	41
4.01 or more (L)	19	39	10	36	31	42	40	39	11	36	32	41	81	44	22	39	33	46
Total	280	36	15	32	29	37	249	36	11	34	30	39	296	40	16	36	31	43

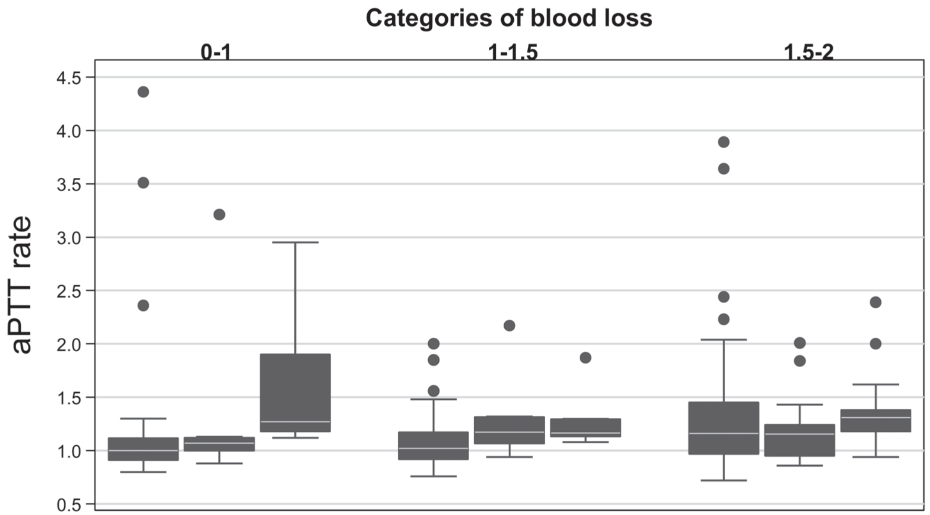
Continuing **S1 Patient count, mean, sd, median and IQR for coagulation parameters in addition to Figure 3**

Blood loss	Fluids category 0-2(L) n	mean	sd	p50	p25	p75	2-3.5(L) n	mean	sd	p50	p25	p75	3.5+(L) n	mean	sd	p50	p25	p75
APTT rate																		
0.00 to 1.0 (L)	36	1.21	0.73	1.00	0.91	1.12	8	1.31	0.77	1.07	1.00	1.12	5	1.68	0.77	1.27	1.18	1.90
1.01 to 1.5 (L)	46	1.09	0.26	1.02	0.92	1.17	12	1.24	0.32	1.17	1.06	1.31	8	1.27	0.26	1.16	1.13	1.29
1.51 to 2.0 (L)	43	1.35	0.67	1.16	0.97	1.45	24	1.17	0.28	1.15	0.95	1.24	15	1.38	0.38	1.31	1.18	1.38
2.01 to 2.5 (L)	41	1.39	0.54	1.21	1.07	1.49	31	1.13	0.22	1.14	0.96	1.28	33	1.34	0.45	1.21	1.04	1.43
2.51 to 3.0 (L)	36	1.21	0.35	1.16	1.01	1.31	55	1.28	0.36	1.20	1.04	1.36	55	1.30	0.48	1.19	1.03	1.45
3.01 to 3.5 (L)	12	1.21	0.27	1.13	1.02	1.40	33	1.20	0.20	1.23	1.07	1.37	54	1.24	0.35	1.21	0.98	1.40
3.51 to 4.0 (L)	13	1.17	0.35	1.05	0.93	1.42	22	1.31	0.53	1.20	1.04	1.37	31	1.31	0.32	1.27	1.17	1.48
4.01 or more (L)	17	1.34	0.36	1.24	1.13	1.41	38	1.35	0.38	1.29	1.13	1.44	73	1.50	0.73	1.31	1.16	1.53
Total	244	1.25	0.51	1.10	0.95	1.33	223	1.25	0.36	1.18	1.04	1.35	274	1.36	0.52	1.25	1.06	1.46



S2 Coagulation parameters according to clear fluid administration (0-2L, 2L-3.5L, >3.5L) and increasing volume of blood loss (0-1.0, 1.0-1.5, 1.5-2.0 L, 2.0-2.5L, 2.5-3.0L, 3.0-3.5L, 3.5-4.0L and >4L).

Laboratory parameters are presented in box plots. Circles are outliers. The box represents the 25th and 75th percentiles and the whiskers are the upper and lower adjacent values.



Fluids	0-2	2-3.5	3.5+	0-2	2-3.5	3.5+	0-2	2-3.5	3.5+
(1)*	36	8	5	46	12	8	43	24	15
(2)	17	38	80	15	75	75	16	42	67
(3)	31	63	100	50	58	88	49	58	80
(4)	2.2	1.9	1.1	2.1	0.9	1.1	1.2	1.0	1.4

S3 aPTT ratio according to clear fluid administration (0-2000mL, 2000mL-3500mL, >3500mL) and increasing blood loss (0-1.0, 1.0-1.5, 1.5-2.0, 2.0-2.5l)

*Statistics: (1) Patient count; (2) Percentage of women who received blood products; (3) Percentage of women who experienced shock surrounding blood sampling; (4) mean bleeding rate in ml/min surrounding blood sampling.