Towards better prognostic and diagnostic strategies for major obstetric haemorrhage

Gillissen, A.

2 PREDICTIVE VALUE OF A BLEEDING SCORE FOR POSTPARTUM HAEMORRHAGE

Ada Gillissen
Thomas van den Akker
Camila Caram-Deelder
Dacia D.C.A. Henriquez
Sebastiaan W.A. Nij Bijvank
Kitty W.M. Bloemenkamp
Jeroen Eikenboom
Johanna G. van der Bom

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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.

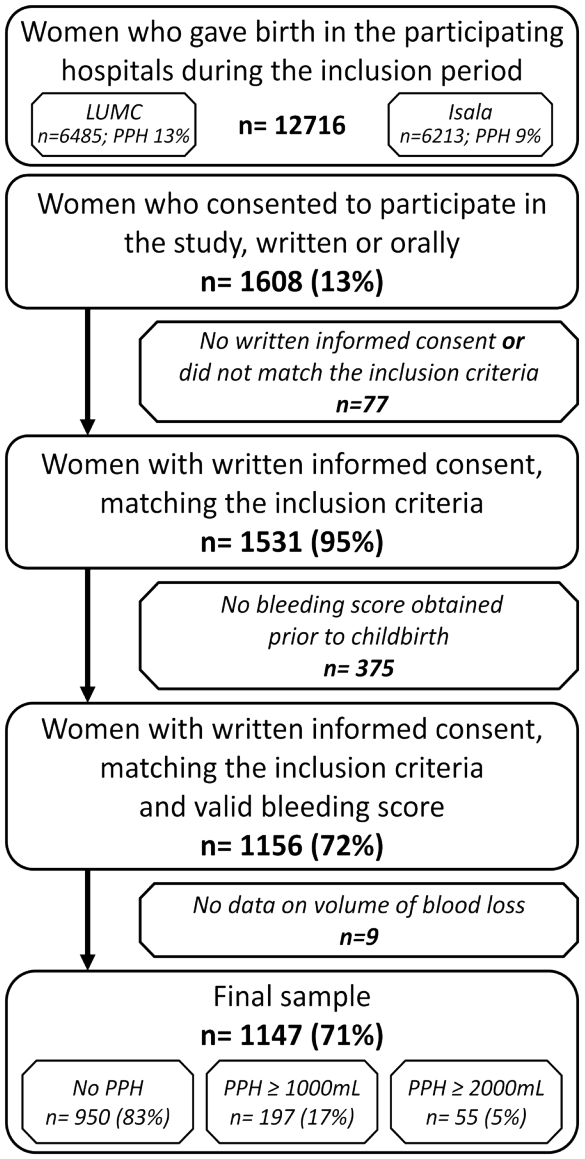

Figure 1. **Inclusion flowchart**

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.

