Postpartum hemorrhage: from insight to action

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PART III

DISCUSSION AND SUMMARY

CHAPTER 7

GENERAL DISCUSSION AND CONCLUSION

DISCUSSION

Childbirth is a major and generally joyous life event. However, every childbearing woman is at risk of postpartum hemorrhage, a serious obstetric complication that is the leading cause of maternal mortality worldwide.[1] Although maternal deaths are rare events in high-income settings, many women suffer from considerable severe maternal morbidity when surviving a life-threatening bleeding following childbirth.[2] The World Health Organization (WHO) has classified a woman who nearly died but survived a complication during pregnancy, childbirth, or within 42 days following termination of pregnancy as a 'maternal near miss'.[3] A maternal near miss reflects a woman surviving a life-threatening obstetric complication with serious and enduring consequences.[3] Identifying and reviewing maternal near misses in addition to confidential enquiries of women who died may help to strengthen maternity care for specific obstetric complications.[4] Investigating postpartum hemorrhage associated with maternal near miss and mortality, and evaluating and improving maternity care at different stages of bleeding in the course of excessive blood loss is key to ultimately improve maternal outcome.

Therefore, the two central themes and purpose of the studies presented in this thesis were:

1. To gain insight into severe postpartum hemorrhages associated with maternal near miss and mortality by investigating women in need of massive blood transfusion due to postpartum hemorrhage.
2. To evaluate maternity care at different stages of bleeding throughout the course of postpartum hemorrhage, specifically at the onset of hemorrhage (timely recognition of women at risk of progression of hemorrhage), during persistent hemorrhage (evaluation of obstetric interventions to cease persistent hemorrhage), and at the end of hemorrhage (learn lessons once a maternal death has occurred due to obstetric hemorrhage).

Part I: Massive blood transfusion in relation to postpartum hemorrhage

It is of great value to investigate these severe bleedings and compare management and severe maternal outcome (i.e. maternal near miss and maternal mortality) between different settings enabling the identification of possible aspects to scrutinize and improve maternity care. Besides obstetric and surgical interventions, management of postpartum hemorrhage also includes transfusion of blood products and fluid resuscitation. In case of a life-threatening postpartum bleeding, massive blood transfusion is needed to maintain adequate perfusion and tissue

oxygenation to survive. Identifying and investigating those women in need of a massive blood transfusion helped to obtain more insight into severe postpartum hemorrhage in order to evaluate and compare management strategies and the maternal outcome across different settings and over time. Nevertheless, a national registration system of women experiencing severe postpartum hemorrhage in the Netherlands is lacking, while routine collection and analysis of such data is the necessary 'next step' to enable a continuous evaluation of the quality of maternity care in case of severe hemorrhage.

Chapter 2 and **Chapter 3** comprised the first part of this thesis and addressed the incidence, causes, management and outcome of women in need of massive blood transfusion due to postpartum hemorrhage in the Netherlands within the time frames 2004-2006 and 2011-2012. Data were used from two nationwide population-based cohort studies: the LEMMoN study and the TeMpOH-1 study.[5,6] This enabled us to include a large number of women with massive blood transfusion allowing for a robust estimation of the incidence, identification of risk factors, and analysis of causes, management and maternal outcome. Only few other population-based studies investigated massive blood transfusion in relation to postpartum hemorrhage.[7-9] The WHO defined massive transfusion as ≥5 units of packed red blood cells in order to identify maternal near miss.[10] However, to date, no consensus exists in the literature as to which definition of massive blood transfusion should be used in maternity care. Multiple definitions varying from ≥8 or ≥10 units of packed red blood cells transfused within a specific time frame and depending on the gestational age at the time of birth were applied in different studies (Table 1). To enable cross-country comparisons, we pragmatically used the definition of ≥8 units of packed cells transfused within 24 hours following birth at a gestational age of ≥20 weeks. This definition was used by the only other population-based study, conducted in the United Kingdom, which investigated massive transfusion within a similar time frame.[7]

Massive blood transfusion in the Netherlands

Our findings showed a decreasing incidence of massive blood transfusion due to postpartum hemorrhage in the Netherlands. Meanwhile, total median blood loss among women who had massive blood transfusion following birth seemingly increased over time and we observed an increase in the proportion of women who had radiological embolization and/or peripartum hysterectomy to stop bleeding. Even more noteworthy was that the case fatality rate among women who received massive blood transfusion increased from 0.9% in 2004-2006 to 2.3% in 2011-2012, a worrying observation that merited further analysis. This was the main

reason to investigate obstetric-related maternal deaths in the Netherlands and led to a collaboration with the Dutch Maternal Mortality and Severe Morbidity Audit Committee (**Chapter 6**). The decrease in massive blood transfusion because of postpartum hemorrhage is in line with the decreasing incidence of women who received an obstetric-related blood transfusion in the Netherlands.[11] The decreasing incidence of massive blood transfusion in combination with an increase in median blood loss and the proportion of women who underwent embolization or hysterectomy between both time frames probably also reflect more pro-active management of postpartum hemorrhage, and/or an ever more restrictive blood transfusion policy after the introduction of the '4-5-6-rule' in the Dutch national guideline on blood transfusion in 2004.[12]

Table 1. Definition and incidence of obstetric-related massive blood transfusion between different settings.

