Postpartum hemorrhage: from insight to action

Ramler, P.I.

POSTPARTUM HEMORRHAGE

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POSTPARTUM HEMORRHAGE

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Voor Ineke

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CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS

INTRODUCTION

"Sarah, pregnant for the first time, gave birth to a healthy daughter by a vacuum extraction because of prolonged pushing with inadequate progress. The placenta followed spontaneously, and appeared to be complete. Following placental expulsion, Sarah had rapid blood loss due to uterine atony (i.e. failure of the uterus to contract after childbirth). Intravenous oxytocin was administered to stimulate the uterine muscles to contract, and clear fluids were infused to maintain an adequate circulating volume. Nevertheless, bleeding persisted and Sarah was transferred to the operating room with an estimated blood loss of 1100mL. Tranexamic acid was given and the obstetrician removed a small placental remnant. However, the bleeding did not cease and bimanual compression of the uterus was performed, while sulprostone was simultaneously administered to promote uterine contraction. This was ineffective and after 4000mL of blood loss, a balloon catheter was inserted inside the uterine cavity to tamponade the bleeding. Meanwhile, the anesthesiologist took coagulation screen tests and activated a massive transfusion protocol. Packed red blood cells and fresh frozen plasma were transfused. By then, Sarah had already lost 7000mL of blood, and because of persistent hemorrhage the uterine arteries were embolized by the radiologist. Fibrinogen (an important protein for clot formation) was supplemented based on a low Clauss fibrinogen level of 0.8 g/L. The clinicians in charge agreed that the next step would be to surgically remove the uterus. Luckily, bleeding stopped following embolization. Sarah had a total blood loss of 11 liters and received 9 units of packed red blood cells altogether. She recovered fully, but slowly."

Postpartum hemorrhage is excessive blood loss following childbirth. It is the leading cause of maternal mortality worldwide[1], and a significant contributor to maternal morbidity, also in high-income countries. Severe postpartum hemorrhage may require invasive interventions to cease the bleeding, including peripartum hysterectomy, and might have serious, psychological impact in those women who survive such a life-threatening bleeding following childbirth.[2-5]

To date, there is no universal definition. The World Health Organization (WHO) has classified postpartum hemorrhage as a bleeding of ≥500mL within 24 hours following birth.[6] The United Kingdom subdivides postpartum bleedings into minor (≥500mL), major (≥1000mL) and severe (≥2000mL)[7], while the national guidelines from the Netherlands and United States of America define postpartum hemorrhage as ≥1000mL of blood loss without a distinction in terms of severity.[8,9] Regardless which definition is applied, multiple high-income countries, including the Netherlands, reported a worrying increasing incidence of postpartum hemorrhage. (Figure 1).[10,11]

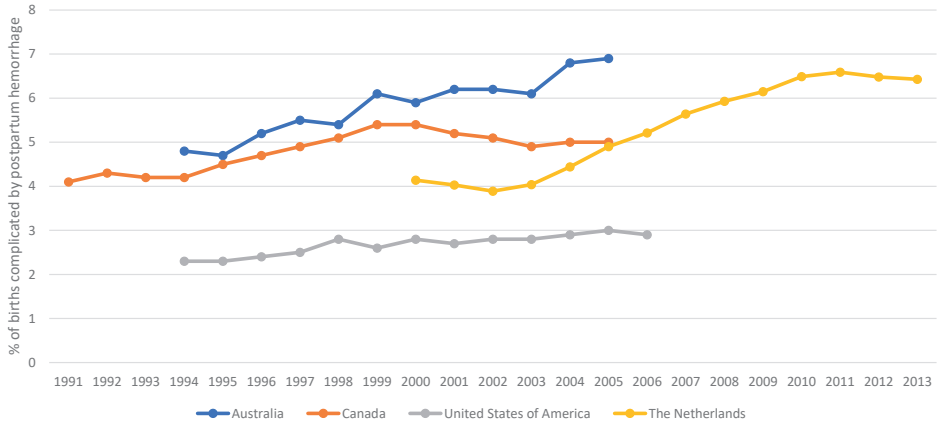

Figure 1. Trends in incidence of postpartum hemorrhage in Australia (defined as ≥500mL after vaginal birth and ≥750mL after cesarean birth), Canada (defined as ≥500mL after vaginal birth and ≥1000mL after cesarean birth), United States of America and the Netherlands (in both settings defined as ≥1000mL irrespective of the mode of birth). Data were retrieved from the studies by Knight, et al. (2009)[10] and van Stralen, et al. (2016)[11].

It has been implied that the rising incidence of postpartum hemorrhage in the Netherlands is the result of an increased incidence of relatively 'mild' bleeding (1000-1500mL), considering that the incidence of women who had an obstetric-related blood transfusion decreased within the same time frame.[11] This remains an assumption, however, as the current definition of postpartum hemorrhage in the Netherlands does not allow differentiation by severity of bleeding and the need for blood transfusion depends on variations in transfusion strategies between different settings. Being able to categorize postpartum hemorrhage according to the severity of bleeding would allow discerning a difference in the incidence of more severe hemorrhage associated with severe maternal morbidity and mortality over time. In addition, obtaining insight into more severe postpartum hemorrhage and thereby generating evidence and formulating recommendations to improve care during severe bleeding is key to reducing hemorrhage-related maternal morbidity and mortality.

Nevertheless, a uniform classification to categorize severity of bleeding is lacking. In the United Kingdom, the severity of postpartum hemorrhage is classified according to different volumes of blood loss.[7] However, visual estimations of blood loss are frequently inaccurate, especially in larger bleedings.[12] This uncertainty limits the ability to adequately categorize postpartum hemorrhage according to severity, and the heterogenous use of definitions for postpartum hemorrhage

also restricts the possibility to compare management and maternal outcome in women who experience severe obstetric-related bleeding between different settings. Therefore, the total number of packed red blood cells transfused has been suggested as a measure for severity of bleeding[13-15], as it may serve as a clear cut-off point to categorize postpartum hemorrhage according to severity and allows for comparisons between different settings. In order to maintain adequate perfusion and tissue oxygenation, severe hemorrhage may require transfusion of a large number of units of donor blood, frequently called 'massive transfusion'. Identifying women like Sarah who had massive blood transfusion as part of the management of postpartum hemorrhage enables identification of a subgroup of women with life-threatening postpartum hemorrhage.

Postpartum hemorrhage requiring massive blood transfusion

Investigating postpartum bleeding in which management included massive blood transfusion allows for assessment of the incidence of postpartum hemorrhage at the severe end of the spectrum, enables cross-country comparisons of obstetric and hematological management. This may help to identify women at risk of massive blood transfusion because of postpartum hemorrhage. While there is no consensus on the definition of massive blood transfusion in obstetric care, it is commonly defined as ≥8 or ≥10 units of packed red blood cells transfused within 24 hours following childbirth.[13-15]

Research from the United Kingdom and the state of New York in the United States of America demonstrated the significant burden of maternal morbidity associated with postpartum hemorrhage in need of massive blood transfusion (respectively defined as ≥8 and ≥10 packed red blood cells transfused).[13,14] Almost half of the women in the United Kingdom and more than one-third of the women from the state of New York that received massive blood transfusion underwent peripartum hysterectomy.[13,14] Abnormal placentation was the most frequent cause of bleeding leading to massive blood transfusion and eventually to peripartum hysterectomy in both settings. [13,14] The researchers in both settings suggested a number of care improvement factors, such as the need for a multidisciplinary massive transfusion protocol with a targeted transfusion strategy depending on the cause of bleeding.[13,14]

Data about frequency, causes, management and outcomes of women in need of massive blood transfusion due to postpartum hemorrhage in the Netherlands are limited. Furthermore, although the Netherlands observed a decrease in the number of women that had an obstetric-related blood transfusion, it is

unknown whether the incidence of postpartum hemorrhage with massive blood transfusion followed the same decreasing pattern.[11] The need for this information is increasingly urgent given the rising incidence of postpartum hemorrhage in the Netherlands[11], and the fact that a similar country like Sweden has reported a concerning rise in the incidence of massive transfusion over time (i.e. ≥10 packed cells transfused).[15] Therefore, it is of utmost importance to investigate postpartum hemorrhage requiring massive transfusion in the Netherlands in order to assess incidence, causes, management and maternal outcome of these life-threatening obstetric hemorrhages, and examine possible trends over time.

However, to reduce the burden of maternal morbidity and mortality because of postpartum hemorrhage, it is crucial to explore all opportunities to evaluate maternity care throughout the whole course of bleeding following childbirth (Figure 2).

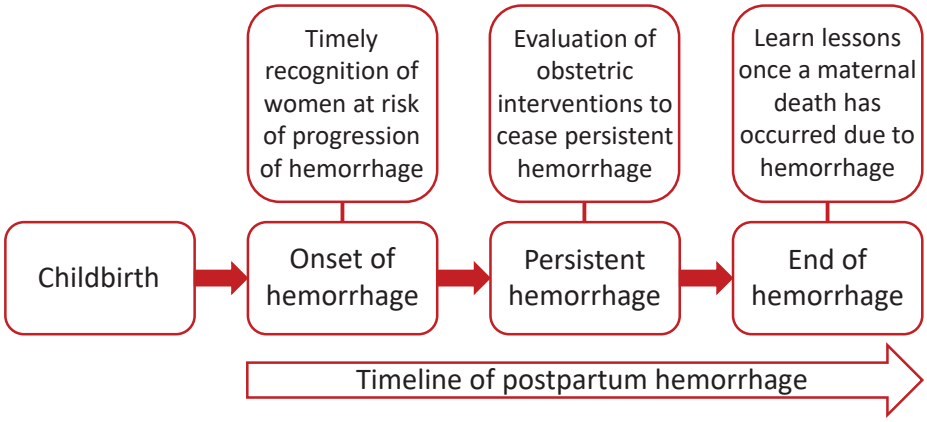

Figure 2. Flowchart of a simplified timeline of postpartum hemorrhage with opportunities to evaluate maternity care at different stages of bleeding in order to reduce the ongoing burden of maternal morbidity and mortality.

Timely recognition of women at risk for progression to severe bleeding

Physiological changes during pregnancy lead to a hypercoagulable state, that may have evolved as an adaptive mechanism to prevent excessive bleeding following childbirth.[16,17] Postpartum hemorrhage is often the result of an obstetric complication, but bleeding may be aggravated by hemostatic impairment.[18] Fibrinogen plays a critical role in clot formation and hemostasis.[19] It is the first coagulation factor that falls early during the course of postpartum hemorrhage.[20] Low fibrinogen concentrations (≤2g/L) have shown to be a predictor of progression

to severe postpartum hemorrhage.[20-22] Thus, early detection of fibrinogen deficiency during onset of hemorrhage could help to identify women at risk of progression to severe bleeding who may benefit from targeted fibrinogen replacement therapy. Clinical applicability, however, of the traditional Clauss fibrinogen assay is limited because of its long turnaround time of 60 minutes, rendering its use unsuitable during rapid blood loss following childbirth.[23]

This stresses the need for fast and reliable tests to monitor fibrinogen during the early stages of postpartum hemorrhage. Viscoelastometric point-of-care testing using rotational fibrin-based thromboelastometry (ROTEM® FIBTEM) measures clot formation through rotational resistance and the amplitude of clot firmness at 5 minutes (A5) provides a surrogate measure of the fibrinogen status with results available within 10 to 15 minutes after blood sampling.[24] Despite scarce evidence for its clinical value in s bleeding following childbirth, ROTEM® FIBTEM has been incorporated in some national guidelines and transfusion algorithms for postpartum hemorrhage.[8,25,26] The Dutch national guideline recommends routine coagulation screening when blood loss exceeds 1000mL and specifically mentions ROTEM® as an option to assess coagulation status.[8] However, robust research is needed to enable evidence-based recommendations for implementation of ROTEM® FIBTEM A5 as part of standard clinical care during onset of bleeding to identify women at risk of progression to severe postpartum hemorrhage. If so, it may be used as an early point-of-care test to detect progression of bleeding due to hemostatic impairment and serve as a trigger for targeted replacement therapy.

Evaluation of obstetric interventions to cease persistent postpartum hemorrhage

Various second-line obstetric interventions exist to cease persistent postpartum hemorrhage, i.e. refractory to first-line therapy according to cause of hemorrhage (Figure 3).[27,28] Intrauterine balloon tamponade is a relatively inexpensive and minimally invasive second-line intervention recommended by the WHO for these refractory bleedings.[6] Nevertheless, most studies that examined the effect of intrauterine balloon tamponade were in uncontrolled observational settings with substantial risk of bias and exaggeration of any possible effect, considering that intrauterine balloon tamponade is also used in women with less severe bleeding that might have stopped with additional uterotonics or by bimanual compression of the uterus.[29-31] Thus, while its use is recommended by the WHO, uncertainty persists as to when and in whom we should apply intrauterine balloon tamponade after first-line therapy failed. For this reason, the WHO states that, if necessary resources are available, use of uterine artery embolization should be considered in case of severe and persisting bleeding.[6] Uterine artery embolization

is an alternative high-tech second-line intervention, but more invasive and expensive.[32-34] This raises the question whether intrauterine balloon tamponade is an effective alternative to uterine artery embolization when both interventions are available and could be considered during the course of a refractory bleeding following childbirth that demands an immediate intervention? This remains an unresolved question considering that both interventions have never been compared to one another. Comparison of second-line interventions is essential to assess the optimal management strategy during persistent postpartum hemorrhage and to reduce the possible risk of adverse maternal outcome.

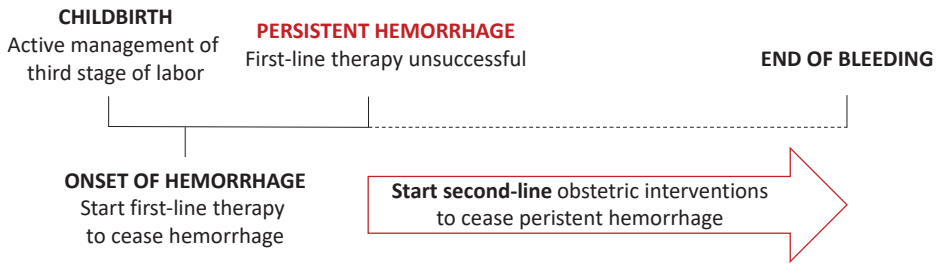

Figure 3. Persistent postpartum hemorrhage is defined as a bleeding refractory to the first-line therapy applied.

However, due to the acute and unpredictable nature of postpartum hemorrhage and the low number of women undergoing uterine artery embolization, there are numerous challenges in identifying eligible women, performing study procedures and obtaining informed consent for a study that compares both interventions in the acute setting. Therefore, we generally rely on cohort studies into postpartum hemorrhage managed by intrauterine balloon tamponade or uterine artery embolization. Such studies are prone to confounding due to differences in relevant characteristics between both intervention groups, which may obscure a possible causal effect, e.g. due to the possibility that intrauterine balloon tamponade is more often used in less severe bleedings. One way to overcome this problem is to use propensity score matching, a statistical technique that establishes a similar distribution of potential confounding between both intervention groups.[35] We postulated that using a propensity score-matched cohort would enable us to compare maternal outcome in women who were initially managed by intrauterine balloon tamponade or uterine artery embolization during persistent hemorrhage.

Learn lessons once a maternal death has occurred due to obstetric hemorrhage

The maternal mortality ratio (MMR) due to obstetric hemorrhage in the Netherlands between 1993-2005 was low.[36] However, this does not mean that we should take the low number of maternal deaths for granted. It is necessary to monitor the MMR in more recent years, especially in light of the increasing incidence of postpartum hemorrhage from 2000 to 2013 in the Netherlands[11], and that the United States of America observed an increase in its MMR because of obstetric hemorrhage.[37] In addition, hemorrhage following birth has been identified as the commonest cause of preventable pregnancy-related deaths.[38,39] Any loss of a mother's life remains a tragedy, and it is a moral imperative to draw lessons from each and every maternal death. A maternal mortality surveillance system with confidential enquiries to assess possible improvable care factors and formulating lessons learned may help to further reduce the risk of fatal outcome from obstetric hemorrhage.[40] A confidential enquiry is an analysis of anonymized data concerning a woman who died in childbirth in order to identify improvable care factors and to devise recommendations to improve care. Through a national collaborative program called 'Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK' (MBRRACE-UK), the United Kingdom examines maternal deaths and publishes a comprehensive annual report with specific key messages to further improve maternity care for specific causes of maternal deaths ever since the fifties of the last century.[41] Scrutinizing their maternity care brought to light important lessons learned and led to a steady decline in the MMR in the United Kingdom.[41]

In the Netherlands, the Dutch Maternal Mortality and Severe Morbidity Audit Committee collects anonymized data on maternal deaths through a nationwide surveillance system and conducts confidential enquiries.[42,43] However, the reporting of improvable care factors and lessons learned based on such confidential enquiries focusing solely on obstetric hemorrhage-related deaths wat not yet done. We assumed that an extensive report with specific key messages to improve maternity care during the course of hemorrhage following childbirth could help to further reduce the risk obstetric hemorrhage-related deaths in the Netherlands.

OBJECTIVES OF THIS THESIS

Postpartum hemorrhage may lead to severe maternal morbidity and mortality. In light of its increasing incidence it is critical to gain insight into severe postpartum hemorrhage associated with severe maternal outcome, and explore all opportunities to evaluate maternity care. As shown, we still face a wide variety of challenges in order to improve maternal safety during and after hemorrhage following childbirth. Hence, our main research objectives were:

1. To examine incidence, causes, management and outcome of women who had massive blood transfusion due to postpartum hemorrhage in the Netherlands, and to discern possible trends over time.
2. To evaluate ROTEM® FIBTEM A5 as a point-of-care parameter during onset of bleeding for predicting progression to severe postpartum hemorrhage.
3. To compare outcome in women with persistent postpartum hemorrhage who were initially managed by intrauterine balloon tamponade or uterine artery embolization.
4. To assess the maternal mortality ratio due to obstetric hemorrhage in the Netherlands in recent years, and to identify improvable care factors and formulate lessons learned from confidential enquiries of maternal deaths due to obstetric hemorrhage.

We used data from three multicenter cohort studies that were conducted in the Netherlands, and collaborated with the Dutch Maternal Mortality and Severe Morbidity Audit Committee:

1. The LEMMoN study (Landelijke studie naar Etnische determinanten van Maternale Morbiditeit in Nederland). A nationwide cohort study in all hospitals with a maternity ward at the time that included women with severe acute maternal morbidity between August 2004 and August 2006. Major obstetric hemorrhage was part of severe acute maternal morbidity and defined as the need for ≥4 units of packed cells, uterine artery embolization, or peripartum hysterectomy. We used the LEMMoN study to construct and investigate a cohort of women who had ≥8 packed red blood cells transfused within 24 hours after birth because of postpartum hemorrhage.
2. The TeMpOH-1 study (Transfusion strategies in women during Major Obstetric Hemorrhage). A nationwide retrospective cohort study in 61 hospitals (71% of all hospitals at the time) that collected data on women who received ≥4 packed red blood cells or a multicomponent blood transfusion because of

postpartum hemorrhage between January 2011 and December 2012. In order to evaluate possible differences over time in obstetric hemorrhage-related massive blood transfusions, we also examined women who had ≥8 packed red blood cells transfused within the TeMpOH-1 study and compared the results to our previous cohort from the LEMMoN study. Furthermore, we constructed a propensity-score matched cohort to compare outcome in women who were initially managed by intrauterine balloon tamponade or uterine artery embolization.

3. The TeMpOH-2 study (Towards better prognostic and diagnostic strategies for Major Obstetric Hemorrhage). A prospective cohort study in three hospitals between February 2015 and April 2018. All women were monitored for the occurrence of postpartum hemorrhage and blood samples were drawn for coagulation screening and thromboelastometry. ROTEM® FIBTEM A5 measurements were performed in women who had 800 to 1500mL of blood loss in order to evaluate the predictive value of ROTEM® FIBTEM A5 for progression to severe hemorrhage.
4. The Dutch Maternal Mortality and Severe Morbidity Audit Committee (Auditcomissie Maternale Sterfte en Ernstige Morbiditeit, AMSM) was instituted by the Dutch Society of Obstetrics and Gynaecology (NVOG) and collects anonymized complete case file copies on maternal deaths through a national surveillance system. Members of the AMSM perform confidential enquiry for each maternal death to identify improvable care factors and formulate lessons learned. We examined all maternal deaths because of obstetric hemorrhage that were reported to the AMSM between 2006 and 2019. Each obstetric hemorrhage-related death was systematically reviewed by the entire AMSM committee to create a comprehensive report with specific key messages to further improve the quality of maternity care. A cross-check with the TeMpOH-1 study was performed to examine possible underreporting to the AMSM.

