Towards better prognostic and diagnostic strategies for major obstetric haemorrhage

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Towards better prognostic and diagnostic strategies for major obstetric haemorrhage

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Ada Gillissen

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1 GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

Introduction

Postpartum haemorrhage, in this thesis defined as blood loss above 1000mL within the first 24 hours after birth, remains a major cause of maternal morbidity and mortality with an incidence that seems to be increasing over the last decade[1-8]. Although risk factors are in many occasions known to be present during pregnancy and birth, postpartum haemorrhage frequently occurs unexpectedly[9-11]. Also, women with known risk factors for postpartum haemorrhage often do not bleed excessively following childbirth. It has therefore proven difficult to predict postpartum haemorrhage based on clinical peripartum risk factors[9,12,13]. Since postpartum haemorrhage remains an event with potentially serious consequences, developing a reliable screening tool for identification of women at increased risk is of utmost importance. Thus far, the best results for prior assessment of bleeding risk come from structured approaches to history taking by means of bleeding assessment tools (BATs) resulting in a bleeding score, originally developed to determine the likelihood of the presence of a bleeding disorder (von Willebrand disease)[14-16]. These bleeding assessment tools might also be useful to identify women with a high risk to bleed excessively *prior* to childbirth[17].

Another moment potentially providing relevant information with respect to prediction and personalized prevention of a severe maternal outcome is the first phase of postpartum haemorrhage. Are we at that time able to identify changes in coagulation parameters that are predictive for severe maternal outcome? Some have suggested that low fibrinogen concentration might be the earliest predictor of progression towards severe postpartum haemorrhage[18,19,20]. In order to determine the optimal strategy to monitor coagulopathy during birth, it is crucial to know patterns of changes in coagulation parameters in relation to the phases of postpartum haemorrhage and identify which parameters show the earliest changes associated with risk of severe maternal outcomes. High volumes of clear fluids may also have detrimental effects on coagulation parameters. International guidelines on management of postpartum haemorrhage elucidate the lack of quantitative evidence on the effect of different fluid management strategies on parameters of coagulopathy. To enable evidence-based recommendations on fluid management strategies in women with severe postpartum haemorrhage, more insight is needed on the changes of coagulation parameters after the administration of different volumes of fluids[21].

By close monitoring of haemostasis, abnormalities in coagulation parameters may be detected soon after their onset. This could contribute to more personalized haemostatic therapy for women experiencing postpartum haemorrhage, potentially leading to better maternal outcomes[22]. Due to long turn-around times of traditional coagulation parameters like Clauss fibrinogen, their clinical applicability in presence of rapid bleeding is limited. A rapid alternative is provided by point-of-care devices using a visco-elastometric

method for haemostasis testing, like ROTEM® thromboelastometry. Selection of the right target population is very important when evaluating the therapeutic value of an applied intervention. A Clauss fibrinogen concentration of ≤2 g/L is often used as an indication for targeted haemostatic treatment[18,23]. When using thromboelastometry, a qualitative assessment of fibrinogen status is provided by the ROTEM® FIBTEM assay. The optimal ROTEM® FIBTEM A5 value corresponding to the cut-off point of a Clauss fibrinogen level of ≤2 g/L has yet to be identified. Recently, the ROTEM® Sigma, a fully automated successor of the ROTEM® Delta device, was launched onto the market. The fact that this device lacks the pipetting procedure of its predecessor, makes it attractive as a point-of-care device to be used at a patient's bedside. Since treatment flowcharts often use exact ROTEM® assay cut-off points, critical evaluation should be performed into the values provided by both the old and the new device to define potential consequences for daily clinical practice.

As part of the management of postpartum haemorrhage, haemostatic agents may be administered to support coagulation and correct for acquired coagulopathy[21,24]. One of these agents is tranexamic acid, an antifibrinolytic agent[25]. In the WOMAN trial, administration of tranexamic acid in an early stage of postpartum haemorrhage was compared to placebo, showing a reduction of maternal mortality due to bleeding from 1.9% to 1.5%[26]. However, since maternal mortality has become a rare event in high-resource countries, it needs to be elucidated whether administration of tranexamic acid early during postpartum haemorrhage also has a positive effect on clinical outcome or amount of blood loss in a high-resource setting.

Aims and objectives

The main aim of the research described in this thesis was to improve prognostic and diagnostic strategies for major obstetric haemorrhage, which may subsequently lead to a reduction of severe maternal morbidity, mortality and need for surgical interventions.

In pursuit of this aim, the following objectives were stated:

1. To examine the predictive value of a bleeding assessment tool for postpartum haemorrhage.
2. To describe the change in coagulation parameters and the influence of fluid management on coagulopathy during the course of postpartum haemorrhage and to examine the predictive value of early changes of coagulation parameters for a severe maternal outcome.
3. To assess correlations between results obtained by thromboelastometry and traditional coagulation parameters in women experiencing postpartum haemorrhage and define cut-off points for detecting women in need of a haemostatic intervention.

In order to answer our research questions, two large multicentre cohort studies were performed. The Transfusion strategies in women during Major Obstetric Haemorrhage-1 (TeMpoH-1) study was a nationwide retrospective cohort study in 61 hospitals in the Netherlands assessing 191.772 births between 2011 and 2013. The TeMpOH-2 (Towards better Prognostic and Diagnostic strategies for Major Obstetric Haemorrhage) study, was a prospective cohort study in three hospitals in the Netherlands between February 2015 and April 2018 assessing 17.203 births. A total of 1982 women experiencing (severe) postpartum haemorrhage were included in both studies. A part of the results of the TeMpOH-1 & 2 studies are described in this thesis.

Outline of this thesis

The first part of this thesis focusses on prediction of postpartum haemorrhage. **Chapter 2** contains results of a prospective evaluation of the predictive value of the TeMpOH-2 self-BAT derived from the condensed MCMDM-1VWD BAT for postpartum haemorrhage. To enable prediction of severe maternal outcome based on early changes in coagulation parameters, changes occurring during postpartum haemorrhage were explored. **Chapter 3** describes coagulation parameters during the course of severe postpartum haemorrhage and compares coagulation parameters during early postpartum haemorrhage between women with and without adverse maternal outcome. The second part of this thesis focusses on improvement of diagnostic strategies for postpartum haemorrhage. **Chapter 4** provides insight in real-world changes in levels of coagulation parameters after administration of different volumes of clear fluids to women suffering from major postpartum haemorrhage. In **Chapter 5** a comparison of thromboelastometry by the ROTEM® Delta versus the Sigma device is described. **Chapter 6** contains the results of a comparison between results of thromboelastometry and traditional coagulation parameters, including Clauss fibrinogen. The optimal cut-off point for ROTEM® FIBTEM A5 is defined to detect women with a Clauss fibrinogen concentration ≤ 2g/L. Finally, in **Chapter 7** the association between tranexamic acid administration at an early stage in the course of persistent postpartum haemorrhage and severe acute maternal morbidity and blood loss in a high-resource setting is quantified.

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2 PREDICTIVE VALUE OF A BLEEDING SCORE FOR POSTPARTUM HAEMORRHAGE

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Abstract

Background: A reliable screening tool that could contribute to the identification of women with an increased risk of postpartum haemorrhage would be of great clinical significance.

Objectives: The aim of this study was to examine the added predictive value of a bleeding assessment tool for postpartum haemorrhage exceeding 1000mL.

Patients/Methods: Prospective two-centre cohort study among 1147 pregnant women visiting the outpatient clinic or the maternity ward who completed a bleeding assessment tool prior to birth. The condensed MCMDM-1VWD bleeding assessment tool was adjusted to a questionnaire that could be used as a self-assessment bleeding tool. A score of ≥ 4 was considered to be abnormal.

Results: In the 1147 pregnant women in our cohort, bleeding scores ranged from -3 to 13, with a median of 1 (IQR -1 to 3); 197 (17%) women developed postpartum haemorrhage. Among women with a history of postpartum haemorrhage 29 percent developed postpartum haemorrhage. Among 147 women with an abnormal bleeding score (≥ 4), 27 (18%) developed postpartum haemorrhage, whereas the remaining 170 cases of postpartum haemorrhage had a normal bleeding score. Despite the high incidence of postpartum haemorrhage, the ability of the bleeding score to predict postpartum haemorrhage was poor: area under Receiver Operating Curve 0.53 (95% CI 0.49 to 0.58) for PPH ≥ 1000mL.

Conclusions: A history of significant postpartum haemorrhage was associated with an increased risk of subsequent postpartum haemorrhage. However, screening with a bleeding assessment tool did not help to discriminate women who will develop postpartum haemorrhage from women who will not.

Introduction

Postpartum haemorrhage continues to be a leading cause of maternal health problems worldwide[1-4]. Although risk factors are often known to be present during pregnancy and birth, postpartum haemorrhage frequently occurs unexpectedly[5-7]. Also, women with known risk factors for postpartum haemorrhage frequently do not bleed excessively following childbirth. It has therefore proven difficult to develop a reliable prediction model for postpartum haemorrhage based on clinical peripartum risk factors[5,8,9].

In general clinical practice, assessment of bleeding risk is performed by assessing clinical history, performing a physical examination and sometimes the use of screening coagulation tests[10,11]. However, coagulation testing to predict bleeding risk prior to invasive procedures was found to be not useful due to limited sensitivity and specificity of the tests and low prevalence of bleeding disorders[12,13]. The best results for prior assessment of bleeding risk come from more structured approaches to history taking by means of bleeding assessment tools (BATs), originally developed to determine the likelihood of the presence of a bleeding disorder (von Willebrand disease)[14-16]. In adults with von Willebrand disease, bleeding assessment tools have shown to be able to predict future bleeding events[17]. Another very useful application of bleeding assessment tools would be the ability contribute to the identification of subjects who are more likely to bleed excessively prior to their exposure to invasive procedures, surgery and also childbirth[18]. The main causes for postpartum haemorrhage are known to be obstetrical, but undiagnosed bleeding disorders can increase the risk of postpartum haemorrhage about threefold[7,19]. Since postpartum haemorrhage remains an event that could have serious consequences including severe acute maternal morbidity and mortality, it would be of great significance to have a reliable screening tool that could contribute to the identification of women with an increased risk of excessive blood loss prior to childbirth.

The aim of this study was to examine the added predictive value of the TeMpOH-2 self-BAT derived from the condensed MCMDM-1VWD (Molecular and Clinical Markers for the Diagnosis and Management of Type 1 von Willebrand disease) BAT in the prediction of postpartum haemorrhage.

Methods

Design and study population

We studied women who had been included in the TeMpOH-2 (Towards better Prognostic and Diagnostic strategies for Major Obstetric Haemorrhage) study, a prospective cohort of pregnant women in the Netherlands between February 2015 and April 2018. The women were recruited during their pregnancy at the outpatient clinics and maternity wards from two of the three participating hospitals, the Leiden University Medical Centre, in Leiden and the Isala Clinics in Zwolle. Included women were monitored for the occurrence of postpartum haemorrhage and followed until discharge from hospital after childbirth. At inclusion women were asked to complete a questionnaire containing a bleeding assessment tool. Answers to the questions of the bleeding assessment tool pertained to a woman's pre-pregnancy condition. Postpartum haemorrhage was defined as any blood loss ≥1000 mL blood loss within 24 hours after childbirth. Blood loss ≥2000 mL was a secondary end point. To include as many women as possible, study information was provided by a trained nurse at a set third trimester consultation that was scheduled for all pregnant women visiting the outpatient clinic. Study information was also handed out to women during regular visits to the outpatient clinic. Moreover, women scheduled for caesarean section, were provided with study information on a second occasion during hospitalization prior to surgery, and women admitted to the maternity ward overnight were visited by a research nurse in the morning and asked to participate in the study. For the present analysis we selected women from the TeMpOH-2 cohort for whom a completed bleeding assessment tool providing us with a valid bleeding score and data on volume of blood loss following childbirth were available. Women below 18 years of age or a gestational age below 24 weeks at the time of birth were excluded. Known coagulation disorders or anticoagulant use were not exclusion criteria. Approval for the study was obtained by the Ethical Committee of the Leiden University Medical Centre (P13.246) and of the committee of the Isala Clinics. The study was registered at ClinicalTrials.gov (NCT02149472). Written informed consent was obtained from all participants. Bleeding assessment tools were completed by all women during pregnancy (always prior to childbirth) because of the possibility of recall bias when completing the bleeding assessment tool after birth.

Bleeding assessment tool

We adjusted the condensed MCMDM-1VWD bleeding assessment tool to a written questionnaire that could be used as a self-assessment bleeding score. Medical terminology was converted into lay language and detail was added to items that needed extra explanation or examples that would otherwise be given by an expert (S1). The agreement between patient self-assessment and expert assessment of the bleeding symptoms was evaluated and found to be excellent: eight women participating in the study completed

the TeMpOH-2 study self-BAT (without assistance) followed by the condensed MCMDM-1VWD (administered by an expert). In both questionnaires, the same scoring key is applied. Scores were equal in seven of the eight participants, and a difference of +1 was found in one woman.

Calculation of bleeding score

The questionnaire (derived from the condensed MCDM-1VWD BAT) comprised twelve areas of bleeding: epistaxis, cutaneous, bleeding from minor wounds, oral cavity, gastrointestinal bleeding, tooth extraction, surgery, menorrhagia, postpartum haemorrhage, muscle hematoma, hemarthrosis, central nervous system bleeding. The condensed MCDM-1VWD BAT as assessed in a primary care setting yielded a mean bleeding score in 100 healthy individuals of 0.16 with a range of normal bleeding scores from -3.2 to + 3.6[15]. Accordingly, we considered a score of ≥ 4 as abnormal.

Data collection

Participants completed the bleeding assessment tool either via a paper-based or web-based questionnaire. Results of the paper-based questionnaire were scanned and evaluated by TeleForm®. TeleForm is a software application that enables the creation of forms for data collection and reads the returned data by use of a scanner. After processing and verifying of the data by a trained operator, data were exported from TeleForm into a SPSS database for further analyses. The web-based questionnaire was created in NetQ, an online questionnaire tool. Data were automatically exported to SPSS and then verified. Bleeding scores were calculated for all participants from the data derived from the bleeding assessment tool. Additional information was collected by well-trained research nurses who performed comprehensive chart reviews. Data were recorded from medical files available at the maternity ward for the following parameters: maternal age at the time of birth, parity, gestational age, mode of birth, presence of pre-eclampsia or HELLP syndrome, presence of a coagulation disorder, anticoagulant use and total volume of blood loss. Blood loss was measured by weighing gauzes and all other soaked materials and by the use of a collector bag and suction system in the operating theatre. In case women had experienced postpartum haemorrhage additional information was collected on cause of bleeding and treatment.

Statistical analyses

Bleeding scores were calculated using the tool specific scoring key. Sensitivity, specificity, positive and negative predictive value and the area under the receiver operator curve (AUC's) were calculated to quantify test characteristics of the bleeding score in relation to the occurrence of postpartum haemorrhage defined as more than 1000mL blood loss (primary endpoint) as well as more than 2000mL blood loss. Positive and negative predictive value were also calculated for all separate items of the bleeding score

(epistaxis, cutaneous, bleeding from minor wounds, oral cavity, gastrointestinal bleeding, tooth extraction, surgery, menorrhagia, postpartum haemorrhage, muscle hematoma, hemarthrosis, central nervous system bleeding). To evaluate the possibility of selection bias due to a high number of women with caesarean sections, sensitivity analyses were performed excluding women who gave birth by elective caesarean section.

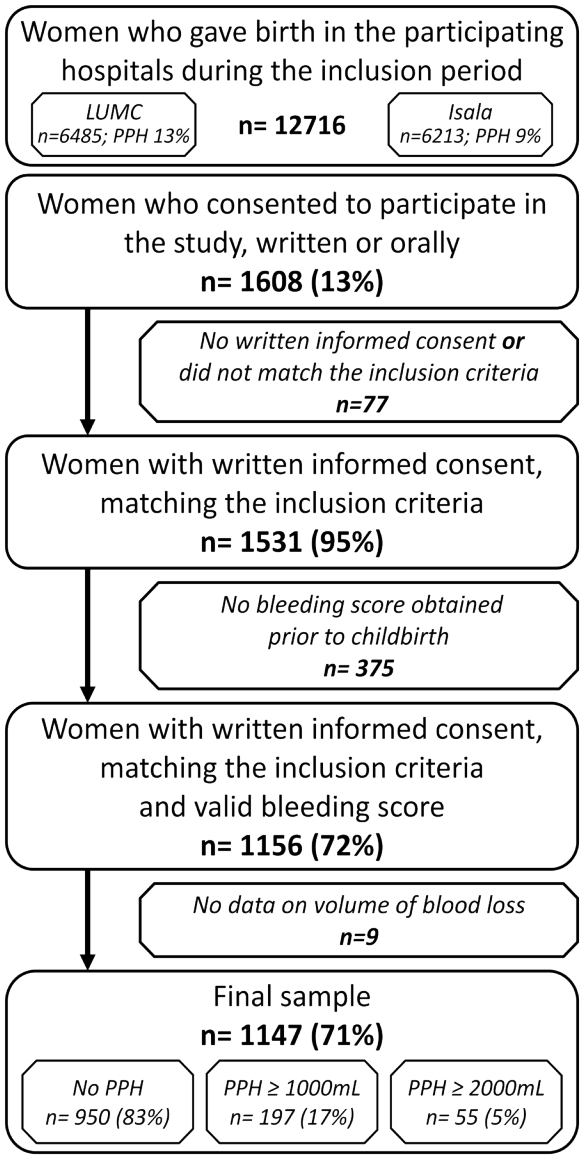

Figure 1. **Inclusion flowchart**

Results

Patient characteristics

Over the three-year TeMpOH-2 inclusion period 1147 women for whom data were available on total volume of blood loss following childbirth, completed the bleeding assessment tool (Figure 1). Baseline characteristics are reported in Table 1. Women were on average 32 years of age (IQR 29-35), gave birth at a median gestational age of 39.0 weeks (IQR 38.1-40.3) and 30% delivered by caesarean section. In our cohort (197/1147) 17.2 % of women experienced postpartum haemorrhage ≥1000 mL and (55/1147) 4.8% of women lost more than 2000mL of blood following birth. Primary cause of postpartum haemorrhage was uterine atony or retained placenta in 68% of women and 25% of bleeds were the result of a surgical cause. Bleeding scores ranged from -3 to 13, with a median of 1 (IQR -1 to 3). Of the women in our cohort, (147/1147) 12.8% had an abnormal bleeding score of ≥ 4. The distribution of bleeding scores plotted to categories of increasing volume of blood loss is shown in Figure 2. The bubble plot displays number of women per bleeding score categorized in increasing volumes of blood loss. Larger bubbles represent a higher patient count.

Discriminative ability of the bleeding score

The ability of the score to discriminate women with postpartum haemorrhage ≥ 1000mL from women without postpartum haemorrhage was poor, area under Receiver Operating Curve 0.53 (95% CI 0.49 to 0.58). For postpartum haemorrhage exceeding 2000mL of blood loss the area under Receiver Operating Curve was 0.60 (95% CI 0.52 to 0.68), showing an increase but still a rather poor discriminative power. Among 147 women with an abnormal bleeding score (≥4) the incidence of postpartum haemorrhage of ≥ 1000mL was 18.4% (n=27), and the incidence of postpartum haemorrhage exceeding 2000mL was 8.8% (n= 13). Of the 1000 women with a normal bleeding score, 170 (17%) developed postpartum haemorrhage ≥1000mL and 42 (4.2%) developed blood losses exceeding 2000mL (Table 2). Results of the sensitivity analyses excluding women with an elective caesarean section were similar to those of the main analyses (S2).

Bleeding symptoms

A history of postpartum haemorrhage was associated with postpartum haemorrhages of ≥ 1000mL and ≥2000mL. Epistaxis, post-surgery blood loss and a history of postpartum haemorrhage were associated with the development of blood loss exceeding 2000mL (Table 3). A total of 122 women had positive score on epistaxis or post-surgery blood loss, 13 (10.7%) of them developed blood loss exceeding 2000mL.

Table 1. Characteristics of participants

				Postpartum haemorrhage ≥ 1000mL	
	Total	**LUMC**	**Isala**	**No**	**Yes**
Patients	1147	818	329	950	197
Age in years	32 (29-35)*	32 (30 to 35)	31 (28 to 35)	32 (29-35)	32 (29-36)
Nulliparity	39%	41%	33%	38%	43%
Gestational age in weeks	39.0 (38.1-40.3)	38.9 (37.9 to 40.1)	39.1 (38.1 to 40.6)	39.0 (38.1 - 40.3)	39.1 (38.0 - 40.6)
Bleeding score	1 (-1 to 2)	1 (-1 to 2)	1 (0 to 2)	1 (-1 to 2)	1 (0 to 3)
Mode of birth					
Caesarean section	30%	33%	23%	30%	27%
Vaginal	70%	67%	77%	70%	73%
Comorbidity					
Pre-eclampsia/HELLP	5%	5%	4%	4%	9%
Anti-coagulant use	8%	10%	3%	8%	7%
Known coagulation disorder (VWD)	1%	5%	2%	1%	0%
Total volume of blood loss in liters	0.4 (0.3-0.7)	0.4 (0.2 to 0.7)	0.4 (0.3 to 0.6	0.3 (0.2 – 0.5)	1.5 (1.2-2.0)
PPH ≥ 1000mL	17%	17%	16%	NA	NA
PPH ≥ 2000mL	5%	4%	4%	NA	NA

*values are median (25-75 IQR), † primary cause of bleeding only reported in case of postpartum hemorrhage

Table 2. Sensitivity and specificity, positive and negativ predictive value of an abnormal bleeding score for the occurrence of postpartum haemorrhage ≥ 1000mL and ≥ 2000mL.

	AUC (95% CI)		**Sensitivity (95% CI)**	**Specificity (95% CI)**	**NPV (95% CI)**	**PPV (95% CI)**
Bleeding score & PPH		**Score ≥ 4 & PPH**				
≥ 1000mL	0.53 (0.49 to 0.58)		13.7 (9.39 to 19.5)	87.4 (85.0 to 89.4)	83.0 (80.5 to 85.2)	18.4 (12.7 to 25.8)
≥ 2000mL	0.60 (0.52 to 0.68)		23.6 (13.7 to 37.3)	87.7 (85.6 to 89.6)	95.8 (94.3 to 96.9)	8.8 (5.0 to 14.9)

AUC, area under the curve; CI, confidence interval; PPH, postpartum hemorrhage.
*abnormal bleeding score is defined as score ≥4.

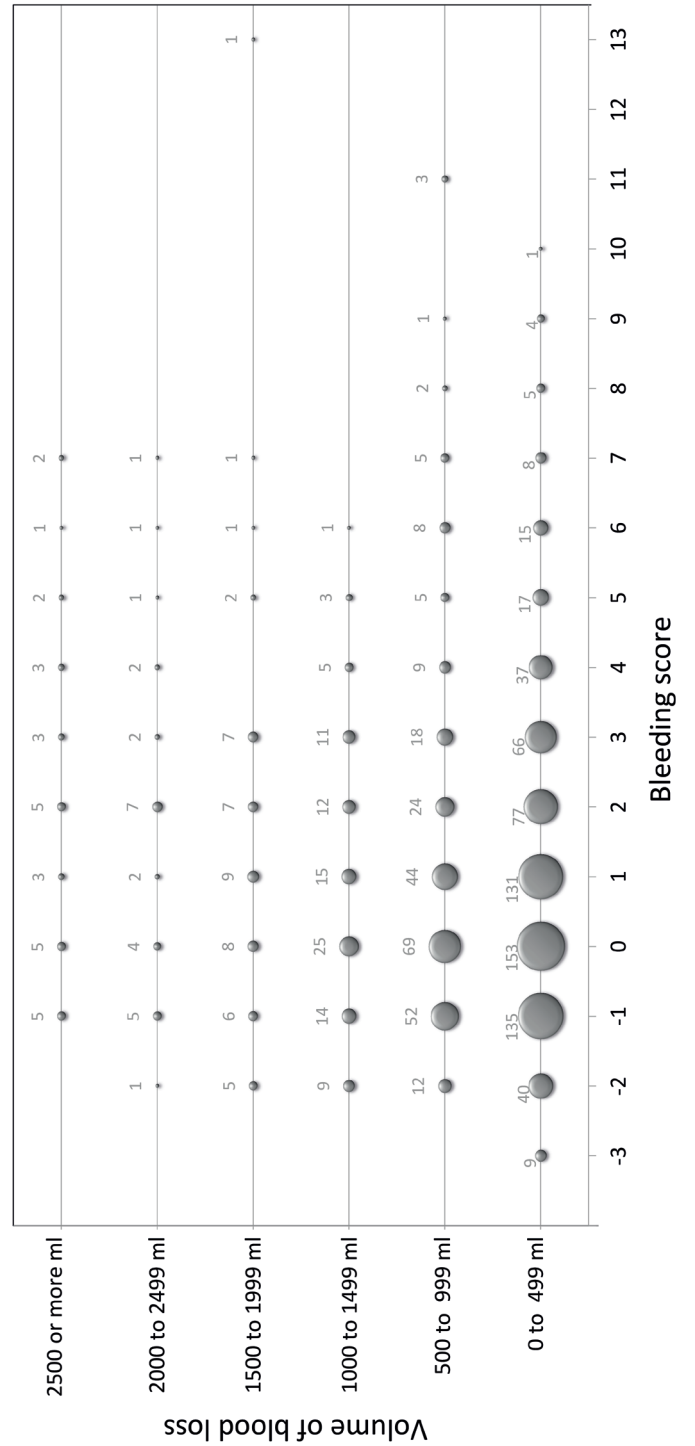

Figure 2. Bubble plot bleeding score versus volume of blood loss

Table 3. Sensitivity and specificity, positive and negative predictive value of bleeding symptoms for the occurrence of postpartum haemorrhage ≥ 1000mL and ≥ 2000mL.

	Sensitivity	Specificity	NPV	PPV
Epistaxis				
PPH 1000	4.6	95.5	82.8	17.3
PPH 2000	10.9	95.8	95.5	11.5
Cutaneous				
PPH 1000	15.2	87.5	83.3	20.1
PPH 2000	18.2	87.3	95.5	6.7
Minor wounds				
PPH 1000	3.6	95.8	82.7	14.9
PPH 2000	3.6	95.9	95.2	4.3
Oral Cavity				
PPH 1000	66.0	31.2	81.5	16.6
PPH 2000	63.6	31.4	95.5	4.5
Gastrointestinal				
PPH 1000	2.5	97.4	82.8	16.7
PPH 2000	1.8	97.3	95.2	3.3
Tooth extraction				
PPH 1000	2.5	95.7	82.6	10.9
PPH 2000	3.6	96.0	95.2	4.3
Surgery				
PPH 1000	8.1	93.5	83.1	20.5
PPH 2000	12.7	93.5	95.5	9.0
Menorrhagia				
PPH 1000	16.2	82.8	82.7	16.4
PPH 2000	14.5	82.9	95.1	4.1
PPH				
PPH 1000	30.5	84.2	85.4	28.6
PPH 2000	40.0	82.8	96.5	10.5
Muscle haematoma				
PPH 1000	4.1	96.4	82.9	19.0
PPH 2000	1.8	96.2	95.1	2.4
Haemarthrosis				
PPH 1000	1.5	99.3	82.9	30.0
PPH 2000	0.0	99.1	NA†	NA
CNS				
PPH 1000	0.0	99.8	NA	NA
PPH 2000	0.0	99.8	NA	NA
Epistaxis & surgery				
PPH 1000	12.2	89.7	83.1	19.7
PPH 2000	10.7	90.0	95.9	10.7

Incidence PPH 1000 mL in cohort 17.2%. Incidence PPH 2000 in cohort 4.2%. *Numbers are percentages.
†Not calculated because of small numbers

AUC, area under the curve; CI, confidence interval; PPH, postpartum haemorrhage. *abnormal bleeding score is defined as score >=4

Discussion

This prospective two-centre cohort study describes the usefulness of a bleeding assessment tool to predict postpartum haemorrhage. In our cohort of 1147 women, the ability of the bleeding score to contribute to the discrimination between women with and without postpartum haemorrhage was poor.

Our results suggest that a questionnaire does not contribute to the identification of women who will develop postpartum haemorrhage. Since the main causes for postpartum haemorrhage are obstetrical it might be not surprising that a tool initially developed for the diagnosis of bleeding disorders does not associate with postpartum haemorrhage. However, adding two questions on history of nosebleeds and post-surgery blood loss to a standard anamnesis does contribute to the identification of women with a higher risk of larger bleeds. Especially in women with already known risk factors for postpartum haemorrhage, knowledge of an abnormal bleeding score could be of added value while composing a personalized birth plan.

Strength and limitations of this study

A strength of our study is that we included a large cohort of 1147 pregnant women who had completed a bleeding assessment tool prior to childbirth with complete follow-up until childbirth. To rule out the possibility of recall bias, the questionnaires were only completed by women before giving birth . Moreover, we used a self- BAT derived from the validated condensed MCMDM-1VWD-BAT which was proven to be a reliable tool.

We can't rule out the presence of bias in our study. A first possible source of bias is selection bias. In our cohort, the incidence of postpartum haemorrhage was higher than expected (17.2% versus expected 6-8%.). This could be a result of the fact that the TeMpOH-2 study included women in a university hospital (LUMC) and a non-university hospital with a NICU department on site, resulting in a population with a higher a priori risk of postpartum haemorrhage. Another possible explanation for the higher incidence of postpartum haemorrhage is the known underestimation of volume of blood loss in case of visual estimation. Volume of blood loss in theTeMpOH-2 study was objectively measured, which could have led to a more realistic, yet higher, incidence of postpartum haemorrhage. Yet, if anything, a higher incidence might have influenced the predictive value of the questionnaire in a positive way[20,21]. We therefore infer that the poor predictive value of our questionnaire is not the result of selection bias.

A second possible source of bias is misclassification of the endpoint postpartum haemorrhage. Volume of blood loss was supposed to be weighed in accordance with the study protocol, but we cannot rule out that sporadically weighing was complemented by

visual estimation. When visual estimation is used, it is well-known that volume of blood loss is in most cases underestimated[22]. This may have led to potential misclassification of women in our cohort, which in this case may have caused an underestimation of incidence of post-partum haemorrhage.

Notwithstanding the high incidence of postpartum haemorrhage, the discriminative power of our bleeding score to detect women with increased risk of postpartum haemorrhage was poor. This could mean, that the predictive ability of the bleeding score in a more general population of pregnant women is even worse. Although a less biased population would have made our results more generalizable, the results of our study into the predictive value of a bleeding score for prediction of postpartum haemorrhage are solid.

Comparison with other studies

To the best of our knowledge, this study is the first to examine the value of bleeding scores acquired during pregnancy as a screening tool for the identification of women with an increased risk of excessive blood loss postpartum. Yet, our findings corroborate results of a previous studies in different patient populations. In a cohort of 7730 paediatric patients undergoing adenotonsillectomy, the efficacy of a preoperative bleeding questionnaire and coagulation screening in predicting haemorrhage associated with the procedure was studied[18]. When both an abnormal bleeding score and positive coagulation screening were combined, a statistically slightly higher likelihood of postoperative bleeding was found. However, an abnormal bleeding score without the additional coagulation screen did not have any predictive value for the occurrence of post-surgery haemorrhage. In a study in von Willebrand disease families (affected and unaffected family members), the association between spontaneous mucocutaneous bleeding symptoms and bleeding after tooth extraction or surgery was evaluated[23]. The mucocutaneous bleeding score showed a predictive value similar to VWF level for bleeding after tooth extraction (AUC 0.71) and an even better value for prediction of bleeding after surgery (AUC 0.78). In the area of von Willebrand disease, bleeding scores are used for their high negative predictive value, indicating that a normal bleeding score can help exclude a clinically significant bleeding disorder[24]. In line with this, in a study of 217 individuals being prospectively investigated for von Willebrand disease, seventeen individuals with negative bleeding scores underwent major surgery, and none experienced significant bleeding. No previous studies were found that examined the predictive value of the use of bleeding scores in the field of childbirth. In contrast with von Willebrand disease, postpartum haemorrhage is a condition that is known for its multi-factorial origin. We have assessed that a high bleeding score can to a certain extent contribute to an individual patients risk assessment prior to birth. However, the question whether postpartum haemorrhage will actually occur,

can only be answered during the course of active bleeding, depending on the obstetric challenges in tone, tissue, trauma and thrombin that will develop along the way [19].

Clinical implications

No evidence was found to support adding a bleeding assessment tool to the review of a pregnant woman's medical history for the prediction of postpartum haemorrhages of ≥ 1000mL. However, adding two questions on history of nosebleeds and post-surgery blood loss to a standard anamnesis could enable a clinician to identify women with a higher risk of postpartum haemorrhage exceeding 2000mL. Clinicians should contemplate whether they find this of clinical significance for individual patients. Especially in women with already known risk factors for postpartum haemorrhage, knowledge of an abnormal bleeding score could be of added value while composing a personalized birth plan.

Conclusion

When used as a screening tool contributing to the identification of pregnant women with an increased risk of postpartum haemorrhage prior to childbirth, a bleeding questionnaire lacks discriminative power. We found no evidence to support the added value of a bleeding assessment tool for the prediction of postpartum haemorrhage.