Setting	*Time period*	*Definition of massive transfusion*	*Incidence*
The Netherlands[5,6]	2004-2006	≥8 packed cells within 24 hours after childbirth at ≥20 weeks of gestation	91 per 100 000 births
	2011-2012	≥8 packed cells within 24 hours after childbirth at ≥20 weeks of gestation	65 per 100 000 births
United Kingdom[7]	2012-2013	≥8 packed cells within 24 hours after childbirth at ≥20 weeks of gestation	23 per 100 000 births
Sweden[8]	1990-2011	≥8 packed cells after birth and the next day at ≥22 weeks of gestation	85 per 100 000 births
	1990-2011	≥10 packed cells after partus and the next day at ≥22 weeks of gestation	53 per 100 000 births
State of New York in the United States of America[9]	1998-2007	≥10 packed cells, irrespective of time and gestational age at time of birth	60 per 100 000 births

Similarities between the Netherlands and other settings

In addition to the substantial risk of peripartum hysterectomy, postpartum hemorrhage with massive blood transfusion was also associated with other forms of severe morbidity. Nearly three-quarters of those in need of massive blood transfusion were admitted to an intensive care unit. This is in accordance with a

study in the United Kingdom on massive blood transfusion in 2012-2013.[7] Uterine atony was the leading cause of bleeding leading to massive blood transfusion in the Netherlands in 2004–2006 and 2011–2012, as was the case in the United Kingdom and Sweden.[7,8] Only the state of New York in the United States of America reported abnormal placentation as the main cause of bleeding leading to massive blood transfusion[9], probably due to the higher cesarean section rate in the United States (around 30% vs 15% in the Netherlands)[13,14]. Cesarean section is an independent risk factor for abnormal placentation.[15,16] Furthermore, our study (**Chapter 3**) along with two other studies on massive blood transfusion following childbirth conducted in Sweden and the state of New York identified a number of risk factors associated with massive blood transfusion in relation to postpartum hemorrhage, including maternal age >35 years, multifetal pregnancies, pregnancies complicated by preeclampsia, and giving birth by cesarean section.[8,9] The latter finding emphasizes that cesarean sections should only be performed on appropriate indication and that clinicians should remain vigilant of severe hemorrhage during and after cesarean section. Early recognition of risk factors may help obstetric caregivers to identify women at risk of severe postpartum hemorrhage and trigger appropriate precautions, such as venous access early during labor with blood sampling for hemoglobin testing and crossmatching with emphasis on active management of the third stage of labor.

Differences between the Netherlands and other settings

The incidence of massive blood transfusion due to postpartum hemorrhage in the Netherlands decreased over time and became lower than the incidence reported in the study on massive blood transfusion in Sweden in 1990–2011 (Table 1).[8] However, contrary to our findings, the incidence of massive blood transfusion in Sweden increased by 30% between 1990–2000 and 2001–2011.[8] The authors of the Swedish study explained this increase by 1) an observed increase in the frequency of women with abnormally invasive placentation, 2) an increase in pregnancies established by in-vitro-fertilization, and 3) more clinicians working in the field of obstetrics with limited surgical skills in performing peripartum hysterectomy leading to a delay in adequate management and more women in need of massive blood transfusion.[8] Although we observed an increase in the proportion of women with massive blood transfusion due to placental pathology, the overall incidence of massive blood transfusion following childbirth in the Netherlands decreased over time. The proportional increase of women with abnormal placentation in our study is likely caused by a larger proportion of high-risk pregnancies due to a more restrictive blood transfusion policy over time. Nevertheless, the incidence of massive blood transfusion following childbirth may increase again in the

future, considering that, although the cesarean section rate in the Netherlands has remained relatively stable around 15%, data suggest that the rate of repeat cesarean sections has been increasing between 2000-2019.[13] Furthermore, senior residents in the Netherlands may lack sufficient surgical skills to perform peripartum hysterectomy. Since the introduction of minimally invasive surgery, a shift from laparotomy towards laparoscopy has been observed. This shift has led to concerns regarding the growing lack of proficiency of clinical caregivers to perform open abdominal surgery, including peripartum hysterectomy.[17] Such concerns have been confirmed in a national survey among French residents, where four out of five residents stated they did not have enough surgical skills to perform peripartum hysterectomy.[18] This is a worrying observation and requires further analysis, also in the Netherlands. This could indicate that the training program for surgical management of severe postpartum hemorrhage is insufficient and has to be improved by e.g. practicing surgical procedures on cadavers or by virtual reality training.[18] However, even by these means, it will likely not be easy to maintain high levels of surgical experience among all clinicians. As open surgery will be required in certain cases of severe postpartum hemorrhage, facilities may require rotations of clinicians who have sufficient surgical skills to perform laparotomy, in order to guarantee 24-hours access to such care if needed.