OUTLINE OF THIS THESIS

Part I: Massive blood transfusion in relation to postpartum hemorrhage
The first part of this thesis provides insight into severe postpartum hemorrhage associated with severe maternal outcome by looking at life-threatening obstetric hemorrhage in women who needed a massive blood transfusion.

Chapter 2 addresses the incidence, causes, management and outcome of women receiving ≥8 packed cells because of postpartum hemorrhage in the Netherlands between 2004 and 2006. Our results are compared with similar studies in the United Kingdom and the state of New York in the United States of America.

In **Chapter 3** we investigate women who had postpartum hemorrhage and received ≥8 packed red blood cells in the Netherlands between 2011 and 2012. These results are compared to our previous findings between 2004 and 2006 in order to examine trends over time. This chapter also explores risk factors for postpartum hemorrhages leading to massive blood transfusion.

Part II: Evaluation of maternity care during and after postpartum hemorrhage
The second part of this thesis focusses on aspects to evaluate maternity care at different stages of bleeding throughout the course of postpartum hemorrhage, as illustrated in Figure 2.

Onset of hemorrhage: timely recognition of women at risk of progression of hemorrhage
Chapter 4 presents the predictive value of ROTEM® FIBTEM A5 for progression to severe postpartum hemorrhage when routinely taken between 800 to 1500mL of blood loss following childbirth. The predictive value of ROTEM® FIBTEM A5 is compared to that of the conventional Clauss fibrinogen assay.

Persistent hemorrhage: evaluation of obstetric interventions to cease persistent hemorrhage
In **Chapter 5** we compare outcomes of women who had intrauterine balloon tamponade with women who underwent uterine artery embolization as initial management for persistent postpartum hemorrhage between 1000 to 7000mL of blood loss. A propensity score-matched cohort was constructed to account for potential confounding.

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

Chapter 6 is a nationwide mixed-methods retrospective cohort study including all obstetric hemorrhage-related deaths in the Netherlands reported to the AMSM between 2006 and 2019. We present the maternal mortality ratio between this time frame and compare it to the previous enquiry between 1993 and 2005. Through confidential enquiries we formulated important lessons learned to improve maternity care during the course of obstetric hemorrhage. De-identified case histories are presented to illustrate specific improvable care factors and lessons learned.

Part III: Discussion and summary

Chapter 7 contains a general discussion and conclusion.

Chapter 8 summarizes the main findings of this thesis.

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PART I

MASSIVE BLOOD TRANSFUSION IN RELATION TO POSTPARTUM HEMORRHAGE

CHAPTER 2

INCIDENCE, MANAGEMENT AND OUTCOME OF WOMEN REQUIRING MASSIVE TRANSFUSION AFTER CHILDBIRTH IN THE NETHERLANDS: A SECONDARY ANALYSIS OF A NATIONWIDE COHORT STUDY BETWEEN 2004 AND 2006

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ABSTRACT

Introduction

Postpartum hemorrhage is the leading cause of maternal morbidity and mortality worldwide. Few population-based studies have examined the epidemiology of massive blood transfusion for postpartum hemorrhage. The aim of this study was to determine incidence, management, and outcomes of women with postpartum hemorrhage who received massive transfusion in the Netherlands between 2004 and 2006.

Material and methods

Data for all women from a gestational age of 20 weeks who had postpartum hemorrhage requiring eight or more packed red blood cells were obtained from a nationwide population-based cohort study including all 98 hospitals with a maternity unit in the Netherlands.

Results

Three hundred twenty-seven women who had postpartum hemorrhage requiring massive transfusion were identified (91 per 100 000 births (95% confidence interval: 81–101)). Median blood loss was 4500mL (interquartile range 3250–6000mL) and median number of packed red blood cells transfused was 11 units (interquartile range 9–16 units). Among women who had massive transfusion, the most common cause of hemorrhage was uterine atony. Eighty-three women (25%) underwent hysterectomy, 227 (69%) were admitted to an intensive care unit, and three women died (case fatality rate 0,9%).

Conclusions

The number of women in the Netherlands who had postpartum hemorrhage with massive blood transfusion was relatively high compared to other comparable settings. Evidence-based uniform management guidelines are necessary.

BACKGROUND

Around the globe, postpartum hemorrhage continues to be a leading cause of both maternal morbidity and mortality.[1,2] In the Netherlands, postpartum hemorrhage is defined by at least 1000 mL blood loss within 24 hours of giving birth. There has been an increase in the incidence of postpartum hemorrhage among all births in the Netherlands from 4.1% in 2000 to 6.4% in 2013.[3] Although case definitions of postpartum hemorrhage vary between countries, this rising incidence of postpartum hemorrhage is also evident in other high-income countries.[4-8] An explanation for the increasing rates of postpartum hemorrhage remains unclear.

In high-income countries, pharmacological, mechanical and surgical methods as well as radiological arterial embolization are available to arrest heavy bleeding. In case of life-threatening postpartum hemorrhage, access to and use of sufficient quantities of blood products for transfusion to treat severe anemia and correct clotting disorder are critical.[9, 10] Clinical benefit of blood transfusion in obstetric hemorrhage was demonstrated in a hypothetical experimental study showing a 6.5-fold increase in risk of maternal death had red blood cell concentrates not been available, as is the case in many low-income settings.[11]

Little is known about the management and outcomes of women who sustain postpartum hemorrhage requiring massive transfusion. A recent population-based study from the United Kingdom) indicated that postpartum hemorrhage requiring massive blood transfusion was associated with high rates of maternal morbidity and peripartum hysterectomy.[12] While the rate of obstetric transfusion in the Netherlands has decreased dramatically over time (from 23% in 2000 to 3.9% in 2013), transfusion rates in other high-income countries increased.[3, 6, 13] If rates of massive transfusion in the Netherlands were to have decreased over time, these data would be important for the discussion about best transfusion practices for postpartum hemorrhage management. The objective of our present study was to determine incidence, causes, management and clinical outcome of women with postpartum hemorrhage requiring massive transfusion in the Netherlands.

METHODS

To determine incidence, causes, management approaches, and clinical outcomes of women who had postpartum hemorrhage requiring massive transfusion in the Netherlands, we performed a secondary analysis of data from the LEMMoN study (Landelijke studie naar Etnische determinanten van Maternale Morbiditeit in Nederland).[14]

The LEMMoN study included 358 874 births with severe acute maternal morbidity that occurred in 98 hospitals with a maternity unit in the Netherlands (100%) between 1st August 2004 and 1st August 2006. The LEMMoN study was approved by the Medical Ethics Committee of Leiden University Medical Centre (P04-020; March 8, 2004). Severe acute maternal morbidity was categorized into five groups: intensive care admission, uterine rupture, eclampsia/HELLP syndrome, major obstetric hemorrhage and a miscellaneous group. Major obstetric hemorrhage was defined as a need for transfusion of four or more units of packed red blood cells or embolization or hysterectomy following postpartum hemorrhage. Detailed information about study design and data collection were described previously.[14] For this specific study, we selected women from the LEMMoN cohort who were classified as 'major obstetric hemorrhage', had a gestational age of at least 20 weeks and received massive transfusion, defined as eight or more packed cells within the first 24 hours after childbirth.

We recorded maternal characteristics (age, body mass index [BMI], geographical ethnic origin (the Netherlands, other European Countries or non-Western immigrants, subdivided into Middle East/North Africa, sub-Saharan Africa, South America and Far East), parity, previous postpartum hemorrhage and prior cesarean section), pregnancy characteristics (gestational age, mode of birth, induction of labor, multiple pregnancy and preeclampsia) and specific data on postpartum hemorrhage (volume of blood loss, number of packed cells transfused, hemoglobin levels at onset of bleeding, after bleeding and at day of discharge). Maternal and pregnancy characteristics of women in this study were compared to the general pregnant population of the Netherlands, obtained from Statistics Netherlands and National Perinatal Database. Incidence figures in the National Perinatal Database were multiplied by 59/100 to also represent all birth under primary care (41% in 2002).[15,16]

Since postpartum hemorrhage is often the result of concurrent causes, we re-examined all cases of massive transfusion within the LEMMoN-cohort and registered up to three causes of postpartum hemorrhage requiring massive transfusion for each individual case. Only those causes that contributed significantly to the hemorrhage were registered. These causes were noted as uterine atony, uterine rupture, iatrogenic during/after cesarean section, placental abnormalities (including retained placenta, placental remnant, placenta previa, abnormally invasive placenta and placental abruption, laceration of vagina and/or cervix, primary clotting disorder with or without amniotic fluid embolism, rupture of the uterine artery, rupture of the liver capsule and uterine inversion. Causes of hemorrhage were analyzed by mode of birth (spontaneous vaginal birth, instrumental vaginal birth, elective cesarean section, emergency cesarean section and by a termination of pregnancy) and number of packed cells transfused ('moderate' (8–12 units), 'high' (13–20 units) and 'immense' (>20 units). The cut-off points for the number of packed cells transfused were identical to those described by Green et al.[12]

Management of postpartum hemorrhage requiring massive transfusion was divided into uterotonic agents (oxytocin, prostaglandin F2α, ergometrine, misoprostol), non-uterotonic drugs (tranexamic acid), mechanical interventions (intrauterine balloon, intrauterine packing and intra-abdominal packing), surgical interventions (removal of the placenta not performed during cesarean section, laparotomy, re-laparotomy, B-Lynch suture, uterine artery ligation and hysterectomy) and uterine artery embolization. Outcome of women was determined by need for peripartum hysterectomy, length of hospitalization, admission to an intensive care unit, morbidity, maternal deaths and case fatality rate.

Statistical analyses were performed using IBM SPSS Statistics (version 22.0; SPSS Inc., Chicago, IL). Discrete data were summarized as frequencies and percentages, while continuous data were noted as medians with an interquartile range (IQR) expressed as the 25th and 75th percentiles. Women with a missing value for a specific parameter were excluded when calculating the rate for that variable.

RESULTS

During the study period, 358 874 births took place in the Netherlands, and 336 women had postpartum hemorrhage and were given eight or more units of packed red blood cells. Of these women, nine were excluded due to a gestational age below 20 weeks, leaving 327 women for analysis. Incidence of massive transfusion due to postpartum hemorrhage was 91 per 100 000 births (95% confidence interval [95% CI]: 81–101). The clinical and demographic baseline characteristics of these women are presented in Table 1 and the characteristics of the pregnancies in Table 2. The median (IQR) age, BMI and gestational age were 33 years (30–36 years), 23 kg/m^2 (21–26 kg/m^2) and 38 weeks (37–41 weeks), respectively.

Characteristics of postpartum hemorrhage requiring massive transfusion
The median (IQR) estimated blood loss was 4500 mL (3250–6000mL), resulting in a median (IQR) hemoglobin drop from 11.6 g/dL (10.8–12.41 g/dL; data missing for 60 women) before hemorrhage to 5.96 g/dL (5–6.77 g/dL; data missing for 34 women) after hemorrhage. The median (IQR, range) number of packed red blood cells transfused was 11 (9–16, 8–52).

The most common cause of postpartum hemorrhage requiring massive transfusion was uterine atony, followed by retained placenta and placenta previa (Table 3). For 117 women (36%), two causes were registered and for 12 women (4%) three causes. The commonest combinations for women with two causes were uterine atony with retained placenta (N=28), uterine atony with a placental remnant (N=21) and uterine atony with a cervical laceration (N=10). For women with three causes, the most frequent combination was uterine atony with a placental remnant and a laceration of the cervix (N=3). For nine women, no cause could be established. The 22 causes in the 'other' category in Table 3 were primary clotting disorder without amniotic fluid embolism (N=7), uterine artery rupture (N=6), live capsule rupture (N=4), clotting disorder due to amniotic fluid embolism (N=4) and uterine inversion (N=1). Massive transfusion occurred during normal working hours (between 08:00 and 16:00 on a weekday) for 196 (65%) women; data were missing for 25 women. The onset of hemorrhage occurred at home for 52 (16%) women; data were missing for 7 women.

Table 1. Characteristics of the women

	N	(%)	General pregnant population in the Netherlands (%)[a]
Age (years)			
20–34	208	(63)	(75.3)
35–39	94	(29)	(21.3)
≥ 40	25	(8)	(3.4)
BMI (kg/m²)			
< 18,5	15	(5)	(3.1)
18,5–24,9	137	(42)	(65.2)
25,0–29,9	39	(12)	(21.9)
≥ 30	24	(7)	(9.8)
Unknown	112	(34)	-
Geographical ethnic origin			
The Netherlands	223	(68)	N/A
Other European Countries	7	(2)	N/A
Non-Western immigrants;	70	(22)	(16.8)
Middle East/North Africa	28	(9)	N/A
Sub-Saharan Africa	17	(5)	N/A
South America	16	(5)	N/A
Far East	9	(3)	N/A
Unknown	27	(8)	-
Parity			
0	158	(48.3)	(45.2)
1–2	145	(44.3)	(49.8)
≥ 3	24	(7.3)	(5.0)
Previous postpartum hemorrhage	40	(12)	N/A
Previous cesarean section	66	(20)	(6.0)

[a]National reference values from Statistics Netherlands[16], N/A: data not available.

Table 4 presents the top three causes of postpartum hemorrhage requiring eight or more units of packed red blood cells according to mode of birth. The commonest cause during elective cesarean section was placenta previa (52%, *N* = 24/46), whereas uterine atony remained the leading cause for the other modes of birth. Categorizing causes of postpartum hemorrhage by number of packed cells transfused, respectively 'moderate' (*N* = 193), 'high (*N* = 89) and 'immense' (*N* = 39), showed no difference in prevalence of causes; uterine atony continued to be the main cause in each group.

Table 2. Characteristics of pregnancy and birth

	N	(%)	General pregnant population in the Netherlands (%)
Gestational age			
Preterm (<37 weeks);	86	(26)	(5.8)[b]
20–24 weeks	6	(2)	N/A
24–32 weeks	18	(5)	N/A
32–37 weeks	62	(19)	N/A
Full Term	241	(74)	(94.2)[b]
Mode of birth[c]			
Vaginal	131	(40)	(78.4)[b]
Instrumental	43	(13)	(8.6)[b]
Cesarean Section;	151	(46)	(13.0)[b]
Elective	46	(14)	N/A
Emergency	105	(32)	N/A
Induction of labor	100	(31)	(12.5)[b]
Multiple pregnancy	37	(11)	(1.7)[a]
Preeclampsia during pregnancy	54	(17)	(4) [22]

[a]National reference values from Statistics Netherlands.[16]
[b]National reference values from the Netherlands Perinatal Registry.[17]
[c]In case of multiple births were the mode of birth differed between the neonates, the mode of birth refers to the most invasive mode.
N/A: data not available.

Management of postpartum hemorrhage requiring massive transfusion

Oxytocin (84%) was the most frequently administered uterotonic agent (prophylactic oxytocin excluded), followed by prostaglandin F2α (70%) and ergometrine (18%) (Table 5). No data regarding which uterotonic agent was administered as first line treatment were retrievable, but of 284 women who received oxytocin, 210 (74%) were given prostaglandin F2α thereafter. Eleven women who had uterine atony received no oxytocin. Instead, these women received prostaglandin F2α and one woman was supplemented with tranexamic acid.

Laparotomy was performed following 42/174 (24%) vaginal births and 82/151 (54%) cesarean sections. Re-laparotomy was necessary in 10/42 (24%) and 20/82 (24%) respectively. Of all 327 women, 83 (25%) underwent peripartum hysterectomy to control bleeding with highest rates in women who had an uterine rupture (N=14/20, 70%) or who had any form of abnormal placentation (N=21/32, 66%).

Table 3. Causes of postpartum hemorrhage cases requiring massive transfusion[a]

	N	(%)
Uterine atony	179	(55)
Placenta abnormalities;	173	(53)
Retained	54	(17)
Previa	37	(11)
Abnormally invasive placenta	32	(10)
Remnant	30	(9)
Abruption	20	(6)
Laceration;	40	(12)
Vagina	23	(7)
Cervix	17	(5)
Uterine rupture	20	(6)
Iatrogenic during/after cesarean section	11	(3)
Other causes	22	(7)
Unknown	9	(3)

[a]Up to three causes per woman could be included.

Table 4. Top three causes categorized by mode of birth[a]

	N	(%)
Vaginal birth *(N = 131)*		
1. Uterine atony	84	(64)
2. Retained placenta	40	(31)
3. Placental remnant	20	(15)
Instrumental vaginal birth *(N = 43)*		
1. Uterine atony	26	(60)
2. Retained placenta	14	(33)
3. Placental remnant	6	(14)
Elective cesarean section *(N = 46)*		
1. Placenta previa	33	(72)
2. Uterine atony	17	(37)
3. Abnormally invasive placenta	13	(28)
Emergency cesarean section *(N = 105)*		
1. Uterine atony	51	(49)
2. Uterine rupture	13	(12)
3. Iatrogenic during/after cesarean	9	(9)
Termination of pregnancy *(n = 2)*		
1. Uterine atony	1	(50)
2. Uterine rupture	1	(50)

[a]Up to three causes could be included.

Table 5. Distribution of obstetric interventions by cause (expressed as percentages)

	Atony (*N=179*)	Rupture (*N=20*)	Previa (*N=37*)	AIP[b] (*N=32*)	Abruption (*N=20*)	Retained (*N=54*)	Total (*N=327*)
Oxytocin	94	70	87	91	70	87	84
Prostaglandin F2α	87	50	54	72	55	85	70
Tranexamic acid	33	5	19	13	5	19	22
Ergometrine	23	15	14	19	20	28	18
Misoprostol	16	5	3	3	20	6	11
Removal of placenta[a]	31	15	11	41	15	100	29
Intrauterine balloon	32	10	14	28	5	19	23
Intrauterine packing	30	15	22	22	5	22	21
Intra-abdominal packing	6	30	0	3	0	4	7
Uterine artery ligation	6	5	8	3	5	4	5
Uterine artery embolization	29	10	19	19	5	22	22
Laparotomy	36	70	51	63	15	13	38
Re-laparotomy	8	30	5	0	0	6	9
B-Lynch suture	5	0	3	3	10	0	2
Hysterectomy	27	70	38	66	5	9	25

[a]Included only removal of the placenta (or remnant) not performed during cesarean section.
[b]Abnormally invasive placenta.

Outcome of women requiring massive transfusion

The median (IQR) length of hospitalization was 9 days (6–13 days; data missing for 14 women) and 227 women (69%) required intensive care admission. The median (IQR) hemoglobin on the day of discharge was 10.15 g/dL (9.02–11.44 g/dL; data was missing for 53 women). One-hundred-and-twenty-one (37%) women experienced some kind of morbidity, of whom 40 (33%) had developed respiratory failure and 13 (11%) experienced renal insufficiency. Other complications were paralytic ileus (N=11), heart failure (N=7), Sheehan syndrome (N=6) and cerebral venous sinus thrombosis (N=2). Maternal death occurred in three women due to hypovolemic shock, ventricular fibrillation and massive pulmonary embolism; case fatality rate of postpartum hemorrhage requiring massive transfusion was 1 in 109 (0,9%).

DISCUSSION

Between 2004 and 2006, the incidence of postpartum hemorrhage treated with massive transfusion was notably high in the Netherlands (91 per 100 000 births). This is four times the incidence reported for the United Kingdom between 2012 and 2013 (23 per 100 000 births), and one-and-a-half times the incidence reported for the state of New York between 1998 and 2007 (60 per 100 000 births).[12, 17] We found that the leading cause of postpartum hemorrhage with massive blood transfusion was uterine atony. One quarter of all the women receiving massive transfusion underwent peripartum hysterectomy to control bleeding.

The difference in incidence of massive transfusion due to postpartum hemorrhage between the Netherlands and the United Kingdom is remarkable. Whereas incidence of major obstetric hemorrhage has differed between various countries as a result of varying inclusion criteria[14, 18, 19], our study applied the same inclusion criteria for massive transfusion described by Green et al.[12] The difference in incidence between the Netherlands and the state of New York is also of note, particularly since Mhyre et al.[17] used a higher threshold for the number of packed cells transfused to define massive transfusion (≥10 units) and included both antepartum and postpartum hemorrhage.