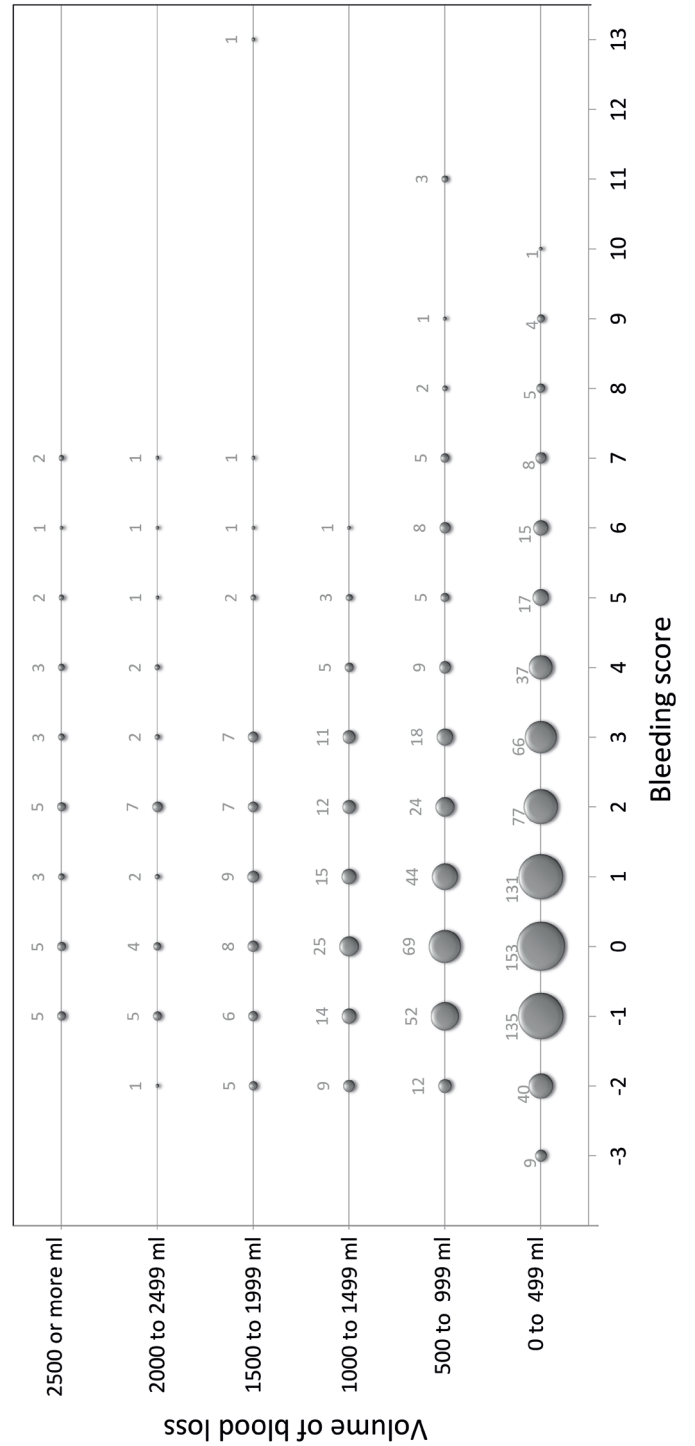

Figure 2. Bubble plot bleeding score versus volume of blood loss

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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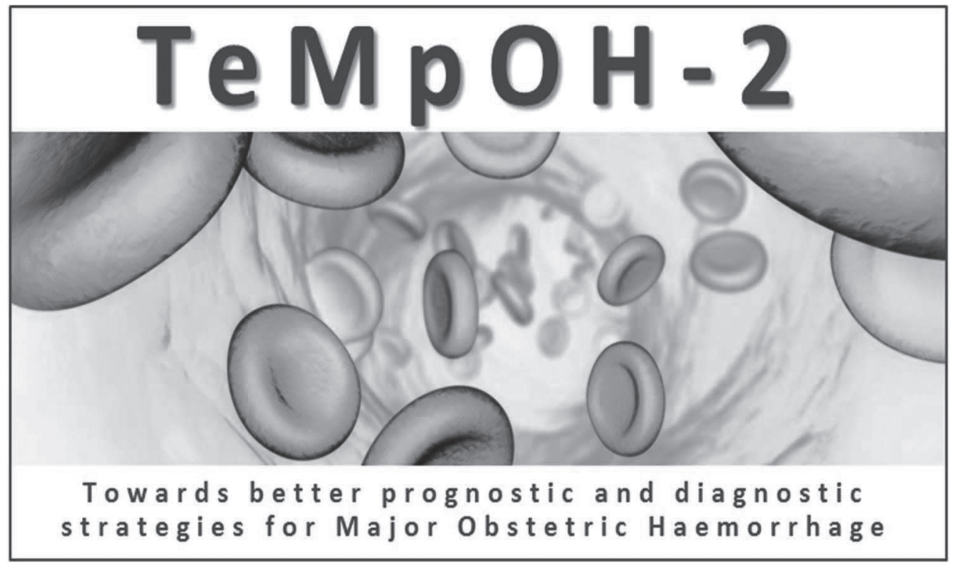
Supplemental material

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

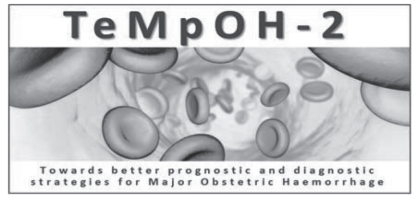
O Black

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.