The incidence of massive blood transfusion in the Netherlands in 2004-2006 and 2011-2012 was considerably higher than the incidence reported in the study in the United Kingdom in 2012-2013 that used the same definition for massive blood transfusion (Table 1).[7] A comparison of our results in 2011-2012 to those in the United Kingdom brought to light remarkable differences in hematological and surgical management. The most distinct difference was the proportion of women who had embolization (16% in the United Kingdom vs 48% in the Netherlands) and peripartum hysterectomy (45% in the United Kingdom vs 30% in the Netherlands).[7] These notable difference may partly be explained by the recommendation '*resort to hysterectomy sooner rather than later*' in the national guideline on postpartum hemorrhage in the United Kingdom without mentioning the option of embolization first, while the Dutch national guideline specifically mentions embolization as a treatment option before resorting to hysterectomy.[19,20] Other possible explanations are country-specific differences in the distribution of facilities with interventional radiology suites and in transport arrangements for referral of a woman to another hospital to undergo embolization. In 2004-2006, 23% of the hospitals with a maternity ward in the Netherlands had unrestricted access to embolization.[21] Furthermore, the Netherlands is a relatively compact country with surmountable distances to facilities that have interventional radiology suites

available, making the threshold to transport women relatively low. Nevertheless, the case fatality rate of women who had massive blood transfusion following birth was notably lower in the United Kingdom in 2012-2013 (0.7%) than in the Netherlands in 2011-2012 (2.3%).[7] This brings into question whether clinicians in the Netherlands may be too focused on preserving women's fertility, ultimately at the cost of a woman's life. Should we actually transport women with postpartum hemorrhage from one hospital to another for radiological embolization? Or does this lead to inappropriate delay? These are important questions that may be answered by routine and structured confidential enquiries of women with severe hemorrhage who had radiological embolization and/or peripartum hysterectomy.

Furthermore, a recent exploratory study with published and non-published data on massive blood transfusion based on regional and national data collection across six countries (France [2012-2013], United Kingdom [2013-2014], Italy [2014-2016], Australia [2014-2015], Denmark [2010-2015], the Netherlands [2011-2012, using data from the TeMpOH-1 study]) from the International Network of Obstetric Survey Systems (INOSS) found considerable variations in the incidence of women with massive blood transfusion because of postpartum hemorrhage, despite using the same definition of ≥8 packed cells transfused within 24 hours following birth at a gestational age of ≥20 weeks across all countries.[22] The incidence of massive blood transfusion was 82 per 100 000 births in Denmark, 69 in France, 21 in Italy as well as in the United Kingdom, and 20 in Australia.[22] This study also observed large disparities in both hematological and surgical management options between countries. The administration of fresh frozen plasma, platelets, tranexamic acid, recombinant factor VIIa and fibrinogen concentrate varied considerably.[22] Intrauterine balloon tamponade was used in at least 50% of the women during bleeding, but lower in France (28%) and Denmark (15%).[22] Embolization and/or vessel ligation (composite endpoint) was high in France (71%) compared to the United Kingdom (16%) and Italy (4%).[22] Although Italy had one of the lowest incidences of massive blood transfusion, the proportion of women who underwent hysterectomy was highest (74%), possibly as a result of a more aggressive management of severe bleeding.[22] Peripartum hysterectomy was performed in 56% of the women in Australia, 46% in France as well as the United Kingdom, 30% in the Netherlands, and 23% Denmark.[22] Denmark reported a similar incidence of massive blood transfusion and a similar proportion of women who underwent peripartum hysterectomy compared to the Netherlands, but the case fatality rate was notably lower (0.7%), while intrauterine balloon tamponade was lower as well (15% vs 56% in the Netherlands) as was embolization and/or ligation (0.7% vs 48% in the Netherlands).[22] These findings indicate considerable

differences in transfusion policies and management of postpartum hemorrhage between the Netherlands and Denmark and should encourage us to scrutinize and compare the clinical pathway leading to massive blood transfusion across settings to improve the quality of maternity care.

Other studies reported a similarly wide variation between countries in the management of severe postpartum hemorrhage, eventually leading to peripartum hysterectomy.[23,24] This is unsurprising considering there are considerable differences in the management guidelines for postpartum hemorrhage and disparities in the access to specific facilities between and within countries.[25,26] The same applies for transfusion recommendations, which have substantial inconsistencies between (non-)obstetrical guidelines.[27] This illustrates that the approach to the management of postpartum hemorrhage is not uniform. This emphasizes the need for high-level (re)search into the optimal management strategies by diligent evaluation of existing and innovative obstetric and hematological treatment possibilities. That may ultimately lead to the establishment of more consistent and evidence-based guidelines. A collaboration within networks such as INOSS could help facilitate population-based studies and enable countries to reference their maternity care against that of other countries in search for the optimization of their management strategies.[28]