A distinct difference between the national guidelines for the management of postpartum hemorrhage between the Netherlands (Dutch Society of Obstetrics and Gynaecology [NVOG]) and the United Kingdom (Royal College of Obstetricians and Gynaecology [RCOG]) is that the RCOG specifically recommends that 'surgical interventions should be initiated sooner rather than later'. Both guidelines are inconclusive concerning the administration of blood products; the NVOG recommends not to deviate from the local guidelines of the hospital, while the RCOG states that the decision to provide blood transfusion 'should be based on both clinical and hematological assessment'.[9, 10, 20] Furthermore, it is noteworthy that the median (IQR) estimated blood loss in the study from Green et al. was 6 L (4.5–8.0 L) versus 4.5 L (3.3–6 L) in our cohort, whilst the massive transfusion rate was four times higher in the Netherlands.[12] This may suggest that the difference in transfusion rate is due to differences in transfusion policy, which would emphasize the need for uniform guidelines.[21]

During the study period, there were 358 874 births in the Netherlands and 145 703 births (40.6%) were under the responsibility of a primary care giver, making the risk of massive blood transfusion because of postpartum hemorrhage 13

per 100 000 births in midwifery care. Comparison of women requiring massive transfusion due to postpartum hemorrhage with the general pregnant population in the Netherlands showed that women requiring massive transfusion had a multiple pregnancy in 11% of all cases vs 1.7% in the general population[15], suffered from preeclampsia in 17% of all cases vs 4% in the general population[22], had labor induced in 31% of all cases vs 12.5% in the general population[16], had a preterm birth in 26% of all cases versus 5.8% in the general population[16] and had a cesarean section in 46% of all cases versus 13% in the general population.[16] These characteristics are known risk factors of postpartum hemorrhage and highlight that the management of postpartum hemorrhage should not only be focused on treatment, but on prevention as well.[23, 24]

Uterine atony was the most frequent cause of postpartum hemorrhage as is consistent with literature.[12, 25, 26] Uterine atony was also the commonest cause of postpartum hemorrhage in home deliveries.[27] In elective cesarean sections the leading cause of massive transfusion due to postpartum hemorrhage was placenta previa. Green et al. reported placenta accreta as the most frequent cause of postpartum hemorrhage in women delivering by elective cesarean section, while Dupont et al. in France found that uterine atony remained the main cause of postpartum hemorrhage regardless of the mode of birth.[12, 26] The higher percentage of laparotomies performed after cesarean section is consistent with previous findings from the LEMMoN-cohort that the risk of postpartum laparotomy was more than 16 times higher in women who delivered by cesarean section compared to those who delivered vaginally.[28]

As a last resort to arrest heavy bleeding, a quarter of all women underwent hysterectomy. This percentage is considerably lower than reported by Green et al. for the United Kingdom, where the overall rate of hysterectomy was 45%.[12] A possible explanation for this difference could be the lower rates of previous cesarean deliveries; 66/327 (20%) in our study versus 73/181 (40%) in the United Kingdom.[12] Two studies showed that the risk of peripartum hysterectomy increased with the number of previous cesarean deliveries.[29, 30] Another contributing factor could be the higher rate of embolization in our study, 72/327 (22%) versus 29/181 (16%) in the United Kingdom, and thereby preventing the need for hysterectomy. Uterine rupture or an abnormally invasive placenta had the highest rates of hysterectomy compared to other causes. This is coherent with the recommendation of the Dutch Society of Obstetrics and Gynaecology guideline that states that hysterectomy should not be postponed if the cause of hemorrhage is related to an invasive placenta or uterine rupture.[10]

The maternal mortality rate of massive blood transfusion due to postpartum hemorrhage in our study was low with 0.84 deaths per 100 000 birth. This is comparable with the maternal mortality rate of postpartum hemorrhage in the Netherlands prior reported by Schutte et al. between 1993 and 2005 (0.7 deaths per 100 000 births).[31] Nearly three-quarters of women who received massive transfusion were admitted to an intensive care unit, and about one-third experienced morbidity. This high rate of morbidity is consistent with other studies.[12, 25] The rate of maternal morbidity may be higher in low-income settings where not all treatment modalities are available or for Jehovah's witnesses who refuse blood products.[3, 14, 32]

A key strength is that our study results were based on a nationwide cohort compromising all hospitals in the Netherlands with a maternity unit. Considering that postpartum hemorrhage cases requiring massive transfusion must have been managed in one of these units, our results are population-based. Furthermore, our results are directly comparable to those of Green et al. who used the same definition for massive transfusion in their analysis.[12]

However, number of packed cells transfused as definition for massive transfusion remains an indicator with shortcomings as well, since it can be influenced by other factors, such as obstetrician's decision-making. We also acknowledge that our data are from 2004 to 2006 and may not reflect the current situation. Since the incidence of postpartum hemorrhage increased significantly throughout the years in many countries, but the incidence of obstetric blood transfusion in the Netherlands decreased[3], it is possible that the incidence of massive transfusion due to postpartum hemorrhage may have reduced in recent years, but this is subject of further assessment. There may have been inclusion bias, since identification and management of cases may differ between obstetricians and hospitals. Underreporting is a concern, however, we have previously observed that there is a negative correlation between the rate of underreporting and the number of red blood cell concentrates transfused.[33] Therefore, we would expect a low rate of underreporting. The considerable number of women without a known Hb-level at discharge is likely due to missing data, as a result of the design of the LEMMoN-database that did not specifically include Hb-level at discharge.

Nevertheless, this study makes clear that the incidence of postpartum hemorrhage requiring massive transfusion was high in the Netherlands at that time compared to other countries and further research of contemporary obstetric cohorts is needed to allow for more up to date international comparisons of rates of transfusion and hemorrhage-related morbidity. Networks such as the International Network of Obstetric Surveillance Systems (INOSS) could facilitate such studies.[34]

CONCLUSION

This study adds to the understanding of causes, management and outcomes of women with postpartum hemorrhage requiring massive transfusion and our results show that massive transfusion due to postpartum hemorrhage is complicated by high rates of morbidity and a considerable risk of hysterectomy. The incidence of massive transfusion due to postpartum hemorrhage appears higher in the Netherlands compared to the United Kingdom and the state of New York. Increased vigilance for women at risk or in early stages of postpartum hemorrhage in the Netherlands is needed, while avoiding unnecessary over-transfusion. Specific reasons for the higher incidence will have to be studied in order to improve care accordingly. Our results show the importance of population-wide studies of severe maternal outcome in general, and those comparing rates of transfusion and outcomes for women with severe postpartum hemorrhage in particular.

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CHAPTER 3

WOMEN RECEIVING MASSIVE TRANSFUSION DUE TO POSTPARTUM HEMORRHAGE: A COMPARISON OVER TIME BETWEEN TWO NATIONWIDE COHORT STUDIES

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ABSTRACT

Introduction

Incidence of massive transfusion following childbirth was high in the Netherlands between 2004 and 2006 compared to other high-income countries. This study investigated incidence, causes, management and outcome of women receiving massive blood transfusion due to postpartum hemorrhage in the Netherlands in more recent years.

Material and methods

Data for all pregnant women who received eight or more units of packed red blood cells from a gestational age of 20 weeks and within the first 24 hours after childbirth, during the period 2011 and 2012, were obtained from a nationwide retrospective cohort study, including 61 hospitals with a maternity unit in the Netherlands.

Results

Incidence of massive transfusion due to postpartum hemorrhage decreased to 65 per 100 000 births (95% Confidence Interval: 56–75) between 2011 and 2012, from 91 per 100 000 births (95% Confidence Interval: 81–101) between 2004 and 2006, while median blood loss increased from 4500mL (Interquartile Range: 3250–6000) to 6000mL (Interquartile Range: 4500–8000). Uterine atony remained the leading cause of hemorrhage. Thirty percent (53/176) underwent peripartum hysterectomy between 2011 and 2012, versus 25% (83/327) between 2004 and 2006. Case fatality rate for women who received massive transfusion due to postpartum hemorrhage was 2.3% (4/176) between 2011 and 2012, compared to 0.9% (3/327) between 2004 and 2006.

Conclusions

The incidence of postpartum hemorrhage with massive transfusion decreased in the Netherlands between both time frames, but remained an important cause of maternal mortality and morbidity, including peripartum hysterectomy. National surveillance of maternal morbidity and mortality due to postpartum hemorrhage through an improved and continuous registration with confidential enquiries may lead to the identification of clear improvements of maternal care.

INTRODUCTION

Postpartum hemorrhage is a serious obstetric complication and a major contributor to maternal morbidity and mortality worldwide.[1] Its incidence seems to be increasing in high-income countries accompanied by increasing rates of severe adverse outcomes.[2] In obstetrics, massive transfusion (defined as eight or more units of packed red blood cells transfused) after birth is associated with high rates of morbidity and hysterectomy.[3, 4] Incidence of massive transfusion due to postpartum hemorrhage was notably high in the Netherlands between 2004 and 2006 (91 per 100 000 births) compared with the United Kingdom (UK) between 2012 and 2013 (23 per 100 000 births) and with the state of New York between 1998 and 2007 (60 per 100 000 births).[3-5]

A nationwide study based on the national perinatal database in the Netherlands showed an increased incidence of postpartum hemorrhage (defined as ≥1000mL blood loss following the first 24 hours after birth) between 2004 and 2013 (from 4.1% to 6.4% of women giving birth), but a decreased incidence of any number of obstetric-related transfusion of packed red blood cells (from 23% to 3.9% of all women with postpartum hemorrhage).[6] It is unknown whether the number of women receiving massive transfusion due to postpartum hemorrhage followed this same decreasing pattern. Assessing such a pattern and discerning possible differences over time in incidence, causes, management and outcome of postpartum hemorrhage leading to massive transfusion could help evaluate maternity care. Moreover, identifying antepartum risk factors may also raise awareness for women at high risk of receiving massive transfusion after birth.

The aim of this study was to describe incidence, causes, management and outcome of women who received massive transfusion due to postpartum hemorrhage in the Netherlands between 2011 and 2012 and compare these to the same parameters previously described in the Netherlands between 2004 and 2006 and to the Dutch general pregnant population of 2012.[3]

MATERIAL AND METHODS

Study design

We performed a secondary analysis of women who received massive transfusion due to postpartum hemorrhage as part of the *Transfusion strategies in women during Major Obstetric Haemorrhage* study (TeMpOH-1). TeMpOH-1 is a nationwide retrospective cohort study in 61 hospitals in the Netherlands (71% of all hospitals in the country at the time) that collected data from women of at least 18 years old, who received four units of packed red blood cells or any transfusion of fresh frozen plasma and/or platelets in addition to packed red blood cells because of obstetric hemorrhage (≥1000mL blood loss during pregnancy or the first 24 hours following childbirth) between January 1st, 2011 and January 1st, 2013.

Population

For the present analysis, women were selected from the TeMpOH-1 cohort who had experienced postpartum hemorrhage and received massive transfusion at a gestational age of at least 20 weeks. Massive transfusion was defined as eight or more units of packed red blood cells transfused within the first 24 hours after childbirth. All results were compared to our previous observations from the LEMMoN cohort (Landelijke studie naar Etnische determinanten van Maternale Morbiditeit in Nederland) between 2004 and 2006, and nationwide statistics obtained from the Netherlands Perinatal Registry (PRN, 2012) were used as national reference values.[3, 7, 8]

Data collection

The TeMpOH-1 study identified eligible women by cross-referencing data from hospitals' blood transfusion services with local birth registers in participating hospitals. Trained medical students and research nurses obtained available data from maternity units, operating theatres and intensive care units. We recorded the following parameters: maternal age at time of birth, body mass index (BMI) at the beginning of pregnancy, parity, ethnicity (Caucasian/non-Caucasian), obstetric medical history (previous cesarean section and/or previous postpartum hemorrhage), gestational age, mode of birth (vaginal birth, instrumental vaginal birth, elective cesarean section or emergency cesarean section), induction of labor, multiple pregnancy, pre-eclampsia in current pregnancy, blood loss (measured by weighing gauzes and by use of a suction system in the operating theatre), number of packed red blood cells transfused, cause of hemorrhage (uterine atony, uterine rupture, placental pathology [including retained placenta, placental remnants, placenta previa,

abnormally invasive placenta and placental abruption], laceration of the birth canal, uterine inversion and clotting disorder with or without amniotic fluid embolism) and management of obstetric hemorrhage (uterotonic agents [oxytocin, sulprostone, ergometrine, misoprostol], non-uterotonic agents [tranexamic acid], intrauterine balloon tamponade, surgical interventions [B-Lynch sutures, uterine artery ligation, peripartum hysterectomy] and uterine artery embolization). Furthermore, since severe postpartum hemorrhage can be the result of concurrent causes, we re-examined all cases of massive transfusion due to postpartum hemorrhage within the TeMpOH-1 cohort, and only included multiple causes for an individual woman if those causes contributed significantly to the bleeding, as was previously done in the LEMMoN study.[3] Causes of postpartum hemorrhage in women who received massive transfusion were further analyzed by mode of birth and the number of packed red blood cells transfused, using the same cut-off points described by Green et al.[4] in the UK: 'moderate' (8–12 units of packed red blood cells), 'high' (13–20 units of packed red blood cells) and 'immense' (more than 20 units of packed red blood cells). Adverse maternal outcome was defined as the need for hysterectomy, admission to an intensive care unit and/or maternal death.

Statistical analyses

All statistical analyses were performed with IBM SPSS Statistics (version 22.0). Categorical data were presented as frequencies with percentages and continuous data as medians with the 25th and 75th interquartile ranges (IQR). The association between possible risk factors and occurrence of postpartum hemorrhage leading to massive transfusion was analyzed by comparing available characteristics from the TeMpOH-1 cohort to characteristics of the general pregnant population in 2012, as obtained from the PRN database.[8] Given that the PRN database only has summary denominator data, odds ratios (OR) were calculated by means of univariate logistic regression models, resulting in crude odds ratios with 95% confidence intervals (CI).[8] Women with missing values for a specific parameter were excluded from analyses that required that parameter. The number of births of the TeMpOH-1 cohort comprised women who gave birth under guidance of obstetricians, but did not include women with low risk pregnancies who had given birth under guidance of their midwives or family physicians (primary care), which represented about 29% of all births in the Netherlands between 2011-2012.[8,9] To estimate a population-based incidence of massive transfusion due to postpartum hemorrhage, number of births in the TeMpOH-1 study was multiplied by 100/71 to represent all births, including those under guidance of primary care.

Ethical approval

The TeMpOH-1 study was approved by the ethics committee of the Leiden University Medical Centre on January 31, 2013 (P12.273) and by the institutional review board of each participating hospital. The study was registered in the Netherlands Trial Register (NTR4079). Need to obtain informed consent was waived by the ethics committee.

RESULTS

The TeMpOH-1 source population comprised 270 101 births (including births under guidance of primary care) in the Netherlands during the two-year inclusion period. A total of 176 women experienced postpartum hemorrhage and received transfusion of eight or more units of packed red blood cells, making the incidence of massive transfusion due to postpartum hemorrhage in the Netherlands 65 per 100 000 births (95% CI; 56 to 75) between 2011 and 2012 (Figure 1)[3-5].

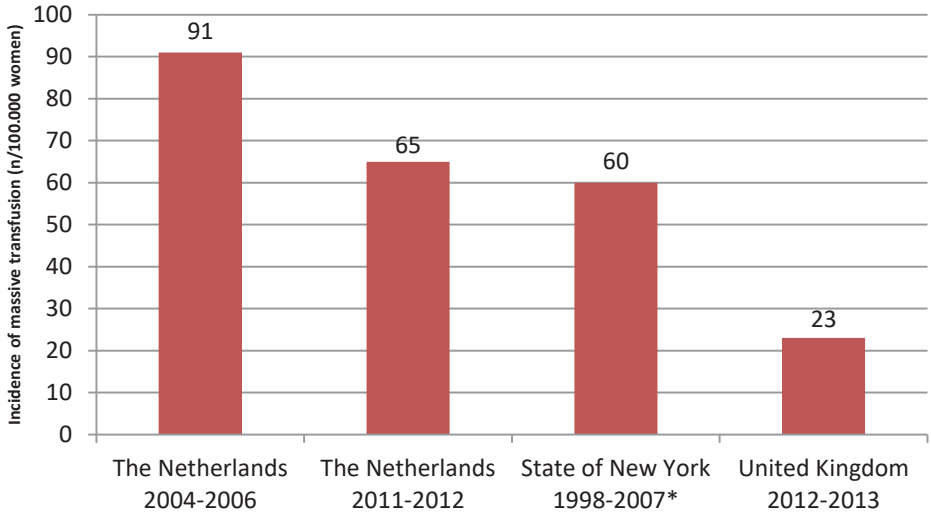

Figure 1. The incidence of women requiring massive transfusion due to postpartum hemorrhage.

*Defined massive transfusion as ≥10 packed cells and included all pregnancy-related hemorrhage.[5]

Characteristics of women and bleeding

Women who received massive transfusion due to postpartum hemorrhage had a median (IQR) age of 32 years (29–37), BMI of 23 kg/m^2 (21–26) and a gestational age of 39 weeks (37–40). The characteristics of women, pregnancy and birth are presented in Table 1 and juxtaposed to the characteristics of women who experienced postpartum hemorrhage and received massive transfusion between 2004 and 2006 in the Netherlands and to the Dutch general pregnant population in 2012.[3, 8, 10, 11] The median (IQR) estimated blood loss was 6000mL (4500–8000).

Table 1. Characteristics of the women, pregnancy and birth

	2004-2006[3] *N=327* N (%)	2011-2012 *N=176* N (%)	General pregnant Dutch population N (%)
Age (years)			
<20	0 (0)	2 (1)	2257 (1.3)[8]
20-34	208 (63)	114 (65)	135.406 (78.2)[8]
35-39	94 (29)	44 (25)	29.562 (17.1)[8]
≥40	25 (8)	16 (9)	5860 (3.4)[8]
BMI (kg/m²)			
<18.5	15 (5)	6 (3)	N/A (N/A)
18.5-24.9	137 (42)	84 (48)	N/A (N/A)
25.0-29.9	39 (12)	30 (17)	N/A (N/A)
≥30	24 (7)	10 (6)	N/A (N/A)
Missing	112 (34)	46 (26)	N/A (N/A)
Ethnicity			
Caucasian	N/A (N/A)	109 (62)	N/A (N/A)
Non-Caucasian	N/A (N/A)	51 (29)	N/A (N/A)
Missing	N/A (N/A)	16 (9)	N/A (N/A)
Parity			
0	158 (48.3)	82 (47)	77.647 (44.9)[8]
1-2	145 (44.3)	83 (47)	93.454 (49.1)[8]
≥3	24 (7.3)	11 (6)	1998 (6.0)[8]
Previous CS	66 (20)	45 (26)	1068 (10.9)[10]
Previous PPH*	40 (12)	15 (9)	N/A (N/A)
Gestational age			
20-24	6 (2)	1 (1)	N/A (N/A)
24-32	18 (5)	10 (6)	N/A (N/A)
32-37	62 (19)	24 (13)	N/A (N/A)
≥37	241 (74)	141 (80)	N/A (N/A)
Mode of birth			
Vaginal	131 (40)	64 (36)	131265 (74.5)[8]
Instrumental	43 (13)	37 (21)	16.210 (9.2)[8]
Cesarean section	151 (46)	75 (43)	28.680 (16.3)[8]
Elective	46 (14)	36 (21)	12.280 (7.1)[8]
Emergency	105 (32)	39 (22)	16.400 (9.2)[8]
Induction of labor	100 (31)	61 (35)	37.510 (21.7)[8]
Multiple pregnancy	37 (11)	11 (6)	2992 (1.7)[8]
Pre-eclampsia	54 (17)	23 (13)	31.560 (2.2)[11]

CS: Cesarean section, PPH: postpartum hemorrhage, N/A: data not available.

*Data about previous experienced PPH were missing for 82 women (47%).

Risk factors and causes of hemorrhage

Women with postpartum hemorrhage leading to massive transfusion were more likely to be aged over 35 years (OR 2.01, 95% CI; 1.47 to 2.74), had a previous cesarean section (OR 2.81, 95% CI; 2.00 to 3.95), suffered from preeclampsia (OR 6.71, 95% CI; 4.33–10.41), had a multiple pregnancy (OR 3.86, 95% CI; 2.10 to 7.12), had induced labor (OR 1.92, 95% CI; 1.41 to 2.62), had an instrumental vaginal birth (OR 2.63, 95% CI; 1.83 to 3.78), or had an elective (OR 3.37, 95% CI; 2.34 to 4.86) or emergency (OR 2.82, 95% CI; 1.97 to 4.02) cesarean section. In figure 2 the proportion of causes of postpartum hemorrhage that led to massive transfusion in 2004 to 2006 and in 2011 to 2012 in the Netherlands are compared.[3] The commonest cause of postpartum hemorrhage leading to massive transfusion remained uterine atony, followed by retained placenta and placenta previa. Compared with 2004 to 2006, it appears that a larger proportion of women between 2011 and 2012 sustained postpartum hemorrhage due to placenta previa (17% [29/176] vs 11% [37/327]), abnormally invasive placenta (13% [22/176] vs 10% [32/327]) and uterine rupture (11% [19/176] vs 6% [20/327]).[3] For 67 women (38%), two causes were registered with uterine atony and placental remnants (N=12) being the commonest combination. The most frequent combination of women with three causes (N=12) was uterine atony with placental remnants and laceration of the birth canal (N=5). The 'other causes' as mentioned in Figure 2 were primary clotting disorder (N=4), amniotic fluid embolism (N=1), uterine inversion (N=1) and liver capsule rupture with uterine atony (N=1). Categorising the top three causes of according to the mode of birth showed no noticeable differences over time with placenta previa (22/36; 61%) remaining the commonest cause during elective cesarean section and uterine atony in other modes of birth (Supporting Information Table S1). Uterine atony also remained a leading cause when causes were grouped by the total units of packed red blood cells transfused: 'moderate' (8–12 units, N=113), 'high' (13–20 units, N=49) and 'immense' (≥20 units, N=14).