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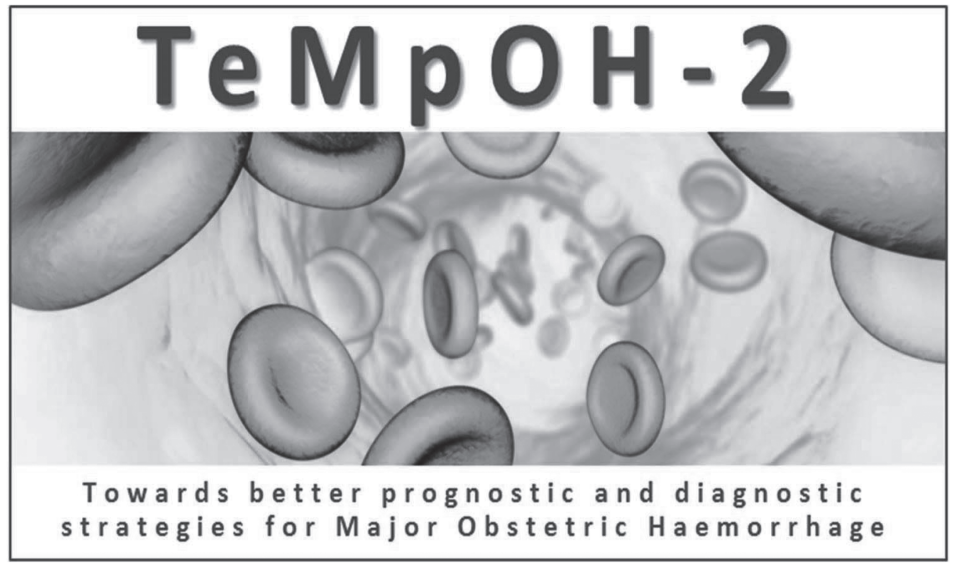
Supplemental material

S1 TeMpOH-2 Self-BAT

S2 Table: Sensitivity analyses: cohort after exclusion of women with elective cesarean section. Sensitivity and specificity, positive and negative predictive value of an abnormal bleeding score for the occurrence of postpartum haemorrhage ≥ 1000mL and ≥ 2000mL.

S1 TeMpOH-2 self-BAT



Questionnaire TeMpOH-2 study

Sanquin LUMC

Thank you very much for participating in the TeMpOH-2 study. It will take no more than 5 minutes to fully complete this questionnaire.

Please do not fold this questionnaire and check all answer boxes with a dark coloured pen so that we can process your questionnaire by using a scanner.

We require your personal information in order to couple the medical information collected during your delivery to the data from this questionnaire. We will not use your personal information for any other purpose except this research project. Your information will be coded and stored in a secure location.

Last name

Date of birth

- -

Patientnumber (as mentioned on your hospital ID card)

Phonenumber

The questions in this questionnaire concern (unless stated otherwise) the period **before your pregnancy.**

It is important to keep in mind while answering the questions, that everyone experiences bruises or gum bleeds every now and then. Try to assess whether you experience these kinds of complaints more frequently or more severely.
Should you answer the first question of a new category with 'no', you may jump to the first question of the next category in most of the cases. If so, you will find these instructions written after the answer you choose.

If you have any questions about this questionnaire, you can contact us via these numbers:
06-10308818 or 071-5685062 or 06-15661456

Or send an email to: tempoh2@lumc.nl

Nosebleeds

1a How many nose bleeds have you experienced during this pregnancy?
O None O 1-2 O 3-5 O 5-10 O 10 or more

1b How many nose bleeds do you typically experience in one year?
O None --> Continue with question 2a
O 1-5 per year
O 5-10 per year
O More than 10 per year

1c How long does an average nose bleeding episode last in your case?
O 1-5 minutes O 5-10 minutes O More than 10 minutes

1d Have you ever consulted with a physician because of nose bleeding?
O No --> continue with question 2a
O Yes

1e How did your physician treat your nose bleed?
O The physician examined me, but in the end treatment wasn't necessary.
O The physician inserted a cotton plug in my nose.
O The physician cauterized (burned) some blood vessels in my nose with a device.
O I received a blood transfusion
O I was treated with medication to improve my coagulation system

2a How often do you experience striking visible bruising?
O Less than once a month --> Continue with question 3a
O More than once a month

2b Do you have bruises larger than 1 centimetre, more than once a month, despite being aware of any impacts/ punches?
O No O Yes

2c Have you ever consulted a physician because of bruising?
O No O Yes

Bleeding from minor injuries/ small wounds

3a How many bleeding episodes from small wounds do you typically have per year?
O None --> Continue with question 4a
O 1-5 persistent bleeds per year
O More than 5 persistent bleeds per year

3b How long do these bleedings typically last in your case?
O 1-5 minutes O More than 5 minutes

3c Have you ever consulted a physician because of persistent bleeding from a small injury? (This doesn't include large injuries that needed to be stitched/closed anyway because of their large size)
O No --> Continue with question 4a
O Yes

3d How did your physician treat your bleeding injury?
O The physician examined me, but in the end treatment wasn't necessary.
O The physician stitched my injury to stop the bleeding
O I received a blood transfusion
O I was treated with medication to improve my coagulation system

Bleeding from the oral cavity (mouth)

4a Have you ever experienced bleeding in your mouth (lips, tongue and gums included)?
O No --> Continue with question 5a
O Yes

4b What was the primary cause of the bleeding from your mouth?
O Bleeding after a (wisdom) tooth came in.
O Spontaneous gum bleeding without a clear cause (clear causes would include toothbrushes)
O Gum bleeding that started after brushing my teeth
O Bleeding after I bit my lip or tongue

4c Have you ever consulted a physician or dentist because of oral bleeding?
O No --> continue with question 5a
O Yes

4d How did your physician or dentist treat this oral bleeding?
O The physician or dentist examined me, but in the end treatment wasn't necessary.
O The physician or dentist stitched the wound in my mouth to stop the bleeding
O I received a blood transfusion
O I was treated with medication to improve my coagulation system

Bleeding after dental extraction

5a Have you ever had a tooth extracted?
O No --> continue with question 6a
O Yes

5b How many tooth extraction procedures have you undergone?
O 1 O 2 O 3 O 4 O 5 O 6 O 7 O 8 O 9 O 10 or more

5c Have you ever experienced extensive bleeding following a tooth extraction?
O No --> continue with question 6a
O Yes

5d How many of these tooth extractions were complicated by a bleeding problem?

O 1 O 2 O 3 O 4 O 5 O 6 O 7 O 8 O 9 O 10 or more

5e Have you ever returned to your physician or dentist because of a bleeding problem after one or more teeth were extracted?

O No --> continue with question 6a

O Yes

5f How did your physician or dentist treat the bleeding problems?

O The physician/ dentist examined me, but in the end treatment wasn't necessary.

O The physician/dentist put some (new) stitches in the wound to stop the bleeding.

O The physician/dentist stuffed the wound with cotton wool or gauze

O I received a blood transfusion

O I was treated with medication to improve my coagulation system

Gastrointestinal bleeding (bleeding from stomach or bowel)

6a Have you ever experienced bleeding from your stomach or bowel?

O No --> Continue with question 7a

O Yes

6b What was the cause of bleeding from your stomach or bowel?

O When I suffered from an ulcer

O When I suffered from liver congestion

O The bleeding in my bowel was caused by haemorrhoids

O The physician couldn't find a clear cause for my stomach or bowel bleeding.

6c What kind of treatment did you receive for this stomach or bowel bleeding?

O The physician examined me, but in the end treatment wasn't necessary.

O I underwent surgery because of the bleeding from my stomach or bowel

O I received a blood transfusion

O I was treated with medication to improve my coagulation system

Surgery

7a Have you ever been operated upon? (this includes tonsillectomy)

O No --> continue with question 8a

O Yes

7b How many times have you been operated upon (including tonsillectomy)?

O 1 O 2 O 3 O 4 O 5 O 6 O 7 O 8 O 9 O 10 or more

7c Where one or more of these operations followed by a bleeding problem?

O No --> continue with question 8a

O Yes

7d How many of these surgical procedures were complicated by a bleeding problem afterwards?

O 1 O 2 O 3 O 4 O 5 O 6 O 7 O 8 O 9 O 10 or more

7e Have you ever required additional treatment due to a bleeding complication following surgery?

O No --> Continue with question 8a

O Yes

7f What kind of treatment did you receive for a bleeding problem after surgery?

O The physician examined me, but an extra treatment to stop the bleeding wasn't necessary

O I received new stitches or underwent a second surgery because of the bleeding

O I received a blood transfusion

O I was treated with medication to improve my coagulation system

Menstruation

8a Have you ever visited a docter because of heavy bleeding during your menstruation?

O No --> Continue with question 9a

O Yes

8b What kind of treatment did you receive for this bleeding problem?

O The docter examined me, but a treatment wasn't necessary.

O I was advised to use oral contraceptives or a Mirena IUD to decrease the amount of blood loss.

O I underwent a curettage, a hysteroscopy, or an endometrial ablation to decrease the bleeding.

O I was advised to have my uterus removed.

8c Have you received one of these treatments because of the large amount of blood loss during your period?

O I was prescribed iron supplements.

O I was treated with medication to improve my coagulation system.

O I received a blood transfusion because of anemia due to my period.

O I received none of these treatments.

Postpartum haemorrhage (blood loss after delivery)

9a Have you ever given birth before? (After at least 16 weeks of pregnancy)

O No --> Continue with question 10a

O Yes

All women loose a small amount of blood during their delivery. Sometimes the amount of blood loss is more than average and extra treatments are necessary to stop the bleeding or to compensate for the amount of blood loss. This is what we consider an excessive amount of blood loss after childbirth.

9b How many times have you given birth? (After at least 16 weeks of pregnancy)

O 1 O 2 O 3 O 4 O 5 O 6 O 7 O 8 O 9 O 10 or more

9c Have you ever experienced an excessive amount of blood loss ater a delivery?

O No --> Continue with question 10a

O Yes

9d How many of these deliveries were complicated by a bleeding problem?

O 1 O 2 O 3 O 4 O 5 O 6 O 7 O 8 O 9 O 10 or more

9e What kind of treatment(s) did you receive for any of these bleeding problems following your delivery? Multiple responses are possible

O The docter or midwife examined me, but a specific treatment wasn't necessary.

O I underwent a curettage.

O (A part of) my placenta was removed in the operating theatre.

O I was treated with iron supplements

O I received a blood transfusion.

Muscle bleeds

A muscle bleed differs from a hematoma or bruising. This bleeding problem occurs deeper in the body and is not typically visible through the skin. It most often causes swelling and a warm, painful sensation in an arm or a leg.

10a Have you ever experienced muscular bleeding?

O No --> continue with question 11a

O Yes

10b What was the cause of the muscular bleed?

O A punch, a fall or an accident (trauma).

O The bleeding occurred spontaneously (without a clear cause/reason).

10c Check the box that applied best to your situation:

O The bleeding started after a trauma (punch/fall/accident) and I did not need any treatment.

O The bleeding started spontaneously, and I didn't need any treatment.

O I was treated with medication to improve my coagulation system.

O I received a blood transfusion.

O I underwent a surgery because of the muscle bleed.

Joint bleeds

11a Have you ever experienced a bleeding in any of your joints?

O No --> continue with question 12 a

O Yes

11b What was the cause of the joint bleeding?

O A punch, a fall, or an accident (trauma)

O The bleeding occurred spontaneously (without any clear cause)

11c Check the box that applies best to your situation:

O The bleeding started after a trauma (punch/fall/accident) and I did not need any treatment.

O The bleeding started spontaneously, and I didn't need any treatment.

O I was treated with medication to improve my coagulation system.

O I received a blood transfusion.

O I underwent a surgery because of the joint bleed.

Brain haemorrhage

12a Have you ever experienced a bleeding in your brain?

O No --> Continue with question 13

O Yes

12b What kind of bleeding occurred in your brain?

O A subdural bleeding (A collection of blood outside the brain, usually caused by head injuries)

O An intracerebral bleeding (A blood vessel within the brain bursts, allowing blood to leak inside the brain)

Some people hypothesize that an association between natural hair colour and bleeding tendency exists. To date, the evidence to proof this statement is lacking. By asking you this question concerning your hair colour, we plan on investigating whether an association between natural hair colour and postpartum haemorrhage exists.

13 What is your natural hair colour?

O Light blond

O Dark blond

O Brown

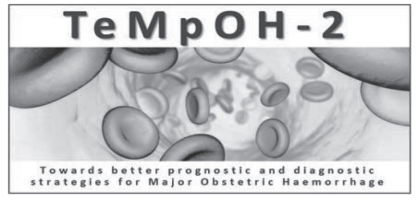
O Black

O Light red

O Dark red

You have now reached the end of the questionnaire!
We would like to thank you very much for taking the time to complete this questionnaire and to participate in the study.

You can return this questionnaire either by using the enclosed self-addressed envelope or by handing it in during your next appointment at the hospital.



Sanquin LUMC

S2 Sensitivity analyses: cohort after exclusion of women with elective caesarean section. Sensitivity and specificity, positive and negative predictive value of an abnormal bleeding score for the occurrence of postpartum haemorrhage ≥ 1000mL and ≥ 2000mL.

	AUC (95% CI) PPH≥1000	AUC (95% CI) PPH≥2000	Sensitivity	Specificity	NPV	PPV
(n=945)	0.52 (0.47 – 0.57)	0.58 (0.50 - 0.66)	NA	NA	NA	NA
PPH ≥ 1000	NA	NA	12.4	87.1	82.0	17.4
PPH ≥ 2000	NA	NA	19.6	95.0	95.0	8.3

AUC, area under the curve; PPH, postpartum haemorraghe, CI, confidence interval.

3 COAGULATION PARAMETERS DURING THE COURSE OF SEVERE POSTPARTUM HAEMORRHAGE: A NATIONWIDE RETROSPECTIVE COHORT STUDY

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Abstract

Background: We describe the pattern of change in coagulation parameters during the course of severe postpartum haemorrhage.

Methods: Retrospective cohort study among 1312 women experiencing severe postpartum haemorrhage necessitating blood transfusion. Levels of haemoglobin, haematocrit, platelet count, fibrinogen, aPTT and PT per categorized volume of blood loss during severe postpartum haemorrhage were described and compared between women with and without the composite adverse outcome. Need for surgical intervention, severe acute maternal morbidity and maternal mortality were jointly considered the composite adverse outcome.

Findings: Of the 1312 women, 463 (35%) developed the composite adverse outcome. The incidence of a fibrinogen level <2 g/L was 26% (342 per 1312). Low fibrinogen and prolonged aPTT during the first two litres of haemorrhage were associated with a subsequent composite adverse outcome; median fibrinogen and aPTT among women with and without the composite endpoint after 1.5-2 L of haemorrhage were 1.5 g/L (IQR 1.0 to 1.9) vs 2.7 g/L (IQR 1.9 to 3.4) and 39s (IQR 30 to 47) vs 32 s (IQR 28 to 36) respectively. PT and platelet count as assessed during the first two litres of haemorrhage were not associated with morbidity or mortality**.**

Interpretation: Our results suggest that detection of low levels of fibrinogen and elevated aPTT levels during early postpartum haemorrhage can contribute to the identification of women that may benefit from targeted haemostatic treatment. Essential in this identification process is *the moment* of reaching a level of fibrinogen of <2 g/L during the course of postpartum haemorrhage.

Introduction

Postpartum haemorrhage is a major cause of maternal morbidity and mortality with an incidence that seems to be increasing over the last decade[1-8] .

Efforts to prevent morbidity and mortality due to postpartum haemorrhage focus among other things on laboratory monitoring of haemostasis in order to enable timely treatment of possible coagulopathy. Haemostasis may be monitored by laboratory-based PT/aPTT, Clauss fibrinogen, platelet count, and point of care testing[9]. Experts recommend that all these may be used simultaneously because there is currently no high level evidence on the best strategy[9]. This advice leads to inefficiency, waste and considerable variation in the care for patients with postpartum haemorrhage.

In order to determine the optimal strategy to monitor coagulopathy, it is crucial to know the patterns of changes in coagulation parameters in relation to the phases of postpartum haemorrhage and to identify which parameters show the fastest changes associated with the risk of severe maternal outcomes. Data on the change in coagulation parameters during the course of postpartum haemorrhage, thus per litre of ongoing haemorrhage, are limited. Earlier studies used repeated measurements at set time points or reported worst values in the course of bleeding[10-12]. Some have suggested that low fibrinogen concentration might be the earliest predictor of progression towards severe postpartum haemorrhage[11,13,14]. Investigators studying women with severe postpartum haemorrhage face the enormous challenge of including women in a life-threatening condition, frequently leading to failure to include the most severe cases.

Diligent observation of present-day monitoring of haemostasis and outcomes among an unselected cohort of women with ongoing postpartum haemorrhage may help to identify the haemostasis parameters that are able to recognize women with a high risk for morbidity and mortality as early as possible during postpartum haemorrhage.

The aim of this study was to describe coagulation parameters including fibrinogen during the course of severe postpartum haemorrhage -per categorized volume of blood loss. Also, coagulation parameters during early postpartum haemorrhage were compared between women with and without severe acute maternal morbidity, mortality and need for surgical intervention.

Methods

Design and study population

The Transfusion strategies in women during Major Obstetric Haemorrhage-1 (TeMpoH-1) study is a nationwide retrospective cohort study in 61 hospitals in the Netherlands. TeMpOH-1 included 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 severe *obstetric haemorrhage* (≥1000 mL blood loss during pregnancy, birth or puerperium). For the present analysis we selected women from the TeMpOH-1 cohort who met criteria for *primary postpartum haemorrhage* (blood loss (≥1000 mL occurring within the first 24 hours after childbirth). We excluded women for whom we did not have any coagulation parameter measured between childbirth and end of active postpartum haemorrhage. Women 18 years of age and older who met the inclusion criteria were selected. Women with a known coagulation disorder or anticoagulant were included in the study. Approval for the TeMpOH-1 study was obtained from the Medical Ethical Research Committee of the Leiden University Medical Centre (P12.273) and from the institutional review board of each participating hospital. The study was registered in the Netherlands Trial Register (NTR4079). Detailed design of the study has been reported elsewhere [15]. Because of the retrospective design of the study, the need to obtain informed consent from eligible women was waived by the ethics committee. Eligible women were selected from transfusion databases and birth registries of participating hospitals with 191.772 births between 2011 and 2013. By cross-referencing electronic data from the hospitals' blood transfusion services with local birth registers in participating hospitals, all women experiencing severe postpartum haemorrhage necessitating blood transfusion during the inclusion period of the study could be included. In most hospitals no pregnancy specific massive transfusion protocol is available and in most cases the normal (non-pregnancy) target values for haemostatic therapy are used: haemoglobin 8 g/dL, PT and aPTT < 1.5x prolonged, platelet count > 50-100 x 10^9/L and fibrinogen > 1.5 g/l.

Data collection

Detailed information on maternal, pregnancy and birth characteristics was collected from medical files. Chart reviews were conducted by trained medical students and research nurses. Data were recorded from files available at the maternity ward, operating theatre and intensive care unit for the following parameters: maternal age at the time of birth, parity, maternal body weight during early pregnancy, maternal height, ethnicity, gestational age, obstetric history, mode of birth, cause of major obstetric haemorrhage, abnormal placentation, shock, timing and volume of fluids and blood products administered, timing of surgical and haemostatic interventions and consecutive measurements of blood loss until cessation of bleeding. Blood loss was measured by weighing gauzes and other soaked materials and by use of a collector bag and suction system in the operating theatre.

Laboratory parameters

Of the included women, we documented available laboratory parameters and data on type and volume as well as timing of clear fluids and blood products administered during the course of postpartum haemorrhage, 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). Laboratory parameters from the first measurement of blood loss onwards were considered, including parameters drawn from women before they had reached 1000mL of blood loss. Unlikely values were verified in the medical records. There was no pre-set protocol for obtaining specimens: blood samples during postpartum haemorrhage had been obtained on request of the care giver leading to different numbers and panels of results of laboratory parameters.

Composite adverse maternal outcome

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 were jointly considered the combined endpoint of severe acute maternal morbidity. Women were compared with regard to whether they had developed a composite adverse maternal outcome consisting of severe acute maternal morbidity, maternal mortality or need for surgical intervention.

Statistical analyses

Coagulation parameters are presented as median and interquartile ranges because of non-Gaussian distribution. The phases of ongoing postpartum haemorrhage were categorized according to increasing volumes of blood loss: 0-1L, 1-1.5L, 1.5-2L, 2-2.5L, 2.5-3L, 3-3.5L, 3.5 and >4L. Each laboratory parameter result was assigned to the category of blood loss at which the respective blood sample had been taken. In case of multiple measurements per woman within one category of volume of blood loss, the mean of those values was used. In order to assign a volume of blood loss for each of the laboratory parameters we imputed volumes of blood loss using linear interpolation of two consecutive blood volume measurements. In case total blood loss was the only available data point, or the blood sample was drawn before the first measurement of blood loss volume, the birth time of the baby was used as the starting point for the interpolation. Levels of coagulation parameters between groups were compared with Mann-Whitney U tests. Reference ranges of aPTT varied somewhat for the 61 participating hospitals as a result of use of different types of reagents. To examine the robustness of aPTT results we repeated the analyses using aPTT ratios, which were calculated by dividing the observed aPTT levels by the mean of the hospital specific reference range.

Results

Patient characteristics

Over the two-year inclusion period of the TeMpOH-1 study, 1391 women had received at least four units of red cells, or fresh frozen plasma or platelets in addition to red cells for postpartum haemorrhage. A total of 1312 women with primary postpartum haemorrhage had at least one valid measurement of coagulation parameters sampled during active bleeding (Figure 1). The median volume of blood loss among these 1312 women was 3 L (interquartile range (IQR) 2.5 to 4.0). Characteristics of the study population and of women with and without the composite adverse outcome are reported in *Table 1*.

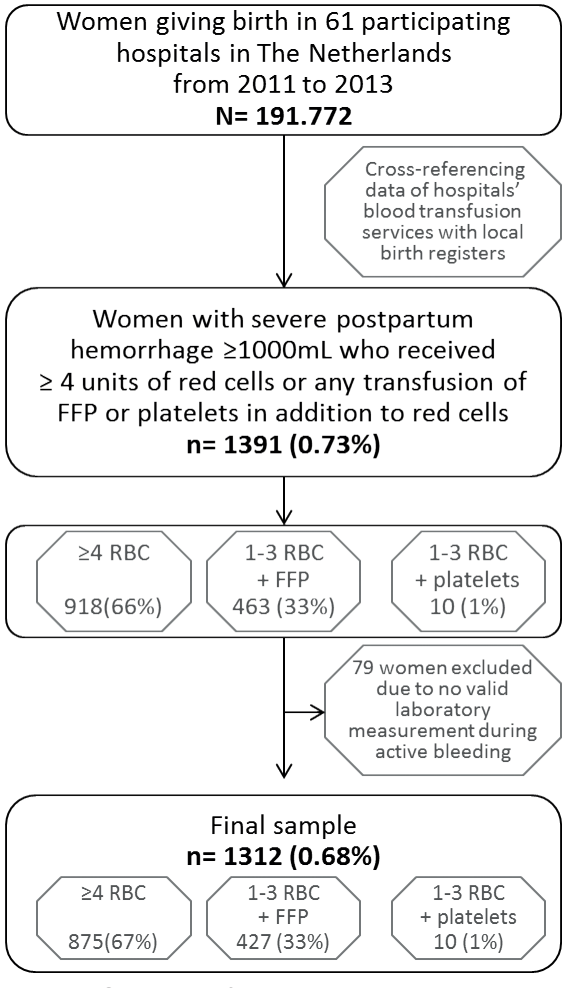

Figure 1. **Inclusion flowchart for 'coagulation parameters during the course of severe postpartum haemorrhage: a nationwide retrospective cohort study'**

Table 1. **Patient and treatment characteristics of the total study population and according to the development of the composite adverse outcome**

		Severe acute maternal morbidity, mortality, and need for surgical intervention	
Patient and treatment characteristics	**Total**	**No**	**Yes**
Patients, n (%)	1312	849 (65)	463 (35)
Maternal characteristics			
Age, y	31.3 (28-35)	31.0 (28-35)	32.0 (29-35)
Body mass index, kg/m2	23.3 (21-26.4)	23.1 (20.9-26.3)	23.5 (21-27)
Ethnicity, white, %	71	75	65
Nulliparity, %	52	54	47
Gestational age, wk	39.6 (38-40.7)	39.7 (38.3-40.9)	39.4 (37.4-40.6)
Mode of birth, %			
Caesarean section	25	19	36
Vaginal	75	81	63
Comorbidity, %			
Preeclampsia/HELLP	11	9	14
Anticoagulant use	0.5	0.5	0.7
Transfer to hospital, %			
Transfer to hospital during labor	14	15	12
Postpartum transfer (birth at home)	12	15	8
Primary cause of bleeding, %			
Uterine atony	65	66	63
Retained placenta	17	21	10
Pathological ingrowth of placenta	8	6	12
Placenta previa	1	1	2
Surgical bleeding	7	5	10
Placental abruption	2	2	2
Coagulopathy	1	0	1
Fibrinogen administered, %	10	4	21
Tranexamic acid administered, %	44	36	59
Recombinant FVIIa-administered, %	3	0.1	8
Bleeding rate, mL/min*	2.4 (1.2-4.6)	2.3 (1.2-4.2)	2.4 (1.3-5.3)
Shock (systolic blood pressure ,90 or heart rate .120), %	85	84	86
Total volume of clear fluids, L	2.5 (1.7-4.0)	2.5 (1.5-3.5)	3.0 (2.0-4.5)

Continuing **Table 1. Patient and treatment characteristics of the total study population and according to the development of the composite adverse outcome**

		Severe acute maternal morbidity, mortality, and need for surgical intervention	
Patient and treatment characteristics	**Total**	**No**	**Yes**
Total units of blood products	6.0 (4.0-8.0)	5.0 (4.0-6.0)	10.0 (6.0-16.0)
Four or more red cells units, n (%)	875 (67)	481 (57)	394 (85)
One to 3 red cells and 1 or more plasma units, n (%)	427 (33)	360 (42)	67 (14)
One to 3 red cells and 1 or more platelets units, n (%)	10 (1)	8 (1)	2 (0.4)
Total volume of blood loss, L	3.0 (2.5-4.0)	2.8 (2.2-3.3)	4.0 (3.0-5.5)

Values are median (IQR), except as noted.
*Maximum.

Laboratory parameters during postpartum haemorrhage

Haemoglobin concentration was measured on 2605 occasions, haematocrit on 2245 occasions, platelet count on 1581 occasions, fibrinogen concentration on 775 occasions, PT on 876 occasions, and aPTT on 1075 occasions. Women had a median amount of 3 (IQR 2 to 5) blood loss measurements during active postpartum haemorrhage. Figure 2 shows results of the laboratory test results according to increasing volumes of haemorrhage.

The accompanying patient count, mean, standard deviation, median, interquartile range, lowest and highest values of laboratory parameters according to increasing volumes of blood loss are presented in supplemental table S1. Levels of haemoglobin tended to decrease up to 2.0-2.5L of blood loss to a haemoglobin level of 7.7 g/dL (IQR 6.4-9.0) and a haematocrit of 0.24 (IQR 0.20-0.28), after which stabilization occurred. At 2.5L of blood loss 203 out of 443 (46%) women had been transfused with blood products.

Platelet counts also decreased with increasing volume of blood loss. Women with 2.0-2.5L of blood loss, had a median platelet count of 146 x10^9/litre (IQR 108-186). Four percent (10/253) of these women had received a platelet transfusion at that time. For 128 women with blood loss of 3.5-4.0L the median platelet count was 115x10^9/litre (IQR 89-143); 21 of these 128 (16%) women had received platelet transfusions and 113/128 (88%) had received a blood product.

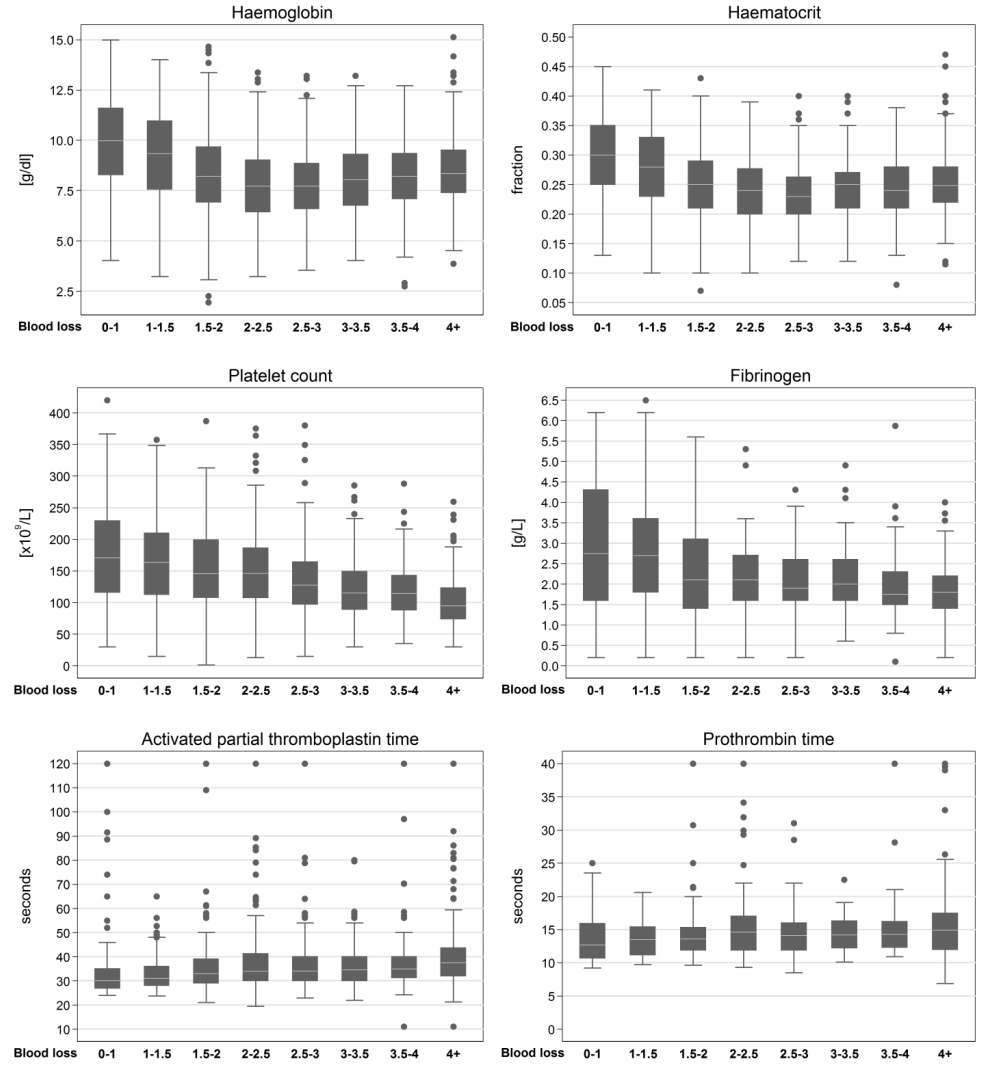

Figure 2. **Coagulation parameters of women during the course of severe postpartum haemorrhage per categorized amount of blood loss.**

Coagulation parameters of women during the course of severe postpartum haemorrhage per categorized amount of blood loss. 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.

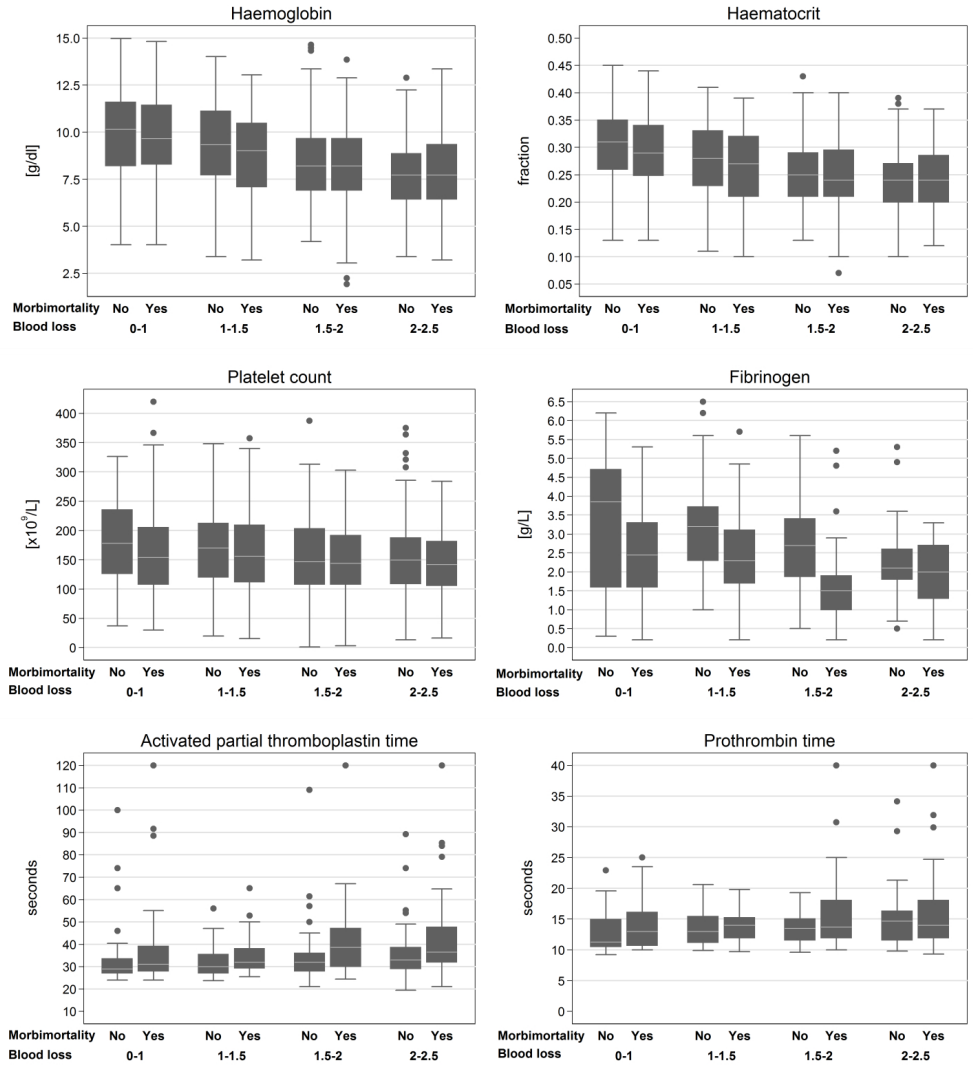

Figure 3. Coagulation parameters of women with and without combined endpoint of severe acute maternal morbidity, mortality or need for surgical intervention per categorized volume of blood loss

Coagulation parameters of women with and without combined endpoint of severe acute maternal morbidity or mortality per categorized amount of blood loss. Box plots of coagulation parameters per categorized amount of blood loss comparing women experiencing postpartum haemorrhage with and without the composite adverse outcome. Morbi-mortality comprises the composite adverse outcome of severe acute maternal morbidity and mortality. Circles are outliers. The box represents the 25th and 75th percentiles and the whiskers are the upper and lower adjacent values.