Strive for a uniform definition of severe postpartum hemorrhage

The definition of severe postpartum hemorrhage has been subject of debate. Using ≥8 or ≥10 packed red blood cells transfused as a definition of massive blood transfusion may reflect severe life-threatening bleeding, but has its limitations. Such a definition reliant on requirement of packed red blood cells, or any other intervention for that matter, could be influenced by differences in clinical decision making and/or availability of specific resources. Furthermore, it can happen that women with severe hemorrhage die or have a peripartum hysterectomy before reaching the threshold of ≥8 or ≥10 units of packed red blood cells transfused, resulting in the exclusion of some of the most severe cases. Other definitions have been proposed to define severe postpartum hemorrhage, such as: blood loss >2000mL[29] or >2500mL[30], ≥4 or ≥5 units of packed red blood cells transfused[2,29,30], need for an obstetric intervention to stop bleeding[21,31] or blood products to treat coagulopathy.[30] Each of these definitions for severe postpartum hemorrhage has its limitations. Quantification of blood loss is difficult in persistent hemorrhage after initial routine measures, while visual estimations of blood loss are frequently inaccurate, and each woman's physiological ability to cope with a certain volume of blood loss is determined

by her health status. Using ≥4 or ≥5 units of packed red blood cells as definition is prone to include many women with less severe bleeding that is not associated with maternal near miss or mortality. Consensus for the definition of severe postpartum hemorrhage is still missing, and use of heterogenous definitions hampers comparisons between settings. It is crucial to arrive at a uniform consensus definition of severe postpartum hemorrhage that is broad enough to identify most women with severe bleeding which led to maternal near miss and mortality to evaluate and compare management and maternal outcome across settings and over time. A composite definition may be most suitable, including women who died from persistent postpartum hemorrhage, who had peripartum hysterectomy or any other invasive intervention to stop the bleeding, or who met a certain number of packed red blood cells transfused.[22]

Routine collection and examination of data on severe postpartum hemorrhage

However, regardless of which definition is applied for severe postpartum hemorrhage, routine and systematic collection and evaluation of data about severe obstetric-related hemorrhage in the Netherlands may help to improve maternity care. The International Federation of Gynecology and Obstetrics (FIGO) specifically recommends to '*collect country-level information, creating advocacy tools, and providing support on national advocacy efforts to reduce deaths and morbidity from postpartum hemorrhage*'.[32] Routine collection of such information may help establish maternal near miss audits of severe postpartum hemorrhage in addition to maternal death audits, in order to monitor and implement further improvements of improve maternity care.[33] The Scottish Confidential Audit of Severe Maternal Morbidity (SCASMM) has reported a steady reduction of severe maternal morbidity after the introduction of maternal near miss-audits in 2003.[34] Although the SCASMM observed a rise in the incidence of major obstetric hemorrhage over the past years, they observed better adherence to the national guideline on postpartum hemorrhage and improved presence of a consultant obstetrician and anesthesiologist during severe blood loss with a significant decline of the proportion of women who underwent peripartum hysterectomy to cease bleeding.[34] This may inspire clinicians in the Netherlands to develop a similar continuous registration system of severe postpartum hemorrhage, preferably on a nationwide scale, and incorporate maternal near miss audit in order to improve the quality of maternity care.[35] The Netherlands Obstetric Surveillance System (NethOSS) could serve as a useful tool to implement a routine prospective registration system of severe postpartum hemorrhage. NethOSS is a nationwide surveillance system of severe maternal morbidity and mortality that sends out monthly emails to clinicians in all hospitals in the Netherlands with a

maternity ward including a link for registration to report cases of severe maternal morbidity or mortality. This may help to reach a 'next level' at which occurrence, management and maternal outcome of severe postpartum hemorrhage are continuously monitored.

The need for such a continuous national registration system for severe postpartum hemorrhage is even more important, considering that a nationwide comparative study in the Netherlands observed large regional differences in the incidence of severe postpartum hemorrhage, from below 2% to over 8%.[36] Another study including 18 hospitals in the Netherlands found that the quality of the guidelines for postpartum hemorrhage varied widely between different hospitals.[37] Routine collection and analysis of data on severe postpartum hemorrhage may help to identify specific differences in the prevention and management of these severe bleedings and opportunities to improve maternity care.

Part II: Evaluation of maternity care during and after postpartum hemorrhage

The second part of this thesis focused on the evaluation of maternity care at different stages of hemorrhage during the course of postpartum hemorrhage (Figure 1). Scrutinizing new and current hematologic and obstetric interventions in search for evidence-based management strategies and learn lessons from obstetric hemorrhage-related maternal deaths is crucial.