Management of postpartum hemorrhage

Median (IQR) number of units of packed red blood cells transfused was 11 (9–16). Distribution of obstetric interventions per cause of hemorrhage in 2004 to 2006 and in 2011 to 2012 are summarized in Table 2.[3] Compared with 2004 to 2006, it seems that proportionally more women received sulprostone between 2011 and 2012 (82% vs 70%), and sulprostone became the most frequent uterotonic drug administered during postpartum hemorrhage leading to massive transfusion.[3] Misoprostol (34% vs 11%) and tranexamic acid (74% vs 22%) were seemingly administered more often as well, while it appears that ergometrine (10% vs 18%) and (non-prophylactic) oxytocin (64% vs 87%) were used less frequently over time.[3]

Table 2. Distribution of obstetric interventions by cause of postpartum hemorrhage

	Uterine atony		Uterine rupture	
	2004-2006[3] *N=179*	2011-2012 *N=105*	2004-2006[3] *N=20*	2011-2012 *N=19*
Oxytocin*	94% (N=168)	66% (N=69)	70% (N=14)	47% (N=9)
Sulprostone	87% (N=156)	88% (N=92)	50% (N=10)	84% (N=16)
Tranexamic acid	33% (N=59)	71% (N=74)	5% (N=1)	74% (N=14)
Ergometrine	23% (N=41)	12% (N=12)	15% (N=3)	11% (N=2)
Misoprostol	16% (N=29)	37% (N=39)	5% (N=1)	37% (N=7)
Intrauterine balloon	32% (N=58)	59% (N=62)	10% (N=2)	16% (N=3)
Uterine artery ligation	6% (N=10)	7% (N=7)	5% (N=1)	5% (N=1)
Uterine artery embolization	29% (N=52)	49% (N=51)	10% (N=2)	37% (N=7)
B-Lynch suture	5% (N=8)	18% (N=19)	0% (N=0)	11% (N=2)
Hysterectomy	27% (N=48)	24% (N=25)	70% (N=14)	63% (N=12)

*Prophylactic oxytocin after childbirth excluded.

Thirty-six women with uterine atony did not receive postpartum oxytocin infusion and of those who gave birth vaginally (N=12), all received sulprostone. Of those women without postpartum oxytocin infusion and who gave birth by cesarean section (N=24), 17 received sulprostone. Among these 24 women, uterine atony co-occurred frequently with placenta previa (N=8), uterine rupture (N=6) and abnormally invasive placenta (N=4), and the hysterectomy rate was considerably high (10/24; 42%). Furthermore, it appears that proportionally more women between 2011 and 2012 received intrauterine balloon tamponade (56% vs 23% between 2004 and 2006), B-Lynch suture (14% vs 2% between 2004 and 2006) and embolization of uterine arteries (48% vs 22% between 2004 and 2006).[3] Hysterectomy rate among all women receiving massive transfusion due to postpartum hemorrhage was allegedly higher in 2011 to 2012 compared with 2004 to 2006 (30% [53/176] vs 25% [83/327])[3], with highest rates among women who endured bleeding due to abnormally invasive placenta (N=18/22), placenta previa (N=20/29) and uterine rupture (N=12/19).

Placenta previa		Invasive placenta		Placental abruption		Total	
2004-2006[3] *N=37*	2011-2012 *N=29*	2004-2006[3] *N=32*	2011-2012 *N=22*	2004-2006[3] *N=20*	2011-2012 *N=5*	2004-2006[3] *N=327*	2011-2012 *N=176*
87% (N=32)	38% (N=11)	91% (N=29)	55% (N=12)	70% (N=14)	40% (N=2)	84% (N=275)	64% (N=112)
54% (N=20)	66% (N=19)	72% (N=23)	73% (N=16)	55% (N=11)	40% (N=2)	70% (N=228)	82% (N=145)
19% (N=7)	62% (N=18)	13% (N=4)	77% (N=17)	5% (N=1)	60% (N=3)	22% (N=72)	74% (N=130)
14% (N=5)	7% (N=2)	19% (N=6)	9% (N=2)	20% (N=4)	0% (N=0)	18% (N=60)	10% (N=18)
3% (N=1)	21% (N=6)	3% (N=1)	18% (N=4)	20% (N=4)	20% (N=1)	11% (N=36)	34% (N=60)
14% (N=5)	45% (N=13)	28% (N=9)	36% (N=8)	5% (N=1)	20% (N=1)	23% (N=75)	56% (N=99)
8% (N=3)	3% (N=1)	3% (N=1)	9% (N=2)	5% (N=1)	0% (N=0)	5% (N=17)	5% (N=9)
19% (N=7)	35% (N=10)	19% (N=6)	32% (N=7)	5% (N=1)	40% (N=2)	22% (N=71)	48% (N=84)
3% (N=1)	21% (N=6)	3% (N=1)	9% (N=2)	10% (N=2)	0% (N=0)	2% (N=8)	14% (N=25)
38% (N=14)	69% (N=20)	66% (N=21)	82% (N=18)	5% (N=1)	0% (N=0)	25% (N=83)	30% (N=53)

Adverse maternal outcome

Of all women, 146 (83%) were admitted to an intensive care unit and 53 (30%) underwent hysterectomy as a last resort to stop bleeding. Four women died (three due to exsanguination caused by uterine atony and one due to liver capsule rupture accompanied by uterine atony), of whom two after hysterectomy. Case fatality rate of postpartum hemorrhage with massive transfusion was 1 in 44 women (2.27%) and case fatality rate of women who underwent peripartum hysterectomy due to major postpartum hemorrhage was 2 in 53 women (3.77%).

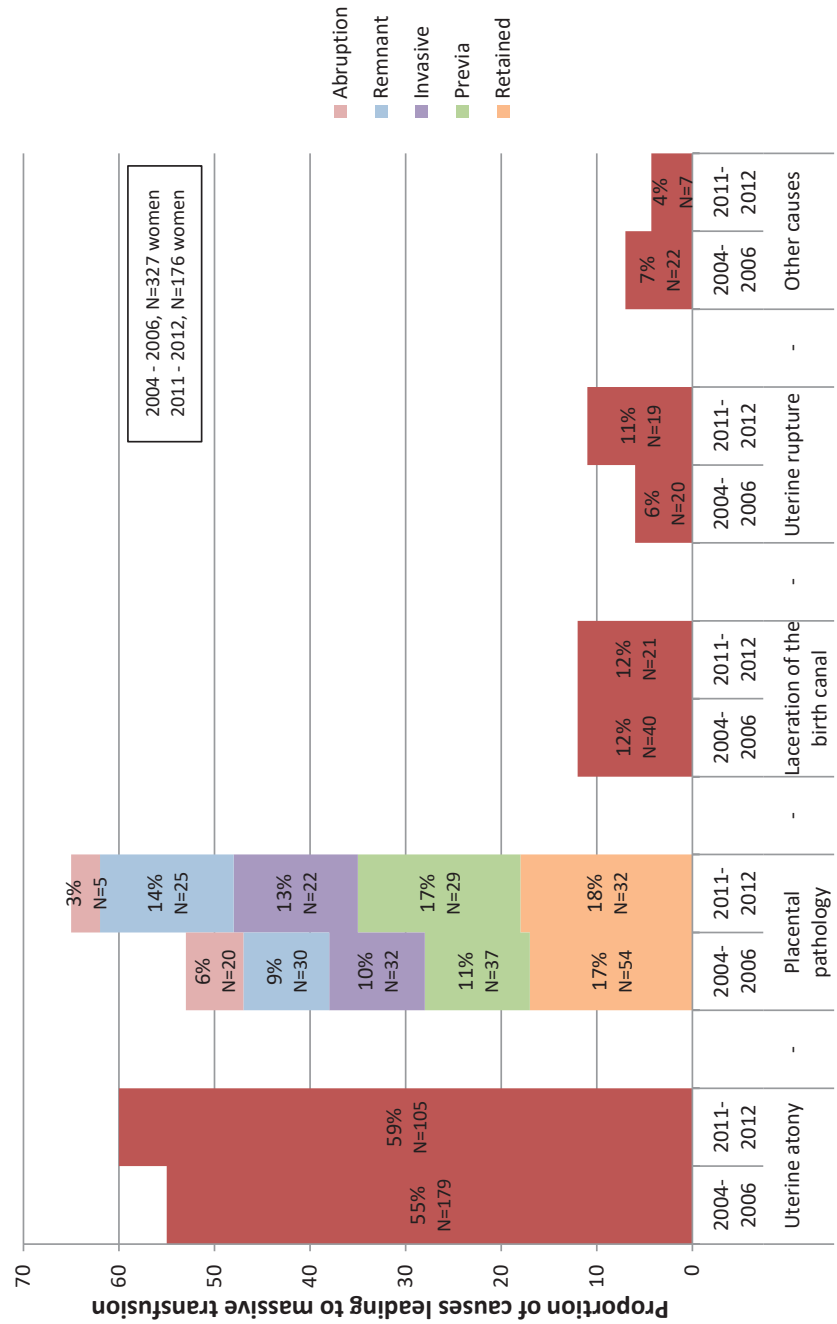

Figure 2. Proportion of causes leading to postpartum hemorrhage with massive transfusion.

DISCUSSION

The incidence of massive blood transfusion due to postpartum hemorrhage decreased in the Netherlands from 91 per 100 000 births (95% CI; 81 to 101) between 2004 and 2006 to 65 per 100 000 births (95% CI; 56 to 75) between 2011 and 2012, while the median (IQR) blood loss increased from 4500mL (3250–6000) to 6000mL (4500–8000).[3] The leading cause of postpartum hemorrhage with massive blood transfusion remained uterine atony. Sulprostone was the most administered uterotonic agent and almost one-third (30%) underwent hysterectomy with highest rates among women with abnormally invasive placenta, placenta previa and uterine rupture. Case fatality rate was 0.9% (3/327) between 2004-2006 vs 2.27% (4/176) between 2011-2012.[3]

Key strengths of this study are that our results are based on a nationwide cohort study (the 71% of the Dutch obstetric units that participated in the TeMpOH-1 were a representative distribution of all obstetric units in the Netherlands at the time, thereby reflecting the general pregnant population in the Netherlands) and that we included all women with postpartum hemorrhage who received massive transfusion by cross-referencing data from hospitals' blood transfusion services with birth registers in local participating hospitals. Additionally, by using the same inclusion criteria and definition of massive transfusion as our previous cohort and the study conducted in the UK, results are directly comparable.[3, 4] However, in applying eight or more units of packed cells as definition of massive transfusion, it must be noted that these numbers can be influenced by clinical decision making. There is still no definite consensus in the literature as to which definition of massive transfusion should be applied.[12-14] Furthermore, number of births used as denominator for calculation of incidence of massive transfusion due to postpartum hemorrhage was estimated by multiplying the number of hospital births in the TeMpOH-1 study by the proportion of births under guidance of primary care. However, since coverage of the PRN registry was about 99% of all births in the Netherlands and all women with hemorrhage receiving massive transfusion will eventually have been referred to a maternity unit, we believe that this estimate of incidence is reliable.[8]

The decreased incidence of postpartum hemorrhage leading to massive transfusion along with an observed increase in median blood loss reflects the more restrictive blood transfusion policy in the Netherlands over time.[6] This gradual change followed, among other things, after the introduction of the '4–5–6 rule' (depending on the presence of co-morbidity, the threshold for transfusion of

packed cells varies between 4.0 mmol/L [6.5 g/dL] and 6.0 mmol/L [9.7 g/dL]) in the Dutch national guideline on blood transfusion in 2004, which implementation probably took time before the effect on the number of blood transfusions became visible.[15] At the same time, the finding that proportionally more women appear to have had peripartum hysterectomy and uterine artery embolization in the recent time frame could either reflect a larger proportion of high-risk pregnancies due to a more restrictive blood transfusion policy, or a more aggressive management of postpartum hemorrhage. Nonetheless, the incidence of massive transfusion due to postpartum hemorrhage in the Netherlands between 2011 and 2012 became comparable to the state of New York between 1998 and 2007 (notwithstanding the higher threshold of 10 or more units of packed cells applied to define massive transfusion in that setting). The incidence, however, remained considerably higher than in the United Kingdom between 2012 and 2013 (23 per 100 000 births, 95% CI; 19 to 26), even though median blood loss in women receiving massive transfusion due to postpartum hemorrhage was similar between the UK and the Netherlands.[4, 5]

Of the women receiving massive transfusion after birth in the Netherlands between 2011 and 2012, there appears to be an increase in the proportion of women who experienced hemorrhage due to placenta previa, abnormally invasive placenta and uterine rupture, and it seems that proportionally more women underwent hysterectomy to control hemorrhage. Although the cesarean section rate remained relatively stable around 16% in the Netherlands[8, 16], these seemingly increased proportions are partly explained by the fact that a larger proportion of women with a prior cesarean birth were present in the TeMpOH-1 cohort (26% compared to 20% between 2004 and 2006).[3] This is known to be associated with increased risks of placenta previa, abnormally invasive placenta and uterine rupture in subsequent pregnancies.[17-19] Furthermore, studies showed that the risk of peripartum hysterectomy increased with the number of prior cesarean births and in presence of an abnormally invasive placenta.[20-22] Other countries have reported increasing prior cesarean birth rates with an increasing trend in incidence of placenta previa, abnormally invasive placenta and uterine rupture, which may suggest that more countries experience the high burden of hysterectomy because of severe postpartum hemorrhage.[23-25]

Nevertheless, the hysterectomy rate in the Netherlands remained substantially lower than in the United Kingdom, where the overall rate was 45%.[4] This difference could be explained by the lower rates of women with previous cesarean births in the Netherlands (26% vs 40% in the UK) and higher rates of embolization

(48% vs 16% in the UK), which may avert hysterectomy in most cases.[4] The national guideline from the Netherlands Society of Obstetrics and Gynecology (NVOG) states that in case of an ongoing hemorrhage, embolization and/or surgical interventions should not be postponed, while the national guideline in the UK made by Royal College of Obstetricians and Gynaecologists (RCOG) specifically recommends to 'resort to hysterectomy sooner rather than later' without explicitly mentioning the option of trying embolization first.[26, 27] This difference could lead to a more restrictive policy of peripartum hysterectomy in the Netherlands.

Furthermore, the incidence of postpartum hemorrhage also depends on prevalence of risk factors in the population. Our findings confirm previous observations that increased maternal age (≥35 years), previous cesarean birth, multiple pregnancy, pre-eclampsia, labor induction, and instrumental or cesarean birth are associated with postpartum hemorrhage leading to massive transfusion.[5, 11, 28, 29] These antepartum risk factors were only present in a certain number of women enduring severe hemorrhage. Considering that uterine atony remained the leading cause of postpartum hemorrhage that required massive transfusion, demonstrates that all obstetric caregivers should acknowledge the possible severity of uterine atony despite absence of risk factors. In this respect, the substantial decrease of oxytocin use among women with postpartum hemorrhage with massive transfusion due to uterine atony is striking, considering that the Dutch national guideline specifically recommends oxytocin as uterotonic agent of first choice.[26] Although our findings rely on the accuracy of data entered into the TeMpOH-1 database, such a decrease is worrying and should be reported to all obstetric caregivers by emphasizing the importance of oxytocin in the Dutch national guideline on the management of postpartum hemorrhage, which may reduce the need to resort to massive transfusion following childbirth.

Despite all changes over time, the maternal mortality ratio (MMR) in women with postpartum hemorrhage leading to massive transfusion in the Netherlands was 1.48 deaths per 100 000 live births between 2011 and 2012 vs 0.84 deaths per 100 000 live births between 2004 and 2006.[3] These results should be viewed with caution, given the substantial uncertainty surrounding these estimates due to the small number of deaths. However, the MMR of postpartum hemorrhage requiring massive transfusion was considerably higher than reported in the United Kingdom between 2012 and 2013 (0.23 deaths per 100 000 live births)[4], and this finding is worrying and merits closer analysis. Our findings are of utmost importance to other high-income countries, where similar patterns may have

occurred. Maternal mortality has become a very rare outcome in these countries, which hampers comparisons over time and between settings. Our findings should encourage researchers in other high-income settings to critically evaluate their clinical management and maternal mortality because of severe postpartum hemorrhage.

National surveillance of maternal morbidity and mortality due to postpartum hemorrhage through improved continuous registration with confidential enquiries and multidisciplinary simulation training of postpartum hemorrhage-related emergencies could improve the quality of maternal care. The MBRRACE-UK reports (Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK) are likely to have contributed to a steady fall of obstetric hemorrhage-related deaths in the United Kingdom and provides a rational framework for how national surveillance may be applied by other countries.[30, 31] Nevertheless, the escalating rates of postpartum hemorrhage in other high-income countries emphasizes the importance of nationwide studies into obstetric hemorrhage-related maternal morbidity and mortality.[29, 32, 33] International comparison of data regarding postpartum hemorrhage that led to massive blood transfusion could reveal variations in the management and outcome between countries, and consequently lead to improvements in maternal care. Collaboration such as the International Network of Obstetric Survey Systems could help facilitate population-based studies.[34]

CONCLUSION

The incidence of postpartum hemorrhage leading to massive blood transfusion decreased in the Netherlands, but continues to be an important cause of maternal morbidity and mortality. Improved continuous registration of severe postpartum hemorrhage with confidential enquiries to identify substandard factors could lead towards better maternal care and may prevent severe maternal outcome from postpartum hemorrhage in the Netherlands. International comparison of our findings could provide high quality evidence for the best management practices of severe postpartum hemorrhage.

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SUPPLEMENTALS

Table S1. Top three causes of postpartum hemorrhage categorized by mode of birth

2004–2006[3]			2011–2012		
	N	(%)		N	(%)
Vaginal birth *(N=131)*			**Vaginal birth *(N=64)***		
1. Uterine atony	84	(64)	1. Uterine atony	32	(50)
2. Retained placenta	40	(31)	2. Retained placenta	21	(33)
3. Placental remnant	20	(15)	3. Placental remnant	18	(28)
Instrumental birth *(N=43)*			**Instrumental birth *(N=37)***		
1. Uterine atony	26	(60)	1. Uterine atony	24	(65)
2. Retained placenta	14	(33)	2. Retained placenta	10	(27)
3. Placental remnant	6	(14)	3. Laceration birth canal	10	(27)
Elective cesarean section *(N=46)*			**Elective cesarean section *(N=36)***		
1. Placenta previa	24	(52)	1. Placenta previa	22	(61)
2. Uterine atony	17	(47)	2. Uterine atony	21	(58)
3. Abnormally invasive placenta	13	(28)	3. Abnormally invasive placenta	13	(36)
Emergency cesarean section *(N=105)*			**Emergency cesarean section *(N=39)***		
1. Uterine atony	51	(49)	1. Uterine atony	28	(72)
2. Uterine rupture	13	(12)	2. Uterine rupture	11	(28)
3. Iatrogenic during cesarean	9	(9)	3. Placenta previa	5	(13)

PART II

EVALUATING MATERNITY CARE DURING AND AFTER POSTPARTUM HEMORRHAGE

CHAPTER 4

CLINICAL VALUE OF EARLY VISCOELASTOMETRIC POINT-OF-CARE TESTING DURING POSTPARTUM HEMORRHAGE FOR THE PREDICTION OF SEVERITY OF BLEEDING: A MULTICENTER PROSPECTIVE COHORT STUDY IN THE NETHERLANDS

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ABSTRACT

Introduction

To evaluate ROTEM® FIBTEM A5 as an early point-of-care parameter for predicting the progression to severe postpartum hemorrhage, and compare its predictive value to that of fibrinogen.

Material and methods

Prospective cohort study in the Netherlands including women with 800 to 1500mL of blood loss within 24 hours after birth. Blood loss was quantitatively measured by weighing blood-soaked items and by using a fluid collector bag in the operating room. Both FIBTEM A5 values and fibrinogen concentrations (Clauss method) were measured between 800 to 1500mL of blood loss. Predictive accuracy of both biomarkers for the progression to severe postpartum hemorrhage was measured by area under the receiver operating curves. Severe postpartum hemorrhage was defined as a composite endpoint of 1) blood loss >2000mL, 2) transfusion of ≥4 packed red blood cells, and/or 3) need for an invasive intervention to cease bleeding.