There were 342 (0.18% of all births in the 61 hospitals and 26% of the women in our study cohort) women who developed a fibrinogen level below 2 g/L. A fibrinogen level below 1 g/L was reached by 78 women. Five percent (70/1312) of the women in our cohort

reached a fibrinogen level below 2 g/L after losing less than 2L of blood. Four women reached this level because of postpartum haemorrhage due to placental abruption. Median baseline fibrinogen level during early postpartum haemorrhage was 2.8 g/L (IQR 1.6-4.3). Fibrinogen levels tended to decrease up to 2-2.5L of blood loss at 2.1 g/L (IQR 1.6-2.7). Among 152 women who had lost more than 4L, median level of fibrinogen was 1.8 g/L (IQR 1.4-2.2); 41% of these women had been treated with fibrinogen concentrates. In the subgroup of patients with postpartum haemorrhage due to uterine atony or retained placenta we observed a similar trend (Figure S4).

Median PT values showed a slight increase with increasing volumes of blood loss. During the earliest phase of postpartum haemorrhage median PT was 12.7 seconds (IQR 10.7-15.9); among women who lost more than 4 L the median PT was 14.9 (IQR 12.0-17.5). Median aPTT increased with increasing volumes of blood loss from 30.0 seconds (IQR, 27.0-35.0) during early bleeding to 37.5 seconds (IQR 32.0-43.6) in the maximum blood loss category. Sensitivity analyses on the aPTT ratio showed similar results (S5).

Laboratory parameters and adverse maternal outcome

Of the 1312 women 463 (35%) developed a combined endpoint of severe acute maternal morbidity mortality or the need for surgical intervention; 37% (172/463 women) of these women developed more than one of the items composing the combined adverse endpoint. To arrest bleeding, hysterectomy was necessary in 72 (5%) women, 164 (13 %) were treated with arterial embolisation, in 46 (4%) women an emergency B-lynch procedure or ligation of arteries was performed. Of the women in our study cohort, 386 (29%) were admitted to the ICU and 7 (0.5%) died as a result of severe haemorrhage. Figure 3 shows laboratory results during postpartum haemorrhage of women with and women without the composite adverse outcome. Women who developed the composite adverse outcome had lower fibrinogen concentrations and longer aPTTs than women who did not develop the endpoint, which was already apparent and most pronounced during the earliest phases of postpartum haemorrhage. There were no noteworthy differences in haemoglobin, haematocrit, PT and platelet levels during the early phases of postpartum haemorrhage (blood loss below 2L, *Table 2*). Women who developed the composite adverse outcome had a median fibrinogen level of <2g/L at 1.5-2L of blood loss, whereas women without the composite adverse outcome had a median fibrinogen of <2 g/L after a volume of more than 3.5L of blood loss. Additional results based on first sample during postpartum haemorrhage, irrespective of blood loss volume and ROC analyses of progression to the severe morbidity endpoint based on the first blood test are provided in the Supplemental Data (Table S2 & S3). Sensitivity analyses with the aPTT-ratio showed similar results (Table S6). Patient characteristics of the women with fibrinogen measurements are also presented (Table S7).

Table 2. **Coagulation parameters during the course of postpartum hemorrhage of women with and without composite adverse maternal outcome**

	Hb, g/dL			Ht (fraction)			Platelet count, 3109/L			Fibrinogen, g/L			aPTT, s			PT, s		
	Composite end point			Composite end point			Composite end point			Composite end point			Composite end point			Composite end point		
Blood loss category, L	No	Yes	P*	No	Yes	P*	No	Yes	P*	No	Yes	P*	No	Yes	P*	No	Yes	P*
0.00 to 1.0	10.1	9.7	0.28	0.31	0.29	0.23	178	154	0.24	3.9	2.5	0.09	29	32	0.11	11	13	0.26
1.01 to 1.5	9.3	9.0	0.04	0.28	0.27	0.04	170	156	0.29	3.2	2.3	0.01	30	33	0.03	13	14	0.44
1.51 to 2.0	8.2	8.2	0.91	0.25	0.24	0.84	147	144	0.47	2.7	1.5	<0.01	32	39	<0.01	14	14	0.26
2.01 to 2.5	7.7	7.7	0.61	0.24	0.24	0.55	150	142	0.32	2.1	2.0	0.19	33	37	<0.01	15	14	0.54
2.51 to 3.0	7.9	7.6	0.29	0.24	0.23	0.13	136	119	0.19	2.0	1.8	<0.01	33	38	<0.01	14	14	0.42
3.01 to 3.5	7.7	8.4	0.01	0.24	0.25	0.02	117	111	0.21	2.2	2.0	0.40	33	36	0.04	15	14	0.82
3.51 to 4.0	8.3	8.2	0.58	0.25	0.24	0.22	128	110	0.06	2.0	1.7	0.05	34	36	0.09	15	14	0.09
4.01 or more	8.2	8.4	0.06	0.24	0.25	0.04	115	93	<0.01	1.7	1.8	0.76	34	38	<0.01	15	15	0.93

*Mann-Whitney U test.

Discussion

Among women with severe postpartum haemorrhage requiring blood transfusion, the occurrence of low levels of fibrinogen and prolonged aPTTs in the earliest phases of haemorrhage was associated with progression toward severe acute maternal morbidity, mortality or need for surgical intervention.

Strength and limitations of this study

Our study describes coagulation parameters and morbidity of women with severe postpartum haemorrhage. The results are therefore only generalizable to women suffering severe postpartum haemorrhage. The unique strength of this retrospective study is that we were able to include all women with severe postpartum haemorrhage necessitating blood transfusion that had occurred in the 61 participating hospitals during the study period, including the most severe cases, enabling reliable and generalizable estimation of percentages of women with coagulopathy during the course of postpartum haemorrhage. In addition, the large sample size allowed us to examine patterns of laboratory parameters throughout the course of on-going postpartum haemorrhage. The retrospective study design also has limitations. We did not have control over the number and specific panels of coagulation samples. Therefore, our results are based on different selections of women in the categories of blood loss. Obviously more blood samples were drawn from women with more severe bleeding. It is therefore possible that women with low fibrinogen or prolonged aPTT were missed in women with lower blood loss as these parameters were not measured, because there were no measurements. This may have led to an underestimation of the occurrence of abnormal laboratory parameters. Moreover, laboratory measurements were performed in local laboratories of the 61 hospitals, leading to significant variation in measurements and possible misclassification. Such variation will also influence the results towards underestimation of the strength of the association of coagulation parameter abnormalities with morbidity and mortality. To be certain of the accuracy of all low fibrinogen values in our study cohort, we returned to the 61 participating hospitals and verified all values of fibrinogen with a level < 2g/L (and all other outliers of laboratory parameters) in the medical files. During the inclusion period of our study none of the participating hospitals used thromboelastometry in women experiencing postpartum haemorrhage.

Comparison with other studies

The occurrence of coagulopathy in postpartum haemorrhage and its association with maternal morbidity and mortality has been studied previously. For a correct interpretation of the results of this study in the context of previous studies, it should be taken into account that our study differs from previous studies as regards to its source population: as opposed to previous studies only women with severe postpartum haemorrhage necessitating the

administration of blood products were included. Fibrinogen levels of lower than 2 g/L were strongly associated with progression towards severe postpartum haemorrhage in a study among 128 women with postpartum haemorrhage[11]. However, in this study measurements were done at predefined hours after enrolment and information on the corresponding amount of blood loss at the time of the measurements was lacking. It therefore remained unclear whether the level of fibrinogen was a predictor of progression towards more severe bleeding or a result of blood loss at time of blood sampling. Another study among 456 women with postpartum haemorrhage from a large UK unit reported results of haemoglobin, platelet count, PT and aPTT tests that were categorized based on the worst value of the total amount of blood loss at the end of bleeding[10]. Fibrinogen was found to be the parameter that best correlated with increasing volume of haemorrhage. PT and aPTT remained within the normal range in most women despite large bleeds. In a review article Collis et al summarized results of five studies that tried to determine a value of fibrinogen that could serve as a biomarker for progression of postpartum haemorrhage[14]. These values varied between studies: fibrinogen level 3.3/3.4/1.8/3.1/2.8 g/L[10,11,13,16,17]. Their overall conclusion was that a fibrinogen level of < 3 g/L and, in particular < 2 g/L was associated with progression towards more severe postpartum haemorrhage.

Another study on women in need of massive transfusion because of postpartum haemorrhage (≥8 units of red cells within 24 hours of delivery) was also based on the first and worst values measured, regardless of volume of blood loss at sampling[12]. Also, in this study a difference was made between levels of coagulation parameters for different primary causes of bleeding. Since the primary cause of bleeding often remains unclear during active postpartum haemorrhage, and in some cases is only clarified when additional tests have been performed after the event, we find it of great clinical importance to study the pattern of change of coagulation parameters over time in relation to volume of blood loss, regardless of primary cause of bleeding.

In our cohort we observe a higher occurrence of a fibrinogen concentration below 2 g/L compared to results suggested in randomized trials. This can be explained by differences in patient selection. In a Danish multicentre double-blind randomized trial, women experiencing severe postpartum haemorrhage were treated with a dose of 2 gram of fibrinogen concentrate or placebo[18]. Of the 244 randomized women, only five had a fibrinogen value less than 2 (mean value in both groups 4.5). A more recent trial randomized 55 women at a FIBTEM® value of 15 mm (considered to be the equivalent to Clauss fibrinogen value of 3 g/L) to fibrinogen concentrate or placebo[19]. No improvement in outcome was observed in women who were administered fibrinogen; only 7 women (out of a cohort of 663 women with postpartum haemorrhage) developed a fibrinogen level below 2 g/L confirming, as discussed by the authors, the challenges related to consenting women with severe bleeding and undertaking trial procedures whilst treating

acutely ill women. This challenge was also experienced by a Finnish research group who aimed to perform a randomized controlled trial comparing prothrombin complex concentrate and fibrinogen concentrate to fresh frozen plasma as a treatment for women experiencing postpartum haemorrhage exceeding 2 litres (NCT01910675). Obtaining informed consent in an acute situation with severe bleeding turned out to be impossible (personal communication).

The results of the TeMpOH-1 study confirm the results of previous studies into this subject, however with one very important addendum for acute clinical decision-making: the dimension of time. We found 342 women with a fibrinogen level ≤ 2 g/L and a further 78 women with a fibrinogen level ≤1 g/L. We have elucidated that women who experienced postpartum haemorrhage without developing a composite outcome of maternal morbidity and mortality only sporadically reached a fibrinogen value of <2 g/L (blood loss above 3.5 litres). Women who did develop the composite adverse outcome reached this low fibrinogen level much earlier (1.5-2L of blood loss) during postpartum haemorrhage. This difference in *the moment* of reaching a level of fibrinogen of <2 g/L during the course of postpartum haemorrhage is essential for the selection of the right target population for future studies into the potential benefit of administering fibrinogen concentrate.

Clinical implications

By the timely detection of changes in levels of relevant coagulation parameters, targeted haemostatic therapy to restore deficiencies could be administered. However, assessment of fibrinogen levels by a standard coagulation test like the Clauss fibrinogen assay has a turn-around time of up to 60 minutes making it unsuitable for acute clinical decision making[20]. Point-of-care devices like ROTEM® thromboelastometry are able to detect essential changes in the coagulation system within 10 minutes after blood sampling[21]. ROTEM FIBTEM could potentially be a worthwhile addition to postpartum haemorrhage management. To make progress in this field we need to monitor women experiencing postpartum haemorrhage closely during the process of active blood loss. In our next currently ongoing study (NCT02149472) we will further elucidate the predictive value of early changes in coagulation parameters (including thromboelastometry) for the development of severe acute maternal morbidity and mortality in women experiencing postpartum haemorrhage. The results provided by this study provide a solid knowledge base to be used when making the transition towards the evidence based use of rapid point of care testing.

Conclusion

In this nationwide retrospective cohort study on the change of coagulation parameters in 1312 women experiencing severe postpartum haemorrhage requiring blood transfusion, we provide a solid knowledge base of common patterns of change in coagulation

parameters during postpartum haemorrhage. Our results suggest that detection of low levels of fibrinogen and elevated aPTT levels during early postpartum haemorrhage can contribute to the identification of women that may benefit from targeted haemostatic treatment. Based on these results we advise to assess levels of fibrinogen and aPTT in all women who experience postpartum haemorrhage with blood loss exceeding 1L.

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Supplemental material

S1 Patient counts, mean, media, IQR per coagulation parameter by category of blood loss

S2 Coagulation parameters during the course of postpartum haemorrhage of women with and without composite adverse maternal outcome including results of the first sample after start of postpartum haemorrhage

S3 ROC analyses and graphs of progression to the severe morbidity endpoint based on the first blood and early blood tests (1-1.5 and 1.5-2L).

S4 Fibrinogen value for postpartum haemorrhage cases due to retained placenta and atony

S5 Sensitivity analyses: patient count, median, IQR and figure for aPTT- ratio

S6 Sensitivity analyses: Adverse maternal outcome & coagulation parameters aPTT- ratio

S7 Patient characteristics per subgroup within blood loss category for fibrinogen values

S1 Patient counts, mean, median, IQR per coagulation parameter

Haemoglobin

Blood loss	n	mean	sd	p50	p25	p75	min	max
0.00 to 1.0 (L)	301	9.8	2.20	10.0	8.3	11.6	4.0	15.0
1.01 to 1.5 (L)	395	9.1	2.18	9.3	7.6	11.0	3.2	14.0
1.51 to 2.0 (L)	430	8.3	2.09	8.2	6.9	9.7	1.9	14.7
2.01 to 2.5 (L)	443	7.8	1.87	7.7	6.4	9.0	3.2	13.4
2.51 to 3.0 (L)	369	7.7	1.68	7.7	6.6	8.9	3.5	13.2
3.01 to 3.5 (L)	256	8.1	1.78	8.1	6.8	9.3	4.0	13.2
3.51 to 4.0 (L)	171	8.1	1.74	8.2	7.1	9.3	2.7	12.7
4.01 or more (L)	240	8.5	1.72	8.4	7.4	9.5	3.9	15.1
Total	2605	8.4	2.06	8.3	7.0	9.7	1.9	15.1

Haematocrit

Blood loss	n	mean	sd	p50	p25	p75	min	max
0.00 to 1.0 (L)	265	0.30	0.06	0.30	0.25	0.35	0.13	0.45
1.01 to 1.5 (L)	357	0.28	0.06	0.28	0.23	0.33	0.10	0.41
1.51 to 2.0 (L)	369	0.25	0.06	0.25	0.21	0.29	0.07	0.43
2.01 to 2.5 (L)	363	0.24	0.05	0.24	0.20	0.28	0.10	0.39
2.51 to 3.0 (L)	320	0.23	0.05	0.23	0.20	0.26	0.12	0.40
3.01 to 3.5 (L)	209	0.25	0.05	0.25	0.21	0.27	0.12	0.40
3.51 to 4.0 (L)	145	0.24	0.05	0.24	0.21	0.28	0.08	0.38
4.01 or more (L)	217	0.25	0.05	0.25	0.22	0.28	0.12	0.47
Total	2245	0.25	0.06	0.25	0.21	0.30	0.07	0.47

Platelet count

Blood loss	n	mean	sd	p50	p25	p75	min	max
0.00 to 1.0 (L)	130	172	75.61	171	116	229	30	420
1.01 to 1.5 (L)	194	164	72.05	164	113	210	15	357
1.51 to 2.0 (L)	226	154	65.21	146	108	199	1	387
2.01 to 2.5 (L)	253	150	60.15	146	108	186	13	375
2.51 to 3.0 (L)	263	132	53.59	128	97	164	15	380
3.01 to 3.5 (L)	167	121	46.47	115	89	149	30	285
3.51 to 4.0 (L)	128	117	44.24	115	89	143	35	288
4.01 or more (L)	220	102	39.85	95	74	123	30	259
Total	1581	138	62.08	130	94	176	1	420

Fibrinogen

Blood loss	n	mean	sd	p50	p25	p75	min	max	n <=1	n <=2
0.00 to 1.0 (L)	52	3.0	1.70	2.8	1.6	4.3	0.2	6.2	8	17
1.01 to 1.5 (L)	75	2.9	1.37	2.7	1.8	3.6	0.2	6.5	6	22
1.51 to 2.0 (L)	79	2.3	1.25	2.1	1.4	3.1	0.2	5.6	13	39
2.01 to 2.5 (L)	115	2.1	0.84	2.1	1.6	2.7	0.2	5.3	10	54
2.51 to 3.0 (L)	133	2.1	0.80	1.9	1.6	2.6	0.2	4.3	11	75
3.01 to 3.5 (L)	94	2.1	0.79	2.0	1.6	2.6	0.6	4.9	7	48
3.51 to 4.0 (L)	75	1.9	0.86	1.8	1.5	2.3	0.1	5.9	7	53
4.01 or more (L)	152	1.8	0.63	1.8	1.4	2.2	0.2	4.0	13	102
Total	775	2.2	1.05	2.0	1.5	2.7	0.1	6.5	75	410

PT

Blood loss	n	mean	sd	p50	p25	p75	min	max
0.00 to 1.0 (L)	49	13.5	3.86	12.7	10.7	15.9	9.2	25.0
1.01 to 1.5 (L)	79	13.6	2.64	13.5	11.2	15.4	9.7	20.6
1.51 to 2.0 (L)	94	14.7	7.02	13.6	11.9	15.3	9.6	74.3
2.01 to 2.5 (L)	130	16.1	9.11	14.7	11.9	17.0	9.3	90.0
2.51 to 3.0 (L)	163	14.5	3.31	14.1	11.9	16.0	8.5	31.0
3.01 to 3.5 (L)	107	14.3	2.58	14.2	12.2	16.3	10.1	22.5
3.51 to 4.0 (L)	87	17.1	15.42	14.3	12.3	16.2	10.9	120.0
4.01 or more (L)	167	16.5	9.00	14.9	12.0	17.5	6.9	79.6
Total	876	15.2	7.87	14.1	11.9	16.3	6.9	120.0

APTT

Blood loss	n	mean	sd	p50	p25	p75	min	max
0.00 to 1.0 (L)	71	36.1	18.28	30.0	27.0	35.0	24.0	120.0
1.01 to 1.5 (L)	105	33.0	7.27	31.0	28.0	36.0	23.7	65.0
1.51 to 2.0 (L)	121	36.4	13.60	33.0	29.0	39.0	21.0	120.0
2.01 to 2.5 (L)	160	37.5	13.70	34.0	30.0	41.3	19.4	120.0
2.51 to 3.0 (L)	199	36.7	10.71	34.1	30.0	40.0	22.9	120.0
3.01 to 3.5 (L)	134	36.0	9.57	34.6	30.0	40.0	21.0	80.0
3.51 to 4.0 (L)	97	38.9	15.81	35.0	31.3	40.0	11.0	120.0
4.01 or more (L)	188	41.7	17.63	37.5	32.0	43.6	11.0	120.0
Total	1075	37.4	13.79	34.0	30.0	40.0	11.0	120.0

S2 Coagulation parameters during the course of postpartum haemorrhage of women with and without composite adverse maternal outcome including results of the first sample after start of postpartum haemorrhage

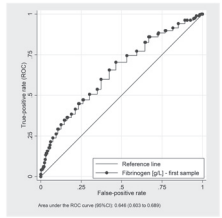
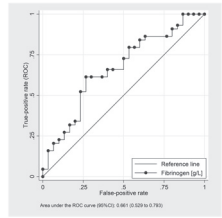
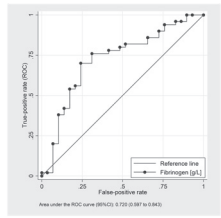
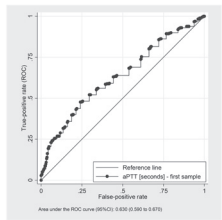
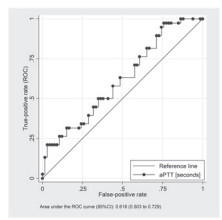
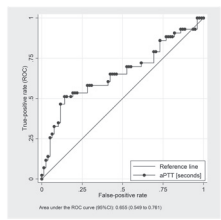
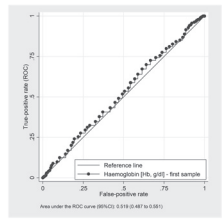
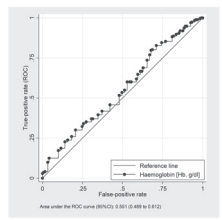
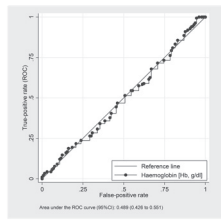
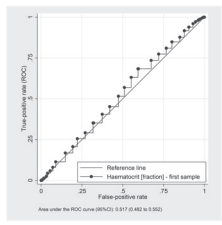
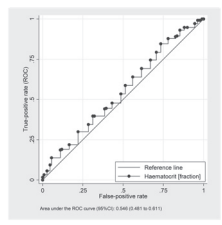
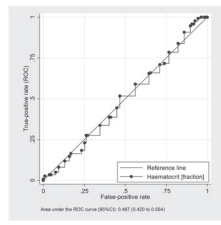
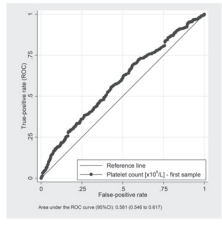
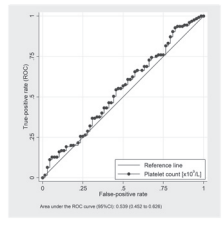
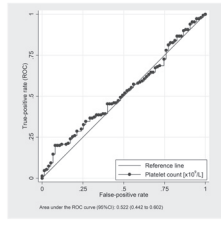
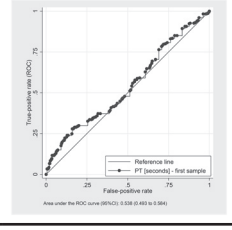
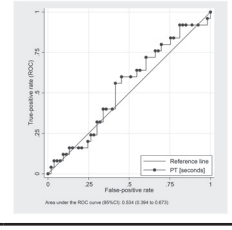
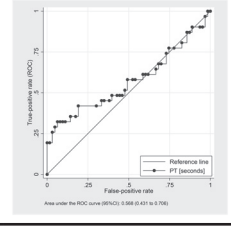
Blood loss Category	Hb [g/dl]			Ht (fraction)			Platelet count [x10^9/L]			Fibrinogen [g/L]			APTT (seconds)			PT (seconds)		
	Composite endpoint			Composite endpoint			Composite endpoint			Composite endpoint			Composite endpoint			Composite endpoint		
	No	**Yes**	***p-value****	**No**	**Yes**	***p-value****	**No**	**Yes**	***p-value****	No	**Yes**	***p-value****	**No**	**Yes**	***p-value****	**No**	**Yes**	***p-value****
0.00 to 1.0 (L)	10.1	9.7	0.28	0.31	0.29	0.23	178	154	0.24	3.9	2.5	0.09	29	32	0.11	11	13	0.26
1.01 to 1.5 (L)	9.3	9.0	0.04	0.28	0.27	0.04	170	156	0.29	3.2	2.3	0.01	30	33	0.03	13	14	0.44
1.51 to 2.0 (L)	8.2	8.2	0.91	0.25	0.24	0.84	147	144	0.47	2.7	1.5	<0.01	32	39	<0.01	14	14	0.26
2.01 to 2.5 (L)	7.7	7.7	0.61	0.24	0.24	0.55	150	142	0.32	2.1	2.0	0.19	33	37	<0.01	15	14	0.54
2.51 to 3.0 (L)	7.9	7.6	0.29	0.24	0.23	0.13	136	119	0.19	2.0	1.8	<0.01	33	38	<0.01	14	14	0.42
3.01 to 3.5 (L)	7.7	8.4	0.01	0.24	0.25	0.02	117	111	0.21	2.2	2.0	0.40	33	36	0.04	15	14	0.82
3.51 to 4.0 (L)	8.3	8.2	0.58	0.25	0.24	0.22	128	110	0.06	2.0	1.7	0.05	34	36	0.09	15	14	0.09
4.01 or more (L)	8.2	8.4	0.06	0.24	0.25	0.04	115	93	<0.01	1.7	1.8	0.76	34	38	<0.01	15	15	0.93
First Sample†	9.2	9.0	0.09	0.28	0.27	0.03	151	136	<0.01	2.3	1.8	<0.01	32	36	<0.01	14	14	0.05

**all p-value reported refers to Mann-Whitney U test, † refers to the first sample irrespective of volume of blood loss*

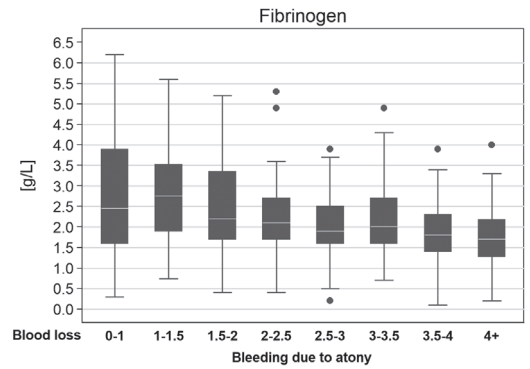
S3 ROC analyses of progression to the severe morbidity endpoint based on the first blood test

AUC	**First sample**	**Blood loss 1.0 to 1.5 (L)**	**Blood loss 1.5 to 2.0 (L)**
Fibrinogen	0.646 (0.603 to 0.689)*	0.661 (0.529 to 0.793)	0.720 (0.597 to 0.843)
aPTT	0.630 (0.590 to 0.670)	0.616 (0.503 to 0.729)	0.655 (0.549 to 0.761)
Haemoglobin	0.519 (0.487 to 0.551)	0.551 (0.489 to 0.612)	0.489 (0.426 to 0.551)
Haematocrit	0.517 (0.482 to 0.552)	0.546 (0.481 to 0.611)	0.487 (0.420 to 0.554)
Platelet count	0.581 (0.546 to 0.617)	0.539 (0.452 to 0.626)	0.522 (0.442 to 0.602)
PT	0.538 (0.493 to 0.584)	0.534 (0.394 to 0.673)	0.568 (0.431 to 0.706)

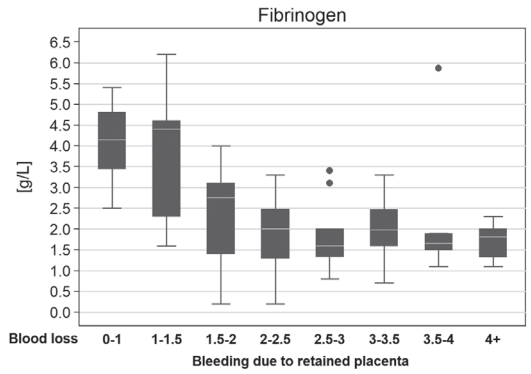
**AUC (95% CI)*

	First sample	1 to 1.5 (L)	1.5 to 2.0 (L)
Fibrinogen			
APTT			
Haemoglobin			
Haematocrit			
Platelet count			
PT			

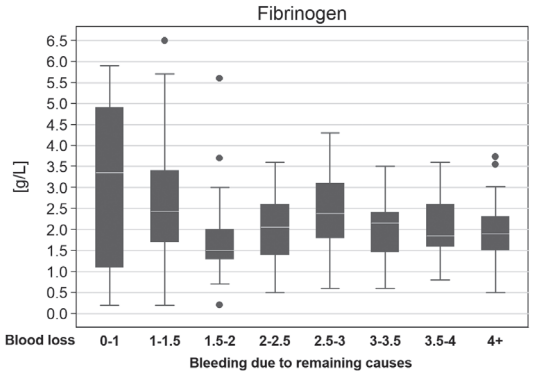
S4 Fibrinogen value for postpartum haemorrhage cases due to retained placenta and atony



Blood loss	n	p50	p25	p75
0.00 to 1.0 (L)	34	2.5	1.6	3.9
1.01 to 1.5 (L)	52	2.8	1.9	3.5
1.51 to 2.0 (L)	48	2.2	1.7	3.4
2.01 to 2.5 (L)	75	2.1	1.7	2.7
2.51 to 3.0 (L)	94	1.9	1.6	2.5
3.01 to 3.5 (L)	62	2.0	1.6	2.7
3.51 to 4.0 (L)	51	1.8	1.4	2.3
4.01 or more (L)	92	1.7	1.3	2.2



Blood loss	n	p50	p25	p75
0.00 to 1.0 (L)	8	4.1	3.5	4.8
1.01 to 1.5 (L)	5	4.4	2.3	4.6
1.51 to 2.0 (L)	14	2.8	1.4	3.1
2.01 to 2.5 (L)	18	2.0	1.3	2.5
2.51 to 3.0 (L)	13	1.6	1.3	2.0
3.01 to 3.5 (L)	16	2.0	1.6	2.5
3.51 to 4.0 (L)	11	1.7	1.5	1.9
4.01 or more (L)	12	1.8	1.3	2.0

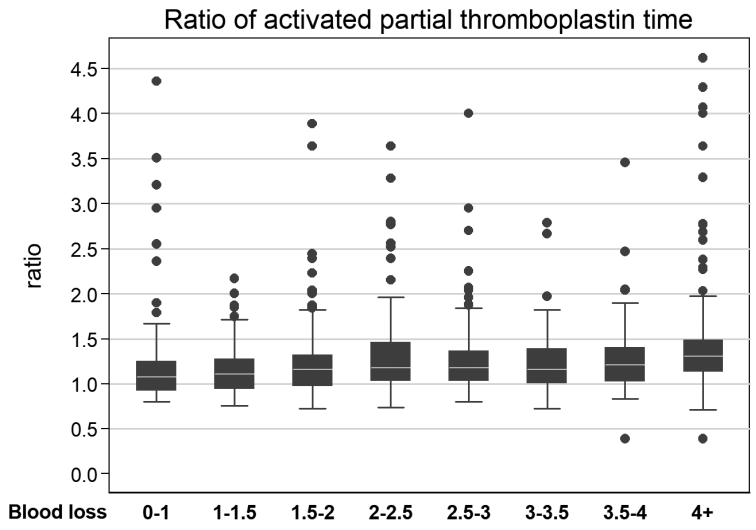


Blood loss	n	p50	p25	p75
0.00 to 1.0 (L)	10	3.4	1.1	4.9
1.01 to 1.5 (L)	18	2.4	1.7	3.4
1.51 to 2.0 (L)	17	1.5	1.3	2.0
2.01 to 2.5 (L)	22	2.0	1.4	2.6
2.51 to 3.0 (L)	26	2.4	1.8	3.1
3.01 to 3.5 (L)	16	2.1	1.5	2.4
3.51 to 4.0 (L)	13	1.9	1.6	2.6
4.01 or more (L)	48	1.9	1.5	2.3

Fibrinogen value for postpartum haemorrhage cases due to atony, retained placenta and other causes. 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.

S5 Sensitivity analyses: patient count, median, IQR and figure for aPTT- ratio

Blood loss	n	mean	sd	p50	p25	p75	min	max
0.00 to 1.0 (L)	68	1.27	0.66	1.08	0.93	1.25	0.80	4.36
1.01 to 1.5 (L)	94	1.14	0.27	1.11	0.95	1.27	0.76	2.17
1.51 to 2.0 (L)	105	1.27	0.49	1.16	0.98	1.32	0.72	3.89
2.01 to 2.5 (L)	135	1.31	0.47	1.18	1.04	1.46	0.74	3.64
2.51 to 3.0 (L)	179	1.27	0.39	1.18	1.04	1.36	0.80	4.00
3.01 to 3.5 (L)	121	1.23	0.33	1.16	1.01	1.39	0.73	2.79
3.51 to 4.0 (L)	83	1.29	0.41	1.21	1.04	1.40	0.39	3.46
4.01 or more (L)	171	1.43	0.61	1.30	1.13	1.49	0.39	4.62
Total	956	1.29	0.47	1.18	1.03	1.40	0.39	4.62

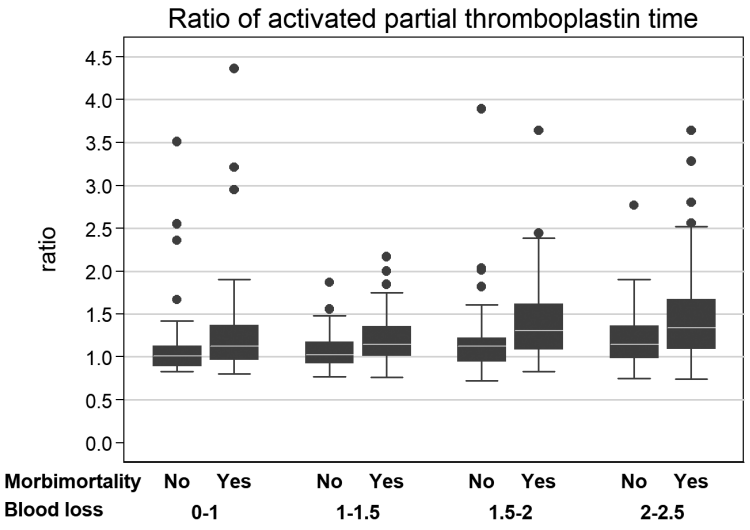


Sensitivity analyses: patient count, median, IQR and figure for aPTT-ratio. Laboratory parameters are presented in box plots. Circles are outliers. The box represents the 25th and 75th percentiles and the whiskers are the upper and lower adjacent values.