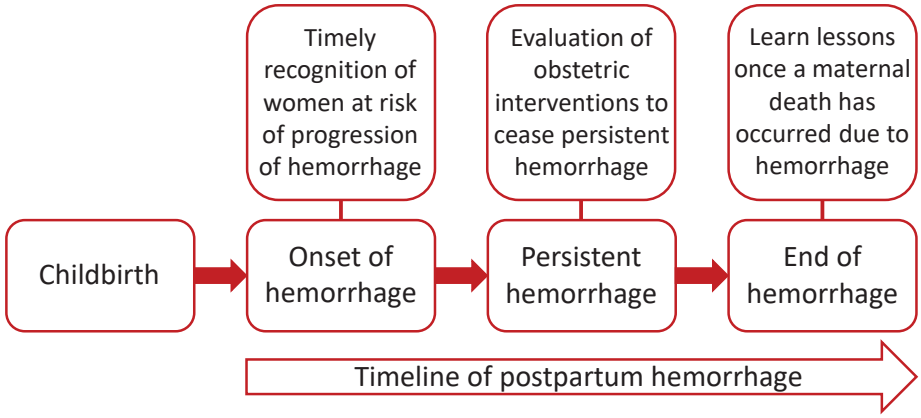

Figure 1. Flowchart of a simplified timeline of postpartum hemorrhage with opportunities to evaluate maternity care at different stages of bleeding in order to reduce the ongoing burden of maternal morbidity and mortality

Onset of hemorrhage: timely recognition of women at risk of progression of hemorrhage

We found no evidence to support the implementation of ROTEM® FIBTEM A5 as part of routine clinical care during onset of postpartum hemorrhage to identify women at risk of progression to severe postpartum hemorrhage (**Chapter 4**). Our results are contradictory to the results of a study from the United Kingdom demonstrating that FIBTEM A5 was predictive of a blood loss >2500mL, transfusion ≥4 packed cells, or need for an invasive intervention.[38] This difference may be explained by the fact that this study in the United Kingdom also included FIBTEM A5 measurements >1500mL of blood loss and women were excluded when bleeding stopped soon after blood sampling.[38] This suggests that the clinical value of a routine FIBTEM A5 measurement during onset of hemorrhage is limited, but FIBTEM A5 might still be useful in a selected target population considering that a fibrinogen deficit is uncommon during postpartum hemorrhage[38-40], and more likely to occur in ongoing bleeding or in presence of known risk factors for coagulopathy.[41-43] A randomized controlled trial comparing pre-emptive treatment with fibrinogen concentrate vs placebo during the onset of bleeding did not show improvement in maternal outcome, possibly explained by a mean baseline fibrinogen concentration of 4.5g/L at the time of the intervention, sufficient to maintain hemostasis.[44] Since the majority of women with postpartum hemorrhage have no hemostatic impairment, a possible added value of ROTEM® is avoidance of unnecessary transfusions. This is especially important considering that fibrinogen levels are elevated to 4-6g/L during pregnancy and that fresh frozen plasma derived from non-pregnant donors have fibrinogen levels of 2g/L.[45-47] Theoretical modeling showed that transfusion of fresh frozen plasma may dilute plasma fibrinogen levels of women with postpartum hemorrhage and could exacerbate bleeding.[48] One study found that withholding fresh frozen plasma in women with postpartum hemorrhage and FIBTEM A5 values >15mm did not result in clinically significant hemostatic impairment.[49] Two other studies demonstrated significantly fewer transfusions of allogeneic blood products after introduction of algorithms for ROTEM-guided transfusions during postpartum hemorrhage.[50,51] This suggests that ROTEM® is useful as a general indicator of a woman's coagulation capacity and that allogeneic blood products may be withheld in women who have normal ROTEM® values, and could help clinicians to differentiate between obstetric or coagulopathic-related hemorrhage. Whether correction of fibrinogen deficiency based on ROTEM® FIBTEM A5 values improves maternal outcome is still unclear. One study found that administration of fibrinogen based on a FIBTEM A5 value ≤15mm did not improve maternal outcome, and a subgroup analysis indicated that targeted fibrinogen replacement is not effective in women with FIBTEM A5 values >12mm.[52]

Moreover, it is important to note that ROTEM® FIBTEM is a qualitative assessment of the fibrinogen status and therefore not interchangeable with Clauss fibrinogen measurements.[53] Although a FIBTEM A5 value of ≤12mm has been identified as the most accurate cut-off to detect fibrinogen concentrations ≤2g/L, FIBTEM A5 lacks specificity.[54] Eighty-one percent of the women with a FIBTEM A5 value ≤12mm had a fibrinogen concentration >2g/L during postpartum hemorrhage.[54] In addition, our study (**Chapter 4**) only found a moderate correlation between FIBTEM A5 values and fibrinogen concentrations, similarly to the study in the United Kingdom.[38] Previous results from the TeMpOH-2 study demonstrated an increase in the correlation between FIBTEM A5 values and fibrinogen concentrations with higher volumes of blood loss.[54] It remains unclear whether ROTEM® FIBTEM is accurate in guiding or withholding blood products in the entire course of postpartum hemorrhage. This raises the question what the right target population is where ROTEM® FIBTEM might be useful and whether the development of a point-of-care test that specifically measures plasma-derived fibrinogen concentration would be of higher clinical significance.