Results

Of the 391 women included, 72 (18%) developed severe postpartum hemorrhage. Median (IQR) volume of blood loss at blood sampling was 1100mL (1000–1300) with a median (IQR) fibrinogen concentration of 3.9g/L (3.4–4.6) and FIBTEM A5 value of 17mm (13–20). The AUC for progression to severe postpartum hemorrhage was 0.53 (95% CI 0.46–0.61) for FIBTEM A5 and 0.58 (95% CI 0.50–0.65) for fibrinogen. Positive predictive values for progression to severe postpartum hemorrhage for FIBTEM A5 ≤12mm was 22.5% (95% CI 14-33) and 50% (95% CI 25-75) for fibrinogen ≤2g/L.

Conclusions

The predictive value of FIBTEM A5 compared to fibrinogen concentrations measured between 800 and 1500mL of blood loss following childbirth to discriminate between women with and without progression towards severe postpartum hemorrhage was poor.

INTRODUCTION

Postpartum hemorrhage is a significant contributor to maternal morbidity in high-income countries and the leading cause of maternal mortality worldwide.[1-4] Hemorrhage following birth most commonly has a primary obstetric cause, and although postpartum hemorrhage should be treated prior to development of coagulopathy, it can be aggravated by hemostatic impairment.[5] Research into the maternal coagulation profile during postpartum hemorrhage has indicated that a low fibrinogen concentration (≤2g/L) is associated with severity of bleeding.[6-9] However, detection of a fibrinogen deficiency during hemorrhage is often delayed due to the long turnaround times of conventional coagulation tests (e.g. Clauss fibrinogen assay), with results generally available following 60 minutes.[10] For this reason, conventional coagulation tests are not suitable for predicting the progression of bleeding and to guide hemostatic interventions (e.g. administration of fibrinogen concentrate) during the acute phase of postpartum hemorrhage.[11]

Viscoelastometric point-of-care testing using rotational thromboelastometry (ROTEM®) provides an alternative approach to detect early changes in coagulation parameters by analyzing clot formation, firmness, and lysis.[12] The ROTEM® FIBTEM assay determines the role of the extrinsic coagulation pathway to clot firmness independent of platelets.[12] The fibrinogen concentration is the major contributing factor in the FIBTEM assay.[12] Results from the FIBTEM amplitude of clot firmness at 5 minutes (A5) can be obtained within 10 to 15 minutes following blood sampling, and correlates well with the plasma-derived fibrinogen concentrations during pregnancy and postpartum hemorrhage.[13, 14] A FIBTEM A5 value of ≤12mm has been suggested as the most accurate cut-off point to select women with a fibrinogen concentration of ≤2g/L during postpartum hemorrhage.[15] In a previous study, FIBTEM A5 was found to be a rapidly available biomarker for predicting progression of postpartum hemorrhage.[16] Nevertheless, it remains unclear whether implementation of FIBTEM A5 measurements as part of standard care during the onset of postpartum hemorrhage has the potential to accurately diagnose low fibrinogen concentrations and is able to discriminate between women with and without progression to severe postpartum hemorrhage. We hypothesized that an early FIBTEM A5 measurement is able to predict the progression to severe hemorrhage for the following reasons. First, a deterioration in FIBTEM A5 measurements during the early stages of postpartum hemorrhage might indicate that blood loss is greater than appreciated. Second, a deterioration in FIBTEM A5 measurements might indicate an impairment in hemostasis suggesting that these women have a higher than average propensity to bleed

in relation to the primary obstetric cause. Early identification of hemostatic impairment allows for earlier use of targeted hemostatic interventions. If so, FIBTEM A5 could be a promising point-of-care parameter to identify women who could possible benefit from targeted fibrinogen replacement therapy during the earliest stages of postpartum hemorrhage, possibly preventing progression to severe bleeding.

National guidelines on the prevention and management of postpartum hemorrhage from the United Kingdom (Royal College of Obstetricians and Gynaecologists [RCOG]) and the Netherlands (Dutch Society of Obstetrics and Gynaecology [NVOG]) recommend routine coagulation testing in case of ongoing bleeding exceeding 1000mL of blood loss following birth.[17, 18] However, in anticipation of postpartum hemorrhage, in some women intravenous access with simultaneous collection of blood for coagulation screening may already have been established before reaching the threshold of 1000mL blood loss. Therefore, the aim of this study was to evaluate the value of FIBTEM A5 as a predictor for progression to severe postpartum hemorrhage when collected between 800 and 1500mL blood loss after birth, and compare its predictive value to that of the conventional Clauss fibrinogen assay.

MATERIALS AND METHODS

This study was part of the *Towards better prognostic and diagnostic strategies for Major Obstetric Hemorrhage* (TeMpOH-2) study. TeMpOH-2 study was a multicenter prospective cohort study of pregnant women in the Netherlands between February, 2015 and April, 2018. Pregnant women of at least 18 years old and with a gestational age of at least 24 weeks were recruited at the outpatient clinics and maternity wards of three participating hospitals; Leiden University Medical Center (tertiary hospital), Erasmus Medical Center Rotterdam (tertiary hospital), and Isala Clinics in Zwolle (secondary hospital). Included women were monitored for the occurrence of postpartum hemorrhage (in the Netherlands defined as ≥1000mL blood loss within 24 hours after birth) and followed until discharge from hospital. In all hospitals, consecutive measurements of blood loss at time of blood sampling and total volume of blood loss when bleeding ceased was measured by weighing gauzes or other soaked materials and by use of a collector bag and suction system in the operating room. The clinician in charge was instructed to take at least one blood sample between 800 to 1500mL of blood loss. These samples were taken for full blood count, fibrinogen measurement (according to the Clauss method)[19], and FIBTEM A5 measurement performed on a ROTEM® Delta device (Tem International GmbH, Munich, Germany). All measurement on the ROTEM® Delta device were conducted with a single use reagent and in accordance with the recommendations of the manufacturer.[15] In one hospital, the ROTEM® Delta device was positioned in a utility room equipped with laboratory devices at the maternity ward and measurements were carried out by well-trained research nurses and clinical midwives. In the other two participating hospitals, the ROTEM® Delta devices were located at the laboratory and samples were handled by laboratory staff. Blood samples were collected before administration of blood components and fibrinogen concentrate. If multiple blood samples were taken between 800 and 1500mL of blood loss, the first sample above 1000mL was selected for analysis as recommended by the Dutch and English national guidelines on management of postpartum hemorrhage, which specifically recommends routine coagulation testing in case of bleeding exceeding 1000mL of blood loss.[17,18] Women who used anticoagulants or had a known coagulation disorder were excluded from the analysis. FIBTEM A5 results were not made available to the clinicians and women were treated according to the Dutch national guideline for postpartum hemorrhage.[18]

Trained research nurses obtained information on maternal and obstetric characteristics from medical files that were available at the maternity ward and operating theatre. The following parameters were recorded: maternal age at time of birth, body mass index (BMI) at beginning of pregnancy, gestational age at

time of birth, parity, ethnicity (Caucasian or non-Caucasian), multiple pregnancy, presence of pre-eclampsia or HELLP syndrome, mode of birth (vaginal birth or cesarean section), cause of hemorrhage (uterine atony, uterine rupture, placental pathology [including placenta previa, retained placenta or placental remnants, abnormally invasive placenta, and placental abruption], laceration of birth canal, and surgical bleeding), administration of uterotonic agents (oxytocin, sulprostone, ergometrine, misoprostol, and carbetocin), administration of non-uterotonic agents (tranexamic acid, fibrinogen concentrate, and recombinant factor VIIa), administration of clear fluids (crystalloids and colloids) and blood products (packed cells, fresh frozen plasma, and platelets), and invasive interventions to control bleeding (including intrauterine balloon tamponade, uterine artery ligation, uterine compression sutures, uterine artery embolization, and peripartum hysterectomy).

Severe postpartum hemorrhage was defined as a composite outcome of a total blood loss exceeding 2000mL, a transfusion of ≥4 packed red blood cells, and/or need for any invasive intervention, defined as intrauterine balloon tamponade, uterine artery ligation, uterine compression sutures, uterine artery embolization, or peripartum hysterectomy. These three outcomes are considered severe postpartum hemorrhage-related core outcome sets based on two international Delphi consensus studies.[20, 21]

Continuous data are presented as medians with interquartile ranges (IQR) and categorical data are summarized as frequencies with percentages (%). The clinical value of FIBTEM A5 and fibrinogen to predict progression to severe postpartum hemorrhage was investigated by area under the receiver operating characteristics curves (AUC) with 95% confidence intervals (CI) and positive and negative predictive values. The correlation between FIBTEM A5 values and fibrinogen concentrations was assessed by the Spearman's rank correlation coefficient (r_s). Considering that the Dutch and English national guidelines are specifically recommending coagulation testing when bleeding exceeds 1000mL, the clinical value of FIBTEM A5 and fibrinogen to predict progression to severe postpartum hemorrhage was also examined in a subgroup including only blood samples taken between 1000 and 1500mL of blood loss. A complete case analysis was performed and missing data were not imputed. Statistical analyses were performed using Stata Statistical Software: Release 14 (StataCorp LP, TX, USA).

Ethical approval

The TeMpOH-2 study was approved by the ethical committee of the Leiden University Medical Center (P13.246; February, 2014) and by the institutional review board of each participating hospital. Written informed consent was obtained antenatally from women included in the study. However, the ethical committee provided the possibility to ask women for verbal informed consent during onset of postpartum hemorrhage in case they had not yet been included during pregnancy. In these cases, written informed consent was obtained when bleeding ceased. The TeMpOH-2 study was registered at ClinicalTrials.gov (NCT02149472).

RESULTS

During the three-year inclusion period of the TeMpOH-2 study there were 17.203 women of at least 18 years old and with a gestational age of 24 weeks onwards who gave birth in one of the three hospitals. Of these women, 1605 (9.3%) had lost at least 1000mL of blood, of whom 391 fulfilled the inclusion criteria, consented to participate, and had a valid corresponding FIBTEM A5 and fibrinogen measurement between 800-1500mL of blood loss after childbirth (Figure 1). Of the 391 women included, 72 women (18%) had severe postpartum hemorrhage.

Baseline characteristics

Characteristics at study entry are presented in Table 1. The main cause of bleeding was either uterine atony (N=145/391, 37%), or retained placenta or placental remnant (N=148/391, 38%). Median (IQR) blood loss at time of blood sampling was 1100mL (1000-1300) with a median (IQR) fibrinogen concentration of 3.9g/L (3.4-4.6) and median (IQR) FIBTEM A5 value of 17mm (13-20). Lowest median (IQR) fibrinogen concentration and FIBTEM A5 value at study entry were associated with placental abruption, respectively 2.5g/L (1.7-3.7) and 13mm (8-16) (see supporting Table S1 for FIBTEM A5 values and fibrinogen concentrations for other postpartum hemorrhage causes). Sixteen (4%) women had a fibrinogen concentration ≤2g/L and 80 (20%) women had a FIBTEM A5 value ≤12mm. Colloids were infused in 28% (N=108, with a median [IQR] volume of 500mL [0-500]) and crystalloids in 62% (N=241, with a median [IQR] volume of 500mL [500-1000]) of the women before blood sampling.

Management of hemorrhage

All women (N=391) received a uterotonic agent, of whom 79 (20%) had a second uterotonic agent, 8 (2%) a third uterotonic agent, and 2 (0.5%) women a fourth uterotonic agent during hemorrhage. Tranexamic acid was administered in 60 (15%) women, fibrinogen concentrate in 12 (3%) women, and recombinant factor VII in none of the women. There were 21 invasive interventions in 19 (5%) women, including 13 intrauterine balloons, 4 uterine compression sutures, 2 uterine artery embolization, and 2 peripartum hysterectomies. One woman had intrauterine balloon tamponade in combination with uterine artery embolization and one woman had intrauterine balloon tamponade followed by peripartum hysterectomy. Seventy-one women (18%) were transfused packed red blood cells, 8 (2%) received fresh frozen plasma, and 9 (2%) received platelet concentrates during bleeding.

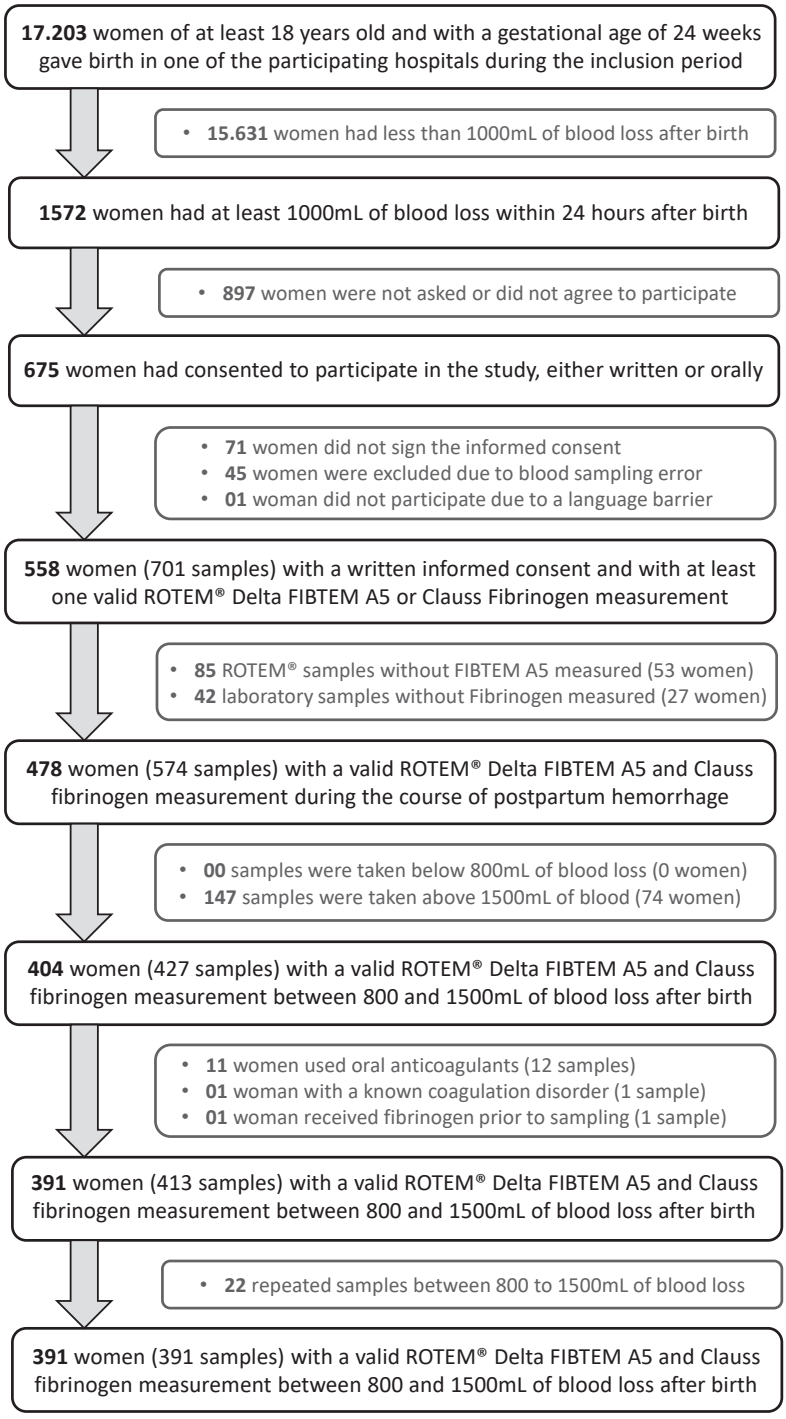

Figure 1. Flowchart of study enrollment.

Table 1. Baseline characteristics for women with postpartum hemorrhage and a valid corresponding FIBTEM A5 and fibrinogen measurement between 800 and 1500mL of blood loss following birth.

		Severe postpartum hemorrhage	
	Total	**No**	**Yes**
	N=391	N=319	N=72
Maternal age, years*	32 (28-35)	32 (28-35)	32 (28-35)
Gestational age, weeks*	39 (38-40)	39 (38-40)	39 (37-40)
Body mass index, kg/m²*	24 (22-28)	24 (22-28)	25 (22-29)
Caucasian, n (%)	336 (86%)	276 (87%)	60 (83%)
Nulliparity, n (%)	201 (51%)	166 (52%)	35 (49%)
Multiple pregnancy, n (%)	34 (9%)	23 (7%)	11 (15%)
Pre-eclampsia, n (%)	32 (8%)	24 (8%)	8 (11%)
Mode of birth, n (%)			
Vaginal birth	304 (78%)	246 (77%)	58 (81%)
Cesarean section	87 (22%)	73 (23%)	14 (19%)
Cause of hemorrhage, n (%)			
Uterine atony	145 (37%)	120 (38%)	25 (35%)
Retained placenta or remnants of placental tissue	148 (38%)	112 (35%)	36 (50%)
Placenta previa	5 (1%)	4 (1%)	1 (1.5%)
Placental abruption	3 (1%)	3 (1%)	0 (0%)
Abnormally invasive placenta	5 (1%)	2 (1%)	3 (4%)
Laceration of the birth canal	42 (11%)	36 (11%)	6 (8%)
Iatrogenic surgical bleeding	39 (10%)	38 (12%)	1 (1.5%)
Uterine rupture	4 (1%)	4 (1%)	0 (0%)
Blood loss at study entry, mL*	1100 (1000-1300)	1100 (1000-1300)	1100 (1000-1300)
Hb level at study entry, g/dL*	10.3 (9.0-11.4)	10.5 (9.4-11.4)	9.5 (8.1-11.1)
Fibrinogen at study entry, g/L*	3.9 (3.4-4.6)	4.0 (3.4-4.7)	3.9 (2.8-4.4)
FIBTEM A5 at study entry, mm*	17 (13-20)	17 (13-20)	16 (13-21)

*Reported as median with (interquartile ranges).

Outcomes

Median (IQR) total blood loss was 1400mL (1100-2000), 66 (17%) women had a total blood loss more than 2000mL and 13 (3%) women had 4 or more packed red blood cells transfused. The number of women with the composite endpoint defined as severe postpartum hemorrhage was 72 (18%). The distribution of outcomes according to increasing fibrinogen concentrations and FIBTEM A5 values at study entry are presented in Table 2 (and visually displayed in Figure S1). Maternal deaths did not occur among women included in this study.

Predictive value

Fibrinogen concentrations and FIBTEM A5 values were moderately correlated (r_s=0.53). The AUC for progression to severe postpartum hemorrhage was 0.58 (95% CI 0.50-0.65) for fibrinogen and 0.53 (95% CI 0.46-0.61) for FIBTEM A5 when measured between 800 and 1500mL of blood loss following childbirth (Figure 2). Fibrinogen had an AUC for progression to total blood loss >2000mL of 0.55 (95% CI 0.47-0.62), AUC for progression to ≥4 packed red blood cells of 0.63 (95% CI 0.44-0.81), and AUC for progression to any invasive intervention of 0.59 (95% CI 0.42-0.75). FIBTEM A5 had an AUC for progression to total blood loss >2000mL of 0.50 (95% CI 0.42-0.58), AUC for progression to ≥4 packed red blood cells of 0.51 (95% CI 0.33-0.70), and AUC for progression to any invasive intervention of 0.53 (95% CI 0.38-0.68) (Figure S2-4). Positive predictive value for progression to severe postpartum hemorrhage for a fibrinogen concentration ≤2g/L was 50% (95% CI 25-75) and 22.5% (95% CI 14-33) for a FIBTEM A5 value ≤12mm when measured between 800 and 1500mL of blood loss. Negative predictive values for a fibrinogen concentration >2g/L and FIBTEM A5 value >12mm were 83% (95% CI 79-87) and 83% (95% CI 78-87), respectively.

Subgroup analysis

There were 306 women with postpartum hemorrhage and a valid corresponding FIBTEM A5 and fibrinogen measurement between 1000 and 1500mL of blood loss following childbirth. Median (IQR) total blood loss was 1500mL (1200-2000) and 61 women (20%) developed severe postpartum hemorrhage. AUCs for progression to severe postpartum hemorrhage was 0.57 (95% CI 0.49-0.65) for fibrinogen and 0.55 (95% CI 0.47-0.64) for FIBTEM A5 (Figure S5), and were indistinguishable from the AUCs for fibrinogen and FIBTEM A5 when measured between 800 and 1500mL of blood loss.

Table 2. Distribution of outcomes categorized to fibrinogen concentrations and FIBTEM A5 values measured between 800 and 1500mL of blood loss following birth.

		Fibrinogen, g/L	
	Total (N=391)	≤2 (N=16)	2.1-3.0 (N=49)
Total volume of blood loss, L*	1.4 (1.1-2.0)	2 (1.8-2.6)	1.5 (1.2-2)
Severe postpartum hemorrhage, n (%)	72 (18%)	8 (50%)	11 (23%)
Women with blood loss >2000mL, n (%)	66 (17%)	7 (44%)	8 (16%)
Women receiving ≥4 packed cells, n (%)	13 (3%)	3 (19%)	2 (4%)
Women with invasive intervention, n (%)	19 (5%)	2 (13%)	6 (12%)

*Reported as median with (interquartile ranges).