S6 Sensitivity analyses: Adverse maternal outcome & coagulation parameters aPTT- ratio

Blood loss Category	aPTT (seconds)			aPTT ratio		
	Composite adverse endpoint			Composite adverse endpoint		
	No	**Yes**	***P****	**No**	**Yes**	***P****
0.00 to 1.0 (L)	29	31	0.11	1.01	1.12	0.04
1.01 to 1.5 (L)	30	32	0.03	1.02	1.14	<0.01
1.51 to 2.0 (L)	32	39	<0.01	1.13	1.31	<0.01
2.01 to 2.5 (L)	33	37	<0.01	1.14	1.34	<0.01
2.51 to 3.0 (L)	33	38	<0.01	1.14	1.30	<0.01
3.01 to 3.5 (L)	33	36	0.04	1.11	1.27	0.04
3.51 to 4.0 (L)	34	36	0.09	1.17	1.22	0.08
4.01 or more (L)	34	38	<0.01	1.20	1.32	0.01

**all p-value reported refers to Mann-Whitney U test.*



Sensitivity analyses: Adverse maternal outcome & coagulation parameters aPTT- ratio. *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.*

S7 Patient characteristics per subgroup within blood loss category for fibrinogen values

	All women			Women per category					
				0-1000mL		1000-1500 mL		1500-2000mL	
	Total	Severe acute maternal morbidity and mortality		Severe acute maternal morbidity and mortality		Severe acute maternal morbidity and mortality		Severe acute maternal morbidity and mortality	
		No	Yes	No	Yes	No	Yes	No	Yes
Patients	1312	849 (65%)	463 (35%)	30	22	44	31	50	29
Maternal characteristics									
Age (years) *	31.3 (28-35)	31.0 (28-35)	32.0 (29-35)	32.0 (29.0-36.0)	30.5 (28.0-36.0)	32.5 (29.0-35.0)	30.0 (27.0-36.0)	31.5 (27.0-35.0)	32.0 (30.0-36.0)
BMI (kg/m2)	23.3 (21-26.4)	23.1 (20.9-26.3)	23.5 (21-27)	25.5 (21.3-27.1)	24.2 (22.3-26.8)	22.6 (20.4-25.6)	24.5 (19.9-26.6)	23.5 (21.9-26.8)	25.0 (22.2-30.0)
Ethnicity Caucasian	71%	75%	65%	63%	55%	61%	52%	72%	66%
Nulliparity (yes)	52%	54%	47%	40%	59%	57%	58%	66%	38%
Gestational age (weeks)	39.6 (38-40.7)	39.7 (38.3-40.9)	39.4 (37.4-40.6)	38.6 (38.0-40.7)	39.3 (37.3-40.6)	39.7 (38.1-40.9)	39.4 (37.6-40.7)	39.7 (38.4-40.9)	39.6 (37.6-40.7)
Mode of birth†									
Caesarean section	25%	19%	36%	13%	55%	34%	52%	24%	41%
Vaginal	75%	81%	63%	87%	41%	64%	48%	76%	59%
Comorbidity									
Pre-eclampsia/ HELLP	11%	9%	14%	10%	32%	18%	32%	12%	28%
Anti-coagulant use	0.5%	0.5%	0.7%	0%	0%	0%	0	2%	0%
Transfer to hospital									
Transfer to hospital during birth	73%	70%	80%	10%	0%	5%	13%	16%	10%

Continuing S7. Patient characteristics per subgroup within blood loss category for fibrinogen values

	All women			Women per category					
				0-1000mL		1000-1500 mL		1500-2000mL	
	Total	Severe acute maternal morbidity and mortality		Severe acute maternal morbidity and mortality		Severe acute maternal morbidity and mortality		Severe acute maternal morbidity and mortality	
		No	Yes	No	Yes	No	Yes	No	Yes
Patients	1312	849 (65%)	463 (35%)	30	22	44	31	50	29
Postpartum transfer (birth at home)	12%	15%	8%	0%	0%	5%	3%	12%	4%
Primary cause of bleeding									
Uterine atony	65%	66%	63%	67%	64%	66%	74%	62%	59%
Retained placenta	17%	21%	10%	23%	5%	11%	0%	24%	7%
Pathological ingrowth of placenta	8%	6%	12%	0%	9%	5%	3%	6%	10%
Surgical bleeding and abruption/coagulopathy	11%	8%	15%	10%	23%	18%	23%	8%	24%
Placentation									
Abnormal localization placenta (yes, placenta previa)	6%	4%	10%	7%	9%	2%	3%	0%	10%
Pathological ingrowth placenta (yes)	9%	6%	14%	0%	9%	5%	6%	6%	10%
Fibrinogen administered	10%	4%	21%	10%	36%	16%	19%	12%	41%
Tranexamic acid administered	44%	36%	59%	40%	55%	48%	65%	44%	55%

Continuing S7. Patient characteristics per subgroup within blood loss category for fibrinogen values

	All women			Women per category					
				0-1000mL		1000-1500 mL		1500-2000mL	
	Total	Severe acute maternal morbidity and mortality		Severe acute maternal morbidity and mortality		Severe acute maternal morbidity and mortality		Severe acute maternal morbidity and mortality	
		No	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
Patients	1312	849 (65%)	463 (35%)	30	22	44	31	50	29
Recombinant FVIIa administered	3%	0.1%	8%	0%	14%	0%	10%	2%	17%
Bleeding rate, ml/min‡	2.4 (1.2-4.6)	2.3 (1.2-4.2)	2.4 (1.3-5.3)	1.3 (0.6-2.4)	0.9 (0.3-1.9)	0.8 (0.4-2.6)	0.7 (0.2-1.4)	0.7 (0.4-2.2)	0.4 (0.3-1.3)
Shock	85%	84%	86%	23%	50%	41%	58%	50%	41%
Total volume of clear fluids (L)	2.5 (1.7-4.0)	2.5 (1.5-3.5)	3 (2.0-4.5)	2.0 (1.3-3.5)	2.5 (1.5-4.0)	2.5 (1.0-3.0)	2.0 (0.5-3.4)	2.5 (1.5-3.0)	3.0 (2.0-4.3)
Total units of blood products (n)	6.0 (4.0-8.0).	5.0 (4.0-6.0)	10.0 (6.0-16.0)	5.0 (4.0-6.0)	12.5 (8.0-20.0)	5.0 (4.0-6.0)	10.0 (6.0 -16.0)	5.0 (4.0-8.0)	13.0 (7.0-18.0)
Total volume of blood loss (L)	3.0 (2.5-4.0)	2.8 (2.2-3.3)	4.0 (3.0-5.5)	2.5 (2.1- 3.0)	3.1 (2.0-5.0)	2.3 (1.6-3.0)	3.0 (1.5-3.8)	2.5 (2.0-3.2)	3.5 (3.0 -4.5)

**All values in the table reported in this format are median and (IQR), † percentage, ‡ maximum*

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*).

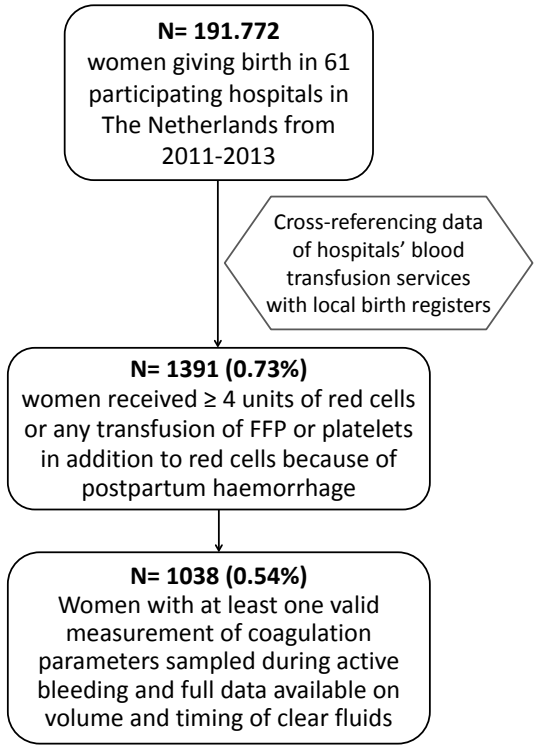


Figure 1. **Inclusion flowchart for 'fluid management and dilutional coagulopathy in severe postpartum haemorrhage: a nationwide retrospective cohort study'**

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).

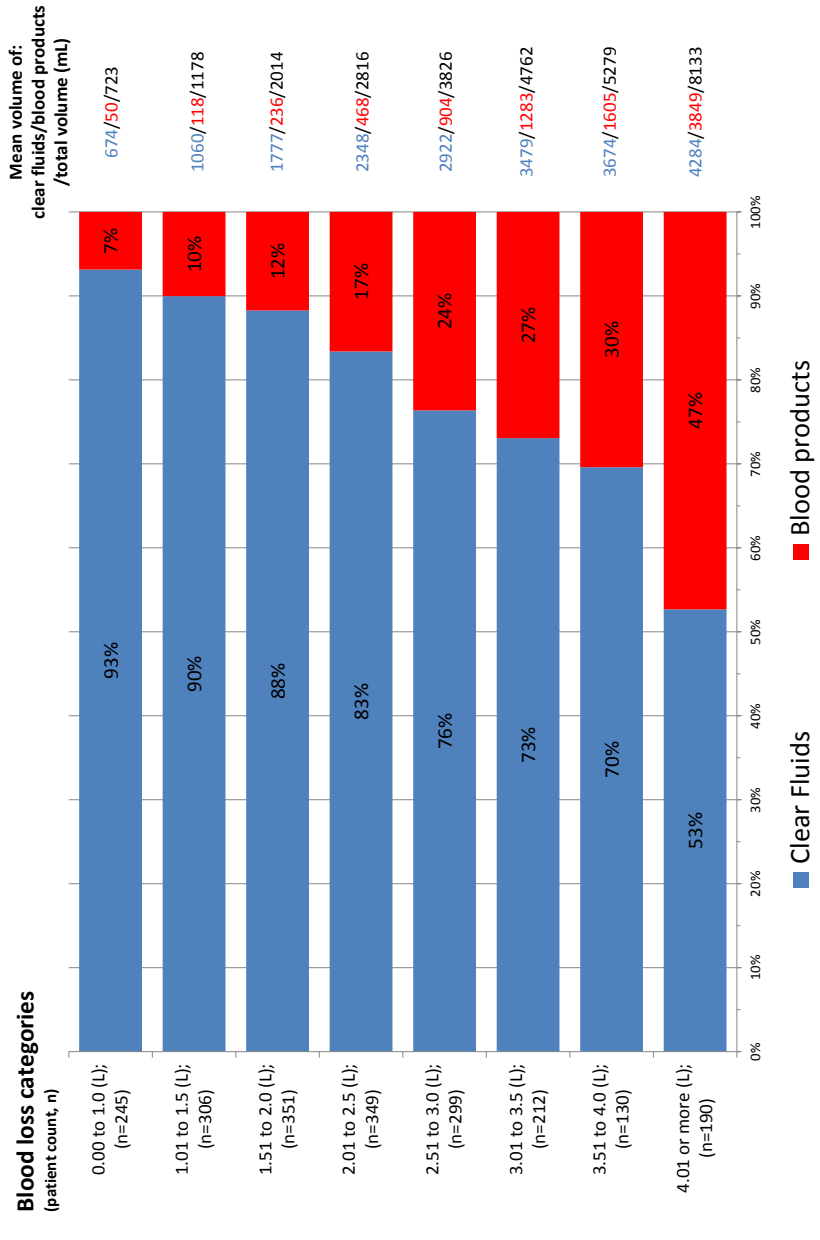
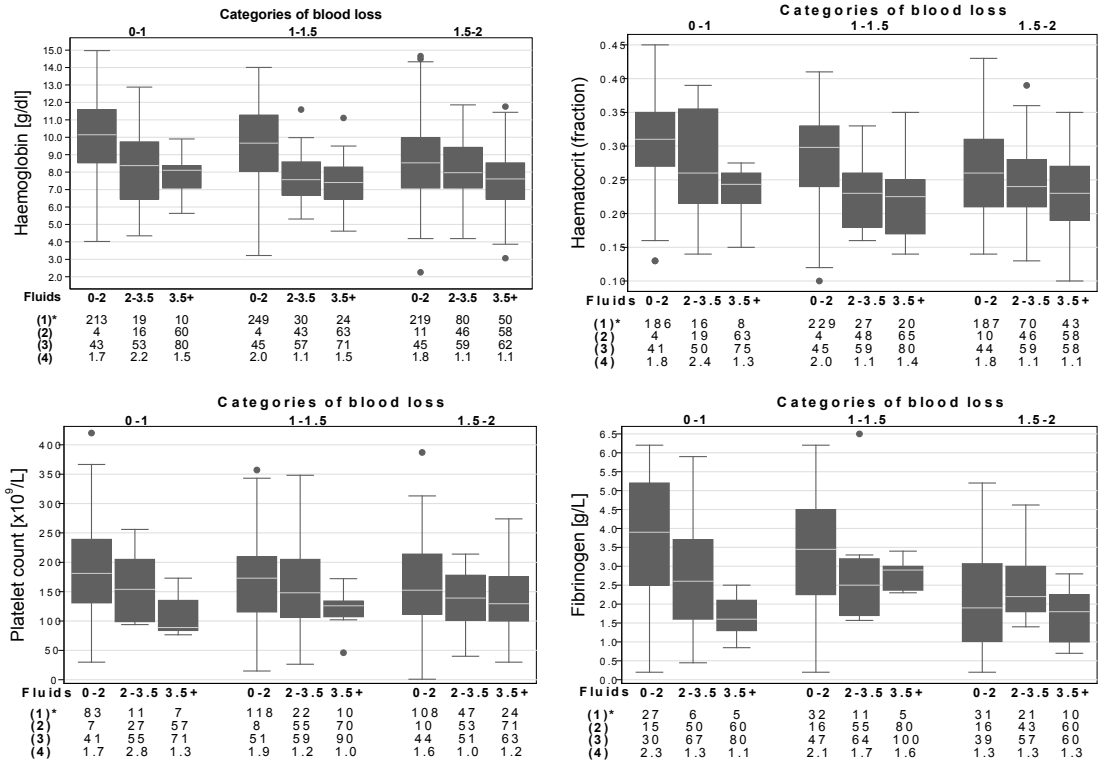


Figure 2. Volume of clear fluids and blood products administered per blood loss category.

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.



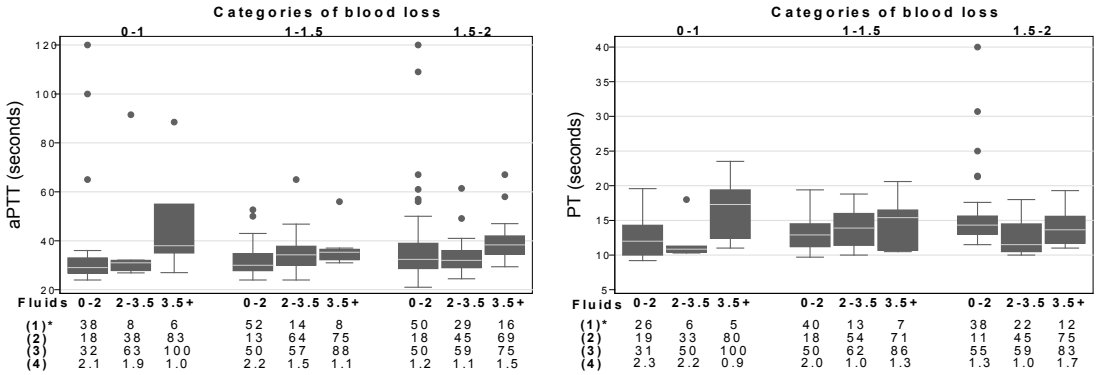


Figure 3. Coagulation parameters according to clear fluid administration (0-2L, 2L-3.5L, >3.5L) and increasing volume of blood loss (0-1.0, 1.0-1.5, 1.5-2.0 L).

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;

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.

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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

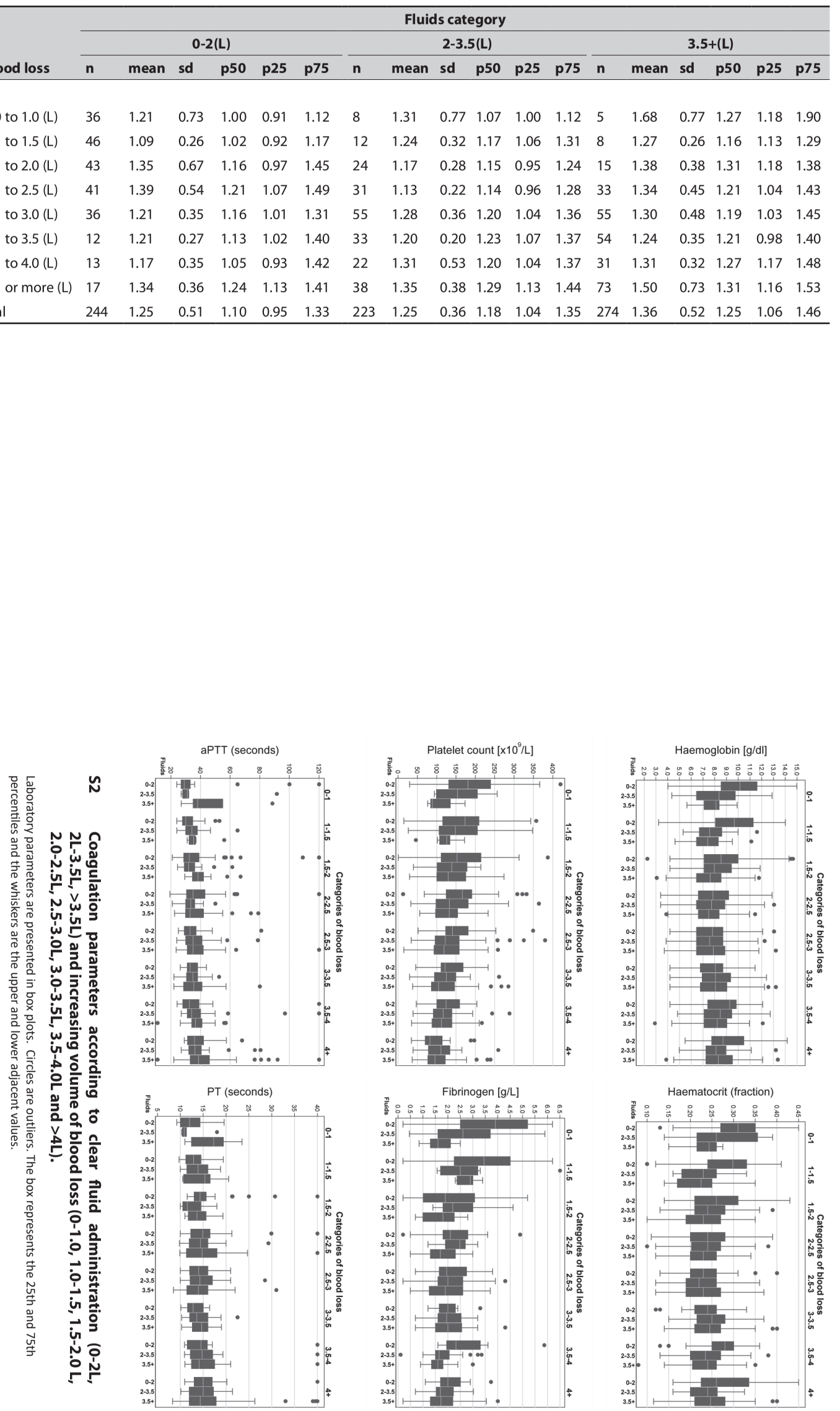
		Fluids category																	
		0-2(L)						2-3.5(L)						3.5+(L)					
	Blood loss	n	mean	sd	p50	p25	p75	n	mean	sd	p50	p25	p75	n	mean	sd	p50	p25	p75
Platelet count																			
	0.00 to 1.0 (L)	83	184	80	181	131	239	11	163	59	154	99	205	7	111	37	89	84	135
	1.01 to 1.5 (L)	118	167	72	173	116	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

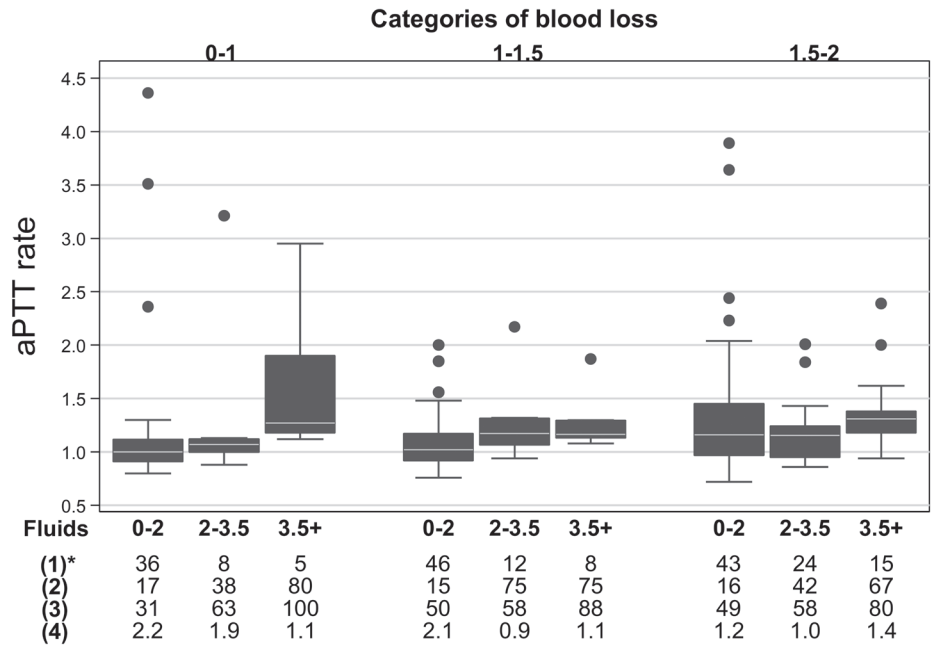
Continuing S1 Patient count, mean, sd, median and IQR for coagulation parameters in addition to Figure 3

		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
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.



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.

5 COMPARISON OF THROMBOELASTOMETRY BY ROTEM® DELTA AND ROTEM® SIGMA IN WOMEN WITH POSTPARTUM HAEMORRHAGE

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Abstract

Background: Haemostatic treatment in women experiencing postpartum haemorrhage is increasingly based on point-of-care devices such as ROTEM® thromboelastometry. Recently, the ROTEM® Sigma was introduced, a fully automated successor of the ROTEM® Delta device. To determine whether these devices provide similar results, we compared ROTEM® parameters using the ROTEM Delta and Sigma devices in women experiencing postpartum haemorrhage.

Methods: Prospective observational cohort study of 23 women experiencing postpartum haemorrhage. ROTEM® INTEM, EXTEM, FIBTEM and APTEM measurements handled by the ROTEM® Delta and Sigma devices were compared. ROTEM® FIBTEM values were also related to Clauss fibrinogen values.

Results: A correlation of Spearman's *r* (r_s) varying between 0.76 and 0.95 was displayed between A5, A10 and A20 measured by EXTEM, INTEM and APTEM assays executed on both devices; A5, A10 and A20 of FIBTEM correlated less well (r_s between 0.71 and 0.74), especially after five and ten minutes. Correlation between both devices regarding clotting time (CT) was poor. The observed correlation between levels of Clauss fibrinogen and FIBTEM A5 was $r_s = 0.70$, (95% confidence interval (CI): 0.38 to 0.87) for Delta and $r_s = 0.85$, (CI 0.65 to 0.94) for Sigma.

Conclusion: A5, A10 and A20 measured in EXTEM, INTEM and APTEM obtained from ROTEM® Delta and Sigma devices were similar. EXTEM, FIBTEM and APTEM CT values from both devices showed no correlation. Substantial variation was found between FIBTEM assays of the devices. Consequently, results of FIBTEM assays should always be interpreted in the context of device-specific reference values. Correlation with Clauss fibrinogen was better in the ROTEM® Sigma device.

Introduction

Postpartum haemorrhage continues to be one of the leading causes of maternal morbidity and mortality worldwide[1]. By close monitoring of haemostasis, abnormalities in coagulation parameters may be detected soon after onset of bleeding. This could contribute to more individually targeted haemostatic therapy for women experiencing postpartum haemorrhage, potentially leading to better maternal outcomes[2]. Some have suggested that a low fibrinogen concentration might be the earliest predictor of progression towards severe postpartum haemorrhage[3-6]. Due to long turn-around times of traditional coagulation parameters like Clauss fibrinogen, their clinical applicability in presence of rapid bleeding is limited. For early detection of changes in coagulation parameters, point-of-care devices using a visco-elastometric method for haemostasis testing like ROTEM® thromboelastometry can be used. Several studies conducted in women during postpartum haemorrhage have confirmed that the ROTEM® FIBTEM A5 assay, available 7 to 10 minutes after sampling, provides an indication of the concentration of fibrinogen during postpartum haemorrhage[2,5,7].

Until recently, the ROTEM® Delta device was the most common device to conduct thromboelastometry. To retrieve quick information on the coagulation status of a woman, users combine blood samples with reagents in several pipetting steps. Although this procedure is relatively user-friendly and the device is marketed as a point-of-care device, the procedure can be quite complicated for non-laboratory trained personnel. Now, the Werfen® company has introduced a fully automated successor of the ROTEM® Delta device, the Sigma. The fact that with this device there is no need for a pipetting procedure, makes it more applicable as a point-of-care device to be used at the bedside. We performed local validation of the new device. To the best of our knowledge no data have been published on comparability of measurements performed on the ROTEM® Delta and ROTEM® Sigma device.

The aim of this study was to compare ROTEM® EXTEM, INTEM, FIBTEM and APTEM measurements conducted by the ROTEM® Delta and Sigma devices in women experiencing postpartum haemorrhage. Moreover, ROTEM® FIBTEM values obtained from both devices were compared to corresponding Clauss fibrinogen concentrations.

Materials and methods

Design and study population

We studied women who had been included in the TeMpOH-2 (Towards better Prognostic and Diagnostic strategies for Major Obstetric Haemorrhage) study, a prospective cohort of pregnant women in the Netherlands between February 2015 and April 2018. Blood samples were drawn from women experiencing postpartum haemorrhage (blood loss ≥ 1000 mL). Up to three samples per woman were available, with the first sample drawn at a volume of blood loss between 800-1500 mL. Subsequent samples were drawn in case of an additional volume of blood loss of 1000-1500mL. Besides ROTEM® assays INTEM, EXTEM, FIBTEM and APTEM, fibrinogen concentration was assessed by the Clauss method. During the inclusion period of the TeMpOH-2 study, the ROTEM® Sigma device was launched onto the market. Subsequently, in one of the study sites measurements were performed simultaneously on both devices between July 2017 and April 2018 to study whether the devices yielded similar results. Data regarding maternal age, BMI, ethnicity, gestational age at birth, mode of birth, primary cause of haemorrhage and total volume of blood loss were recorded from medical files available at the maternity ward and operating theatre. Approval for the study was obtained from the Ethical Committee of the Leiden University Medical Centre (P13.246). The study was registered at ClinicalTrials.gov (NCT02149472). Written informed consent was obtained from all women participating in the study. Women below 18 years of age or with a gestational age below 24 weeks at the time of birth were excluded. Women with coagulation disorders or who used anticoagulants were not excluded.

Handling of ROTEM® devices and measurements

Both the ROTEM® Delta and Sigma device were positioned in a utility room equipped to locate laboratory devices at the maternity ward. ROTEM® measurements were performed by well-trained study personnel including research nurses and clinical midwives. In case measurements could not be started immediately, citrated blood samples were stored and handled at 37°C. Results were only taken into consideration when measurements had started within 4 hours after blood sampling as sample stability up to 4-6 hours has been confirmed in previous studies [8,9]. Blood withdrawal was performed by venepuncture using a 21 gauge blood collection needle or following insertion of a peripheral vein cannulation. Blood was collected in vacuum tubes (BD Vacutainer® Citrate tubes 3.2% and BD Vacutainer® spray-coated K2EDTA tubes), always discarding the first 3 mL of blood. Citrated tubes were collected before EDTA tubes. Visual inspection was conducted to verify if the minimum acquired volume of blood was collected, otherwise the tube was discarded. The citrated tubes for ROTEM analyses were handled at the maternity ward, whereas tubes containing blood for other coagulation parameters were send to the laboratory by pneumatic tube system transport. Blood samples for Clauss fibrinogen assays were handled immediately after arriving at the laboratory and centrifuged for 10 minutes at 2700g at a temperature of 20°C. External quality control for Clauss fibrinogen, APTT and PT was secured by participation in the international External Quality Assessment Programme (EQAP). Internal quality control was performed weekly by using the quality control reagents 'ROTROL N' (normal control) and 'ROTROL P' (abnormal control) provided by the manufacturer. Also, daily, quarterly and yearly maintenance on the devices was carried out according to the manufacturer's instructions. Single use reagents were used in the ROTEM® Delta device.

ROTEM® measurements

The ROTEM® Delta and Sigma analyses were performed according to the instructions provided by the manufacturer resulting in a visual display of the coagulation process (Figure 1). Parameters considered include clotting time (CT) in seconds and amplitudes of clot firmness measured in millimetres at 5 (A5), 10 (A10) and 20 (A20) minutes after start of clot formation including maximum clot firmness (MCF). The following reagents were used: EXTEM to activate the extrinsic coagulation pathway, INTEM to analyse the intrinsic part of the coagulation cascade, FIBTEM to provide an indication of the fibrinogen concentration and APTEM to detect hyperfibrinolysis. All measurements on the ROTEM Delta® device were conducted with single use reagent. On the ROTEM® Sigma device, the same measurements can be performed in a fully automated manner: a citrated tube with whole blood is inserted into a cartridge holding balls containing the four different reagents, which is then entered into the device initiating the measurements.

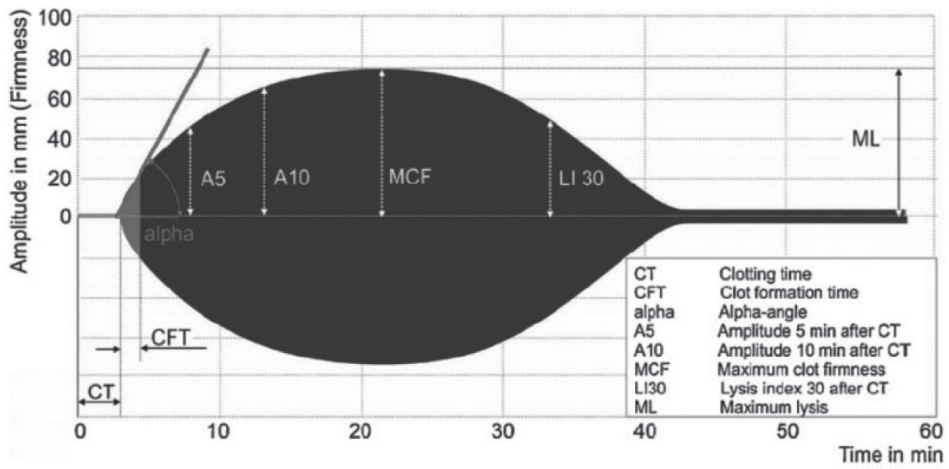

Figure 1. Graphical display of coagulation as provided by ROTEM® devices

Statistical analyses

Characteristics of the women included are reported using descriptive statistics. Coagulation parameters are presented as median and interquartile ranges because of their non-Gaussian distribution. Non-Gaussian distribution was established by graphical visualisation and confirmed via Kolmogorov-Smirnov test. All ROTEM® parameters were verified by visually inspecting their corresponding temograms for normal lay-out and by checking all parameters for error codes. Unlikely values were excluded from the analyses. We first calculated the differences between values of ROTEM® parameters CT, A5, A10, A20 and maximum clot firmness (MCF) from the same samples on each of the two devices. Since the ROTEM® Sigma device was newly launched, the Delta was considered the reference. Statistical significance of the differences between the results from the two devices was tested with the Wilcoxon signed rank test. We also assessed Spearman's rank correlation coefficients of ROTEM® Sigma and Delta results (r_s) and for the correlation between ROTEM® FIBTEM values of both devices and fibrinogen concentration as obtained by the Clauss assay[10].

Results

Characteristics of the women included

During the inclusion period of this sub-study of the TeMpOH-2 study, samples of 23 women experiencing postpartum haemorrhage were analysed, simultaneously in both ROTEM® devices. Baseline characteristics of the study population are reported in Table 1. Women were on average 35 years of age (interquartile range (IQR) 31 to 38), gave birth at a median gestational age of 39 weeks (IQR 37.4 to 39.3) and in 43% (10/23) by caesarean section. Median total volume of blood loss was 1400 mL (IQR 1200 to 1800). One sample was available for 23 women, and a second sample for three women. For EXTEM and INTEM assays, 26 valid measurements executed on both devices were available. For FIBTEM and APTEM assays, 23 and 25 valid combinations of measurements could be obtained. Of the total of 26 measurements, three FIBTEM and one APTEM measurement had to be excluded because of measurement errors, providing no valid result. Clauss fibrinogen assays were available for 21 women, with a median value of 4.3 (IQR 4.1 to 4.8).