Nonetheless, ROTEM® has been incorporated in postpartum hemorrhage care bundles and its use during postpartum hemorrhage has significantly increased over time[55,56]. However, the Royal College of Obstetricians and Gynaecologists and the National Institute of Health and Care Excellence both do not support the use of ROTEM® during postpartum bleedings, and state that to date there is insufficient evidence to recommend routine adoption of ROTEM® during postpartum hemorrhage.[19,57] Investigating the role of ROTEM® and establishing the right target population are especially important, given the high costs that come with running ROTEM® and the need for continuous technical support. Although we found no evidence to support the implementation of ROTEM® FIBTEM A5 as part of standard clinical care during the onset of bleeding to identify women at risk of progression to severe postpartum hemorrhage, targeted use might still be useful to identify women at risk of progression and to withhold blood products and surpass formulaic transfusion protocols. However, before ROTEM® may be implemented into the national guidelines on the management of postpartum hemorrhage we need evidence-based answers to the following clinically relevant questions:

- What is the right target population where implementation of ROTEM® FIBTEM may adequately help to identify women at risk for progression of hemorrhage because of hemostatic impairment and who may benefit from replacement therapy?

- Will targeted fibrinogen replacement based on ROTEM® FIBTEM measurements during the course of postpartum hemorrhage lead to better maternal outcome?
- Is ROTEM® FIBTEM accurate enough to guide or withhold blood products throughout the whole course of postpartum hemorrhage, or do we need more accurate point-of-care tests to quantify plasma fibrinogen concentrations?

Persistent hemorrhage: evaluation of obstetric interventions to cease persistent hemorrhage

In **chapter 5** we compared the outcomes of women who had intrauterine balloon tamponade with women who underwent uterine artery embolization as initial management for persistent postpartum hemorrhage (i.e. refractory to first-line therapy according to cause of bleeding)[58] in whom immediate intervention was deemed necessary. Both intrauterine balloon tamponade and uterine artery embolization are second-line interventions developed to reduce the need for peripartum hysterectomy and lower the risk of maternal mortality.[59] However, studies comparing intrauterine balloon tamponade to uterine artery embolization are missing, resulting in uncertainty as to whether intrauterine balloon tamponade is an effective alternative to uterine artery embolization in the course of persistent postpartum hemorrhage.

Our results (**Chapter 5**) showed that initial management by intrauterine balloon tamponade during persistent postpartum hemorrhage has the potential to cease bleeding and obviate the need for uterine artery embolization in the majority of women without an increased risk of hysterectomy and/or maternal mortality. Furthermore, there were no significant differences in total blood loss or units of packed cells transfused between both management groups. Thus, by using intrauterine balloon tamponade as the intervention of first choice during persistent postpartum hemorrhage, most women can be spared uterine artery embolization (an intervention that is more invasive, expensive and prone to a number of long and short-term complications) without increased risk of severe maternal outcome.

This is an important finding and highlights the need for other studies comparing second-line obstetric interventions in order to assess the optimal management strategy during persistent postpartum hemorrhage. Whilst a treatment effect is commonly investigated in a randomized controlled trial, such trials following childbirth are hampered by the acute and unpredictable nature of postpartum hemorrhage and by the low number of women undergoing certain obstetric interventions, making it challenging to reach sufficient power, obtain informed

consent, and randomly assign women to specific treatment arms. For these reasons, we could rely on deferred consent procedures[60], or observational cohort studies on postpartum bleeding managed by the obstetric interventions of interest.[61] Well-designed cohort studies have been shown to provide results similar to controlled triala.[62,63] However, these studies may be limited by differences in relevant characteristics between the intervention groups because of potential selection bias or bias by indication that could obscure a possible causal effect.

Propensity score matching is a statistical method used to ensure comparability between the intervention groups.[64] Using propensity score matching enabled us to construct a cohort of women with persistent postpartum hemorrhage who were initially managed by intrauterine balloon tamponade or uterine artery embolization with a similar distribution of potential confounders. This allowed us to compare both interventions in terms of effectiveness of preventing severe maternal outcome. Our study (**Chapter 5**) was the first study that compared intrauterine balloon tamponade to another obstetric intervention, and its design provides a useful framework for other studies when comparing obstetric interventions during the course of persistent postpartum hemorrhage where randomized trials are not likely to be feasible. This may encourage other clinical researchers to compare obstetric interventions in search of an optimal management strategy when facing persistent postpartum hemorrhage.

Our propensity score-matched cohort, however, was underpowered due to the small sample size. We can therefore only make cautious statements about the effect of both interventions on risk of severe maternal outcome. The problem of reaching sufficient power was encountered in the only other study that assessed the effectiveness of intrauterine balloon tamponade as adjunct to misoprostol.[65] This emphasizes the need for international research collaboration and our results confirm the increasing need for a continuous and systematical registration system of severe postpartum hemorrhage in the Netherlands, but also demonstrates how obstetric interventions may be compared.

Furthermore, it is important to examine whether it is possible to develop new interventions to cease hemorrhage, such as the Jada® System[66] (an intrauterine device that establishes vacuum within the uterus causing the uterine walls to collapse and compress the bleeding vessels), or to improve existing obstetric interventions. In search of an intrauterine balloon tamponade device that is less likely to fail in presence of coagulopathy[67], we are currently collaborating with the Clinical Technology bachelor degree program of the Delft University of Technology

bringing together the medical and the technological field.[68] A dedicated group of clinical technician students are investigating if it is possible to combine an intrauterine balloon with chitosan-covered gauze, a promising pro-hemostatic agent in the treatment of ongoing blood loss following childbirth.[69-71] A previous collaboration with the Delft University of Technology led to a preliminary concept of an automated uterine massage device that could be used during transport to the hospital or an operating room. Such innovative projects involve clinicians and technicians to invent and optimize interventions for the management of bleeding. Integration of the medical and technological fields may transform healthcare approaches.