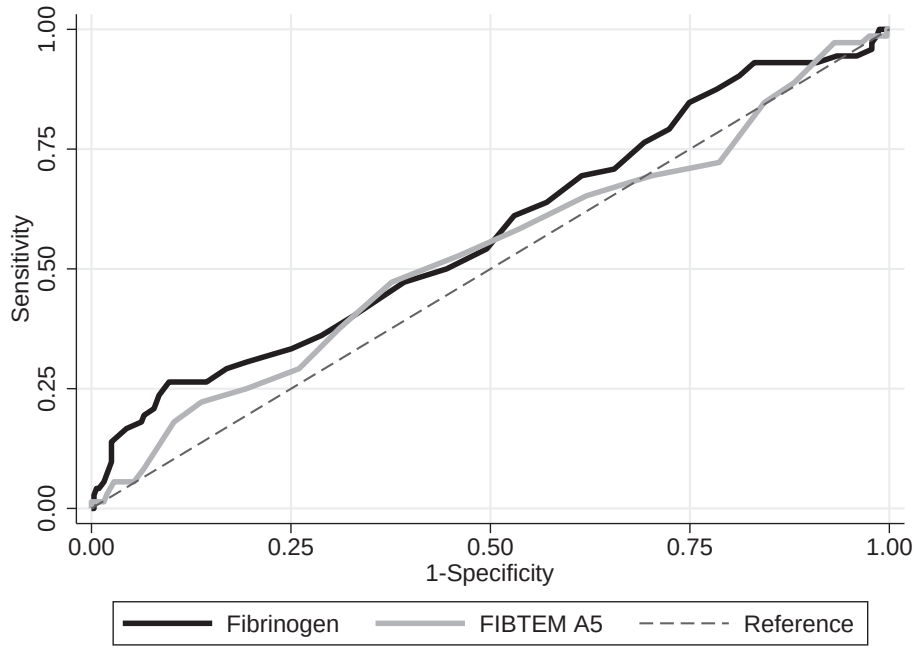

Figure 2. ROC curves for fibrinogen (black) and fibrin-based thromboelastometry amplitude of clot firmness at 5 min (FIBTEM A5) (gray) for progression to severe postpartum hemorrhage when measured between 800 and 1500mL of blood loss following childbirth.

		FIBTEM A5, mm			
3.1-4.0 (N=138)	>4 g/L (N=178)	≤12 (N=80)	13-15 (N=74)	16-22 (N=191)	≥23 (N=46)
1.5 (1.2-1.9)	1.3 (1.1-1.7)	1.6 (1.3-2.0)	1.5 (1.2-1.9)	1.3 (1.1-1.7)	1.5 (1.2-2.0)
23 (17%)	28 (16%)	18 (23%)	16 (22%)	30 (16%)	8 (17%)
21 (15%)	28 (16%)	14 (18%)	14 (19%)	30 (16%)	8 (17%)
3 (2%)	5 (3%)	4 (5%)	1 (1%)	6 (3%)	2 (4%)
3 (2%)	8 (5%)	5 (6%)	5 (7%)	6 (3%)	3 (7%)

DISCUSSION

This multicenter, prospective cohort study found that the point-of-care test FIBTEM A5 correlates only moderately with the Clauss fibrinogen assay and lacks the ability to single out women who develop severe postpartum hemorrhage when routinely measured between 800 and 1500mL. Women with a fibrinogen concentration ≤2g/L had a 50 percent risk to develop severe postpartum hemorrhage, vs 23 percent of women with a FIBTEM A5 value ≤12mm.

Main strength was that we prospectively collected fibrinogen and FIBTEM A5 measurements in a large cohort, within a specific range of blood loss during the onset of hemorrhage. By using postpartum hemorrhage-related core outcome sets, our results may be used in systematic reviews and/or meta-analyses regarding viscoelastometric point-of-care testing.[20, 21] Our median (IQR) FIBTEM A5 value of 17mm (13-20) measured between 800 to 1500mL of blood loss appeared lower than the median (IQR) FIBTEM A5 value of 21mm (18-23) measured in healthy laboring women.[22] This is not surprising given that fibrinogen, for which FIBTEM A5 is a surrogate measure, falls early in the course of postpartum hemorrhage.[6] Generalizability is hampered by challenges in having women provide consent and executing trial procedures in acute situations where women had rapid blood loss, a problem previously encountered.[23, 24] An examination of potential cases showed that women who lost large volumes of blood in short time frames were more frequently not included. Trial procedures were hampered in more serious bleedings leading to 74 women with blood samples solely taken >1500mL and 80 with only one valid FIBTEM A5 or Clauss fibrinogen measurement. This could have resulted in underestimation of fibrinogen concentrations ≤2g/L or FIBTEM A5 values ≤12mm, and fewer women with severe postpartum hemorrhage. However, the proportion of women who had a fibrinogen concentration ≤2g/L (4%) was similar to that in the United Kingdom and Denmark.[16, 23] Given that we collected a limited number of variables, we were unable to present all known risk factors associated with severe postpartum hemorrhage as baseline characteristics. In addition, numbers of women with specific characteristics predisposing to coagulopathy or severe postpartum hemorrhage were small, restricting possible subgroup analyses to determine whether FIBTEM A5 might be more predictive in some, e.g. women with a placental abruption (N=3). Managing clinicians were intended to be blinded for the FIBTEM A5 results. However, it appeared that clinicians from one of the participating hospitals had been able to see FIBTEM A5 results. The finding that of the 19 women

with a FIBTEM A5 value ≤12mm in this hospital, none received fibrinogen concentrate suggests that little was done with this information. No noticeable differences were found between hospitals regarding patient characteristics, FIBTEM A5 values, fibrinogen concentrations, incidence and management of postpartum hemorrhage.

Clinical utility of FIBTEM A5 as a predictor for progression of postpartum hemorrhage has only been described once.[16] Contrary to our results, this study from the United Kingdom found that FIBTEM A5 could be used as a predictive biomarker for progression to transfusion of ≥4 packed cells (AUC 0.78, 95% CI 0.69-0.88), need for invasive intervention (AUC 0.69, 95% CI 0.52-0.86), and total blood loss >2500mL (AUC 0.75, 95% CI 0.66-0.85).[16] However, this study also included samples taken above 1500mL and women were not enrolled when bleeding stopped simultaneously or soon after reaching the entry criteria.[16] The fact that we did include such women may explain the lower proportion of women in our study with ≥4 packed cells (3% versus 9%) or any invasive intervention (5% versus 11%).[16] However, these findings could also indicate differences in management or transfusion policies. Nevertheless, the proportion of women with fibrinogen concentrations ≤2g/L appeared to be the same in the United Kingdom (4%, N=12/341).[16] These combined findings suggest that FIBTEM A5 is not a good predictor for progression of bleeding when routinely taken during the onset of postpartum hemorrhage at a blood loss ≤1500mL.

The low number of women with fibrinogen concentration ≤2g/L reflects the hypercoagulable state of pregnancy.[25-27] Although low fibrinogen concentrations are associated with severity of bleeding[6, 7, 28], the likelihood of a fibrinogen concentration ≤2g/L ≤1500mL is low.[8, 9, 29] Our study population was relatively low risk; only a small proportion of women had a fibrinogen concentration ≤2g/L or FIBTEM A5 value ≤12mm. Hemostatic impairment is more likely to occur in the presence of more severe persistent bleeding or risk factors for coagulopathy. Furthermore, in our study many women stopped bleeding soon after 1000mL. Therefore, the role of a single routine FIBTEM A5 measurement during onset of hemorrhage ≤1500mL appears limited, and may explain the poor predictive value of FIBTEM A5 for progression to severe postpartum hemorrhage. However, multiple consecutive measurements during an ongoing bleeding might still detect a downfall in FIBTEM A5 values indicating fibrinogen deficiency and could identify women who may benefit from targeted fibrinogen replacement therapy. Additionally, FIBTEM A5 might be useful in specific causes of ongoing bleeding more likely to involve coagulopathy, such as trauma-related hemorrhage.

Whether correction of fibrinogen based on FIBTEM A5 improves maternal outcome is still being investigated. The OBS2 trial showed that infusion of fibrinogen concentrate in women with FIBTEM A5 value ≤15mm and a bleeding exceeding 1500mL did not improve outcome.[24] Subgroup analyses showed that FIBTEM A5 values >12mm or fibrinogen concentrations >2g/L are sufficient to maintain hemostasis.[24] Another study from the United Kingdom compared a fixed-ratio transfusion protocol with targeted fibrinogen replacement therapy on the basis of FIBTEM A5 results and obstetric hemorrhage >1500mL.[30] A significant reduction in total use of allogeneic blood products was found when fibrinogen concentrate was infused based on FIBTEM A5 values <7mm, or values <12mm with ongoing bleeding.[30]

This is important considering that guidelines on postpartum bleeding are recommending the use of fixed-ratio protocols. The observational counterpart of the OBS2 found no significant hemostatic impairment when fresh frozen plasma was withheld in FIBTEM A5 values >15mm.[31] Therefore, FIBTEM A5 seems to have potential to avoid unnecessary transfusion of blood products. However, our study found a moderate correlation between FIBTEM A5 values and fibrinogen concentrations. The same moderate correlation (r_s=0.59) was found between both test results in the study from the United Kingdom that evaluated FIBTEM A5 as a predictive biomarker.[16] Only one small observational study found a strong correlation (r_s=0.86) between FIBTEM A5 values and fibrinogen concentrations, but volume of blood loss at time of blood sampling was not described, an important omission considering that an increase in correlation between FIBTEM A5 values and fibrinogen concentrations in higher volumes of blood loss was previously found.[14,15] This raises the question whether FIBTEM A5 is accurate enough in guiding or withholding hemostatic interventions during the whole course of postpartum hemorrhage. This requires further study and calls for the need of more accurate point-of-care tests to quantify plasma fibrinogen concentrations.[32]

Our results show that the clinical utility of FIBTEM in postpartum bleedings below 1500mL is limited and should encourage researchers and clinical caregivers to reserve the use of FIBTEM A5 to more severe bleedings, especially considering the high costs associated with ROTEM® tests. FIBTEM A5 might still be useful in a selected population of women at high risk of coagulopathy or with ongoing bleeding reaching a certain, yet undefined but presumably >1500mL, volume of blood loss. Further research in these situations is needed as to whether FIBTEM A5 is able to detect development of fibrinogen deficiency in order to identify women at risk of progression to severe postpartum hemorrhage and who may

benefit from targeted fibrinogen replacement. As stated by the RCOG and National Institute of Health and Care Excellence, the role of viscoelastometric point-of-care testing during postpartum hemorrhage requires evaluation before FIBTEM A5 may be implemented into guidelines.[17, 33]

CONCLUSION

Our study results suggest that FIBTEM A5 is not a good predictor for progression of bleeding when routinely measured as part of standard clinical care during the onset of postpartum hemorrhage. Nevertheless, FIBTEM A5 might still be a promising point-of-care test with clinical advantages in women with ongoing hemorrhage exceeding 1500mL of blood loss, especially considering the potential to provide rapid results at which blood products can be withheld. However, given the moderate correlation between FIBTEM A5 values and fibrinogen concentrations, and the costs that come with running and interpreting ROTEM® tests, more clinical and cost effectiveness research is needed before FIBTEM A5 may be implemented into guidelines on prevention and management of postpartum hemorrhage.

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SUPPLEMENTALS

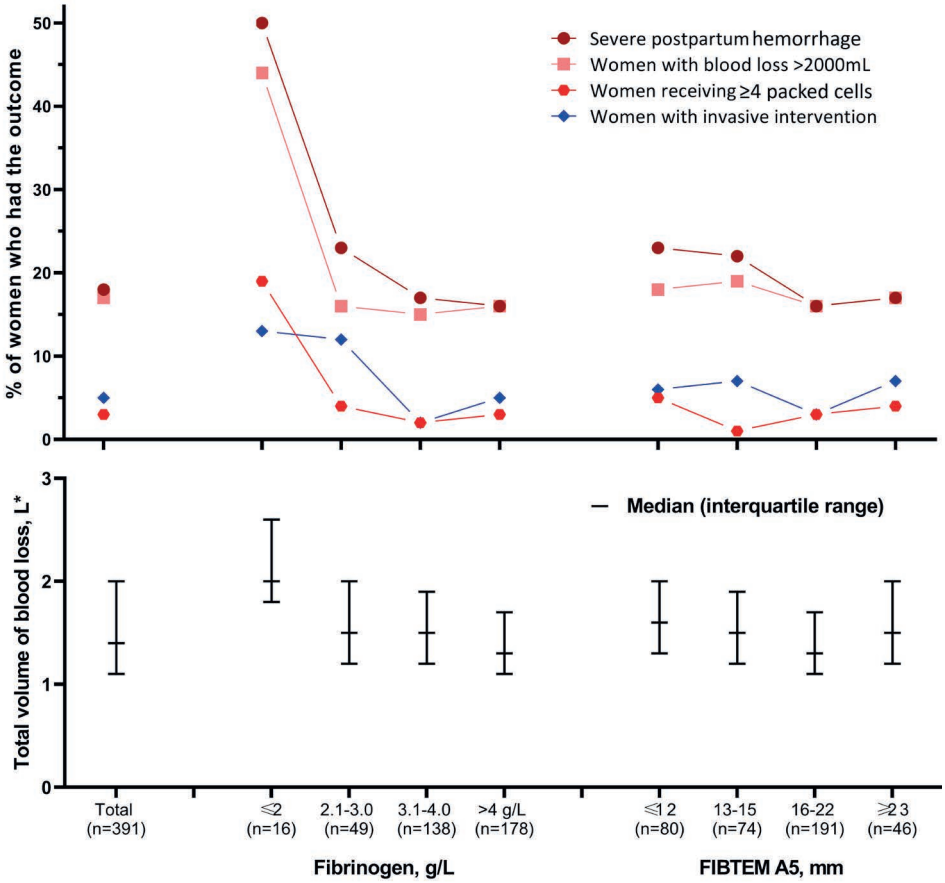

Figure S1. Visual display of the distribution of the outcomes categorized to fibrinogen concentrations and fibrin-based thromboelastometry amplitude of clot firmness at 5 min (FIBTEM A5) values measured between 800 and 1500mL of blood loss following childbirth.

Table S1. Fibrinogen concentrations and FIBTEM A5 values for each cause of hemorrhage separately when measured between 800 and 1500mL of blood loss following childbirth.

Cause of hemorrhage	**N**	**Fibrinogen**, g/L*	**FIBTEM A5**, mm*
Uterine atony	145	4.1 (3.4-4.7)	18 (14-20)
Retained placenta or remnants of placental tissue	148	3.8 (3.3-4.4)	16 (12-21)
Placenta previa	5	4.4 (3.7-5.8)	21 (14-21)
Placental abruption	3	2.5 (1.7-3.7)	13 (8-16)
Abnormally invasive placenta	5	3.5 (3.1-4.0)	15 (13-17)
Laceration of the birth canal	42	4.1 (3.5-4.6)	18 (15-20)
Iatrogenic surgical bleeding	39	4.1 (3.5-4.7)	15 (13-18)
Uterine rupture	4	4.6 (4.1-5.4)	15 (10-23)

*Reported as median with (interquartile ranges).

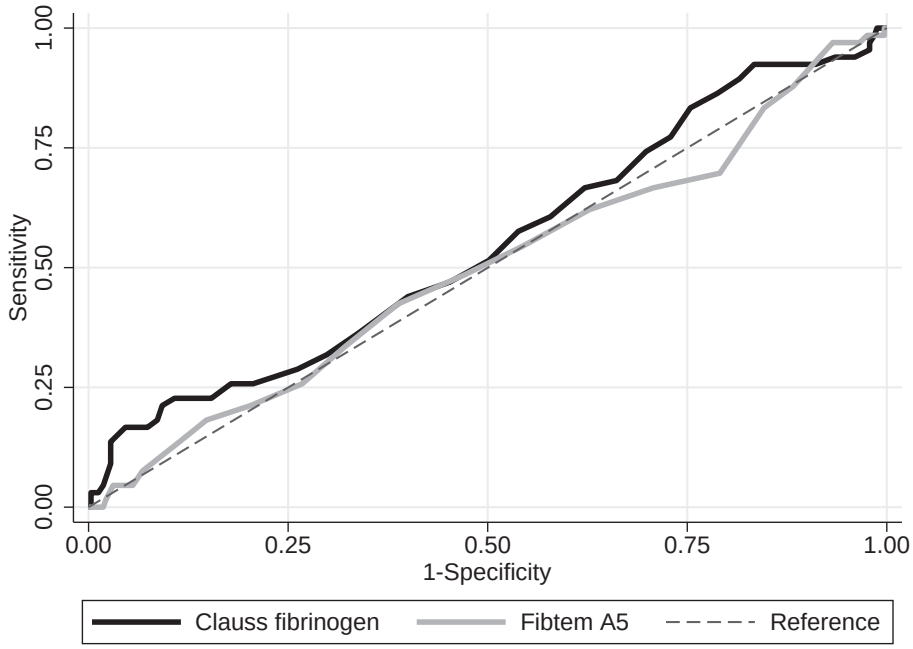

Figure S2. ROC curves for fibrinogen (black) and fibrin-based thromboelastometry amplitude of clot firmness at 5 min (FIBTEM A5) (gray) for progression to a total blood loss >2000mL when measured between 800 and 1500mL of blood loss following childbirth.

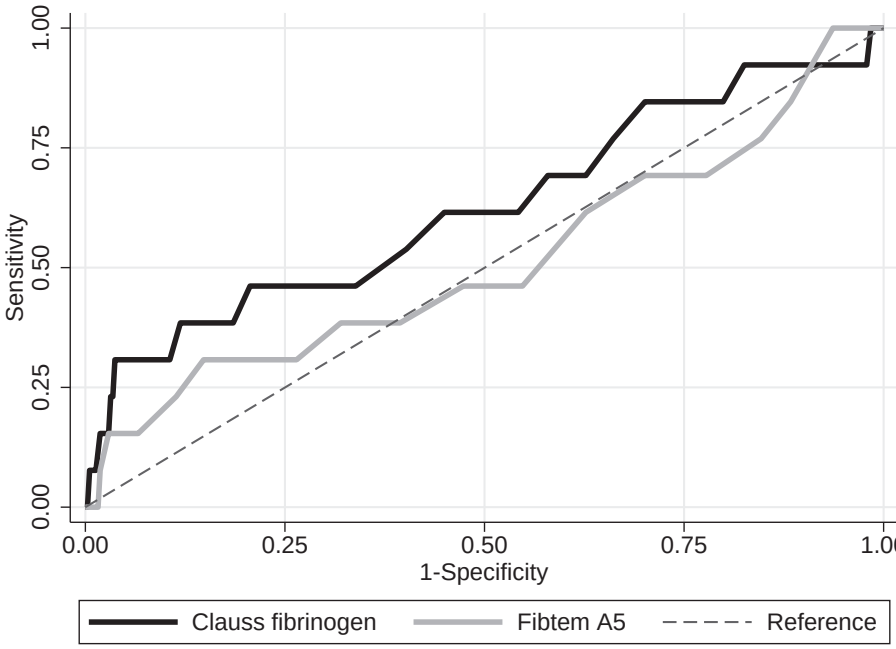

Figure S3. ROC curves for fibrinogen (black) and fibrin-based thromboelastometry amplitude of clot firmness at 5 min (FIBTEM A5) (gray) for the progression to a transfusion of ≥4 packed cells when measured between 800 and 1500mL of blood loss following childbirth.

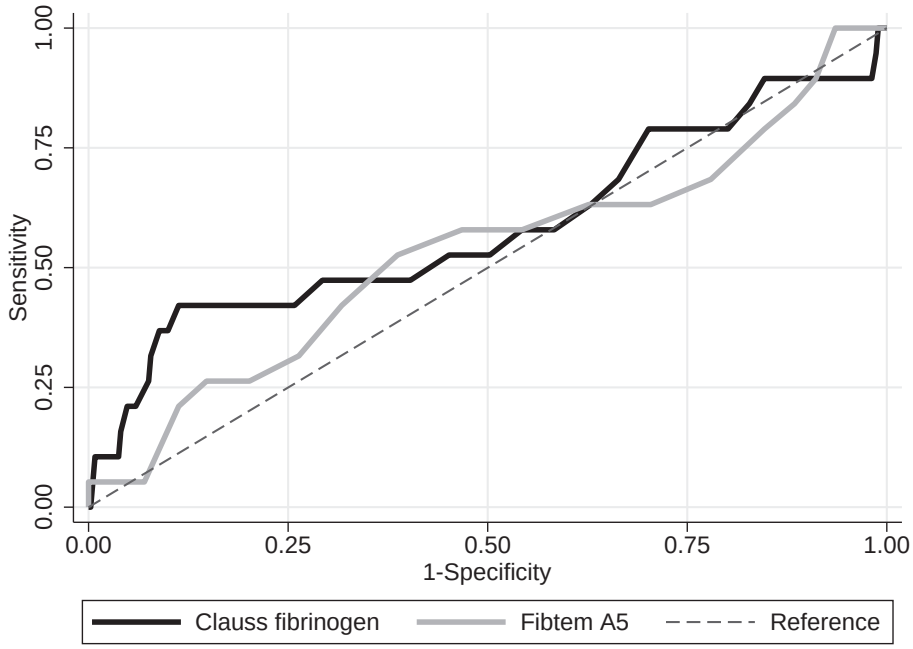

Figure S4. ROC curves for fibrinogen (black) and fibrin-based thromboelastometry amplitude of clot firmness at 5 min (FIBTEM A5) (gray) for progression to any invasive intervention when measured between 800 and 1500mL of blood loss following childbirth.