Table 1. Characteristics of the women included

Patients	**n=23**
Maternal characteristics	
Age in years	35 (31 to 38)*
BMI in kg/m^2	23 (21 to 28)
Ethnicity, Caucasian	17 (74%)
Gestational age in weeks	39.0 (37.4 to 39.3)
Mode of birth	
Caesarean section	10 (43) †
Vaginal	13 (57)
Primary cause of bleeding	
Uterine atony	7 (30)
Retained placenta	8 (35)
Surgical bleeding	6 (26)
Genital tract trauma	1 (4)
Placental abruption	1 (4)
Pathological ingrowth of placenta/placenta praevia/uterine rupture/ coagulopathy	-
Bleeding characteristics	
Total volume blood loss in mL	1400 (1200 to 1800)

* Values are median (interquartile range), †(percentage)

EXTEM

Median difference between both devices for EXTEM CT was -6.5 seconds (IQR -9.25 to -1.75) with a poor Spearman's correlation coefficient, r_s = 0.18 (Figure 2, Table 2 and S1). Median differences between amplitudes at 5 (A5), 10 (A10) and 20 (A20) minutes and MCF were minor and statistically non-significant: -1.5 mm(IQR -3.25 to 2.0), 0.5mm (IQR -1.0 to 1.25), 0.0mm (IQR -1.25 to 1.25) and -0.5mm (-2.25 to 1.0) respectively; corresponding Spearman's correlation coefficients were excellent (Table 3).

INTEM

INTEM values showed a median difference in CT between devices of +3.5 seconds (IQR -2.0 to 7.0), Spearman's r_s = 0.86. Differences between amplitudes diminished over time: +2.0mm (IQR 1.0 to 3.0) after 5 (A5) and 10 (A10) minutes, and +1mm (IQR 0.0 to 2.0) at 20 (A20) minutes and MCF, with excellent Spearman's correlation coefficients. Although the absolute differences between amplitudes were relatively small, these were statistically significant.

FIBTEM

The median FIBTEM CT value, performed on the ROTEM® Delta device, was 6 seconds (IQR -1 to -10) lower when compared to the values of the Sigma, r_s = 0.42. This difference was also displayed in the amplitudes at 5, 10 and 20 minutes where some stabilisation occurred over time: A5 -4.0mm (IQR -5.0 to -2.0), A10 -3mm (IQR -3.0 to -1.0) and A20 -2mm (IQR -3.0 to -1.0). The differences at A5 and A10, relevant for acute clinical decision making, were statistically significant. Spearman's correlation coefficients for all FIBTEM measurements were only moderate compared to the results from the other assays, reflecting substantial variation between measurements.

APTEM

Variation between APTEM CT values on both devices was large, with a very poor Spearman's correlation coefficient of -0.09. Median differences between amplitudes over time were small, but did show variation over time: A5 0.0mm(IQR -1.0 to 3.0), A10 2.0mm (IQR 1.0 to 4.0), A20 2.0mm (IQR 0.5 to 2.5) and MCF 0.0mm (IQR -1.0 to 2.0).

Correlation between Clauss fibrinogen and ROTEM® FIBTEM parameters

To determine the correlation between fibrinogen concentration measured according to Clauss and ROTEM® FIBTEM parameters A5, A10, A20 and MCF, these values were compared for both devices. Spearman's correlation coefficients for fibrinogen and FIBTEM A5 samples were *r* = 0.70, (95% CI: 0.377 to 0.867) for the Delta device and *r*=0.85, (95% CI: 0.651 to 0.935) for the Sigma, presented in the supplemental material (S2, S3).

Table 2. Differences between Delta and Sigma for CT, A5, A10, A20 and MCF

	EXTEM			INTEM			FIBTEM			APTEM		
	Δ	IQR	p*	Δ	IQR	p*	Δ	IQR	p*	Δ	IQR	p*
CT s	-6.5	-9.25 to -1.75	<0.01	3.5	-2.0 to 7.0	0.01	-6.0	-10.0 to -1.0	<0.01	-4.0	-7.0 to 4.5	0.17
A5 mm	-1.5	-3.25 to 2.0	0.16	2.0	1.0 to 3.0	<0.01	-4.0	-5.0 to -2.0	<0.01	0.0	-1.0 to 3.0	0.17
A10 mm	0.5	-1.0 to 1.25	0.32	2.0	1.0 to 3.0	< 0.01	-3.0	-3.0 to -1.0	0.01	2.0	1.0 to 4.0	<0.01
A 20 mm	0.0	-1.25 to 1.25	0.77	1.0	0.0 to 2.0	<0.01	-2.0	-3.0 to -1.0	0.07	2.0	0.5 to 2.5	0.02
MCF mm	-0.5	-2.25 to 1.0	0.18	1.0	0.0 to 1.0	<0.01	-1.0	-2.0 to 0.0	0.12	0.0	-1.0 to 2.0	0.52

Values are median (interquartile range), Δ difference, IQR interquartile range, *p-values of Wilcoxon signed-rank test, CT clotting time, MCF maximum clot firmness

Table 3. Correlation between Delta and Sigma for CT, A5, A10, A20 and MCF

	EXTEM			INTEM			FIBTEM			APTEM		
	n	r_s	p*	n	r_s	p*	n	r_s	p*	n	r_s	p*
CT s	26	0.180	0.38	26	0.855	<0.01	23	0.416	0.05	25	-0.87	0.68
A5 mm	26	0.904	<0.01	26	0.950	<0.01	23	0.712	<0.01	25	0.850	<0.01
A10 mm	26	0.905	<0.01	26	0.910	<0.01	23	0.738	<0.01	25	0.805	<0.01
A 20 mm	26	0.885	<0.01	26	0.907	<0.01	23	0.733	<0.01	25	0.759	<0.01
MCF mm	26	0.840	<0.01	26	0.940	<0.01	23	0.769	<0.01	25	0.736	<0.01

r_s Spearman's correlation coefficient, *correlation coefficients and p-value by Spearman's rank test, CT Clotting Time, MCF Maximum Clot Firmness

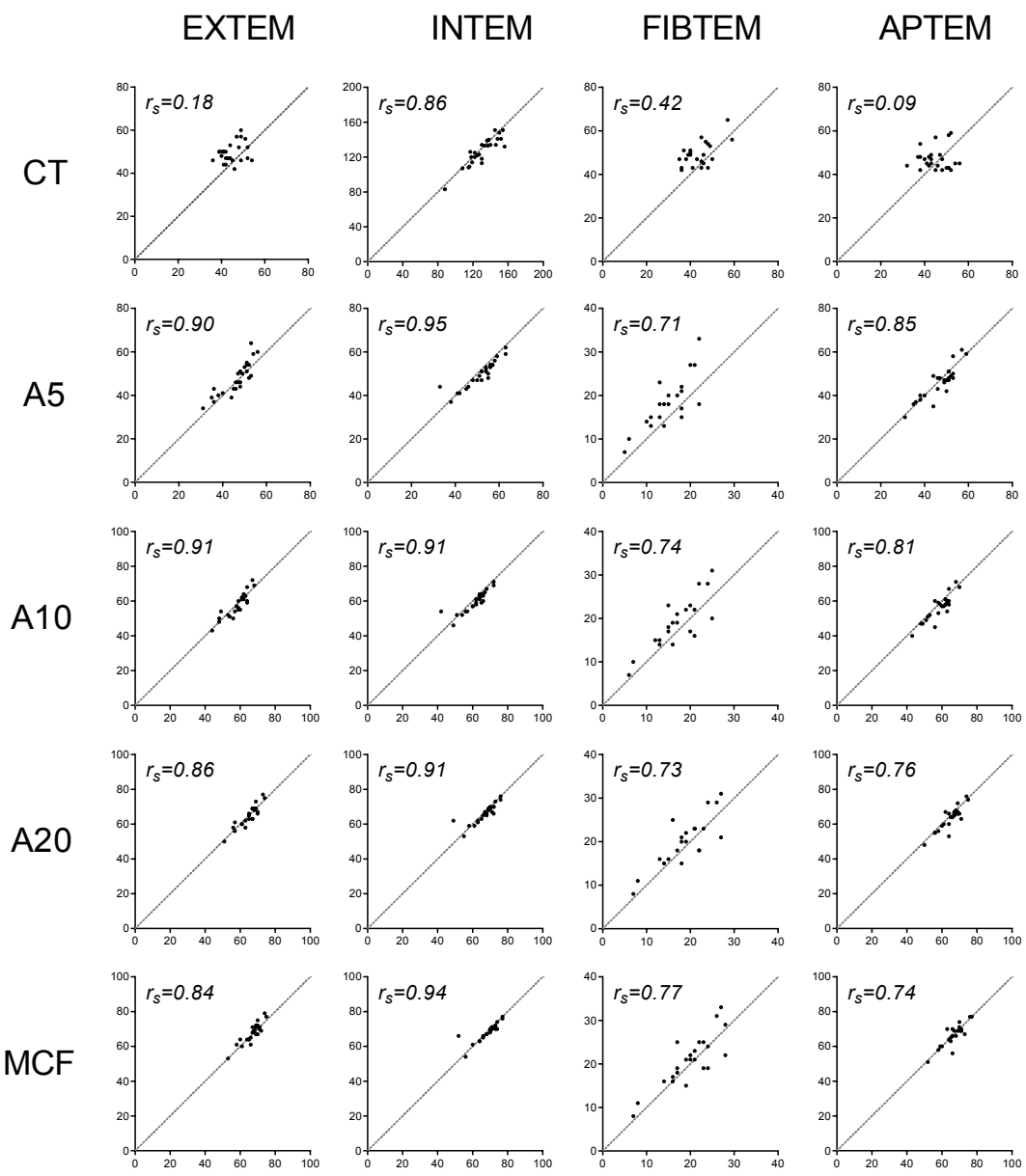

Figure 2. **Scatterplots and Spearman's correlation coefficients (r_s) for EXTEM, INTEM, FIBTEM and APTEM parameters measured on ROTEM® Delta and Sigma devices**

Discussion

A positive correlation was found for MCF, A5, A10 and A20 measured by ROTEM® assays EXTEM, INTEM and APTEM, executed on both the ROTEM® Delta and Sigma device in women experiencing postpartum haemorrhage. FIBTEM parameters however, showed rather wide variation, and only moderate correlation. Moreover, statistically significant differences were found between devices at A5 and A10, the most relevant parameters for acute clinical decision making. FIBTEM measurements from both devices showed moderate to good correlation with Clauss fibrinogen concentration, with a better result for the Sigma device.

Strength and limitations of this study

A strength of our study is that we were able to prospectively study ROTEM® measurements performed in women experiencing postpartum haemorrhage. Samples were handled on ROTEM® Delta and Sigma devices simultaneously and were not only compared to each other but also to the traditional Clauss fibrinogen assay. A limitation of our study is the small sample size, specifically a limited number of low fibrinogen concentrations. Since low fibrinogen concentrations represent women who are potentially in need of a haemostatic intervention, it is of high importance to also assess validity of samples in women with low fibrinogen concentrations.

Interpretation of results

The ability to perform point-of-care coagulation tests in acutely bleeding patients potentially provides a considerable clinical advantage. Yet, specifically in an acute situation, reliability of measurements is of utmost importance. For EXTEM, INTEM and APTEM assays, comparability was found to be excellent between both devices. This confirms the reliability of our measurements and study procedures. However, a statistically significant difference was found between FIBTEM measurements A5 and A10, the most relevant parameters for acute clinical decision making. For example, the use of an algorithm based on FIBTEM A5 on a Delta device will tend to provide a lower result for a given Clauss fibrinogen value. This will result in overtreatment and unnecessary interventions in case this difference remains unrecognized and the algorithm is not amended to account for this device specific difference. Consequently we can conclude that the two devices are not directly interchangeable and intervention points for algorithms must be tailored to the device used. When looking at the performance of both devices in our cohort of women experiencing postpartum haemorrhage, we did observe a better correlation with Clauss fibrinogen in the ROTEM® Sigma device (r_s range 0.82-0.86) as compared to the Delta (r_s range 0.66-0.70).

The question that remains unanswered is why this effect is only observed in FIBTEM measurements and not in EXTEM, INTEM and APTEM. Potentially, the absence of platelets in the FIBTEM assay, resulting in lower amplitudes when compared to the other assays increases the sensitivity of the FIBTEM measurement. This finding needs further evaluation because of its high importance to clinical practice with the use of practice flow-charts using exact FIBTEM cut-off points to initiate (haemostatic) treatments.

Very poor correlation between CT measured on both devices was observed for EXTEM, FIBTEM and APTEM assays. Correlation for INTEM CT however, was strong. A new mode of presenting the reagent (a ball constituted of reagent, located at the bottom of the cartridge) on top of a rather short dissolving time as currently programmed in the Sigma device seems to be a possible explanation for this problem . INTEM CT takes considerably longer compared to CT's of the other assays, thereby providing more time for the process of liquefying. We conclude that CT values obtained by the Sigma device are unreliable. Future adaptation of the cartridge and elongation of the period of reagent dissolving are possible solutions for this issue.

Comparison with other studies

To the best of our knowledge no previous studies have been conducted into the agreement between ROTEM® Delta and Sigma measurements in women experiencing postpartum haemorrhage. When looking at a non-pregnant population, we only found a trial registered by Tem Innovations GmbH (NCT02379104) into the method comparison of the ROTEM® Sigma with its predecessor model ROTEM® Delta to confirm equality of reference intervals; results are expected in December 2018. Some have studied agreement between ROTEM® FIBTEM parameters and Clauss fibrinogen concentrations. The peripartum use of thromboelastometry and ROTEM® Delta were studied among 153 women and compared with fibrinogen concentrations assessed by the Clauss method[11]. Samples drawn within one hour after childbirth showed only moderate correlation between ROTEM® FIBTEM parameters and fibrinogen concentrations: Spearman's rank correlation coefficients were 0.57 (A10), 0.56 (A20) and 0.56 (MCF). Another study into the bedside assessment of fibrinogen concentration in postpartum haemorrhage by thromboelastometry reported on results of 37 women experiencing postpartum haemorrhage[12]. Correlation between Clauss fibrinogen concentration and ROTEM® FIBTEM parameters A 5, A15 and MCF was found to be strong (r_s 0.84 to 0.86). The correlation between ROTEM® FIBTEM and Clauss fibrinogen displayed in our cohort lies between values of correlation described in these earlier studies. In both articles, the authors did not state whether single or multiple-use reagent was used.

Clinical implications

During acute situations like postpartum haemorrhage, clinicians are keen to get fast, yet reliable results on a patient's fibrinogen status. Results from ROTEM® FIBTEM assays of the devices differed significantly, especially in the earlier measurements (A5 and A10) emphasizing the need to validate new devices before implementation and obtain device specific reference ranges, to inform appropriate device specific intervention points on an algorithm. Results of FIBTEM assays should be used with caution and should always be interpreted in the context of the specific device used, and all available patient and bleeding characteristics, because of the potential variation between measurements. Parallel sampling of Clauss fibrinogen level is advised to be used as a comparison in the course of ongoing haemorrhage.

Conclusion

In our cohort of 23 women experiencing postpartum haemorrhage, we displayed a positive correlation between thromboelastometry assays EXTEM, INTEM and APTEM executed on the ROTEM® Delta and Sigma device: results of these assays from both devices are similar. CT values as obtained by the Sigma device are unreliable. A wide variation was shown between ROTEM® FIBTEM assays performed on both devices, especially in the earlier measurements (A5 and A10), important to acute clinical decision-making. Consequently, results of FIBTEM assays should be interpreted with caution and always in the context of device-specific reference values determining the intervention points on an algorithm. Correlation with Clauss fibrinogen was better in the ROTEM® Sigma device as compared to the Delta.

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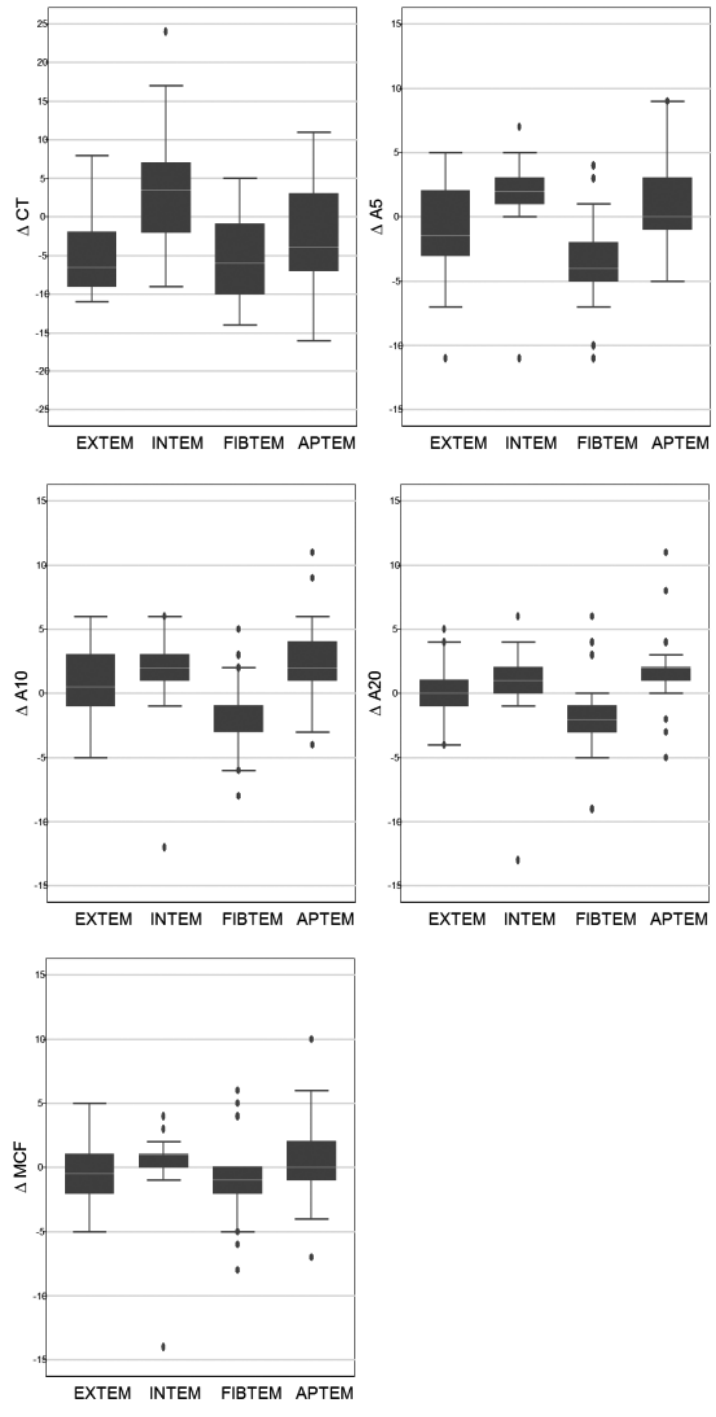
Supplemental material

S1 Figure 1 Median differences between EXTEM, INTEM, FIBTEM and APTEM parameters measured on ROTEM Delta and Sigma devices

S2 Table 1 Correlation between FIBTEM and Clauss fibrinogen for Delta and Sigma device

S3 Figure 2 Correlation Clauss fibrinogen and ROTEM® FIBTEM measurements

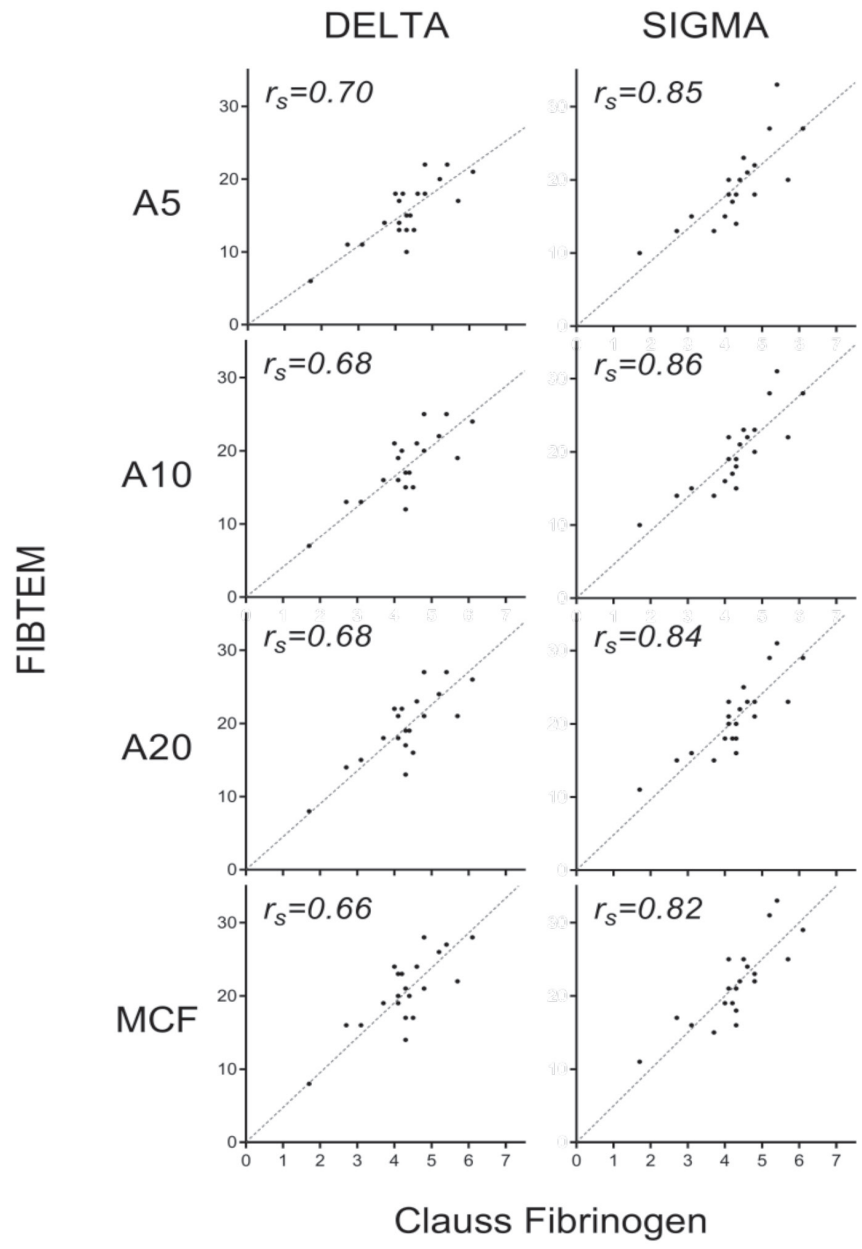


S1. Figure. Median differences between EXTEM, INTEM, FIBTEM and APTEM parameters measured on ROTEM® Delta and Sigma devices

S2. Table Correlation between FIBTEM and Clauss fibrinogen for Delta and Sigma device

	Delta			Sigma		
	n	r_s	p*	n	r_s	p*
CT s	21	-0.163	0.48	21	-0.011	0.96
A5 mm	21	0.695	<0.01	21	0.845	<0.01
A10 mm	21	0.681	<0.01	21	0.862	<0.01
A 20 mm	21	0.680	<0.01	21	0.841	<0.01
MCF mm	21	0.655	<0.01	21	0.821	<0.01

r_s Spearman's correlation coefficient, *correlation coefficients and p-value by Spearman's rank test, CT Clotting Time, MCF Maximum Clot Firmness



S3. Figure Correlation Clauss fibrinogen and ROTEM® FIBTEM measurements

6 ASSOCIATION BETWEEN CLAUSS FIBRINOGEN CONCENTRATION AND ROTEM® FIBTEM A5 IN WOMEN WITH POSTPARTUM HAEMORRHAGE: VALIDATION OF CUT-OFF POINTS

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Submitted

Abstract

Background: Point-of-care tests like FIBTEM A5 have been proposed to guide the treatment of patients who might have low fibrinogen concentrations (≤2 g/L). The aim of this study was to describe fibrinogen concentrations according to previously proposed FIBTEM A5 cut-off points in blood samples collected from women during persistent postpartum haemorrhage.

Methods: Prospective multicentre cohort study in 511 women sustaining postpartum haemorrhage. A total of 637 blood samples were drawn during haemorrhage. Clauss fibrinogen concentrations and ROTEM® FIBTEM A5 values were studied to assess the diagnostic properties of previously proposed FIBTEM A5 cut-off points for the detection of low fibrinogen concentrations.

Results: Of 511 women with a median total volume of blood loss of 1500 mL (IQR 1200 to 2000) 31 women (6%) developed Clauss fibrinogen concentrations below 2 g/L. Using FIBTEM A 5 cut-off of ≤ 7 mm: 48% of cases with Clauss fibrinogen ≤2 g/L were missed (FIBTEM A5 > 7mm), and of the 28 samples with FIBTEM A5 ≤ 7mm, 12 (43%) samples had Clauss fibrinogen >2 g/L. Using FIBTEM A5 cut-off of ≤12mm: 13% of cases with Clauss fibrinogen ≤2 g/L were missed and of the 145 samples with a FIBTEM A5 ≤12 mm, 118 had Clauss fibrinogen >2 g/L, resulting in false positive selection of 81% of women. Using FIBTEM A5 ≤ 15 mm: 97% (30/31) of the samples with Clauss fibrinogen ≤2 g/L were accurately selected; yet 89% (248/278) of samples that were selected had a fibrinogen concentration of >2 g/L. Based on the Youden index, the optimal cut-off point in our cohort was a FIBTEM A5 of 12mm with sensitivity 87% and specificity 81%.

Conclusions: Our findings suggest that if FIBTEM A5 lower than 12 mm would have been used to detect women with fibrinogen concentrations below 2 g/L in order to treat them with fibrinogen concentrate, 87 % of the women with fibrinogen below 2 g/L would correctly have received fibrinogen. However, most women (81%) receiving fibrinogen concentrate would not have needed it, because they had plasma fibrinogen concentrations above 2 g/L.

Introduction

Postpartum haemorrhage remains one of the leading maternal health problems worldwide[1, 2]. Although in most women the primary cause is obstetric, acquired haemostatic impairment may aggravate bleeding[3, 4]. From previous studies, a low fibrinogen concentration emerges as the earliest predictor of progression towards severe postpartum haemorrhage[5, 6,7-10]. By timely detection of low fibrinogen concentrations, targeted haemostatic therapy may be administered to restore adequate concentrations of fibrinogen. The Clauss fibrinogen assay is the standard coagulation test to assess fibrinogen concentration. Its downside is a turn-around time of up to 60 minutes, rendering this test unsuitable for clinical decision making in the acute setting[11]. Point-of-care devices like ROTEM® thromboelastometry can detect changes in the coagulation system within ten minutes from blood sampling[4]. In trauma, cardiac and liver surgery, thromboelastometry is increasingly used to predict bleeding, diagnose fibrinogen deficiency and guide fibrinogen administration. Evidence is emerging that ROTEM-guided transfusion strategies may reduce the need for blood products and bleeding-associated morbidity[12]. ROTEM® devices are becoming more widely available in maternity wards, where treatment is generally dependent on local algorithms. Several studies in women sustaining postpartum haemorrhage found that fibrinogen concentrations below 2 g/L were associated with progression towards more severe postpartum haemorrhage[5-9, 13]. The ROTEM® FIBTEM A5 assay, available within 7 to 10 minutes after sampling, may provide a quantitative assessment of the plasma concentration of fibrinogen of women during postpartum haemorrhage and has been established as an early biomarker for progression towards more severe postpartum haemorrhage[4, 13, 14]. However, the diagnostic properties of FIBTEM A5 to accurately identify Clauss fibrinogen concentrations ≤2 g/L remain unclear. In a previous trial comparing administration of fibrinogen concentrate with placebo in women with postpartum haemorrhage, a FIBTEM A5 cut-off of 15 mm was used and no difference was observed between groups with regard to number of units of red blood cells, plasma, cryoprecipitate and platelets transfused[15]. An earlier study in women with postpartum haemorrhage suggested a FIBTEM A5 value of 6 mm as the cut-off point that correlates best with Clauss fibrinogen below 2 g/L. To create reliable ROTEM®- based treatment algorithms for use during postpartum haemorrhage, the properties of the FIBTEM A5 test to detect Clauss fibrinogen concentrations below 2 g/L among women at risk of severe outcome of postpartum haemorrhage needs to be established.

The aim of this study was to describe fibrinogen concentrations according to previously proposed FIBTEM A5 cut-off points in blood samples collected from women suffering persistent postpartum haemorrhage.

Methods

Design and study population

We studied women who had been included in the TeMpOH-2 (Towards better Prognostic and Diagnostic strategies for Major Obstetric Haemorrhage) study, a prospective cohort of pregnant women in the Netherlands between February 2015 and April 2018. Women were recruited during pregnancy at the outpatient clinics and maternity wards of three participating hospitals: the Leiden University Medical Center, the Erasmus Medical Centre Rotterdam and the Zwolle Isala Clinics.

Included women were monitored for the occurrence of postpartum haemorrhage (≥1000 mL blood loss within 24 hours from childbirth) and followed until discharge from hospital. All subjects were treated according to the Dutch regulations for prevention and management of postpartum haemorrhage[16]. Blood samples were drawn from women in case they developed postpartum haemorrhage. Up to three samples per woman were sampled, with the first sample drawn at a blood loss between 1000-1500mL, but in some cases pragmatically drawn from 800mL of blood loss at time of achieving intravenous access. Subsequent samples were drawn in case of an additional volume of blood loss of 1000-1500mL. Both a ROTEM® FIBTEM assay and fibrinogen concentration assessed by the Clauss method were performed. A Clauss fibrinogen concentration of ≤2g/L was considered to be a low fibrinogen level. FIBTEM cut-off points of 7, 12 and 15 mm that were used in previous studies as an equivalent of a low fibrinogen (≤2g/L) were compared to Clauss fibrinogen concentrations. ROTEM thromboelastometry results were not available to treating clinicians. During the inclusion period of the TeMpOH-2 study, the ROTEM® Delta was replaced by the ROTEM® Sigma device. On the ROTEM® Sigma device, measurements are performed in a fully automated manner. In one of the study sites measurements were performed simultaneously with both devices[17]. Approval for the study was obtained from the Ethical Committee of the Leiden University Medical Centre (P13.246) and from the institutional review board of each participating hospital. The study was registered at ClinicalTrials.gov (NCT02149472). The ethical committee provided the possibility to ask women for verbal informed consent during early postpartum haemorrhage in case they had not yet been included in the study during pregnancy. The present analysis was restricted to data from women who provided written informed consent for their data to be used in the study. Women below 18 years of age or with a gestational age below 24 weeks at the time of birth were excluded. Women with coagulation disorders or who used anticoagulants were not excluded.

Data collection

Information on maternal and obstetric characteristics was collected by well-trained research nurses who performed comprehensive chart reviews. Data were recorded from medical files available at the maternity ward for the following parameters: maternal age at the time of birth, parity, gestational age, mode of birth, presence of pre-eclampsia or HELLP syndrome, presence of a coagulation disorder, anticoagulant use and total volume of blood loss, primary cause of major obstetric haemorrhage, abnormal placentation, shock, volume and timing of administration of fluids and blood products, performance and timing of surgical and haemostatic interventions, and consecutive measurements of blood loss until cessation of bleeding. Blood loss was measured by weighing gauzes and all other soaked materials and by use of a collector bag and suction system in the operating theatre.

Handling of ROTEM® devices and measurements

In two of the participating hospitals, the ROTEM® devices were positioned at the laboratory and samples were handled by laboratory staff. In the other hospital, the devices were positioned in a utility room equipped to house laboratory devices at the maternity ward. Here, ROTEM® measurements were performed by well-trained study personnel including research nurses and well-trained clinical midwives. In case measurements could not be started immediately, citrated blood samples were stored and handled at 37°C. Results were only taken into consideration when measurements had started within 4 hours after blood sampling, since sample stability up to 4-6 hours has been confirmed in previous studies[18,19]. Blood draw was performed by venepuncture using a 21 -gauge blood collection needle or following insertion of a peripheral vein cannula. Blood was collected in vacuum tubes (BD Vacutainer® Citrate tubes 3.2% and BD Vacutainer® spray-coated K2EDTA tubes), always discarding the first 3 mL of blood. Citrated tubes were collected before EDTA tubes. Visual inspection was conducted to verify if the minimum acquired volume of blood had been collected. If not, the tube was discarded. In case samples were not handled directly at the maternity ward, tubes were sent to the laboratory by pneumatic tube system transport. Blood samples for Clauss fibrinogen assays were handled immediately after arriving at the laboratory and centrifuged for 10 minutes at 2700 g at a temperature of 20°C. External quality control for Clauss fibrinogen, APTT and PT and (in two of three participating hospitals) ROTEM® parameters was secured by participation in the international External Quality Assessment Programme (EQAP) by ECAT. Internal quality control was performed weekly by using the quality control reagents 'ROTROL N' (normal control) and 'ROTROL P' (abnormal control) provided by the manufacturer. Also, daily, quarterly and yearly maintenance on the devices was carried out according to the manufacturer's instructions. Single use reagents were used in the ROTEM® Delta device.

Statistical analyses

Characteristics of women are reported using descriptive statistics. Clauss fibrinogen and ROTEM® parameters are presented as median and interquartile ranges because of their non-Gaussian distribution. In case of multiple samples per woman these were all taken into account in the analysis. All ROTEM® parameters were verified by visually inspecting corresponding temograms for normal lay-out and by checking all parameters for error codes. Incorrect values were excluded from analysis. Spearman's rank correlation coefficients (r_s) were assessed for the correlation between ROTEM® FIBTEM values of both devices and fibrinogen concentration as obtained by Clauss assay[20]. Sensitivity, specificity, positive and negative predictive value and the area under the receiver operator curve (AUC's) were calculated to assess the diagnostic properties of FIBTEM A5 to discriminate women with and without a fibrinogen concentration of ≤2g/L. The cut-off with the highest sensitivity and specificity was determined by use of the Youden index, which defines the maximum potential effectiveness of a test[21]. A complete case analysis was performed, data were not imputed.