End of hemorrhage: learn lessons from obstetric hemorrhage-related maternal deaths

Maternal deaths due to obstetric hemorrhage are rare in high-income settings, such as the Netherlands. However, these maternal deaths remain tragic and obstetric hemorrhage has been identified as the commonest cause of preventable pregnancy-related death.[72] Although we argued for reviewing maternal near miss cases, it remains just as important to draw qualitative lessons from maternal deaths due to obstetric hemorrhage in order to identify improvable care factors and to take appropriate actions to further improve the quality of maternity care during severe bleeding. The potential preventability makes obstetric hemorrhage an important target for continuous efforts to improve maternal outcome.

Chapter 6 contains a nationwide mixed-methods prospective case-series of maternal deaths because of obstetric hemorrhage in the Netherlands that were reported to the Dutch Maternal Mortality and Severe Morbidity Audit Committee in 2006-2019. We studied both women where obstetric hemorrhage was classified as the underlying cause of death (defined as the initial event that initiated the chain of events ultimately leading to death) according to the International Classification of Diseases-Maternal Mortality, tenth revision (ICD-MM)[73], as well as women who died due to obstetric hemorrhage at any point in the chain of events, although the underlying cause of death was deemed otherwise by the Dutch Audit Committee. Identification of maternal deaths because of obstetric hemorrhage solely based on the assigned underlying cause of death will lead to underestimation of the true impact of obstetric hemorrhage leading to death. Reviewing cases of death due to obstetric hemorrhage in the chain of events but with a different underlying cause is also crucial to identify lessons learned in order to recognize and act appropriately to such bleedings, and should be part of confidential enquiries focused on obstetric hemorrhage-related maternal deaths.

We found that 37% of the women who died because of obstetric hemorrhage had different underlying causes of death. These deaths were the result of disseminated intravascular coagulation-related bleeding in women who had amniotic fluid embolism, sepsis, or preeclampsia. This emphasizes that clinical caregivers need to be aware of the risk of excessive bleeding due to hemostatic impairment in such women, and that correction of coagulopathy at an early stage during hemorrhage is of vital importance.[74-76]

The maternal mortality ratio (MMR) due to obstetric hemorrhage in the Netherlands in 2006-2019 was low, and comparable to the MMR in the Netherlands in 1993-2005[77] and to other high-income settings.[78-80] The MMR because of obstetric hemorrhage in the Netherlands showed a non-significant trend to decline over the last 26 years and indicates leaving room for lessons to be learned and avoid maternal deaths during obstetric-related bleedings. A capture-recapture analysis of underreporting of maternal mortality in the Netherlands in 1993-2005 revealed 0% underreporting of obstetric hemorrhage-related maternal deaths to the Dutch Audit Committee when compared to cases collected by Statistics Netherlands, a governmental institution that collects perinatal statistics about the Netherlands.[81] This contrasts with our time frame in 2006-2019 in which 11% of the obstetric hemorrhage-related deaths were not reported and only identified after a cross-check with the TeMpOH-1 study. This is a worrying finding implying that the MMR due to obstetric hemorrhage in the Netherlands may be considerably higher, and underestimation is an actual problem. Considering, however, that since 2016 maternal deaths are reported electronically to the Dutch Audit Committee through NethOSS, it is less likely that underreporting may have taken place at similar levels in more recent years. Cross-checking maternal deaths reported to the Dutch Audit Committee with Statistics Netherlands is no longer possible after 2011 because of alleged privacy issues. Our worrying results of underreporting may be a reason to reestablish the possibility to cross-check data with Statistic Netherlands.

Improvable factors in care were identified in 75% of the obstetric hemorrhage-related deaths, suggesting room for improvement of care in the majority of women who died from obstetric hemorrhage. Our confidential enquiries brought to light clear lessons learned and resulted in several recommendations that may help clinical caregivers to improve maternity care and maternal outcome during the course of postpartum hemorrhage. Our key recommendations to prevent specific care factors during hemorrhage that may have attributed to these deaths are extensively described in **chapter 6** along with de-identified case histories.