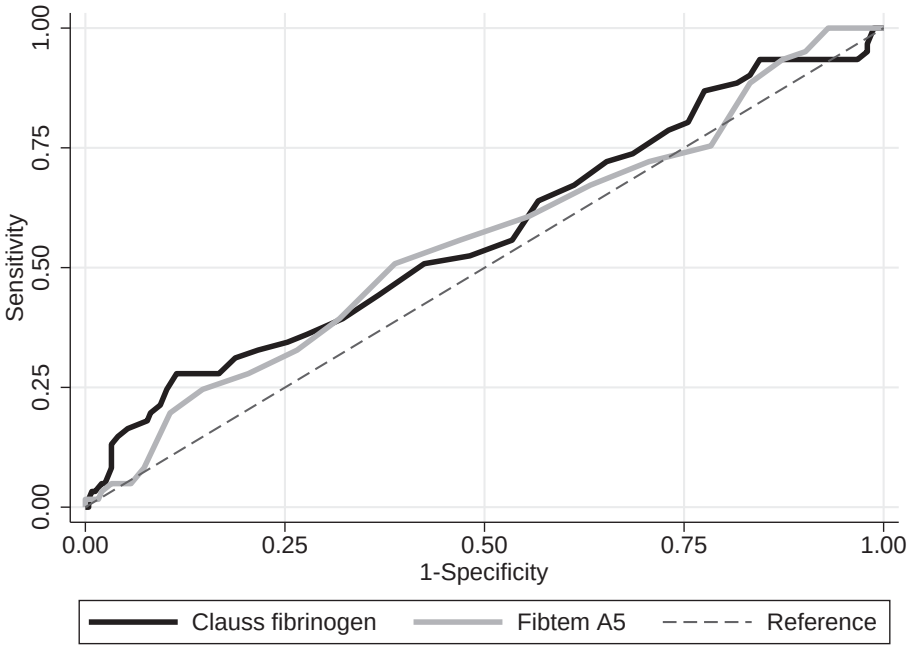

Figure S5. ROC curves for fibrinogen (black) and fibrin-based thromboelastometry amplitude of clot firmness at 5 min (FIBTEM A5) (gray) for progression to severe postpartum hemorrhage when measured between 1000 and 1500mL of blood loss following birth.

CHAPTER 5

COMPARISON OF OUTCOME BETWEEN INTRAUTERINE BALLOON TAMPONADE AND UTERINE ARTERY EMBOLIZATION IN THE MANAGEMENT OF PERSISTENT POSTPARTUM HEMORRHAGE: A PROPENSITY SCORE-MATCHED COHORT STUDY

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ABSTRACT

Introduction

To compare the outcomes of women who were initially managed by intrauterine balloon tamponade or uterine artery embolization because of persistent postpartum hemorrhage demanding an immediate intervention to control bleeding.

Material and methods

Propensity score matched cohort study including women who had intrauterine balloon tamponade or uterine artery embolization as initial management strategy to control persistent postpartum hemorrhage, i.e. refractory to first-line therapy combined with at least one uterotonic agent. The primary outcome measure was a composite of peripartum hysterectomy and/or maternal mortality. Secondary outcomes measures were total volume of blood loss and total number of packed red blood cells transfused.

Results

Our 1:1 propensity score matched cohort comprised of 50 women who had intrauterine balloon tamponade and 50 women who underwent uterine artery embolization at a blood loss between 1000 and 7000mL. There was no statistically significant difference in the hysterectomy risk between both groups (N=6 in each group, OR 1.00, 95% CI; 0.30 to 3.34), nor in total volume of blood loss (median 4500mL [IQR; 3600 to 5400] for balloon versus 4000mL [IQR; 3250 to 5000] for embolization, p=0.382), nor in total units of packed red blood cells transfused (median 7 [IQR; 5 to 10] for balloon versus 6 [IQR; 4 to 9] for embolization, p=0.319). Fifteen women (30%) who were initially managed by an intrauterine balloon still underwent uterine artery embolization, of whom one had an embolization-related thrombo-embolic event. Maternal mortality occurred in neither of the intervention groups.

Conclusions

No difference in the risk of hysterectomy and/or maternal death was observed between women who had intrauterine balloon tamponade and women who underwent uterine artery embolization as an initial management for persistent postpartum hemorrhage. Although this study was underpowered to demonstrate equivalence, our study design provides a rational framework for future research in which intrauterine balloon tamponade may prove to be a suitable intervention of first choice in the management of persistent postpartum hemorrhage.

INTRODUCTION

Postpartum hemorrhage remains the leading cause of maternal mortality around the world.[1] There is an international call for improving maternal safety and the evaluation of obstetric care is crucial to answer this call and reduce maternal deaths, which are often preventable.[2] Peripartum hysterectomy can be performed as a life-saving procedure of last resort, but leads to infertility, accompanied by substantial morbidity and psychosocial sequelae.[3-5] Various invasive and less invasive management strategies were developed to reduce the need for hysterectomy, including intrauterine balloon tamponade, uterine compression sutures, and devascularisation of the uterine artery by surgical ligation or radiological embolization.[6]

Uterine artery embolization may be used to manage persistent postpartum hemorrhage that demands immediate intervention before proceeding to hysterectomy, but it is considered as a relatively costly and invasive procedure that is prone to a number of complications (e.g. post-embolization syndrome, thrombo-embolic events, or uterine necrosis).[7-10] On the other hand, intrauterine balloon tamponade has emerged as an inexpensive and less invasive option to control ongoing bleeding.[11-13] Insertion of an intrauterine balloon for the purpose of tamponade during postpartum hemorrhage could potentially obviate the need for uterine artery embolization, and reduce health care costs. However, these interventions have never been compared in terms of their effectiveness of preventing severe maternal outcome (i.e. maternal death or a near miss averted by a peripartum hysterectomy), and thus uncertainty persists as to whether intrauterine balloon tamponade is an effective alternative to uterine artery embolization when both interventions are considered as possible options during the course of postpartum hemorrhage.

Aim of this study was to compare severe maternal outcome in women who received intrauterine balloon tamponade with women who had uterine artery embolization as initial management for persistent postpartum hemorrhage in whom immediate intervention was deemed necessary.

MATERIALS AND METHODS

Given the fact that intrauterine tamponade with a balloon-like device is less invasive and much easier to perform than uterine artery embolization, it is possible that intrauterine balloon tamponade is more often used in women with less severe bleeding. Women receiving intrauterine balloon tamponade may also differ in various ways from women undergoing uterine artery embolization. For these reasons, we used propensity score matching to correct for any confounding by indication. Using this technique, we constructed a cohort of women who differed with respect to the management strategy applied, but were similar with respect to all other clinically relevant characteristics that could have influenced the clinician's decision to apply either one of the interventions during persistent postpartum hemorrhage.[14]

Data source

This study used data from the *Transfusion strategies in women during Major Obstetric Haemorrhage* study (TeMpOH-1). The TeMpOH-1 study was a nationwide retrospective cohort study in 61 hospitals in the Netherlands (71% of all hospitals in the country) in which data from medical files of pregnant women of at least 18 years old were included. These women had received at least four units of packed red blood cells or any transfusion of fresh frozen plasma and/or platelets in addition to packed red blood cells because of obstetric hemorrhage (≥1000mL blood loss during pregnancy or the first 24 hours following birth) between January 1st, 2011 and January 1st, 2013. Eligible women were identified by cross-referencing data from hospitals' blood transfusion services with the local birth registers in participating hospitals. Trained medical students and research nurses obtained available data from medical records present in maternity units, operating theatres, and intensive care units.

Cohort selection

From the TeMpOH-1 database, we identified all women who were initially managed by intrauterine balloon tamponade or uterine artery embolization during persistent postpartum hemorrhage. Persistent postpartum hemorrhage was defined as ongoing hemorrhage within the first 24 hours following birth, refractory to first-line therapy (previously defined per primary cause of hemorrhage, Table S1)[15] combined with the administration of at least one uterotonic agent (including oxytocin [prophylactic use of oxytocin following childbirth excluded], ergometrine, misoprostol, or sulprostone). By using this definition of persistent postpartum hemorrhage, we avoided a definition solely based on mere estimation of blood loss and ensured that women included in

this study received minimally necessary care per cause of hemorrhage prior to use of intrauterine balloon tamponade or uterine artery embolization. However, since no uterine artery embolizations were performed below 1000mL of blood loss and no intrauterine balloons were inserted above 7000mL of blood loss (Figure S1), we restricted our analyses to women who had intrauterine balloon tamponade or uterine artery embolization between these limits of blood loss. Furthermore, although the Bakri® balloon (Cook Medical, Bloomington, USA) is the type of intrauterine balloon device mostly used in the Netherlands, the TeMpoH-1 study did not specifically register which type of device was inserted. Therefore, this study defined intrauterine balloon tamponade as insertion of any type of balloon catheter into the uterine cavity for the purpose of tamponade. Women were classified depending on the intervention (i.e. balloon or embolization) that was first applied and they were considered to remain in that intervention group until the end of hemorrhage or occurrence of the primary outcome.

Outcome measures

The World Health Organisation developed the Maternal Near Miss (MNM) tool to enable uniform identification of those women who nearly died but survived a complication during pregnancy, childbirth, or within 42 days of termination of pregnancy.[16] In this approach, women who underwent hysterectomy due to hemorrhage are considered as MNM. The reason to perform uterine balloon tamponade or uterine artery embolization is to control intractable bleeding, and avert severe maternal outcome (i.e. maternal death or MNM). Hence, we used a composite of maternal death or MNM averted by hysterectomy as the *primary outcome measure*. If this primary outcome did not occur, end of bleeding was defined as the time of the last estimated blood loss measurement. *Secondary outcome measures* were total estimated volume of blood loss and total number of packed red blood cells transfused.

Statistical analyses

The propensity score, representing the probability of receiving intrauterine balloon tamponade during the course of persistent postpartum hemorrhage, was estimated by a logistic regression model with intrauterine balloon tamponade inserted between an estimated blood loss of 1000 to 7000mL as the dependent variable. Characteristics considered as potential confounders for the association between use of intrauterine balloon tamponade or use of uterine artery embolization, or characteristics considered to be risk factors for the occurrence of the primary outcome measure alone, were included as covariates in the propensity score model.[17]

Characteristics included as covariates that were available at the moment the clinician decided to use an intrauterine balloon tamponade or to perform uterine artery embolization were: maternal age, gestational age, parity (nulliparity or multiparity), preeclampsia, multiple pregnancy, prior cesarean birth, mode of birth (vaginal birth or cesarean section), cause of hemorrhage (categorized as uterine atony, retained placenta, abnormally invasive placenta, and other causes [composite of placenta previa, placental abruption, and uterine rupture due to small numbers]), presence of coagulopathy (defined as a fibrinogen level ≤2 g/L during bleeding), symptoms of shock (defined as at least one measurement of a systolic blood pressure ≤90mmHg and/or heart rate ≥120 beats per minute during bleeding), volume of blood loss at time of intervention (measured by weighing gauzes or other soaked material and use of suction in the operating theatre), hemostatic interventions used at the time of intrauterine balloon tamponade or uterine artery embolization (the number of uterotonic agents given [including oxytocin, ergometrine, misoprostol, and sulprostone], the administration of non-uterotonic agents [tranexamic acid, fibrinogen concentrate, and recombinant factor VIIa], and number of packed red blood cells, fresh frozen plasma, and platelets transfused), and other surgical interventions that had already been applied at the time of intrauterine balloon insertion or uterine artery embolization (composite of B-Lynch suture and uterine artery ligation). These clinically relevant characteristics were a priori selected based on literature[4, 5, 7, 12, 13, 18-23] and clinical reasoning. Missing variables were imputed using median and logically derived imputation (see Appendix 1 for the rationale behind the imputation method applied per missing variable).

To balance all characteristics over the course of persistent postpartum hemorrhage, estimated blood loss was stratified into increments of 500mL and women were matched within the same increment of blood loss in which they had the intervention. Thus, women who had intrauterine balloon tamponade during persistent postpartum hemorrhage were matched to women with *the same chance* (i.e. same propensity score) of receiving intrauterine balloon tamponade, but who underwent uterine artery embolization instead within the same increment of blood loss at the time of intervention. By matching in the same increments of blood loss, we ensured that women who had intrauterine balloon tamponade were matched to women who had uterine artery embolization at approximately the same amount of blood loss. Matching was performed by a 1:1 sequential greedy algorithm without replacement using a calliper of 0.2 times the standard deviation of the logit of the propensity score.[24] Balance in distribution of clinically relevant characteristics between both groups was assessed by standardized differences,

where distributions of characteristics were considered comparable when the standardized difference was less than 10% after propensity score matching.[25, 26] Interaction terms were included in the propensity score model if they improved balance between the comparison groups after propensity score matching.[27]

The primary outcome was compared between women who were managed by intrauterine balloon tamponade and women who underwent uterine artery embolization using a logistic regression model, resulting in estimated odds ratios (OR) with 95% confidence intervals (CI).[28] Differences in secondary outcome measures were estimated by Mann-Whitney U testing before propensity score matching, and by the Wilcoxon signed-rank test after propensity score matching, where a two-tailed p-value less than 0.05 was considered statistically significant.[29] To evaluate the robustness of our study findings with regard to propensity score matching, a sensitivity analysis was performed of the primary outcome measure by including the propensity score as a covariate in the logistic regression model to compare the primary outcome measure between both intervention groups, under the assumption that the propensity score has a linear functional relation with the log odds of the primary outcome.[30]

All continuous variables were summarised as medians with interquartile ranges (IQR), and categorical variables were presented as frequencies with percentages (%). All statistical analyses were performed using the Stata Statistical Software: Release 14 (College Station, TX: StataCorp LP, USA). The statistical analysis plan was approved by the Scientific Committee of the Sanquin Center for Clinical Transfusion Research before execution of the analyses.

Ethical approval

The TeMpOH-1 study was approved by the Ethical Committee of the Leiden University Medical Centre (P12.273, 2013) and by the institutional review boards of all participating hospitals. The TeMpOH-1 study was registered in the Netherlands Trial Register (Trial NL3909, 2013) and need to obtain informed consent was waived by the ethics committee.

RESULTS

Of the 270 101 women who gave birth in the Netherlands during the two-year inclusion period, 1391 women endured postpartum hemorrhage and fulfilled the inclusion criteria of the TeMpOH-1 study, of whom 1260 had ongoing hemorrhage despite first-line therapy combined with at least one uterotonic agent. We identified a total of 373 women who were initially managed by intrauterine balloon tamponade and 82 women who initially had uterine artery embolization at an estimated blood loss between 1000-7000mL to control bleeding. Eleven balloons were inserted below 1000mL of blood loss and five women underwent uterine artery embolization at a blood loss >7000mL. Out of the 373 women who initially had intrauterine balloon tamponade, 50 were propensity score matched to 50 of 82 women who initially underwent embolization during persistent postpartum hemorrhage (Figure 1).

Comparison of characteristics

Clinically relevant characteristics of women who were managed by intrauterine balloon tamponade and uterine artery embolization before and after propensity score matching are presented in Table 1. Before propensity score matching, multiple characteristics differed significantly between intervention groups, as indicated by a standardized difference above 10%. Women who were initially managed by intrauterine balloon tamponade were more likely to have a vaginal birth (80% vs 60% of women in the embolization group), and had less blood loss at the time of balloon insertion (median 2500mL [IQR; 2000 to 3000]) compared with women who initially had uterine artery embolization (median 3500mL [IQR; 3000 to 4500]). Furthermore, women who initially underwent uterine artery embolization were more likely to have coagulopathy (43% vs 11% of women in the balloon group), were more often treated with non-uterotonic agents, and received more blood components than women who were managed by intrauterine balloon tamponade. Uterine atony was the leading cause in both intervention groups. Characteristics were well balanced in the propensity score matched cohort, with standardized differences for all characteristics less than 10% (Table 1).

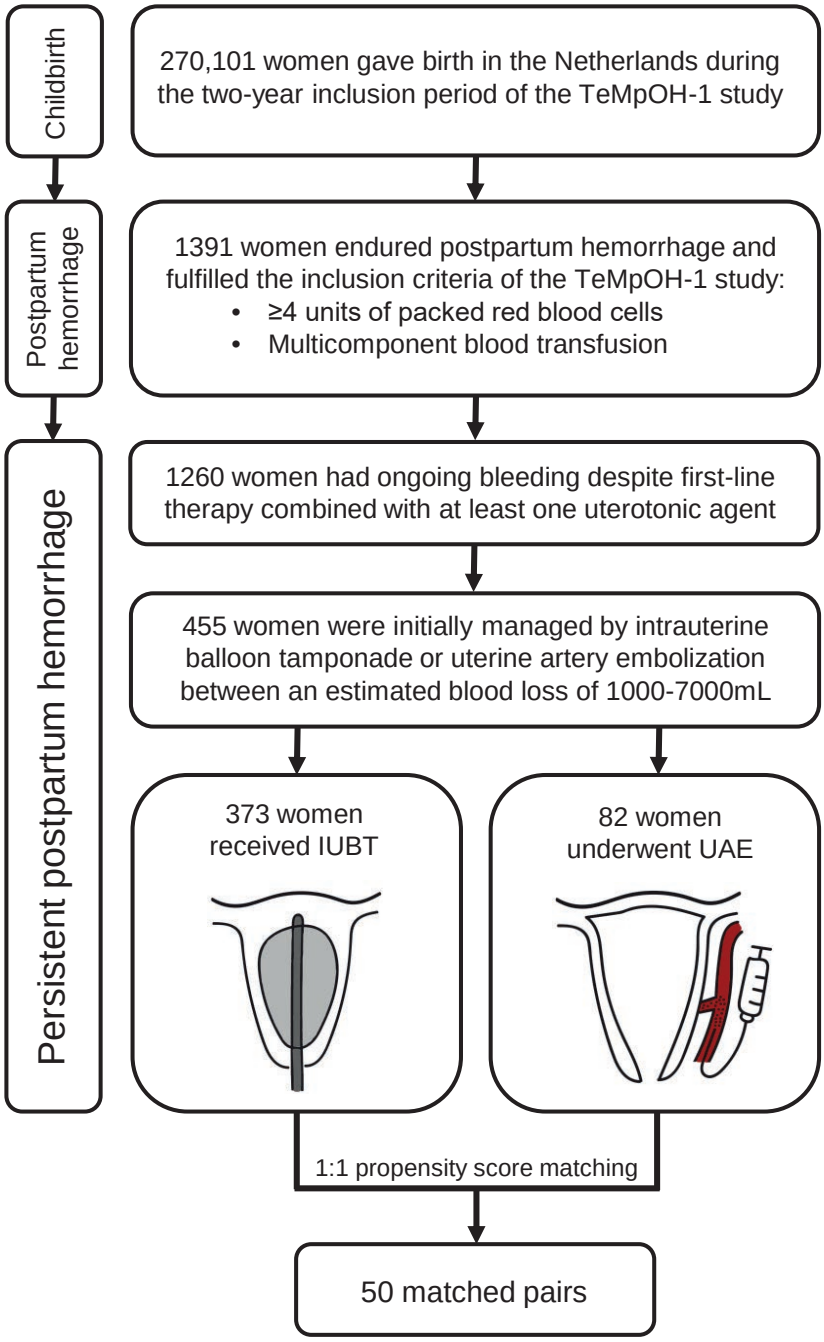

Figure 1. Flowchart of study enrolment and propensity score matching.
IUBT: Intrauterine balloon tamponade, UAE: Uterine Artery Embolization.

Table 1. Clinically relevant characteristics for women who had intrauterine balloon tamponade or who underwent uterine artery embolization between an estimated blood loss of 1000-7000mL because of persistent postpartum hemorrhage before and after propensity score matching.