Results

Women characteristics

Over the three-year inclusion period, 17203 women gave birth in the participating hospitals. Of all women, 1605 suffered postpartum haemorrhage defined as a volume of blood loss of ≥1000 mL within 24 hours from childbirth and 591 women agreed to participate in the study. For 511 women, valid corresponding measurements of fibrinogen and FIBTEM A5 were available resulting in 637 samples (Figure 1). Baseline characteristics are reported in *Table 1*. Women were on average 32 years of age (interquartile range (IQR) 28 to 35), gave birth at a median gestational age of 39.4 weeks (IQR 38.0 to 40.6) and in 23% by caesarean section. Median total volume of blood loss was 1500mL (IQR 1200 to 2000) and the most prevalent causes of haemorrhage were atony and/or retained placenta in 76% of women. One sample was available for 397 women, a second sample for 102 and a third sample for 12 women.

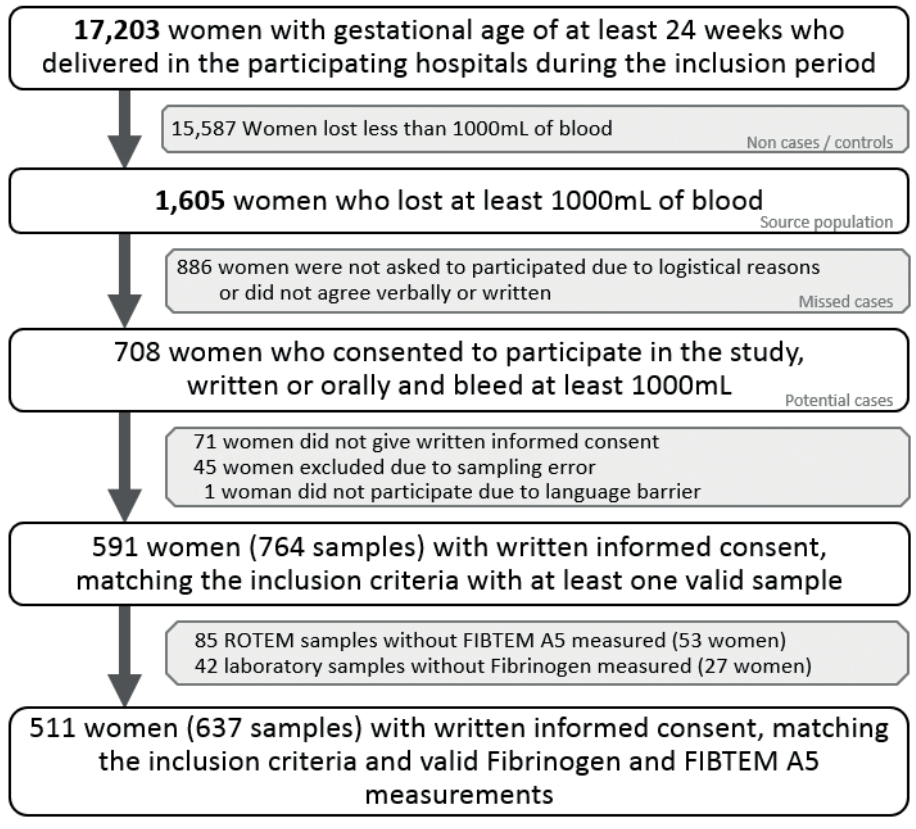

Figure 1. Inclusion flowchart

Table 1. Women characteristics

	Women
Maternal characteristics	n =511
Age in years	32 (28 to 35)*
BMI in kg/m^2	24 (22 to 28) *
Ethnicity, Caucasian	86%
Gestational age in weeks	39.4 (38.0 to 40.4) *
Nulliparity	51%
Risk factors PPH	
Pre-eclampsia/HELLP	4%
Anti-coagulant use	3%
Known coagulation disorder	
Multiple pregnancy	9%
Mode of birth	
Vaginal	77%
Caesarean section	23%
Primary cause of bleeding	
Uterine atony	35%
Retained placenta or remnants of placental tissue	41%
Surgical bleeding	9%
Genital tract trauma	9%
Placenta praevia	2%
Pathological ingrowth of placenta	1%
Placental abruption	2%
Uterine rupture	1%
Coagulopathy	0%
Bleeding	
Total volume of clear fluids (L)	1.0 (0.5 to 2.0) *
Total units of blood products (n)	0 (0 to 0) *
Total volume of blood loss (n)	1500 (1200 to 2000) *
Samples	
Sample 1000-1500mL	n=412
Blood loss at sampling time (L)	1.0 (0.9 to 1.2) *
Units of RBC received at sampling time (n)	0.0 (0.0 to 0.0) *
Fluids received at sampling time (L)	1.0 (0.0 to 2.0) *

Continuing. Table 1. Women characteristics

	Women
Sample 1500-2500mL	n=185
Blood loss at sampling time (L)	1.8 (1.5 to 2.0) *
Units of RBC received at sampling time (n)	0.0 (0.0 to 0.0) *
Fluids received at sampling time (L)	2.0 (1.0 to 4.0) *
Sample >2500mL	n=40
Blood loss at sampling time (L)	2.7 (2.5 to 3.4) *
Units of RBC received at sampling time (n)	0.0 (0.0 to 2.0) *
Fluids received at sampling time (L)	3.0 (2.0 to 6.0) *
Total	n=637
Blood loss at sampling time (L)	1.2 (1.0 to 1.6) *
RBC received at sampling time	0.0 (0.0 to 0.0) *
Fluids received at sampling time (L)	1.0 (1.0 to 3.0) *

* All values in the table reported in this format are median and (IQR)

Clauss Fibrinogen and FIBTEM A5 levels observed in cohort

In total 637 valid combinations of measurements of Clauss fibrinogen and FIBTEM levels were obtained. Median FIBTEM A5 level was 17mm (IQR 13 to 20) and median Clauss fibrinogen concentration 3.9 g/L (IQR 3.1 to 4.5). Of the 511 women, 31 (6%) had a Clauss fibrinogen concentration of ≤2 g/L.

Correlation Clauss fibrinogen ROTEM® FIBTEM A5

In the 637 samples, overall correlation between Clauss fibrinogen concentration and FIBTEM A5 showed a Spearman's correlation coefficient (r_s) of 0.64 (95% Confidence Interval (CI): 0.60 to 0.69). Spearman's correlation coefficient between Claus fibrinogen concentration and FIBTEM measured on the ROTEM® Delta and Sigma device were (r_s) 0.63 (95% CI: 0.58 to 0.67) and (r_s) 0.76 (95% CI: 0.63 to 0.85) respectively (Figure 2). Within the three sample categories, Spearman's correlation coefficients improved with increasing volumes of blood loss (Table 2).

Table 2. **Fibrinogen concentration as assessed with the Clauss assay, ROTEM® FIBTEM A5 values and their correlations according to increasing volumes of blood loss among 511 women with postpartum haemorrhage.**

Samples	Volume of blood loss* (L)	Clauss Fibrinogen* (g/L)	FIBTEM A5* (mm)	Spearman's correlation (r_s) (95% CI) †
1.0-1.5 L (n = 412)	1.0 (0.9 to 1.2)	4.1 (3.5 to 4.7)	18 (14 to 20)	0.56 (0.48 to 0.62)
1.5-2.5 L (n = 185)	1.8 (1.5 to 2.0)	3.5 (2.9 to 4.1)	15 (12 to 18)	0.67 (0.58 to 0.74)
> 2.5 L (n = 40)	2.7 (2.5 to 3.4)	2.7 (2.2 to 3.3)	12 (10 to 16)	0.79 (0.64 to 0.89)
All samples (n = 637)	1.2 (1.0 to 1.6)	3.9 (3.1 to 4.5)	17 (13 to 20)	0.64 (0.60 to 0.69)

* Values in the table reported in this format are median and (IQR), † Spearman's correlation (r_s) (95% CI)

Discriminative ability of FIBTEM A5 for low fibrinogen concentration and cut-off points

The ability of FIBTEM A5 to select observations with a Clauss fibrinogen concentration of ≤2 g/L was good, area under Receiver Operating Curve 0.92 (95% confidence interval (CI) 0.87 to 0.97). Based on the Youden index, the best cut-off point in our cohort was 12mm with a sensitivity of 87% and specificity of 81%, missing 4 of the 31 cases (13%) of a Clauss fibrinogen ≤2 g/L and false positively selecting 118 cases (81%) (Table 3). When 15 mm was used as FIBTEM A5 cut-off point, 97% (30/31) of the samples with a Clauss fibrinogen ≤2 g/L were accurately selected, but 89% (248/278) of selected samples had a fibrinogen concentration >2 g/L. When a lower cut-off value for FIBTEM A5 was chosen, these numbers changed: a cut-off value of FIBTEM A5 of 6 mm accurately selected 26% (8/31) of samples with a Clauss fibrinogen concentration of ≤2 g/L and 74% (23/31) of samples with a low fibrinogen were missed. Yet, a lower percentage of 53% (9/17) of samples that were selected based on FIBTEM A5 value < 7 mm had corresponding Clauss fibrinogen values of >2g/L.

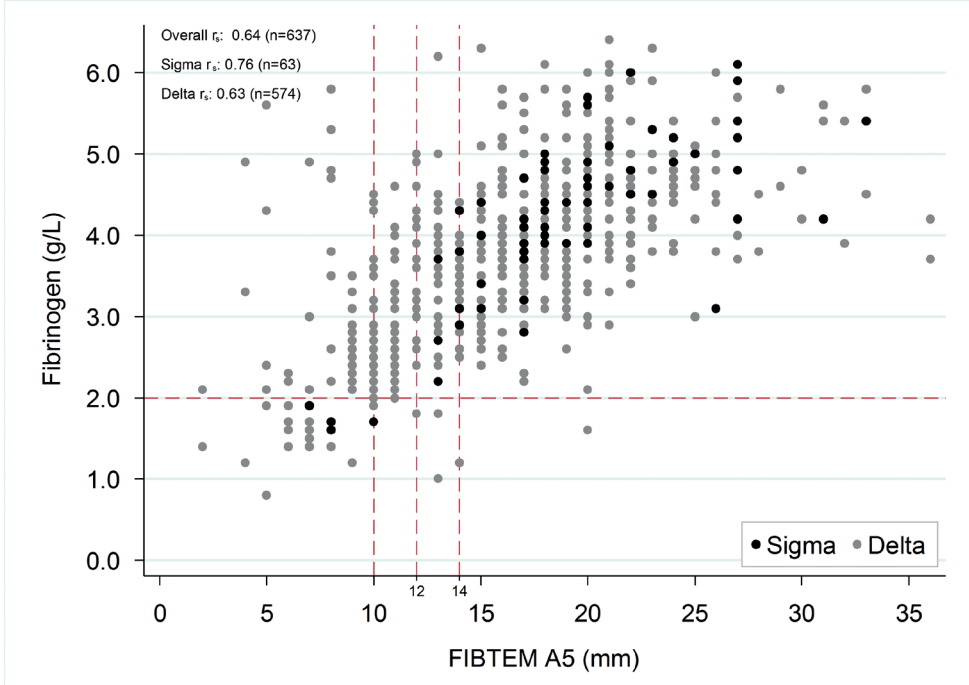

Figure 2. **Scatterplot correlation Clauss fibrinogen and FIBTEM A 5**

Table 3. Diagnostic test characteristics for FIBTEM A5 at various cut-off values to detect Clauss fibrinogen ≤2g/L

FIBTEM (mm)	Sensitivity	Specificity	Proportion of samples with fibrinogen ≤2 g/L incorrectly classified as fibrinogen >2 g/L* False negative	Proportion of samples with FIBTEM A5 below cut-off, incorrectly classified fibrinogen ≤ 2 g/l† False positive
A5 ≤ 6	26%	99%	74% (23/31)	53% (9/17)
A5 ≤ 7	52%	98%	48% (15/31)	43% (12/28)
A5 ≤ 8	65%	97%	36% (11/31)	50% (20/40)
A5 ≤ 9	68%	94%	32% (10/31)	63% (36/57)
A5 ≤ 10	77%	90%	23% (7/31)	71% (60/84)
A5 ≤ 11	81%	85%	19% (6/31)	79% (92/117)
A5 ≤ 12	87%	81%	13% (4/31)	81% (118/145)
A5 ≤ 13	94%	73%	6% (2/31)	85% (162/191)
A5 ≤ 14	97%	67%	3% (1/31)	87% (202/232)
A5 ≤ 15	97%	59%	3% (1/31)	89% (248/278)

* In the numerator the number of women with a FIBTEM at or below the cut-off and a fibrinogen concentration ≤2 g/L, in the denominator the total number of women with a fibrinogen concentration ≤2 g/L.

† In the numerator the number of women with a FIBTEM at or below the cut-off and a fibrinogen concentration >2 g/L, in the denominator the total number of women with a FIBTEM at or below the cut-off.

Discussion

Based on the Youden index, the optimal cut-off point in our cohort was a FIBTEM A5 of 12mm. If FIBTEM A5 would have been used to detect women with a low fibrinogen concentration in a treatment algorithm that uses the 12 mm cut-off to initiate administration of fibrinogen concentrate, 87 percent of women in need of fibrinogen would have been treated. However, a large majority of women (81%) would have received fibrinogen concentrate despite normal plasma fibrinogen concentrations.

Strengths and limitations

To the best of our knowledge this is the largest study to date to describe fibrinogen concentrations according to previously proposed FIBTEM A5 cut-off points in blood samples collected from women suffering postpartum haemorrhage. The strength of this prospective study is that we were able to include a large cohort of women sustaining postpartum haemorrhage with repeated blood samples containing set panels at established times during postpartum haemorrhage. This enables for reliable and generalizable estimation of correlation and determination of interventional cut-off points based on Clauss fibrinogen and FIBTEM A5 levels. The prospective design of our study also has limitations: although the majority of women consented to participate in the study during their pregnancy, or in case they did not give consent yet, the opportunity was created to provide verbal consent during early postpartum haemorrhage, we did experience the challenge of performing study procedures in acutely ill women as described by others[15]. A total of 31 (6.1%) of the 511 women in our cohort developed a Clauss fibrinogen concentration ≤2g/L. Keeping track of missed cases that could have been included in the study, we noticed that women who lost a large volume of blood in a short period of time were more frequently not included in the study due to lack of time and personnel to perform study procedures in such an acute situation. This may have led to an underestimation of the incidence of a Clauss fibrinogen concentration ≤2g/L. However, the incidence of a Clauss fibrinogen concentration ≤2g/L in our source population of women giving birth during in the participating hospitals during the inclusion period was 0.2% (31/17203) which is exactly the same (0.2%, 342/191772) as observed in a previous study with the same source population (women giving birth in the Netherlands)[10].

Comparison with other studies

Correlation between Clauss fibrinogen concentration and FIBTEM A5 in women experiencing postpartum haemorrhage has been described in two previous studies. One observational study with postpartum haemorrhage (>500mL after vaginal birth or >1000mL after caesarean section) found a Spearman's correlation coefficient (r_s) of 0.86 for the haemorrhage group and r_s 0.83 for the control group[22]. No information was provided with regard to volume of blood loss at the time of sampling and number of

samples with a Clauss fibrinogen ≤2g/L, yet correlation coefficients were similar for both groups, whereas we found an increase in correlation with higher volumes of blood loss. Another study into FIBTEM A5 as a biomarker for progression of postpartum haemorrhage found a moderate correlation in 312 paired Clauss fibrinogen and FIBTEM A5 assays of r_s 0.59[13]. These assays were sampled at study entry, at a median volume of blood loss of 1200mL. Our findings corroborate these results with a r_s of 0.55 at 1000mL and r_s of 0.67 at 1800mL. The choice for a cut-off point for a diagnostic test depends on the risks for adverse outcomes when patients are incorrectly classified and/or incorrectly treated. Since the risk of adverse outcomes is very high when fibrinogen concentrations are below 2 g/L, sensitivity of the test to diagnose all women with fibrinogen below 2 g/L should be high. At the time of writing, there is no consensus on an optimal cut-off point for FIBTEM A5 and results of previous studies lack conformity in their conclusions. In the previously cited study with high correlation between FIBTEM A5 and Clauss fibrinogen, a FIBTEM A5 level of 6 mm was found to correspond best (sensitivity 100%, specificity 87%) to the threshold of Clauss fibrinogen ≤2g/L[22]. Yet, in other studies, a FIBTEM A5 level of 12mm and 15 mm were considered the equivalent of a Clauss fibrinogen concentration of 2 and 3 g/L respectively[13, 15, 23]. No additional explanation was provided to support the choice for these thresholds. In a double-blind randomised controlled trial (OBS2), the effect of early fibrinogen replacement in women during postpartum haemorrhage guided by thromboelastometry was examined[15]. In this study women, with a FIBTEM A5 value of ≤15mm were randomised to treatment with fibrinogen concentrate or placebo based on an earlier observational study of the same research group, which found that a FIBTEM A5 value of ≤ 15mm was associated with progression of postpartum haemorrhage. No reduction of allogeneic blood product transfusion or volume of blood loss was observed. Also, a subgroup analysis in women with a FIBTEM A5 value of ≤ 12mm showed no significant differences between groups. However, in this study only seven women developed a Clauss fibrinogen concentration ≤2 g/L.

Clinical implications

During acute situations like postpartum haemorrhage, clinicians are keen to get fast, reliable results on a woman's coagulation status. FIBTEM A5 has been promoted to diagnose fibrinogen deficiency and guide treatment with fibrinogen concentrate. Assuming that women suffering postpartum haemorrhage with a Clauss fibrinogen concentration of ≤2 g/L require administration of fibrinogen concentrate, FIBTEM A5 is useful but lacks specificity. Using FIBTEM A5 with a cut-off point of 12 mm will lead to large numbers of women receiving fibrinogen concentrate in vain. The development of a point-of-care test that accurately and rapidly measures fibrinogen concentrations could be of considerable clinical significance.

Conclusion

Based on the Youden index, the best cut-off point to accurately select women with a Clauss fibrinogen concentration of ≤2 g/L is FIBTEM A5 of 12mm. Yet, treatment of all women with FIBTEM A5 lower or equal than 12 mm with fibrinogen concentrate will lead to inappropriate use of fibrinogen in about 80 percent of women with postpartum haemorrhage treated with fibrinogen concentrate.

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7 THE EFFECT OF TRANEXAMIC ACID ON BLOOD LOSS AND MATERNAL OUTCOME IN THE TREATMENT OF PERSISTENT POSTPARTUM HAEMORRHAGE: A NATIONWIDE RETROSPECTIVE COHORT STUDY

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Abstract

Background: Recent results show a protective effect of tranexamic acid on death due to bleeding in patients with postpartum haemorrhage in low- and middle-resource countries. We quantify the association between early administration of tranexamic acid compared to late or no administration and severe acute maternal morbidity and blood loss among women suffering from persistent severe postpartum haemorrhage in a high-income country.

Methods and findings: We performed a nationwide retrospective cohort study in 61 hospitals in the Netherlands. The study population consisted of 1260 women with persistent postpartum haemorrhage who had received at least four units of red cells, or fresh frozen plasma or platelets in addition to red cells. A review of medical records was performed and cross-referenced with blood bank data. The composite endpoint comprised maternal morbidity (hysterectomy, ligation of the uterine arteries, emergency B-Lynch suture, arterial embolization or admission into an intensive care unit) and mortality.

Results: 247 women received early tranexamic acid treatment. After adjustment for confounding, odds ratio for the composite endpoint for early tranexamic acid (n = 247) versus no/late tranexamic acid (n = 984) was 0.92 (95% confidence interval (CI) 0.66 to 1.27). Propensity matched analysis confirmed the absence of a difference between women with and without tranexamic acid. Blood loss after administration of first line therapy did not differ significantly between the two groups (adjusted difference -177 mL, CI -509.4 to +155.0).

Conclusions: Our findings suggest that in a high-resource country the effect of tranexamic acid on both blood loss and the combined endpoint of maternal mortality and morbidity may be disappointing.

Introduction

Major obstetric haemorrhage during pregnancy, delivery and puerperium continues to be an important health problem around the world. In low-resource countries, it remains the leading cause of maternal mortality. In high-resource countries it accounts for almost half of all severe acute maternal morbidity[1-4]

As part of management of major blood loss, haemostatic agents may be administered to support coagulation and correct for acquired coagulopathy[5,6]. One of these is tranexamic acid, an antifibrinolytic agent inhibiting dissolution of the fibrin clot by binding to plasminogen and blocking the interaction of plasmin(ogen) with fibrin[7]. Tranexamic acid has been shown to reduce blood loss and the need for blood transfusion in both elective and emergency surgery[8]. Blood loss after caesarean and vaginal births was also found to be somewhat reduced by administration of tranexamic acid in absence of significant maternal and neonatal complications[9]. In severely bleeding trauma patients, tranexamic acid was found to reduce mortality by 10–15%[10]. Moreover, the CRASH-2 trial and the WOMAN trial have shown that treatment with tranexamic acid should be started as early as possible to result in the largest effect[11,12].

In theory, postpartum haemorrhage provides an additional indication for tranexamic acid because rapid degradation of fibrinogen and fibrin and increased activation of plasminogen activators occur at placental expulsion[7,13]. Tranexamic acid has a half-life of three hours and adequate therapeutic levels persist for 7–8 hours following intravenous injection.

Tranexamic acid is inexpensive, available in many settings, and has a good safety profile. Given the hypercoagulable status of pregnant women, possible thromboembolic side effects of tranexamic acid administration have been the subject of earlies studies. Reported adverse events were mainly minor and no clear evidence was found for an increase of thromboembolic events in pregnant women who were administered with a low dose of tranexamic acid[9].

Recently, the results of the WOMAN trial that compared tranexamic acid in an early stage of postpartum haemorrhage to placebo, showed a reduction of maternal mortality due to bleeding from 1.9% to 1.5%. However, this trial was conducted primarily in low-resource settings and no differences were found in all-cause mortality or other clinical endpoints concerning maternal morbidity. Also, the effect of tranexamic acid on the amount of blood loss was not studied. Since maternal mortality has become a rare event in high-resource countries, it remains unclear whether administration of tranexamic acid at an early stage in

the course of postpartum haemorrhage has a positive effect on clinical outcome or amount of blood loss in a high- resource setting.

The aim of this study was to quantify the association between tranexamic acid administration at an early stage in the course of persistent postpartum haemorrhage and severe acute maternal morbidity and blood loss in a high-resource setting.

Methods

Design and study population

We performed a retrospective cohort study among women who experienced postpartum haemorrhage as part of the *Transfusion strategies in women during Major Obstetric Haemorrhage study* (TeMpOH-1). TeMpOH-1 is a nationwide retrospective cohort study in 61 hospitals in the Netherlands (75% of all hospitals in the country). The TeMpOH-1 study was approved by the Ethical Committee of the Leiden University Medical Center (P12.273) and by the institutional review board of each participating hospital. Because of the retrospective design of the study, the need to obtain informed consent was waived by the ethics committee. Data were collected retrospectively from medical files of women ≥18 years old, who had received four units of red blood cells or any transfusion of fresh frozen plasma (FFP) and/or platelets in addition to red blood cells because of obstetric haemorrhage between January 1st, 2011 and January 1st, 2013. Women were identified by cross-referencing electronic data from the hospitals' blood transfusion services with local birth registers in participating hospitals. Data were recorded from medical files available at the delivery ward, operating theatre and intensive care unit for the following parameters: maternal age at the time of delivery, parity, maternal body weight during early pregnancy, maternal height, ethnicity, gestational age, obstetric history, mode of delivery, cause of major obstetric haemorrhage, abnormal placentation, shock, timing and volume of fluids and blood products transfused, medical and surgical interventions and repeated measurements of blood loss until cessation of bleeding. Blood loss was measured by weighing gauzes and all other soaked materials and by the use of a collector bag and suction system in the operating theatre. Information on possible side effects of treatment with tranexamic acid was not available due to the design of the study.

Selection of women with persistent postpartum haemorrhage

In order to avoid use of case definitions based on mere estimations of blood loss and in absence of a universal definition of severe postpartum haemorrhage, we opted for a practically derived definition. First, we selected those women from our cohort, who had primary postpartum haemorrhage within 24 hours after birth. To meet the criteria of severe postpartum haemorrhage, bleeding had to persist despite the timely administration of first line therapy[14].

Women were treated according to the Dutch national guideline on postpartum haemorrhage, which advises to initiate first line therapy without delay in case of persisting haemorrhage despite administration of prophylactic uterotonic agents. First line therapy was defined as per primary cause of bleeding (Table 1). By applying this pragmatic definition to our cohort, only cases of ongoing haemorrhage (despite administration of first line therapy) were included for analysis.

Table 1. First line therapy as per primary cause of bleeding.

Primary cause of bleeding	Corresponding first line therapy
Uterine atony	Administration of uterotonic agents* and/ or inspection of the uterine cavity
Retained placenta	Manual removal of placenta
Traumatic cause (uterine rupture, trauma of the birth canal)	Surgical repair
Surgical cause	Surgical repair
Placental abruption and placenta praevia	Caesarean section †

* The uterotonic agents administered were Oxytocin or Misoprostol.

† In case of stillbirth no caesarean section was performed

Early versus late/no tranexamic acid

In our study, the effect of tranexamic acid was compared between patients who had received tranexamic acid early during persistent postpartum haemorrhage and patients who had not received tranexamic acid or who had received tranexamic acid at a later stage. Women who received tranexamic acid late were grouped with women who did not receive tranexamic acid at all. This allocation was chosen because at the early decision moment whether to administer tranexamic acid or not, the choice in these both groups was to refrain from administration of tranexamic acid. Thus, a control group was created of women who did not receive tranexamic acid at the early decision moment. The administration of tranexamic acid within one hour after the start of first line therapy was considered "early" administration. This cut-off point was based on the results of the CRASH-2 trial, which showed a positive effect on mortality in women who received tranexamic acid within an hour and between one and three hours after trauma. In patients who received tranexamic acid after three hours this positive effect disappeared[12,15]. Because administration of tranexamic acid in the late treatment group of the TeMpOH-2 cohort exceeded this three hours' time limit, these women were analysed together with the women that did not receive tranexamic acid at all.

Outcome definitions

The primary outcome was a combined endpoint of maternal mortality and severe acute maternal morbidity. 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 were considered endpoints of maternal morbidity. Secondary outcomes were total blood loss (blood loss at the end of postpartum haemorrhage), additional blood loss (additional blood loss between administration of first line therapy and the end of postpartum haemorrhage), volume and number of blood products transfused.

Confounding and effect modifiers

The following parameters were pre-defined as possible confounders for the association between administration of tranexamic acid and outcomes: maternal age, body mass index (BMI), mode of delivery, primary cause of major obstetric haemorrhage and abnormal placentation. Also, the following bleeding characteristics at first line therapy were regarded as potential confounder: amount of blood loss, bleeding rate, shock, administration of other haemostatic agents, amount of fluids and amount of blood products that had been administered at first line therapy.

Haemorrhagic shock was defined as systolic blood pressure of 90 mmHg or less, or a heart rate of 120 bpm or higher[16]. Bleeding rate was calculated as the amount of blood loss in millilitres per minute. In the cohort, active management of labour (standard administration of oxytocin, controlled cord traction and uterine massage for prevention of postpartum haemorrhage) was practiced according to the Dutch national guidelines.

Statistical analyses

Characteristics and outcomes are reported using descriptive statistics. In order to prevent bias due to missing data in covariates, we used multiple imputation. The associations between early versus no/late tranexamic acid administration and outcomes were assessed using logistic and linear regression models. The multivariate models were adjusted for measured, pre-defined confounders based on observed differences between the comparison groups.

Results

Patient characteristics

The TeMpOH-1 cohort comprised 1391 women who had received at least four units of red cells (66%), or fresh frozen plasma or platelets in addition to red cells, for postpartum haemorrhage. For the present analysis, we selected all 1260 women who fulfilled the definition of *persistent post- partum haemorrhage*. Patient selection is presented in Figure 1. Uterine atony was the primary cause of bleeding in 789 (62%) and retained placenta in 215 (17%) women. The median total blood loss was 3000 mL (IQR 2500–4000 mL). Primary causes of bleeding and other patient characteristics are presented in Table 2. Median amount of blood loss after administration of first line therapy in the selected cohort with persistent bleeding was 2125 ml (IQR 1200–3021 ml).

Early versus late/no tranexamic acid administration

Of 1260 women with persistent postpartum haemorrhage 540 (42.8%) were treated with tranexamic acid, of whom 247 at an early stage, i.e. within one hour after the start of first line therapy. Among women who had received tranexamic acid early, 73% had received it at a single occasion and 21% had received tranexamic acid twice. The mean dosage per tranexamic acid gift was 1.1 grams (range 0.1 to 3.0 grams) and administration occurred intravenously. In the early treatment group, administration of tranexamic acid occurred 1.6 hours after birth (95%CI 1.3–1.9), compared to 4.6 hours (95%CI 4.1–5.1) in the late treatment group. Because of the presumed absence of benefits of administration of tranexamic acid beyond the 3-hour time interval as described in the Crash-2 trial, women in the late treatment group were analysed together with women who did not receive tranexamic acid at all.

Table 2 presents patient characteristics according to early versus late/no tranexamic acid administration. Given the relatively large proportion of women in the Dutch maternity care system delivering with a midwife outside a hospital setting, data on location of delivery and transfer to a hospital were studied between groups. No statistically significant differences were found. Delivery by caesarean section and bleeding due to atony had occurred more frequently among women with early tranexamic acid administration, compared to women with late/no tranexamic acid administration (29% vs 21%, and 68% vs 63% respectively). In addition, women who had received tranexamic acid early, bled more severely at onset of first line therapy: bleeding rate (24 vs 19 ml/min), blood loss at diagnosis of first line therapy (1300 ml vs 800 ml) and incidence of haemorrhagic shock (31% vs 21%) were all higher compared to late/ no tranexamic acid administration.

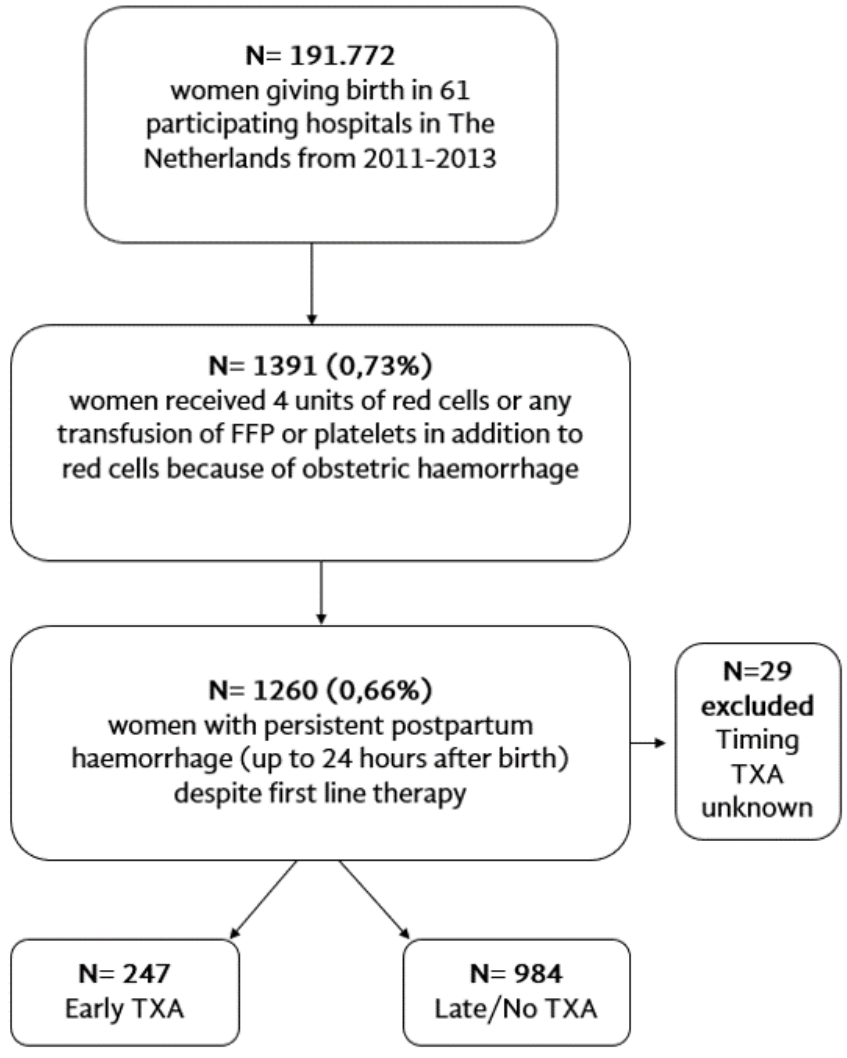

Figure 1. Inclusion flowchart.

FFP Fresh frozen plasma, TXA Tranexamic acid.