Although maternal deaths due to obstetric hemorrhage are rare events in the Netherlands, our findings reveal that there are still multiple opportunities to reduce the risk of obstetric hemorrhage-related deaths. **Chapter 6** is a comprehensive report that enables clinical caregivers to improve maternity care during obstetric hemorrhage and should encourage them adopt our recommendations based on lessons learned identified by confidential enquiries on a nationwide scale. A previous enquiry in the Netherlands about maternal mortality due to cardiovascular diseases led to modifications in the national guideline. This may have contributed to a reduction in the number of maternal deaths due to cardiovascular diseases.[82]

However, luckily, too few women die from obstetric hemorrhage in the Netherlands each year to yield meaningful information to evaluate possible trends and make clear recommendations to improve maternity care. Implementation of a recurrent (e.g. 5-year) cycle of confidential enquiries in which data on maternal deaths because of obstetric hemorrhage are shared and trended over time would provide valuable insight into improvable factors of obstetric care of which lessons learned could be drawn and allows for more robust comparisons and evaluation of previously formulated lessons learned and recommendations. Such a recurrent theme-based approach of confidential enquiries into maternal deaths have led to a steadily decline in the maternal mortality ratio in the United Kingdom through their national collaborative program called 'Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK' (MBRRACE-UK).[80] This approach should serve as an example on how to examine maternal deaths in a structured and recurrent manner, with the publication of a comprehensive report with key messages that could improve maternity care and maternal outcome.

CONCLUSION

This thesis provides valuable insight into severe postpartum hemorrhage leading to massive transfusion in the Netherlands, and highlighted differences in incidence and management of severe bleeding over time in comparison to other settings. Our results have contributed to the evaluation of maternity care at different stages of bleeding and may serve as a reference for future assessment of hematologic and obstetric interventions, e.g. by using our framework of propensity score matching when a randomized controlled trial may not be feasible. Finally, our confidential enquiries into maternal deaths due to obstetric hemorrhage brought to light important lessons learned and recommendations to further improve maternity care.

In this thesis we also pledge for the need of an international consensus definition of severe postpartum hemorrhage that could enable cross-country comparisons in search for optimal management strategies. It is essential to collect robust data through continuous and systematic registration of severe postpartum hemorrhage at a nationwide scale. This is a necessary 'next step', so that the occurrence and management of severe postpartum hemorrhage may be continuously monitored and the quality of maternity care improved. Figure 2 is an extension of the flowchart which was previously introduced in the introduction of this thesis. Figure 2 is a comprehensive timeline of postpartum hemorrhage illustrating the opportunities to evaluate maternity care at different stage of obstetric hemorrhage combined with the increasing need for surveillance of severe postpartum hemorrhage in order to evaluate these opportunities and perform confidential enquiries of maternal near miss in addition to those of maternal deaths.

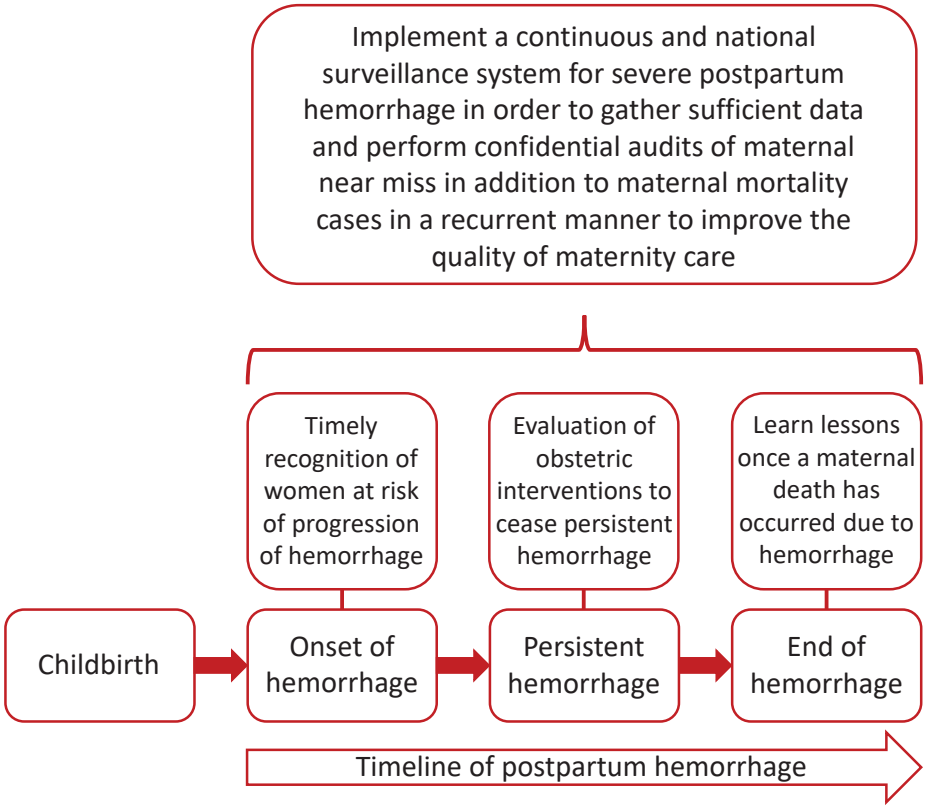

Figure 2. Flowchart of a simplified illustration of the timeline of postpartum hemorrhage that combines the opportunities to evaluate maternity care at different stages of bleeding and the increasing need for national surveillance of severe postpartum hemorrhage to evaluate these opportunities and perform confidential enquiries of maternal near miss in addition to maternal mortality cases.

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