Towards better prognostic and diagnostic strategies for major obstetric haemorrhage

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8 GENERAL DISCUSSION AND SUMMARY

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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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