Table 2. **Patient characteristics and treatment characteristics at first line therapy according to whether women had received tranexamic acid early (within one hour after the start of first line therapy) or not early (later and no tranexamic acid).**

	Early TXA n = 247	Late/No TXA n = 984
Maternal characteristics		
Age, years*	33 (29–36)	31 (28–35)
BMI (kg/m^2)*	23 (21–26)	23 (21–27)
Ethnicity†		
Caucasian	181 (73)	698 (71)
Non-Caucasian	53 (21)	219 (22)
Unknown	13 (5)	67 (7)
Obstetric Characteristics		
Nulliparity† (yes)	133 (54)	511 (52)
Gestational age (weeks)*	40 (38–41)	40 (38–41)
Labour characteristics		
Mode of delivery†		
Vaginal	175 (71)	769 (78)
Caesarean section	71 (29)	208 (21)
Transfer to hospital		
No transfer (birth with midwife)	162 (66)	647 (66)
Postpartum transfer	34 (14)	125 (13)
Primary cause of bleeding†		
Uterine atony	168 (68)	621 (63)
Retained placenta	39 (16)	176 (18)
Other	40 (16)	187 (19)
Placentation†		
Abnormal localisation placenta	34 (14)	124 (13)
Pathological ingrowth placenta	22 (9)	94 (10)
Treatment characteristics at first line therapy		
Fibrinogen-previously†	4 (2)	3 (0)
Recombinant FVIIa-previously†	0 (0)	0 (0)
Estimated blood loss previously, ml*	1300 (450–1933)	800 (150–1400)
Bleeding rate, ml/min*	24 (14–43)	19 (9.2–38)
Shock any time before first line therapy †	76 (31)	203 (21)

* median and (IQR)
† number and %

Morbidity and mortality according to tranexamic acid administration

Six women died due to major postpartum haemorrhage (0.5%), of whom two had received early tranexamic acid. There was no clear consistent difference between women who had and those who had not received tranexamic acid early (Table 3). Adjusted odds ratio for the composite endpoint of maternal morbidity and mortality was 0.92 (95% confidence interval (CI) 0.66–1.27). There were no differences between early and late/no tranexamic acid in subsets of women with uterine atony, shock before first line therapy, blood loss above 2 litres, or by mode of delivery. (Table 4)

Table 3. **Numbers and odds ratios (OR) of severe maternal morbidity, maternal mortality, blood loss and transfusions after first line therapy according to TXA administration.**

	Early TXA n = 247	Late/No TXA n = 984	Crude OR (95% CI) or crude difference	Adjusted OR (95% CI) or difference*
Maternal mortality	2 (0,8)	4 (0,4)	2,00 (0,36–10,98)	1,31 (0,20–8,73)
Hysterectomy/ligation arteries/B-lynch	28 (11,2)	68 (6,7)	1,71 (1,07–2,75)	1,10 (0,63–1,95)
Embolisation	33 (13,1)	132 (13,1)	1,00 (0,66–1,52)	0,76 (0,48–1,22)
ICU admission	75 (29,9)	287 (28,4)	1,07 (0,78–145)	0,85 (0,60–1,19)
Composite morbidity mortality†	96 (38,2)	345 (34,2)	1,21 (0,90–1,61)	0,92 (0,66–1,27)
Additional blood loss after first line therapy (mL)‡	2150 (1058–3115)	2100 (1244–3001)	+145,7 (-167,1–458,5)	-177,2§ (-509,4–155,0)
Total units of RBC ‖	4 (2–6)	4 (3–5)	0,35 (-0,20–0,90)	-0,73 (-1,35–0,10)
Total units of FFP	2 (2–4)	2 (2–3)	0,56 (0,17–0,95)	-0,12 (-0,55–0,31)
Total units of platelets	1 (1–2)	1 (1–2)	-0,03 (-0,42–0,36)	-0,40 (-0,80–0,00)
Total units of blood products	6 (4–10)	6 (4–8)	1,33 (0,33–2,32)	-0,62 (-1,72–0,48)

*ORs and differences were adjusted for pre-defined confounders: bleeding rate, measured blood loss, fluids and blood products administered at first line therapy; Occurrence of shock before first line therapy, primary cause of major obstetric haemorrhage abnormal placentation, maternal age, mode of delivery, previous administration of fibrinogen and rec FVIIa. Multiple imputation was used.
† Patients that reached at least one of the predefined clinical endpoints (maternal mortality, hysterectomy/B-lynch/arterial ligation, embolization, ICU admission.
‡ Blood loss in ml, median & IQR are reported
§ Difference between groups calculated by linear regression analysis
‖ Median and IQR are reported

Blood loss after first line therapy

The volume of additional blood loss after first line therapy was 2150 mL among women who had received tranexamic acid early whereas among women who had not received tranexamic acid early the additional blood loss was 2100 mL, amounting to a total blood loss of 3300 mL (+65% increase) vs 3000mL (+70% increase) in women who received early vs no/late tranexamic acid respectively. After adjustment for confounding the blood loss after first line therapy was slightly, but not statistically significant, lower among the women who had received early tranexamic acid (adjusted difference -177 mL, CI -509 to +155). Women who had received early tranexamic acid had been transfused 6 (IQR 4 to 10) units of blood products, which was similar to women who had not received tranexamic acid early (6 units, IQR 4 to 8).

Table 4. Association between early administration of tranexamic acid versus late/no tranexamic acid and outcomes among women with atony, shock before first line therapy, volume of postpartum haemorrhage more than 2 litres, after caesarean section, or vaginal delivery.

Subgroup women with	Composite endpoint Adj. OR (95%CI)	Additional bleeding (mL) Adj. difference (95%CI)
Atony (n = 789)	0,95 (0,65–1,41)	-270 (-649–110)
Shock present before first line therapy (n = 279)	0,96 (0,52–1,79)	-105 (-662–452)
Postpartum haemorrhage > 2 litres (n = 1121)	1,71 (0,79–3,68)	-243 (-871–384)
Caesarean section (n = 279)	0,81 (0,44–1,46)	-381 (-1407–645)
Vaginal delivery (n = 944)	1,02 (0,69–1,50)	+26 (-277–329)

Sensitivity analyses

As a sensitivity analysis, we calculated propensity scores for receiving tranexamic acid early according to bleeding rate, measured blood loss, fluids and blood products administered at first line therapy, occurrence of shock before first line therapy, primary cause of major postpartum haemorrhage, abnormal placentation, maternal age, mode of delivery and previous administration of fibrinogen and recombinant FVIIa. Using nearest neighbour propensity score matching we could match 201 women who had received tranexamic acid early with women who had not received tranexamic acid early. Results of these analyses were similar to those of the main analysis. Results are provided in Table 5.

Table 5. Outcomes according to TXA early or late/no among women selected and matched according to the propensity score for early TXA administration.

	Early TXA n = 201	Late/No TXA n = 201	OR PS matching N = 402
Maternal mortality*	-	-	-
Hysterectomy	13 (6,5)	8 (4,0)	1,71 (0,69–4,24)
Embolization	22 (10,9)	25 (12,4)	0,87 (0,47–1,60)
ICU admission	58 (28,9)	56 (27,9)	1,06 (0,68–1,64)
Composite morbidity/Mortality	72 (35,8)	66 (32,8)	1,16 (0,76–1,77)

*Not applicable due to low numbers

Discussion

In this nationwide study in a high-resource country, tranexamic acid administration at an early stage during the course of persistent postpartum haemorrhage was associated neither with lower maternal morbidity nor with reduced blood loss. Despite the large number of women in our cohort the confidence intervals were wide and the findings may indicate a protective as well as absence of any effect of tranexamic acid. Subgroup analyses did not reveal any particular group of women with persistent postpartum haemorrhage that might benefit from early tranexamic acidadministration.

To the best of our knowledge this is the largest study to date into the effect of early treatment with tranexamic acid in patients with persistent postpartum haemorrhage in a high- resource setting. Our large sample size enables us to provide information on clinical endpoints in addition to volume of blood loss. In our study, women were included when in need of transfusion of at least 4 red blood cells or additional blood products because of persistent postpartum haemorrhage. Therefore, our results are generalizable to and may be included in meta-analyses examining women with severe postpartum haemorrhage. Some limitations to our study need to be discussed. Inherent to our observational design is bias due to confounding by indication. Such confounding bias will lead to underestimation of a possible protective effect of tranexamic acid. Despite the fact that timing of first line therapy will be similar between cases, severe cases of postpartum haemorrhage are more likely to receive early tranexamic acid as compared to less severe cases of postpartum haemorrhage. To minimize this bias, we measured and adjusted for all known and measurable confounders. In addition, we evaluated the robustness of our findings by matching women receiving early tranexamic acid with women with the same propensity scores. Nevertheless, we cannot exclude bias due to residual confounding and therefore our findings may be an underestimate of a possible truly protective effect of tranexamic acid in some women with postpartum haemorrhage. Previous studies focused on the use of tranexamic acid for *prevention* of postpartum haemorrhage, rather than treatment of postpartum haemorrhage[6]. Our results corroborate the findings of these studies. A recent systematic review and meta-analysis of RCTs that studied the effect of the *prophylactic* use of tranexamic acid for postpartum haemorrhage, showed a similar reduction in mean blood loss of 149 ml[17]. So far, few studies have looked at the effect of tranexamic acid on maternal outcome in the *treatment* of postpartum haemorrhage. The most important one is the recently published WOMAN trial, in which 20 060 women from mostly low-resource settings with blood loss above 500 ml were included. A reduction in maternal death due to bleeding from 1.9% to 1.5% was found. The largest effect occurred in the group of patients that received tranexamic acid within 1–3 hours after birth. Surprisingly no difference was found on (severe) maternal morbidity. The amount of brace sutures/ligation/embolization and blood products transfused was equal in the treatment and placebo group. And, the

number of hysterectomies was higher in the tranexamic acid group. The different study settings and populations make it difficult to come to a fair comparison of the results of the studies. As also mentioned by the authors of the WOMAN trial, hysterectomy to stop postpartum haemorrhage often is a first line treatment option in low resource setting, where in a high resource setting this treatment counts as a last resort. In the WOMAN trial treatment with tranexamic acid occurred at a lower level of blood loss, which is in line with the setting of the study and the relative lack of treatment and transfusion options. Despite these differences, in both settings no significant treatment effect was found of tranexamic acid on the outcome (severe) maternal morbidity. Since maternal mortality is rare in a high resource setting, the treatment effect on mortality as found in the WOMAN trial is expected to be negligible when translated to our study population, which is in line with our results on mortality. The effect of treatment with tranexamic acid on total amount of blood loss was not studied in the WOMAN trial[18].

A French randomized controlled open-label trial studied the effect of high dose tranexamic acid (4 grams in 1 hour) versus placebo in 144 women with postpartum haemorrhage of more than 800 ml. Blood loss six hours after enrolment was lower in the tranexamic acid group, but the difference was only 48 ml, which seems clinically irrelevant[19]. A pre- and post-implementation study from the same country compared high dose tranexamic acid (4 grams in 1 hour) in 159 women with postpartum haemorrhage of more than 800 ml after vaginal birth and showed no difference in amount of blood loss, duration of bleeding or need for transfusion[20]. Both studies were rather small, and contained women with less severe post- partum haemorrhage compared to our cohort, making it difficult to assess major clinical outcomes. After the first trial some concern arose with regard to a possible association between high dosages of tranexamic acid and unexplained renal failure[20]. Treatment of postpartum haemorrhage with these high dosages of tranexamic acid was therefore discontinued in several French hospitals. Given the relatively low mean dose of tranexamic acid administered in our cohort, the chance of developing negative side effects due to tranexamic acid was considered to be low. The infusion strategy of tranexamic acid that was used in our cohort is similar to the protocol used in the Crash-2 and WOMAN trials. In the previous RCTs that evaluated the use of tranexamic acid in treatment of postpartum haemorrhage, a much higher dose (4 gram tranexamic acid in 1 hour, followed by infusion of 1 gram per hour over 6 hours) was used, based on available data on reducing haemorrhage in cardiac surgery[19]. Taking into account the pro-coagulant status of pregnancy, limiting the dosage of tranexamic acid appears to be a safer choice.

The results of our study appear plausible given the underlying mechanisms and causes of postpartum haemorrhage[21]. Administration of tranexamic acid may partially block degradation of the fibrin clot, resulting in a decrease in the amount of blood loss. However, the primary cause of bleeding in postpartum haemorrhage is in almost all cases of obstetric

origin[21]. Treatment of postpartum haemorrhage should, therefore, focus on solving the underlying obstetric cause first.

This study suggests no difference or a small reduction in blood loss after administration of first line therapy in women who are treated with tranexamic acid early during persistent postpartum haemorrhage. Early treatment with tranexamic acid during persistent postpartum haemorrhage does not demonstrate a significant favourable effect on the frequency of composite maternal morbidity and mortality. Judging from the promising results of early tranexamic acid treatment in trauma medicine and elective and acute surgery and the results of the WOMAN trial, its good safety profile (when administered in dosages of 15mg/kg) and the fact that tranexamic acid is inexpensive, there seem to be few reasons not to administer tranexamic acid early during the course of persistent postpartum haemorrhage, yet the effect on clinical endpoints may be limited or absent[8,10].

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8 GENERAL DISCUSSION AND SUMMARY

General Discussion and Summary

While looking at the magnitude of health problems occurring in women experiencing postpartum haemorrhage worldwide, the overall goal of this thesis was to contribute to a reduction of the incidence of subsequent adverse maternal outcomes. In pursuit of this aim, research questions were posed corresponding to all three phases leading up to adverse outcome due to postpartum haemorrhage: (1) pregnancy (prior to childbirth), (2) early postpartum haemorrhage and (3) persistent postpartum haemorrhage.

Ad 1. Prediction prior to childbirth: are we able to predict -during the pregnancy- who is going to bleed excessively following childbirth?

Ad 2. Prediction and diagnosis during early postpartum haemorrhage: can we identify women who will end up with adverse outcome during early postpartum haemorrhage and moreover, how will we be able to diagnose these women in a reliable and fast manner?

Ad 3. Treatment options during persistent postpartum haemorrhage: when persistent bleeding has developed, do we have adequate haemostatic therapy to stop bleeding?

The findings of this thesis can be summarized as follows:

- The predictive value of a bleeding score for postpartum haemorrhage was found to be poor (**chapter 2**).
- Detection of low levels of fibrinogen and elevated aPTT levels during early postpartum haemorrhage (1.5-2L blood loss) can contribute to the identification of women that may benefit from targeted haemostatic treatment (**chapter 3**).
- The administration of larger volumes of clear fluids is associated with more severe deterioration of coagulation parameters corresponding to dilution, which is most pronounced during the earlier phases of postpartum haemorrhage (**chapter 4**).
- Comparability between ROTEM® parameters from the Delta and Sigma device varies per assay. The early FIBTEM assays in particular should be interpreted with caution (**chapter 5**).
- The optimal cut-off point to detect women with a low fibrinogen concentration (≤2 g/L) was identified at a FIBTEM A5 value of 12mm. By using this cut-off, 87 percent of women who need fibrinogen (Clauss fibrinogen concentration ≤2 g/L) will be treated. Downside is that a large majority of women (81%) will be treated with fibrinogen concentrate, although these women in fact have high fibrinogen concentrations (**chapter 6)**
- In a high-resource setting, the effect of administration of tranexamic acid during postpartum haemorrhage on both blood loss and the combined endpoint of maternal mortality and morbidity may be disappointing (**chapter 7**).

Prediction prior to childbirth

Major obstetric haemorrhage during pregnancy, childbirth and puerperium continues to be an important health problem around the world. In low-resource countries, it remains the leading cause of maternal mortality, whereas in high-resource countries it accounts for almost half of all severe acute maternal morbidity[1-4]. Despite improvements initiated by the worldwide implementation of postpartum haemorrhage protocols, recent studies suggest a steady increase of postpartum haemorrhage in high-resource countries, which can only be partially explained by an increase in maternal age, multiple pregnancies and caesarean sections ratesCanada, 2001-2009.\n\nPOPULATION: All women with live births or stillbirths.\n\nMETHODS: Detailed clinical information was obtained for 371\u00a0193 women from the British Columbia Perinatal Data Registry. Outcomes of interest were atonic PPH and severe atonic PPH (atonic PPH with blood transfusion \ u22651 unit; atonic PPH with blood transfusion \u22653 units or procedures to control bleeding[4-11]. Although risk factors are often known to be present during pregnancy and birth, postpartum haemorrhage frequently occurs unexpectedly[12-14]. Also, women with known risk factors for postpartum haemorrhage often do not bleed excessively following childbirth. It has therefore proven difficult to develop a reliable prediction model for postpartum haemorrhage based on clinical risk factors[12, 15, 16]. From studies on von Willebrand disease it is known that the best results for prior assessment of bleeding risk come from more structured approaches to history taking by means of bleeding assessment tools (BATs)[17-19]. The TeMpOH-2 study was the first study to examine the value of a bleeding score acquired during pregnancy as a screening tool for the identification of women with an increased risk of excessive blood loss postpartum. An already existing and validated bleeding assessment tool (the condensed MCMDM-1VWD) was adjusted to a written questionnaire that could be used as a self-assessment bleeding score. Medical terminology was converted into lay language and detail was added to items that needed additional explanation or examples that would otherwise be given by an expert[18]. In the 1147 pregnant women in the TeMpOH-2 study who completed a bleeding assessment tool during pregnancy, the ability of the score to discriminate between women with and without postpartum haemorrhage was found to be poor. This finding did not come as an utter surprise, since in the area of von Willebrand disease, bleeding scores are used because of their high negative predictive value, indicating that a normal bleeding score can help exclude a clinically significant bleeding disorder[20]. In line with this, in a study of 217 individuals screened for von Willebrand disease, seventeen individuals with negative bleeding scores underwent major surgery, and none experienced significant bleeding. In another study in a cohort of paediatric patients undergoing adenotonsillectomy, an abnormal bleeding score without the addition of a coagulation screen did not have any predictive value for the occurrence of post-surgery haemorrhage[21]. No previous studies were found that examined the predictive value of the use of bleeding scores in the field of

childbirth. In the TeMpOH-2 study no evidence was found to support adding a bleeding assessment tool to the review of a pregnant woman's medical history for the prediction of postpartum haemorrhage of ≥ 1000mL. However, adding two questions on history of nosebleeds and post-surgery blood loss to a standard anamnesis did contribute to the identification of women with a higher risk of postpartum haemorrhage exceeding 2000mL. The downside of this approach is that, looking at its relatively low positive predictive value (11%), this approach would in many cases be false alarm leading to unnecessary preventive measures.

Prediction and diagnosis during early postpartum haemorrhage

Since a bleeding score prior to childbirth was not found to be useful in the prediction of postpartum haemorrhage, another potential predictor to look into was coagulopathy occurring during postpartum haemorrhage. From earlier studies into coagulopathy developing during postpartum haemorrhage several important methodological challenges had become apparent: identifying whether the observed change in a coagulation parameter is a predictor or rather the result of postpartum haemorrhage, asking for informed consent in an acute clinical setting, and last but not least selection of the appropriate target population.

By close monitoring of haemostasis, abnormalities in coagulation parameters may be detected soon after their onset. This could contribute to more individually targeted haemostatic therapy for women experiencing postpartum haemorrhage, potentially leading to better maternal outcomes[22]. Previous studies have suggested that a low fibrinogen concentration might be the earliest predictor of progression towards severe postpartum haemorrhage[23-26]. A review article summarizing results of five studies concluded that a fibrinogen concentration of ≤ 3 g/L and, in particular ≤2 g/L was associated with progression towards more severe postpartum haemorrhage[26]. These studies had several drawbacks: either the volume of blood loss at blood sampling was not known, or only first and worst values of levels of coagulation parameters were reported. Therefore, it has remained unclear whether an observed change in concentration of a coagulation parameter is the result of bleeding or a predictor of progression towards more severe bleeding. Also, most studies had a prospective design, leading to challenges related to obtaining informed consent from women with severe bleeding and undertaking trial procedures whilst treating them. Because of these challenges, the most severe cases of postpartum haemorrhage remained unstudied.

The unique strength of the retrospective design of the TeMpOH-1 study was that it enabled us to include all women with severe postpartum haemorrhage from 61 participating hospitals during the study period, including the most severe cases. This allowed for reliable and generalizable estimation of proportions of women with coagulopathy during the course of postpartum haemorrhage. In the women of the TeMpOH-1 study cohort, we mapped patterns of change in coagulation parameters in relation to the phases of postpartum haemorrhage and were able to identify timing of these changes associated with risk of severe maternal outcomes. This enabled us to distinguish between a change in coagulation parameter concentration as a predictor of excessive bleeding versus a change as a result of volume of blood loss. Included were 1312 women who experienced severe postpartum haemorrhage and had at least one valid measurement of coagulation parameters sampled during active bleeding. We have elucidated that women who experienced postpartum haemorrhage without developing a composite outcome of maternal morbidity and mortality only sporadically reached a fibrinogen value of ≤2 g/L (blood loss above 3.5 litres). Women who did develop the composite adverse outcome reached such low fibrinogen levels much earlier (1.5-2L of blood loss) during postpartum haemorrhage. A similar pattern was observed for aPTT levels. This difference in *the moment* of reaching a level of fibrinogen of ≤2 g/L during the course of postpartum haemorrhage is essential for the selection of the target population for future studies into the potential benefit of administering fibrinogen concentrate. The results of the TeMpOH-1 study confirm the results of previous studies into this subject, but with one very important addition for acute clinical decision-making: the dimension of time. In our cohort, we observed higher occurrence of fibrinogen concentrations below 2 g/L compared to results suggested in previous prospective studies[27, 28]. This confirms the unique strength of our retrospective study and once more emphasizes the challenges for (future) prospective studies into potential treatment effects of fibrinogen concentrate, as previously experienced by research groups in Denmark and the UK: both groups had trouble selecting the appropriate target population (few women had fibrinogen levels ≤ 2 g/L) for their intervention (fibrinogen concentrate versus placebo in women experiencing postpartum haemorrhage) and both were therefore unable to draw conclusions on treatment effect of fibrinogen concentrate[27, 28].

The TeMpOH-1 cohort also allowed for a description of changes in coagulation parameters after applying different fluid management strategies during various phases of severe postpartum haemorrhage. No previous studies described this association in women experiencing haemorrhage. International guidelines on management of women with severe postpartum haemorrhage highlight the lack of evidence on the effect of different fluid management strategies. In our cohort of women experiencing postpartum haemorrhage, changes were displayed in coagulation parameters 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 haemorrhage. These findings corroborate results of previous in vitro studies into the effect of dilution on coagulation parameters, where PT and aPTT were significantly prolonged after 60% and 80% dilution and levels of dilution-dependent coagulation factors and aPTT were found to decrease in an almost linear manner reaching critically low levels of coagulation parameters at dilutions of between 60% and 75%[29, 30]. Our findings provide evidence to reinforce expert opinion-based guidelines recommending restrictive fluid resuscitation strategies in case of postpartum haemorrhage; when clinical conditions allow for it, administration of large volumes of clear fluids should be avoided, because of their deteriorating impact on coagulation parameter levels.

From these studies in women of the TeMpOH-1 cohort, we have learned that timely detection of changes in levels of relevant coagulation parameters could play an essential role in the management of postpartum haemorrhage. From previous studies, a low fibrinogen concentration emerges as the earliest predictor of progression towards severe postpartum haemorrhage[23, 24, 26, 31-33]. By timely detection of low fibrinogen concentrations, targeted haemostatic therapy may be administered to restore adequate concentrations of fibrinogen. The Clauss fibrinogen assay is the standard coagulation test to assess fibrinogen concentrations. Its downside is a turn-around time of up to 60 minutes, rendering it unsuitable for acute clinical decision making[34]. Point-of-care devices like ROTEM® thromboelastometry can detect changes in the coagulation system within ten minutes from blood sampling[22]. Evidence on correlation between fibrinogen concentration measured by the Clauss fibrinogen assay and the ROTEM® equivalent FIBTEM® and stability of the measurements in women experiencing postpartum haemorrhage was limited[35, 36]. Several studies conducted in women during postpartum haemorrhage have confirmed that the ROTEM® FIBTEM A5 assay, available 7 to 10 minutes after sampling, provides an indication of the fibrinogen concentration during postpartum haemorrhage[22, 25, 37]. In contrast with the evidence-based consensus on the Clauss fibrinogen concentration of ≤ 2 g/L as predictor of adverse outcome, this level of agreement is lacking for the corresponding ROTEM® FIBTEM A5 cut-off value. From a literature search we learned that several (research) groups working with thromboelastometry composed their own treatment flowcharts containing various FIBTEM cut-off points to initiate administration of fibrinogen concentrate. These flowcharts are often based on expert opinion rather than data[28, 38]. As discussed earlier, one of the problems that will occur while investigating an intervention in the wrong target population, is the impossibility to draw valid conclusions on the added value of the intervention. Once more, this expresses the importance of assessing the correct level of ROTEM® FIBTEM corresponding to women with fibrinogen concentrations ≤2 g/L.

Another important topic while working with laboratory devices is the introduction of a new version of a device. Until recently, the ROTEM® Delta device was the most common device to conduct thromboelastometry. Now, a fully automated successor of the ROTEM® Delta device, the Sigma was introduced. The fact that with this device there is no need for a pipetting procedure, makes it more applicable as a point-of-care device to be used at bedside. When a successor of a device is launched onto the market it is of great clinical importance to perform validations to review whether the newly introduced device provides exactly the same values as its predecessor. Because ROTEM® values within the millimetre of accuracy are commonly used in (postpartum) haemorrhage treatment flowcharts, excellent correlation between values from the old and new device is extremely important.

Therefore, we conducted a prospective multicentre study, TeMpOH-2, comprising a large cohort of unselected pregnant women and following them until discharge from hospital after childbirth. To overcome issues concerning the informed consent procedure whilst treating women in an acute situation, consent had already been obtained during pregnancy or could be obtained verbally during early postpartum haemorrhage. In women experiencing blood loss exceeding 800mL, repeated blood sampling was performed with a maximum of three samples, comprising traditional coagulation parameters and ROTEM® assays. First, a sub-study was performed to compare values provided by the two ROTEM® devices, Delta and Sigma. In the cohort of 23 women experiencing postpartum haemorrhage, a strong positive correlation was displayed between thromboelastometry assays EXTEM, INTEM and APTEM executed on the ROTEM® Delta and Sigma device: results of these assays from both devices are similar. Clotting time (CT) values as obtained by the Sigma device were unreliable. Wide variation was shown between ROTEM® FIBTEM assays performed on both devices, especially in the earlier measurements (A5 and A10), important to acute clinical decision-making. No other studies have been published on this subject, making this a very important message for the ROTEM user community. Given the fact that exact FIBTEM A5 values are used in (postpartum haemorrhage) flowcharts around the world, we advise to re-evaluate the values used in a treatment flowchart when switching to the new device.

Subsequently, we assessed the optimal ROTEM® FIBTEM A5 value for detecting women with a Clauss fibrinogen concentration ≤2 g/L in our TeMpOH-2 cohort. Over the three-year inclusion period, 17203 women gave birth in the participating hospitals. Of these women, 1605 experienced postpartum haemorrhage and 591 women agreed to participate in the study. For 511 women valid corresponding measurements of fibrinogen and FIBTEM A5 were available resulting in 637 samples. When comparing ROTEM® FIBTEM A5 results to Clauss fibrinogen levels, we found a moderate Spearman's correlation coefficient of 0.64 (95% Confidence Interval (CI): 0.60 to 0.69). Spearman's correlation coefficients for

measurements on the ROTEM® Delta and Sigma device were (r_s) 0.63 (95% CI: 0.58 to 0.67) and (r_s) 0.76 (95% CI: 0.63 to 0.85) respectively. These results corroborate results of a previous study in women experiencing postpartum haemorrhage, where a similar correlation was found[25]. The choice for a cut-off point for a diagnostic test depends on the risk of adverse outcomes when patients are incorrectly classified and/or incorrectly treated. Since the risk of adverse outcomes was found to be very high when fibrinogen concentrations are below 2 g/L, sensitivity of the test to detect women with fibrinogen below 2 g/L should be high. Our most important aim was to describe fibrinogen concentrations according to previously proposed FIBTEM A5 cut-off points in blood samples collected from women suffering postpartum haemorrhage since there was no consensus on the optimal cut-off point for FIBTEM A5 and results of previous studies lacked conformity in their conclusions. In a previous trial comparing administration of fibrinogen concentrate to placebo in women with postpartum haemorrhage, a cut-off of 15 mm was used and no difference observed between groups with regard to number of units of red blood cells, plasma, cryoprecipitate and platelets transfused[28]. An earlier study in women with postpartum haemorrhage suggested a FIBTEM A5 value of 6 mm as the cut-off point that correlates best with a Clauss fibrinogen ≤2 g/L (sensitivity 100%, specificity 87%).

In the TeMpOH-2 cohort, the ability of FIBTEM A5 to discriminate observations with a Clauss fibrinogen concentration of ≤2 g/L was good, area under Receiver Operating Curve 0.92 (95% confidence interval (CI) 0.87 to 0.97). The best cut-off point in the TeMpOH-2 cohort was 12mm with sensitivity of 87% and specificity of 81%, missing 4 of 31 cases (13%) of Clauss fibrinogen ≤2 g/L and incorrectly selecting 118 (81%) (Table 3). When 15 mm was applied as FIBTEM A5 cut-off point, 97% (30/31) of samples with Clauss fibrinogen ≤2 g/L were accurately selected, but 89% (248/278) of selected samples had fibrinogen concentrations >2 g/L. When a lower cut-off value for FIBTEM A5 was chosen, these numbers changed: a cut-off value of FIBTEM A5 of 6 mm accurately selected 26% (8/31) of samples with Clauss fibrinogen concentrations ≤2 g/L and 74% (23/31) of samples with a low fibrinogen were missed. Yet, a lower percentage of 53% (9/17) of samples that were selected based on FIBTEM A5 value < 7 mm had corresponding Clauss fibrinogen values of >2g/L.

Since FIBTEM A5 has been promoted to diagnose fibrinogen deficiency and guide treatment with fibrinogen concentrate and assuming that women suffering postpartum haemorrhage with Clauss fibrinogen concentrations ≤2 g/L require administration of fibrinogen concentrate, we conclude that FIBTEM A5 is useful but lacks specificity. Using FIBTEM A5 with a cut-off point of 12 mm will lead to a large number of women receiving fibrinogen concentrate in vain. The development of a point-of-care test that truly measures fibrinogen concentration could be of considerable clinical significance.

Treatment options during persistent postpartum haemorrhage

When the situation occurs that postpartum haemorrhage does develop, despite all prognostic and preventive measures, time has come to focus on interventions with haemostatic agents[39,40]. One of these is tranexamic acid, an antifibrinolytic agent inhibiting dissolution of the fibrin clot by binding to plasminogen and blocking the interaction of plasmin(ogen) with fibrin [41]. Tranexamic acid has been shown to reduce blood loss and need for blood transfusion in both elective and emergency surgery[42]. Blood loss after caesarean and vaginal births was also found to be somewhat reduced by administration of tranexamic acid in absence of significant maternal and neonatal complications[43]. In severely bleeding trauma patients, tranexamic acid was found to reduce mortality by 10-15% [44]. The WOMAN trial, which compared tranexamic acid in an early stage of postpartum haemorrhage to placebo, showed a reduction of maternal mortality due to bleeding from 1.9% to 1.5%. However, this trial was conducted primarily in low-resource settings and no differences were found in all-cause mortality or other clinical endpoints concerning maternal morbidity. Also, the effect of tranexamic acid on volume of blood loss was not studied. Since maternal mortality has become a rare event in high-resource countries, it remains unclear whether administration of tranexamic acid at an early stage in the course of postpartum haemorrhage has a positive effect on clinical outcome or volume of blood loss in a high-resource setting.

In the TeMpOH-1 cohort we quantified the association between tranexamic acid administration at an early stage in the course of persistent postpartum haemorrhage and severe acute maternal morbidity and blood loss in a high-resource setting. Women not responding to first line therapy were considered to suffer from persistent postpartum haemorrhage. In a cohort of 1260 women we found no difference or a clinically irrelevant reduction in blood loss in women who were treated with tranexamic acid early during persistent postpartum haemorrhage. Also, early treatment with tranexamic acid during persistent postpartum haemorrhage did not demonstrate a significant favourable effect on the frequency of composite acute maternal morbidity and mortality.

Previous studies focused on the use of tranexamic acid for *prevention* of postpartum haemorrhage, rather than treatment of postpartum haemorrhage[40]. Our results corroborate the findings of these studies. A systematic review and meta-analysis of RCTs that studied the effect of the *prophylactic* use of tranexamic acid for postpartum haemorrhage, showed a similar reduction in mean blood loss of 149 ml[45]. So far, few studies have looked at the effect of tranexamic acid on maternal outcome in the *treatment* of postpartum haemorrhage. The most important one is the already mentioned WOMAN trial, in which 20 060 women from mostly low-resource settings with blood loss above 500 ml were included. A reduction in maternal death due to bleeding from 1.9% to 1.5%

was found. The largest effect occurred in the group of patients that received tranexamic acid within 1-3 hours after birth. Surprisingly, no difference was found with regard to (severe) maternal morbidity. Since maternal mortality is rare in a high resource setting, the treatment effect on mortality as found in the WOMAN trial is expected to be negligible when translated to our study population. Based on our results and the promising results of early tranexamic acid treatment in trauma medicine and elective and acute surgery and the results of the WOMAN trial, its good safety profile (when administered in dosages of 15mg/kg) and the fact that tranexamic acid is inexpensive, there seem to be few reasons not to administer tranexamic acid early during the course of persistent postpartum haemorrhage, yet the effect on clinical endpoints may be limited or absent[42,44].

Strengths and limitations

The unique strength of the retrospective design of the TeMpOH-1 study was that it enabled us to include all women with severe postpartum haemorrhage from the 61 participating hospitals during the study period, including the most severe cases. This allowed for reliable and generalizable estimation of proportions of women with coagulopathy during the course of postpartum haemorrhage. When looking at limitations of the studies in this thesis, for both the TeMpOH-1 and TeMpOH-2 cohort the main limitation is selection bias. TeMpOH-1 included 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* (≥1000 mL blood loss during pregnancy, birth or puerperium). Results of the studies in the TeMpOH-1 cohort are thus derived from women suffering from severe postpartum haemorrhage necessitating blood transfusion. This should be taken into account while interpreting the results and applying these to other settings. Besides the fact that the retrospective design enabled us to study the most severe cases of haemorrhage, this design also has limitations: we did not have control over the number and specific panels of coagulation samples. Therefore, our results are based on different selections of women in the categories of blood loss.

Two out of three hospitals participating in the TeMpOH-2 study were university hospitals. This may have led to selection bias because of a difference in source population. Although we were able to include a large cohort of pregnant women with a broad range of gestational ages and pregnancy risk-profiles the high incidence of postpartum haemorrhage shows that our study population comprises a relatively high number of women with a high risk of postpartum haemorrhage. Also, additional counselling to obtain informed consent was performed during admissions preceding elective caesarean sections, potentially leading to overrepresentation of women who underwent caesarean section. In studies comparing ROTEM® assays to traditional coagulation parameters, this type of bias was irrelevant. In the

study on the predictive value of bleeding scores, the presence of selection bias is obvious from the relatively high incidence of women suffering from postpartum haemorrhage as opposed to the general population. Yet, if anything, a higher incidence might have influenced the predictive value of the questionnaire in a positive way. We therefore infer that the poor predictive value of our questionnaire is not the result of selection bias.

Future perspectives

When confronted with women who develop postpartum haemorrhage, obviously the first actions to be taken are measures leading to cessation of bleeding.

Questions Whilst treating acutely bleeding women, several important questions will spring to the mind of caregivers: is this woman going to continue bleeding? Will she develop more severe postpartum haemorrhage with a subsequent adverse outcome? What can I do to prevent her from reaching these severe stages of postpartum haemorrhage?

Required tests An answer to these questions can be provided by diagnostic and prognostic tests. These diagnostic and prognostic tests support caregivers in their capacity to distinguish between postpartum haemorrhages with and without an increased risk of subsequent adverse maternal outcome.

Current knowledge From the results as described in this thesis we have learned that a bleeding assessment tool providing a bleeding score does not contribute to prediction of postpartum haemorrhage whereas history of postpartum haemorrhage does. Monitoring coagulation was shown to be a relevant diagnostic test that could serve as a useful application in the prediction of development of severe postpartum haemorrhage, when taken into account one important addendum: the essence of the difference in the moment of reaching a level of fibrinogen of ≤2 g/L during the course of postpartum haemorrhage.

Opportunities Thus, a great deal of opportunities exist in the field of close monitoring of coagulation. Quick yet stable and reliable tests to establish levels of coagulation parameters are necessary to cope with the challenges of acutely bleeding women. Also, the effects of targeted haemostatic interventions aimed to reverse acquired coagulopathy need to be further evaluated.

Until now, it remains unclear whether implementation of thromboelastometry in peripartum care, indeed does lead to better maternal outcomes. Future studies should focus on evaluation of the added value of implementation of thromboelastometry as standard care at the maternity ward. Thromboelastometry provides a faster indication of a patient's coagulation status compared to traditional coagulation testing methods. It could provide close monitoring of haemostasis by detecting abnormalities in coagulation parameters soon after onset. However, in contrast with traditional coagulation tests providing exact levels of coagulation parameters, thromboelastometry provides 'qualitative assessments of clot formation and fibrinogen status'. Notably, these two results are not the same and cannot be used and interpreted interchangeably. Before implementation into daily clinical practice, thorough evaluation is necessary to determine whether values provided by thromboelastometry correspond to their traditional counterparts. In this thesis, we have determined these ROTEM® FIBTEM cut-off values for corresponding levels of Clauss fibrinogen in women experiencing postpartum haemorrhage. The next step before decisions can be made upon their incorporation in postpartum haemorrhage treatment flow-charts, is to establish their predictive value. For Clauss fibrinogen, it is already known that a level of ≤2 g/L serves as predictor for adverse maternal outcome. This level has yet to be determined for FIBTEM. Moreover, from our studies in the TeMpOH-1 and TeMpOH-2 cohort we have learned, that the incidence of a fibrinogen concentration ≤2 g/L in women giving birth in the Netherlands is rather low: 0.18%. This once more emphasises the need for a reliable, quick, yet inexpensive test, since many women have to be tested to accurately select the ones in actual need of treatment with fibrinogen concentrate.

Moreover, a very important action to be taken is the evaluation of the association between the implementation of thromboelastometry in clinical practice and maternal outcomes of postpartum haemorrhage. A distinction that has to be made during this evaluation, is whether an observed (positive or negative) effect on maternal outcome did occur because of the use of thromboelastometry or as a result of the commissioning of a strict postpartum haemorrhage treatment protocol. Given the difficulties of randomising women during an acute situation like postpartum haemorrhage, in particular the most severe cases, choice of an appropriate study design is of utmost importance. A way to study this in an epidemiologically sound manner without the challenges of undertaking study procedures in an acute situation would be to perform a trial using a stepped wedge design. In the first phase of the study a postpartum haemorrhage protocol with haemostatic interventions at set times will have to be implemented in maternity wards that have not yet been exposed to thromboelastometry. In the second phase of the study, these hospitals will get the availability of a ROTEM® device, and now the interventions of the postpartum haemorrhage protocol will be based on the set ROTEM® cut-off values. This study design enables reliable assessment of the added value of thromboelastometry to standard postpartum haemorrhage care as to maternal outcomes and amount of

blood products transfused. Based on our experiences with thromboelastometry in the TeMpOH-2 study, this trial is a necessary step to be taken before implementation of thromboelastometry in standard postpartum haemorrhage care protocols.

Coming to the end of this theses we can conclude that the results have provided many answers, but also led to new questions: is there a *future* for thromboelastometry in peripartum care? That answer seems easy: thromboelastometry is not likely to ever become an indispensable part of postpartum haemorrhage care, if only for the fact that it will never become available for a large part of the clinics providing maternity care worldwide, because of its high price and need for continuous technical support and monitoring. When looking into the technique that is used in thromboelastometry one could wonder to what extent the 'qualitative assessment of clot formation' by thromboelastometry differs from the visual inspection of clot formation that can be performed by collecting blood in a non-citrated tube and wait to see what happens. Obviously, visual inspection does not provide an estimation of a woman's fibrinogen concentration. However, we have learned from the studies in this thesis, that FIBTEM A5 also seems to lack specificity in providing a correct estimation. Yet, FIBTEM A5 has proven to be useful as a more general indicator of coagulation capacity in a cohort of women experiencing postpartum haemorrhage, leading to reduction of FFP use[46]. For more accurate estimations of a woman's fibrinogen concentration, in case treatment with fibrinogen concentrate is considered, a fast and stable fibrinogen assay could serve as a useful addition to visual inspection of clot formation and should therefore be an important subject of future studies.

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APPENDICES

Summary

Postpartum haemorrhage, in this thesis defined as blood loss above 1000mL within the first 24 hours after birth, remains a major cause of maternal morbidity and mortality with an incidence that seems to be increasing over the last decade[1-8]. In this thesis we focussed on improvement of prognostic and diagnostic strategies for major obstetric haemorrhage, which may subsequently lead to a reduction of severe maternal morbidity, mortality and need for surgical interventions. In pursuit of this aim, research questions were posed corresponding to all three phases leading up to adverse outcome due to postpartum haemorrhage: pregnancy (prior to childbirth), early postpartum haemorrhage and persistent postpartum haemorrhage. In the first part of this thesis we focused on prediction of postpartum haemorrhage

In **Chapter 2** we prospectively evaluated the predictive value of a bleeding assessment tool for postpartum haemorrhage. In our cohort of 1147 women, the ability of the bleeding score to contribute to the discrimination between women with and without postpartum haemorrhage was poor. The most important reasons for this negative result were a high negative predictive value of the bleeding score, and obstetrical factors as main primary causes of postpartum haemorrhage. Hence, no evidence was found to support adding a bleeding assessment tool to the review of a pregnant woman's medical history for the prediction of postpartum hemorrhages of ≥1000 mL. However, adding two questions on medical history of nosebleeds and post-surgery blood loss to a standard anamnesis could enable a clinician to identify women with a higher risk of postpartum hemorrhage exceeding 2000 mL. Clinicians should contemplate whether they find this of clinical significance for individual patients.

In **Chapter 3** coagulation parameters during the course of severe postpartum haemorrhage were described, comparing coagulation parameters during early postpartum haemorrhage between women with and without adverse maternal outcome. Our findings demonstrate that detection of low levels of fibrinogen and elevated aPTT levels during early postpartum hemorrhage can contribute to the identification of women that may benefit from targeted hemostatic treatment. Essential in this identification process is *the moment* of reaching a level of fibrinogen of ≤2g/L during the course of postpartum hemorrhage. Based on these results we advise to assess levels of fibrinogen and aPTT in all women who experience postpartum hemorrhage with blood loss exceeding 1000mL.
In the second part of the thesis we focused on improvement of diagnostic strategies for postpartum haemorrhage. In **Chapter 4** changes in levels of coagulation parameters after administration of different volumes of clear fluids to women suffering from major postpartum haemorrhage were described. 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.

By the timely detection of changes in levels of relevant coagulation parameters, targeted hemostatic therapy to restore deficiencies could be administered. However, assessment of fibrinogen levels by a standard coagulation test like the Clauss fibrinogen assay has a turn-around time of up to 60 minutes making it unsuitable for acute clinical decision making[20]. Point-of-care devices like ROTEM® thromboelastometry are able to detect essential changes in the coagulation system within 10 minutes after blood sampling[21]. During the course of the TeMpOH-2 study, the ROTEM® Sigma was introduced, a fully automated successor of the ROTEM® Delta device.

In **Chapter 5** we compared ROTEM® parameters using the ROTEM Delta and Sigma devices in women experiencing postpartum haemorrhage to determine whether these devices provided similar results. We found that results from ROTEM® FIBTEM assays of the devices differed significantly, especially in the earlier measurements (A5 and A10) emphasizing the need to validate new devices before implementation and obtain device specific reference ranges, to inform appropriate device specific intervention points on an algorithm.
FIBTEM A5 has been promoted as the ROTEM equivalent to the Clauss fibrinogen assay which could be used to diagnose fibrinogen deficiency and guide treatment with fibrinogen concentrate.

In **Chapter 6** fibrinogen concentrations were described according to previously proposed FIBTEM A5 cut-off points in blood samples collected from women suffering postpartum haemorrhage. Our findings suggest that the best cut-off point to accurately select women with a Clauss fibrinogen concentration of ≤2 g/L in our cohort was a FIBTEM A5 value of 12mm. When this cut-off was applied, 87 percent of women in need of fibrinogen were treated. Downside is that a large majority of women (81%) was treated with fibrinogen concentrate, although they in fact had high fibrinogen concentrations. The development of a point-of-care test that really measures fibrinogen concentration could be of considerable clinical significance.

The last part of this thesis focussed on haemostatic treatment in case of persistent postpartum haemorrhage. In **Chapter 7** the association between tranexamic acid administration at an early stage in the course of persistent postpartum haemorrhage and severe acute maternal morbidity and blood loss in a high-resource setting was quantified. Our findings suggest that in a high-resource setting, the effect of administration of tranexamic acid during postpartum haemorrhage on both blood loss and the combined

endpoint of maternal mortality and morbidity may be disappointing. Judging from the promising results of early tranexamic acid treatment in trauma medicine and elective and acute surgery and the results of the WOMAN trial, its good safety profile (when administered in dosages of 15mg/kg) and the fact that tranexamic acid is inexpensive, there seem to be few reasons not to administer tranexamic acid early during the course of persistent postpartum hemorrhage, yet the effect on clinical endpoints may be limited or absent.

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Nederlandse samenvatting

Fluxus postpartum, in dit proefschrift gedefinieerd als een hoeveelheid bloedverlies van tenminste 1000 ml binnen de eerste 24 uur na de bevalling, blijft één van de belangrijkste oorzaken van maternale morbiditeit en mortaliteit wereldwijd, waarbij er ook nog steeds sprake lijkt te zijn van een toenemende incidentie. De focus van dit proefschrift ligt op het verbeteren van prognostische en diagnostische strategieën rondom fluxus postpartum, met als overkoepelend doel het bewerkstelligen van een reductie van ernstige maternale morbiditeit, mortaliteit en noodzaak tot het doen van chirurgische interventies. Om dit doel te kunnen bereiken werden onderzoeksvragen opgesteld corresponderend met drie perioden rondom zwangerschap en geboorte waarin prognostische en diagnostische strategieën kunnen worden ingezet: (1) zwangerschap (de fase voorafgaand aan de geboorte), (2) de beginfase van fluxus postpartum en (3) persisterende fluxus postpartum.

Ad 1. Predictie tijdens zwangerschap: zijn er mogelijkheden om al tijdens de zwangerschap te voorspellen welke vrouwen een verhoogd risico hebben op fluxus postpartum?

Ad 2. Predictie en diagnose tijdens de beginfasen van fluxus postpartum: is het mogelijk om al in de beginfase van fluxus postpartum vrouwen te identificeren, met een verhoogd risico op een ernstige afloop van fluxus postpartum? Maar ook, zijn er mogelijkheden om deze vrouwen op een snelle én betrouwbare manier te identificeren?

Ad 3. Behandelopties in het geval van persisterende fluxus postpartum: kunnen we vrouwen met persisterend bloedverlies tijdens fluxus postpartum adequaat behandelen met hemostatica om het bloedverlies een halt toe te roepen?

Om deze onderzoeksvragen te beantwoorden werden twee grote multicenter cohort studies opgezet. De Transfusion strategies in women during Major Obstetric Haemorrhage-1 (TeMpoH-1) studie was een nationale retrospectieve cohort studie in 61 ziekenhuizen in Nederland, waarin tussen 2011 en 2013 191.772 bevallingen zijn geëvalueerd. De TeMpOH-2 (Towards better Prognostic and Diagnostic strategies for Major Obstetric Haemorrhage) studie was een prospectief cohort onderzoek in drie ziekenhuizen in Nederland waarin tussen februari 2015 en april 2018 17.203 bevallingen zijn geanalyseerd. In totaal werden in beide studies 1982 vrouwen met (ernstige) fluxus postpartum geïncludeerd. Een deel van de resultaten van de TeMpOH-1 & 2 studies zijn beschreven in dit proefschrift.

In het eerste deel van dit proefschrift ligt de focus op predictie van fluxus postpartum. In **hoofdstuk 2** presenteren we de prospectieve evaluatie van de voorspellende waarde van een bloedingsscore voor fluxus postpartum. Uit onderzoek is gebleken dat het inschatten van a priori bloedingsrisico in een subpopulatie met milde stollingsziekten zoals de ziekte van Von Willebrand het beste gedaan kan worden door gebruik te maken van gestructureerde anamnesevoering. Dit gebeurt door middel van een bleeding-assessment tool (BAT) waarmee een bloedingsscore wordt gegenereerd. Wij hebben als eerste onderzocht of een tijdens de zwangerschap verkregen bloedingsscore kan bijdragen aan de identificatie van vrouwen met een verhoogd risico op het optreden van fluxus postpartum. In ons cohort van 1147 zwangere vrouwen, bleek het discriminerend vermogen van de bloedingsscore tussen vrouwen met en zonder uitkomst van fluxus postpartum slecht te zijn. De belangrijkste verklaringen voor dit negatieve resultaat waren de met name hoge *negatief* voorspellende waarde van de bloedingsscore en het feit dat verreweg de meeste gevallen van fluxus postpartum primair een obstetrische oorzaak hebben. Er werd dus geen bewijs gevonden dat het toevoegen van een gestructureerde anamnese op het gebied van bloedingssymptomen bijdraagt aan de identificatie van vrouwen met een verhoogd risico op fluxus postpartum. Uit ons onderzoek bleek wel dat het tijdens de zwangerschap positief beantwoorden van twee vragen t.a.v. frequent optreden van neusbloedingen en het hebben ervaren van een nabloeding na een eerdere chirurgische interventie een klein deel van de vrouwen (10%) met een fluxus postpartum >2000 ml op voorhand detecteerde. In de dagelijkse klinische praktijk zal de afweging gemaakt moeten worden, of dit klinisch relevant is voor het opstellen van een behandelplan voor een individuele patiënt.

In **hoofdstuk 3** presenteren we het beloop van stollingsfactoren over de tijd bij vrouwen die een ernstige fluxus postpartum hebben doorgemaakt. De hoeveelheid bloedverlies werd ingedeeld in categorieën, waarna de bloedafnames werden geanalyseerd in de categorie corresponderend met de hoeveelheid bloedverlies ten tijde van de bloedafname. Daarnaast werd een vergelijking gemaakt tussen de concentraties van stollingsfactoren gemeten tijdens vroege fluxus postpartum van vrouwen die mét en zonder gecombineerd eindpunt van ernstige maternale morbiditeit en mortaliteit eindigden. Onze bevindingen laten zien dat het meten van een laag Clauss fibrinogeengehalte (≤ 2g/L) of een verlengde APTT *vroeg* tijdens fluxus postpartum (1.5-2.0 L) kan bijdragen aan de identificatie van vrouwen met een verhoogde kans op een ernstig beloop van fluxus postpartum. Dit zijn de vrouwen die mogelijk baat hebben bij een geïndividualiseerde behandeling door middel van het gericht toedienen van hemostatica. Een fibrinogeen van ≤2g/L is in eerdere studies ook gevonden als voorspeller van een ernstiger beloop van fluxus postpartum. Essentieel in de bevindingen die wij presenteren is *het moment* waarop dit lage fibrinogeen gehalte bereikt wordt tijdens fluxus postpartum. Als een verlaagd fibrinogeen gehalte gemeten wordt bij een relatief 'beperkte' hoeveelheid bloedverlies van 1500ml is het een duidelijke

voorspeller van een slechtere maternale uitkomst van fluxus postpartum. Op basis van deze resultaten is ons advies om in geval van een persisterende fluxus postpartum bij een hoeveelheid bloedverlies van 1500ml een stollingsstatus te laten bepalen, waarbij in ieder geval fibrinogeen en APTT bepaald moeten worden.

In het tweede gedeelte van dit proefschrift staat de verbetering van diagnostische methoden tijdens fluxus postpartum centraal.

In **hoofdstuk 4** beschrijven we de veranderingen optredend in concentraties van stollingsparameters als een gevolg van volumesuppletie door middel van kristalloïden en colloïden (clear fluids) tijdens fluxus postpartum. Er werden drie categorieën gevormd (toediening van <2.0L, 2-3.5L en >3.5L helder vocht ten tijde van de bloedafname) op basis van adviezen ten aanzien van volumesuppletie tijdens fluxus postpartum door de Royal College of Obstetricians and Gynaecologists (RCOG). Concentraties van stollingsparameters werden ook in deze studie gecategoriseerd op basis van hoeveelheid bloedverlies op het moment van bloedafname. Een meer liberaal vochtbeleid (toediening van >2.0L ten tijde van de bloedafname) bleek geassocieerd te zijn met een duidelijke verslechtering van hemoglobine, hematocriet, trombocytengetal, fibrinogeen, aPTT en PT, waarbij de grootste veranderingen werden gezien tijdens de vroege fase van fluxus postpartum (bloedverlies 1-1.5L). Onze bevindingen bieden kwantitatief bewijs ter ondersteuning van de vooralsnog alleen op meningen van experts gebaseerde richtlijnen die een restrictief beleid t.a.v. volumesuppletie adviseren tijdens fluxus postpartum ter voorkoming van verdunningscoagulopathie.

Door de vroegtijdige detectie van veranderingen van relevante stollingsparameters, kan doelgerichte behandeling met hemostatica worden toegepast om ontstane deficiënties in stollingsparameters aan te vullen. Een belangrijke factor daarbij is de tijd die het duurt tussen bloedafname en het uiteindelijke verkrijgen van het resultaat (turn-around time). Een standaard stollingstest, zoals bijvoorbeeld de Clauss fibrinogeen test, heeft een turn-around time van 60 minuten, waardoor deze test in de praktijk niet geschikt is om acute klinische beslissingen op te baseren. Stollings point-of care apparaten zoals ROTEM® waarbij er door middel van tromboelastometrie een kwalitatieve inschatting van de bloedstolling wordt verkregen, kunnen binnen 10 minuten essentiële veranderingen in de stollingsstatus detecteren. Ze worden dan ook in toenemende mate gebruikt bij cardiothoracale, lever- en traumachirurgie. In de verloskunde is de toegevoegde waarde van het gebruik van tromboelastometrie nog onduidelijk. In de onderzoeken zoals beschreven in dit proefschrift werd het gebruik van tromboelastometrie tijdens fluxus postpartum onderzocht. Aangezien een Clauss fibrinogeengehalte ≤ 2g/L een voorspeller blijkt te zijn van een ernstige afloop van fluxus postpartum, ging onze interesse met name

uit naar het onderzoeken van de fibrinogeen equivalent van ROTEM®, die bekend is na 7-10 minuten: FIBTEM A5.

Tijdens het uitvoeren van deze studies werd de ROTEM® Sigma geïntroduceerd, de volledig geautomatiseerde opvolger van de eerder gebruikte ROTEM® Delta, waarbij er handmatig gepipetteerd diende te worden. In **hoofdstuk 5** beschrijven we een vergelijking van ROTEM® parameters gemeten met de Delta en de Sigma bij vrouwen tijdens fluxus postpartum. Aangezien de Sigma werd geïntroduceerd als de opvolger van de Delta, was onze aanname dat de metingen die tegelijkertijd werden uitgevoerd op beide apparaten vergelijkbaar zouden zijn. In ons cohort bleek dat er significante verschillen waren tussen waarden voor FIBTEM van beide apparaten. Het verschil bleek het grootst te zijn in de voor de kliniek meest relevante waarden met een uitslag die bekend is na 5 en na 10 minuten, FIBTEM A5 en FIBTEM A 10. Onze bevindingen benadrukken de noodzaak om voorafgaand aan introductie en implementatie van een nieuw apparaat in de klinische praktijk, een validatieprocedure te doorlopen. Hierbij kunnen apparaat specifieke referentiewaarden worden vastgesteld, om te gebruiken in behandelalgoritmes.

Zoals eerder beschreven wordt ROTEM® FIBTEM A5 gezien als het snelle equivalent van Clauss fibrinogeen, om op een snelle manier een fibrinogeendeficiëntie vast te stellen en te gebruiken als een maat om toediening van fibrinogeenconcentraat te doseren. Het is in dit geval belangrijk om een maat te hebben waarmee zoveel mogelijk vrouwen met een daadwerkelijk laag fibrinogeen gehalte worden geïdentificeerd, zonder dat er aan de andere kant veel vrouwen fout-positief worden geselecteerd, terwijl ze in de praktijk een hoog genoeg fibrinogeen gehalte hebben.

In **hoofdstuk 6** beschrijven we de associatie tussen Clauss fibrinogeen concentratie en ROTEM® FIBTEM A5 gemeten bij vrouwen tijdens fluxus postpartum. Daarnaast werden eerder beschreven afkappunten van FIBTEM A5 om vrouwen met een lage Clauss fibrinogeen concentratie (≤ 2g/L) te identificeren geanalyseerd. In ons cohort bleek een FIBTEM A5 waarde van 12mm het beste afkappunt te zijn om zoveel mogelijk vrouwen met een laag Clauss fibrinogeen gehalte te detecteren, met een sensitiviteit 87% van en een specificiteit van 81%. Als dit afkappunt wordt toegepast om vrouwen te selecteren met een laag fibrinogeen gehalte, waarbij er een noodzaak bestaat om fibrinogeen concentraat toe te dienen, wordt 87% van de vrouwen met een daadwerkelijk laag fibrinogeen geselecteerd. De keerzijde is, dat bij het hanteren van een afkapwaarde van FIBTEM A5 van 12 mm ook veel vrouwen worden geselecteerd die in de praktijk toch geen laag fibrinogeen blijken te hebben. Dit laatste is het geval voor 81% van de vrouwen. Dit betekent dat in ons cohort voor de heel gerichte toepassing van het identificeren van vrouwen met een noodzaak tot behandeling met fibrinogeenconcentraat, ROTEM®

FIBTEM A5 geen accurate meetmethode is gebleken. De ontwikkeling van een snelle én betrouwbare fibrinogeen point-of -care test is dan ook van groot klinisch belang.

Het laatste deel van dit proefschrift heeft als focus het toepassen van behandeling met hemostatica bij vrouwen met persisterende fluxus postpartum.

In **hoofdstuk 7** presenteren we de resultaten van ons onderzoek naar de associatie tussen het vroegtijdig toedienen van tranexaminezuur tijdens persisterende fluxus postpartum en het optreden van een gecombineerd eindpunt van ernstige maternale morbiditeit en mortaliteit in een setting met een hoog voorzieningen niveau. Persisterende fluxus postpartum werd gedefinieerd als persisterend bloedverlies ondanks het toepassen van eerstelijns maatregelen. Als voorbeeld werd bij een vastzittende placenta een manuele placentaverwijdering beschouwd als eerstelijns behandeling. Onze resultaten laten zien dat in deze setting de toegevoegde waarde van het vroeg toedienen van tranexaminezuur beperkt lijkt wat betreft vermindering van bloedverlies (min 177 ml). Daarnaast werd geen verschil gevonden in het optreden van het gecombineerde eindpunt van ernstige maternale morbiditeit en mortaliteit. Op basis van onze bevindingen, maar zeker ook kijkend naar de veelbelovende resultaten van de WOMAN trial, het goede veiligheidsprofiel van tranexaminezuur en de lage kostprijs, lijken er weinig redenen te zijn om geen tranexaminezuur toe te dienen vroeg tijdens fluxus postpartum. Kanttekening daarbij is dat het effect op klinische eindpunten beperkt kan zijn.

List of publications

In this thesis

Gillissen A, van den Akker T, Caram-Deelder C, et al. Predictive value of a bleeding score for postpartum hemorrhage. Research and practice in thrombosis and haemostasis. 2019;3(2):277-284.

Gillissen A, van den Akker T, Caram-Deelder C, et al. Comparison of thromboelastometry by ROTEM((R)) Delta and ROTEM((R)) Sigma in women with postpartum haemorrhage. Scandinavian journal of clinical and laboratory investigation. 2019:1-7.

Gillissen A, van den Akker T, Caram-Deelder C, et al. Association between fluid management and dilutional coagulopathy in severe postpartum haemorrhage: a nationwide retrospective cohort study. BMC pregnancy and childbirth. 2018;18(1):398.

Gillissen A, van den Akker T, Caram-Deelder C, et al. Coagulation parameters during the course of severe postpartum hemorrhage: a nationwide retrospective cohort study. Blood advances. 2018;2(19):2433-2442.

Gillissen A, Henriquez D, van den Akker T, et al. 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.

Other publications

Oosterhuis JJ, **Gillissen A,** Snijder CA, Stiggelbout A, Haak MC. Decision-making in the referral process of sonographers in primary care screening centers. Prenatal diagnosis. 2016;36(6):555-560.

Gillissen A, Sueters M, van Lith JM, Walther FJ, Lopriore E. Acute hemorrhage in monochorionic twins with ruptured velamentous vessels: anemic twin resuscitated by its co-twin through placental vascular anastomoses? Fetal diagnosis and therapy. 2013;34(1):56-58.

Curriculum Vitae

Ada Gillissen was born on December 2nd 1982 in Kerkrade. She graduated from secondary school (gymnasium) at the Bernardinus College in 2000. In the same year she moved to Maastricht to study at the Medical Faculty of the University of Maastricht. During her study she went to Canada for a research project at the Child and Family research institute of the University of British Columbia (Prof. M.C. Klein), in Vancouver Canada. In 2006 she conducted a combined scientific and clinical internship at the LUMC (Prof. Dr. A.A.W. Peters). In 2006 she attained her medical degree and started to work as a physician (ANIOS) at the department of Obstetrics and Gynaecology at the Groene Hart Ziekenhuis, Gouda. In 2008 she started her residency in Obstetrics and Gynaecology at the same department. (Dr. J.C.M. van Huisseling). She continued her residency at the LUMC (Prof. J.M.M. van Lith). In 2013 she was given the opportunity to work as a full time researcher for the Towards better prognostic and diagnostic strategies for Major Obstetric Haemorrhage (TeMpOH-2) study at the Center for Clinical Transfusion Research, of Sanquin Research, Leiden in collaboration with the department of Obstetrics and Gynaecology of the LUMC that led to her thesis under supervision of Professor J.G. van der Bom, Prof. T.H. van den Akker and Dr. C. Caram-Deelder. She is currently continuing her residency at the department of Obstetrics and Gynaecology, Groene Hart Ziekenhuis, Gouda (Dr. C.A.H. Janssen).

Ada lives together with Koen van Deudekom and their sons Hugo, Timme and Olivier in Voorburg.

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Aad, Yavanna, Debby, Ouisam

Afdelingen verloskunde
LUMC, EMC & Isala

Vrienden & vriendinnen

De allerliefsten ♥
Koen, Hugo, Timme & Olivier

Papa & Mama

Freek & Bernard

Familie & schoonfamilie

International Safe Motherhood & Reproductive Health

The Dutch Working Party 'International Safe Motherhood and Reproductive Health' aims to contribute to improvement of the reproductive health status of women around the globe, in particular by collaborating with local health workers (http://www.safemotherhood.nl). The Working Party is part of both the Dutch Society of Obstetrics and Gynaecology (NVOG) and the Dutch Society for International Health and Tropical Medicine (NVTG). The activities that are undertaken under the umbrella of the Working Party can be grouped into four pillars: education, patient care, research and advocacy.
Research activities are undertaken by (medical) students, Medical Doctors International Health and Tropical Medicine and many others. Some research activities develop into PhD-trajectories. PhD- candidates all over the world, Dutch and non-Dutch, work on finding locally acceptable and achievable ways to improve the quality of maternal health services, supervised by different members of the Working Party. Professor Jos van Roosmalen initiated the Safe Motherhood Series, which started in 1995.

The Safe Motherhood Series

- Safe motherhood: The role of oral (methyl)ergometrin in the prevention of postpartum haemorrhage. (Akosua N.J.A. de Groot), Nijmegen, 1995
- Safe motherhood: Perinatal assessment in rural Tanzania. (Gijs E.L. Walraven), Nijmegen, 1995
- Safe motherhood: Confidential enquiries into Maternal Deaths in the Netherlands, 1983-1992. (Nico W.E. Schuitemaker), Leiden, 1998
- Safe motherhood: Confidential enquiries into Maternal Deaths in Surinam. (Ashok S. Mungra), Leiden, 1999
- Safe motherhood: Reproductive health matters in rural Ghana. (Diederike W. Geelhoed), Leiden, 2003
- Safe Motherhood: Vaginal birth after caesarean section in Zimbabwe and The Netherlands (Wilbert A. Spaans), Amsterdam AMC, 2004
- Safe Motherhood and Health systems research: Health care seeking behaviour and utilisation of health services in Kalabo District (Jelle Stekelenburg), VU University Medical Centre, Amsterdam, 2004
- Safe Motherhood. Enhancing survival of mothers and their newborns in Tanzania (Godfrey Mbaruku), Karolinska Institute, Stockholm, Sweden, 2005
- Safe Motherhood. Beyond the numbers: confidential enquiries into maternal deaths in Accra- Ghana (Afisah Yakubu Zakariah, Accra, Ghana), Vrije Universiteit Brussel, Belgie, 2008
- Safe Motherhood. Severe maternal morbidity in the Netherlands: the LEMMoN study (Joost Zwart), Leiden University Medical Centre, the Netherlands, 2009
- Safe Motherhood. Obstetric audit in Namibia and the Netherlands (Jeroen van Dillen), VU University Medical Centre, Amsterdam, the Netherlands, 2009
- Safe Motherhood. Confidential enquiries into maternal deaths in the Netherlands 1993-2005 (Joke Schutte), VU University Medical Centre, Amsterdam, the Netherlands, 2010
- Delay in Safe Motherhood (Luc van Lonkhuijzen), University Medical Centre Groningen, the Netherlands, 2011
- Safe Motherhood: Medical Mirrors: Maternal care in a Malawian district (Thomas van den Akker), VU University Medical Centre, Amsterdam, the Netherlands, 2012
- Safe Motherhood: Leading change in the maternal health care system in Tanzania: application of operations research (Angelo Nyamtema, Ifakara, Tanzania), VU University Medical Center, Amsterdam, the Netherlands, 2012
- Safe Motherhood: Health professionals and maternal health in Malawi: mortality and morbidity at district level (Jogchum Beltman), VU University Medical Center, Amsterdam, the Netherlands, 2013
- Safe Motherhood: Obstetric emergencies in primary midwifery care in the Netherlands (Marrit Smit), Leiden University Medical Center, the Netherlands, 2014
- Safe Motherhood: Improving maternal outcome in rural Tanzania using obstetric simulation based training (Ellen Nelissen), VU University Amsterdam, the Netherlands, 2014
- Safe Motherhood: The aberrant third stage of labour (Giel van Stralen), Leiden University Medical Center, the Netherlands, 2015
- Safe Motherhood: Terugvinden van waardigheid, community-based sociotherapie in Rwanda, Oost-Congo en Liberia (Cora Bakker), VU University Amsterdam, the Netherlands, 2016
- Safe Motherhood: Severe acute maternal morbidity, risk factors in the Netherlands and validation of the WHO Maternal Near-Miss Tool (Tom Witteveen), Leiden University Medical Center, the Netherlands, 2016
- Safe Motherhood: Getting the job done, providing lifelong HIV-treatment in settings with limited human resources for health: innovative approaches (Marielle Bemelmans), VU University Amsterdam, the Netherlands, 2016
- Safe Motherhood: Identifying needs for optimizing the health work force in Ethiopia (Tegbar Yigzaw Sindekie), VU University Amsterdam, the Netherlands, 2017
- Safe Motherhood: Improving frontline health workers' performance in low resource settings; the case of Ethiopia (Firew Ayalew Desta), VU University Amsterdam, the Netherlands, 2017
- Safe Motherhood: Increasing access to anesthaesia in Ethiopia: task shifting (Sharon J.N. Kibwana), VU University Amsterdam, the Netherlands, 2017

- Safe Motherhood: Diagnostic and clinical decision support systems for antenatal care: is mHealth the future in low-resource settings? (Ibukun-Oluwa O. Abejirinde), VU Amsterdam, the Netherlands, 2018
- Safe Motherhood: Assisting birth attendants in providing acceptable care under unacceptable clinical realities: The Partoma Intervention Study at Zanzibar's Tertiary Hospital (Nanna Maaløe), University of Kopenhagen, Denmark, 2019
- Safe Motherhood: Severe Maternal Morbidity and Mortality in Eastern Ethiopia (Abera Kenay Tura), University Medical Centre Groningen, the Netherlands, 2019
- Safe Motherhood: Maternity Waiting Homes in Ethiopia to improve women's access to maternity care (Tienke Vermeiden), University Medical Centre Groningen, the Netherlands, 2019
- Safe Motherhood: Improving access to quality maternal and newborn care in low-resource settings: the case of Tanzania (Dunstan Raphael Bishanga), University Medical Centre Groningen, the Netherlands, 2019

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