	Before PS matching	
	IUBT N=373	UAE N=82
Maternal age, years*	31 (28-35)	32 (29-36)
Gestational age, weeks*	39 (38-40)	38 (37-40)
Multiparity, n (%)	170 (46)	43 (52)
Preeclampsia, n (%)	36 (10)	10 (12)
Multiple pregnancy, n (%)	23 (6)	6 (7)
Prior cesarean birth, n (%)	44 (12)	16 (20)
Mode of birth, n (%)	-	-
Vaginal delivery	300 (80)	49 (60)
Cesarean section	73 (20)	33 (40)
Cause of hemorrhage, n (%)	-	-
Uterine atony	293 (79)	53 (64)
Retained placenta	45 (12)	7 (9)
Abnormally invasive placenta	24 (6)	7 (9)
Other causes	11 (3)	15 (18)
Placental abruption	*2*	*1*
Placenta previa	*2*	*3*
Uterine rupture	*7*	*11*
Estimated blood loss at the time of the intervention, mL*	2500 (2000-3000)	3500 (3000-4500)
Coagulopathy, n (%)	42 (11)	35 (43)
Symptoms of shock, n (%)	304 (82)	68 (83)
Number of uterotonics given*	2 (2-3)	2 (1-3)
Non-uterotonic agents, n (%)	-	-
Tranexamic acid	132 (35)	42 (51)
Fibrinogen concentrate	6 (2)	13 (16)
Recombinant factor VIIa	3 (1)	3 (4)
Blood components*	-	-
Packed red blood cells	1 (0-2)	4 (3-7)
Fresh frozen plasma	0 (0-1)	2 (1-4)
Platelets transfusion	0 (0-0)	0 (0-1)
Surgical interventions, n (%)	3 (1)	2 (2)
B-Lynch suture	*3*	*2*
Uterine artery ligation	*0*	*1*

PS: Propensity Score, IUBT: Intrauterine Balloon Tamponade, UAE: Uterine artery embolization, SMD: Standardized Mean Difference, Ref: Reference.
*Reported as median with (interquartile ranges).

	After PS matching		
SMD (%)	IUBT N=50	UAE N=50	SMD (%)
15.6	32 (29-37)	31 (29-36)	5.7
28.9	39 (37-40)	38 (37-40)	6.9
16.8	28 (56)	27 (54)	4.0
7.5	6 (12)	6 (12)	0.0
7.1	4 (8)	4 (8)	0.0
22.4	9 (18)	10 (20)	5.0
54.0	-	-	0.0
-	28 (56)	28 (56)	-
-	22 (44)	22 (44)	-
-	-	-	-
Ref	32 (64)	33 (66)	Ref
6.6	5 (10)	5 (10)	0.0
19.2	6 (12)	6 (12)	0.0
34.7	7 (14)	6 (12)	5.9
-	*2*	*0*	-
-	*2*	*1*	-
-	*3*	*5*	-
62.5	3250 (2500-4000)	3250 (2500-4000)	0.0
60.4	18 (36)	18 (36)	0.0
1.3	40 (80)	41 (82)	5.0
28.0	2 (1-2)	2 (1-3)	5.2
-	-	-	-
13.5	23 (46)	21 (42)	8.0
30.0	4 (8)	4 (8)	0.0
10.1	1 (2)	1 (2)	0.0
-	-	-	-
88.7	4 (2-6)	4 (2-5)	9.2
80.1	2 (0-2)	2 (0-2)	5.5
48.7	0 (0-0)	0 (0-0)	6.3
20.8	2 (4)	2 (4)	0.0
-	*2*	*2*	-
-	*0*	*1*	-

Table 2. Outcomes for women with persistent postpartum hemorrhage who initially received intrauterine balloon tamponade versus women who initially underwent uterine artery embolization between an estimated blood loss of 1000-7000mL after birth.

	Unadjusted analysis	
	IUBT (N=373)	UAE (N=82)
Composite primary outcome, n (%)	21 (5.5)	10 (12)
Peripartum hysterectomy	19 (5.0)	10 (12)
Maternal mortality	2 (0.5)	0 (0)
Secondary outcome measures*	-	-
Total number of packed cells, units	4 (3–7)	7 (5–11)
Total volume of blood loss, mL	3500 (3000–4500)	4500 (3350–6000)

IUBT: Intrauterine Balloon Tamponade, UAE: Uterine Artery Embolization, OR: Odds Ratio, MWU: Mann-Whitney U, WSR: Wilcoxon signed-rank.
*Reported as median with (interquartile ranges).

Comparison of outcomes

Among the 373 women who initially had intrauterine balloon tamponade, 262 women (70%) required no additional intervention and bleeding was adequately treated. After intrauterine balloon insertion, 12 women (3%) had a B-Lynch suture, four women (1%) had uterine artery ligation, and 81 women (22%) still had to undergo uterine artery embolization, of whom seven eventually underwent hysterectomy. The total number of women who had a peripartum hysterectomy after intrauterine balloon tamponade was 19 (5%) and two women (0.5%) died because of exsanguination before additional interventions could be performed. Of the 82 women who initially underwent uterine artery embolization, 14 women (17%) endured ongoing hemorrhage, of whom three (4%) had a B-Lynch suture, one (1%) had uterine artery ligation, and ten (12%) required peripartum hysterectomy. None of the women who primarily had uterine artery embolization died. In the unadjusted analysis, the risk of the composite primary outcome (peripartum hysterectomy and or maternal mortality) was higher for women who underwent uterine artery embolization compared to women who received intrauterine balloon tamponade (12% vs 5.5% [OR 2.33, 95% CI; 1.05 to 5.15]). In addition, total volume of blood loss (median 4500mL [IQR; 3350 to 6000] vs 3500mL [IQR; 3000 to 4500] respectively, p<.001) and total number of packed red blood cells transfused (median 7 units [IQR; 5 to 11] vs 4 units [IQR; 3 to 7] respectively, p<.001) were higher for women who underwent uterine artery embolization compared to women who had an intrauterine balloon as initial management during persistent postpartum hemorrhage (Table 2). Of all women who had uterine

	Propensity score matched adjusted analysis		
OR (95% CI)	IUBT (N=50)	UAE (N=50)	OR (95% CI)
2.33 (1.05–5.15)	6 (12)	6 (12)	1.00 (0.30–3.34)
-	6 (12)	6 (12)	-
-	0 (0)	0 (0)	-
MWU p-value	-	-	WSR p-value
<.001	7 (5–10)	6 (4–9)	0.319
<.001	4500 (3600-5400)	4000 (3250-5000)	0.382

artery embolization (82 as initial management and 81 after intrauterine balloon tamponade), three (1.8%) suffered an embolization-related thrombo-embolic event, of whom one had received intrauterine balloon tamponade before embolization was performed.

In the propensity score matched cohort, 29 of the 50 women (58%) who were initially managed by an intrauterine balloon required no additional intervention to control bleeding. Two women (4%) had a B-Lynch suture after intrauterine balloon insertion and 15 (30%) underwent uterine artery embolization after intrauterine balloon tamponade, of whom two required hysterectomy. The total number of women who underwent hysterectomy to arrest hemorrhage was 6 (12%) for both women who initially had intrauterine balloon tamponade and women who initially had uterine artery embolization. Maternal deaths occurred in neither of the intervention groups. In the propensity score matched adjusted analyses, there was no significant difference in the risk of the composite primary outcome between the intervention groups (12% in each group [OR 1.00, 95% CI; 0.30 to 3.34]). Neither did total volume of blood loss (median 4500mL [IQR; 3600 to 5400] vs 4000mL [IQR; 3250 to 5000] respectively, p=0.382) or total number of packed red blood cells transfused (median 7 units [IQR; 5 to 10] vs 6 units [IQR; 4 to 9] respectively, p=0.319) differ significantly between both women who had intrauterine balloon tamponade and women who underwent uterine artery embolization (Table 2). One woman in the propensity score matched cohort had a thrombo-embolic event related to the uterine artery embolization performed after initial management with intrauterine balloon tamponade failed.

Sensitivity analysis

The sensitivity analysis yielded results similar to our primary analysis. When the propensity score was used as the only covariate in the logistic regression model to compare the primary outcome measure between all women who had intrauterine balloon tamponade (N=373) and all women who underwent uterine artery embolization (N=82) as the initial management for persistent postpartum hemorrhage between an estimated blood loss of 1000 to 7000mL, the risk of the composite primary outcome was slightly, but still not statistically significant, lower among women who were managed by intrauterine balloon tamponade compared to women who underwent uterine artery embolization (OR 0.77, 95% CI; 0.27 to 2.21).

DISCUSSION

This propensity score matched cohort study found no significant difference in the risk of the composite outcome of hysterectomy and/or maternal death between women with persistent postpartum hemorrhage and who were initially managed by intrauterine balloon tamponade or uterine artery embolization between a blood loss of 1000 and 7000mL. Neither did we find significant differences in total volume of blood loss and total number of packed red blood cells transfused. Thirty-four percent (17/50) of the women who were initially managed by an intrauterine balloon tamponade had an additional intervention, of whom 15 had uterine artery embolization. One woman suffered an embolization-related thrombo-embolic event.

To the best of our knowledge, this is the first study comparing the effect of intrauterine balloon tamponade with another invasive management strategy to control bleeding and avert peripartum hysterectomy and maternal death during persistent postpartum hemorrhage. By using propensity score matching, we ensured a similar distribution of potential confounding variables between the two intervention groups. The definition of persistent postpartum hemorrhage enabled us to overcome differences between caregivers regarding estimation of blood loss and establish a clear point in time at which an additional intervention (i.e. intrauterine balloon tamponade or uterine artery embolization) was deemed necessary following failure of initial management. Another key strength is that the composite primary outcome consisted of two postpartum hemorrhage-related core outcome sets (peripartum hysterectomy and maternal death), allowing our results to be potentially included in systematic reviews or meta-analyses on persistent postpartum hemorrhage.[31] Furthermore, the extensive TeMpOH-1 database made it possible to include many characteristics as potential confounders in the propensity score model. Nonetheless, even though this is the first study that compares the effectiveness of intrauterine balloon tamponade to another invasive management strategy, our propensity score matched sample size was limited to 50 pairs. This resulted in confidence intervals too broad to rule out type II error for the composite primary outcome measure between both intervention groups. Limited statistical power also restricted possible comparative analyses of subgroups to determine which characteristics may modify the effect of intrauterine balloon tamponade. However, consistency between the results of our primary analysis and the sensitivity analysis strengthens the credibility of our findings. Nevertheless, our results should be interpreted with caution considering several other limitations in relation to the observational design. We

were unable to collect data regarding type of intrauterine balloon device inserted, volume of fluid used to inflate the intrauterine balloon, and the reason of failure of intrauterine balloon tamponade or uterine artery embolization. Additionally, although we are confident to have included all clinically relevant characteristics associated with the clinical decision to use intrauterine balloon tamponade or uterine artery embolization, residual confounding cannot be ruled out. Finally, women were included when in need of four or more units of packed red blood cells or a multicomponent blood transfusion, and who had an estimated blood loss of 1000 to 7000mL at the time of intervention. Our results can therefore not be generalized to all women who satisfy the criteria for persistent postpartum hemorrhage, but are still applicable to the large majority in settings where both interventions and packed cells are available.

Intrauterine balloon tamponade has been incorporated as a management option into multiple national guidelines for postpartum hemorrhage.[32-35] In non-comparative studies, success rates of intrauterine balloon tamponade to control bleeding after birth varied between 67% to 91%.[6, 12, 13, 36] However, evidence for the benefits of intrauterine balloon tamponade compared to other invasive management strategies is lacking, resulting in uncertainty whether intrauterine balloon tamponade is effective during the course of persistent hemorrhage.[37]

Our reported success rate of 70% among all women who were initially managed by an intrauterine balloon tamponade between an estimated blood loss of 1000 to 7000mL is in accordance with prior literature. However, success rate of women who had intrauterine balloon tamponade and required no additional intervention to control hemorrhage was 58% in the propensity score matched cohort. The explanation for this apparent lower success rate could be due to the difference in severity of bleeding. Volume of blood loss at time of intrauterine balloon insertion was lower for the total cohort of women who had intrauterine balloon tamponade (median 2500mL [IQR; 2000 to 3000]) compared to women in the propensity score matched cohort (median 3250mL [IQR; 2500 to 4000]). This is due to the fact that we matched women who had intrauterine balloon tamponade with women who had uterine artery embolization within the same increment of blood loss at the time of the intervention. Consequently, there were proportionally more women with intrauterine balloon tamponade in the propensity score matched cohort who had more severe bleeding than in the total cohort of women who were initially managed by intrauterine balloon tamponade. Nevertheless, early timing of intrauterine balloon tamponade during the course of postpartum hemorrhage has been associated with improved maternal outcome, whereas early timing

of uterine artery embolization seems to be unrelated to maternal outcome.[19, 38] However, in these studies, early timing of intrauterine balloon tamponade in absence of a control group could also have led to an overestimation of the effectiveness due to the possibility that the use of intrauterine balloon tamponade was not absolutely necessary.

Nevertheless, although 34% of women who initially received intrauterine balloon tamponade had an additional intervention, there was no significant difference in the risk of peripartum hysterectomy and or maternal death compared to women who initially underwent uterine artery embolization. Therefore, our results indicate that initial management by intrauterine balloon tamponade during persistent postpartum hemorrhage has the potential to control bleeding and obviate the need for uterine artery embolization in most women, without an increased risk of severe maternal outcome. By using intrauterine balloon tamponade as intervention of first choice during persistent hemorrhage, a majority of women can be spared a more invasive and expensive intervention, i.e. embolization. Two studies corroborate our study findings, reporting a significant drop in the number of invasive procedures following introduction of intrauterine balloon tamponade into their guidelines on the management of postpartum hemorrhage after an initial treatment with uterotonic agents failed.[39, 40]

However, since our propensity score matched sample size was small, we can only make cautious statements regarding the effect of both management options on the risk of hysterectomy and or maternal mortality. Furthermore, it is specifically important to note that if uterine artery embolization was not available, it is possible that a larger proportion of women who were initially managed by intrauterine balloon tamponade had hysterectomy or died. In addition, although intrauterine balloon tamponade seems to be a readily available intervention of first choice in the management of persistent postpartum hemorrhage, it should not delay or be considered as replacement for embolization or hysterectomy if that procedure is deemed necessary to control bleeding. On the other hand, balloon tamponade could also be used as temporizing measure while awaiting embolization or surgery.[41]

The World Health Organisation acknowledges the need for further research into the efficacy of intrauterine balloon tamponade in the management of postpartum hemorrhage.[42] Considering that uterine artery embolization is not widely available, comparative research of intrauterine balloon tamponade to other management strategies is warranted, particularly in low-resource settings where

intrauterine balloon tamponade could be used as cost-saving option to control ongoing bleeding. One randomized trial evaluated the effectiveness of intrauterine balloon tamponade as an adjunct to misoprostol, but was underpowered to demonstrate a significant treatment effect.[43] This inability to resolve the research question whether intrauterine balloon tamponade is as good as or superior to other management strategies due to small sample sizes, highlights the need for larger studies comparing intrauterine balloon tamponade to other management strategies for a good substantiated implementation of intrauterine balloon tamponade into the guidelines for management of postpartum hemorrhage. International research collaboration may be the key to overcome the problem of low statistical power and determine whether and when intrauterine balloon tamponade should be used during the course of postpartum hemorrhage. Our study design provides a useful framework and could serve as a starting point for future comparative effectiveness research of intrauterine balloon tamponade to control intractable postpartum hemorrhage in clinical as well as observational studies.

CONCLUSION

The risk of the composite outcome of peripartum hysterectomy and/or maternal death, total volume of blood loss, and total number of packed red blood cells transfused did not significantly differ between women who had intrauterine balloon tamponade and women who had uterine artery embolization as initial management for persistent postpartum hemorrhage. Intrauterine balloon tamponade seems to be a readily available intervention of first choice in the management of persistent postpartum hemorrhage that could obviate the need for uterine artery embolization in most women. However, limited sample size made it difficult to demonstrate equivalence between both interventions and our results emphasize the need for larger studies comparing intrauterine balloon tamponade to other management options for a substantiated implementation of balloon tamponade into clinical guidelines for management of postpartum hemorrhage.

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SUPPLEMENTALS

Table S1. First-line therapy as defined per primary cause of hemorrhage[15]

Primary cause of hemorrhage	*Corresponding first-line therapy*
Uterine atony	Administration of uterotonic agents with or without inspection of the uterine cavity
Retained placenta(l) (remnant)	Manual removal of the placenta(l) (remnant)
Placenta previa with/without accreta	Cesarean section
Placental abruption	Cesarean section*
Traumatic cause	Surgical repair
Surgical cause	Surgical repair

*In case of stillbirth no cesarean section was performed, a vaginal birth was then pursued.

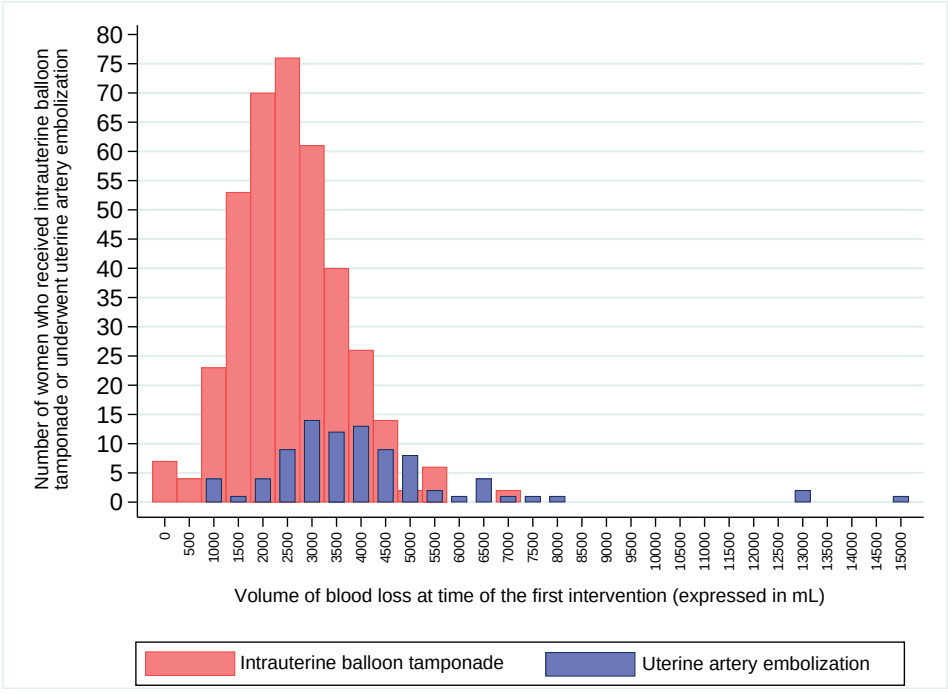

Figure S1. Number of women with persistent postpartum hemorrhage and who were initially managed by intrauterine balloon tamponade or uterine artery embolization according to volume of blood loss at the time of intervention (stratified into increments of 500mL).

APPENDIX 1

Out of the 373 women who were initially managed by intrauterine balloon tamponade at an estimated blood loss between 1000 to 7000mL, 11 women (3%) had only one of the following variables missing: prior cesarean birth (N=3), gestational age (N=3), mode of birth (N=2), multiple pregnancy (N=2), and parity (N=1). Only prior cesarean birth was missing for one of 82 women (1%) who initially underwent uterine artery embolization. Missing data for gestational age were imputed using median imputation and all other missing variables were logically derived from information in the TeMpOH-1 database.

Median imputation:
Gestational age (N=3): In the absence of a clear deterministic approach to estimate pregnancy duration based on other available characteristics and because of the small number of missing, we replaced missing values with the median gestational age of all women who had intrauterine balloon tamponade between 1000 to 7000mL of blood loss. The median of 39 weeks (interquartile range: 38 to 40 weeks) was chosen due to the non-normal distribution of gestational age.

Logically derived imputation:
Prior cesarean birth (N=4): It was assumed that none of the women had a prior cesarean birth. Two women were primigravida, and the other two women had a planned home birth, but were transferred to the hospital during labour. Considering that women in the Netherlands will give birth under guidance of an obstetrician during the consecutive pregnancies when they have a cesarean section in the past, it was assumable that these women had no prior cesarean birth.

Mode of birth (N=2): According to free-text fields in the TeMpOH-1 database, both women had a vaginal birth. One woman had a planned home birth and was referred to the hospital because of postpartum hemorrhage, while the other woman had a vaginal birth in the hospital, which was followed by a manual removal of the placenta.

Multiple pregnancy (N=2): Both women were assumed to have no multiple pregnancy. In the Netherlands, multiple pregnancy is an indication to have prenatal check-ups in the hospital. Both women had no such indication, making it unlikely that these women had a multiple pregnancy.

Parity (N=1): This woman was classified as a primigravida in the TeMpOH-1 database. Therefore, we considered her as a nulliparous woman.

CHAPTER 6

NATIONWIDE CONFIDENTIAL ENQUIRIES INTO MATERNAL DEATHS BECAUSE OF OBSTETRIC HEMORRHAGE IN THE NETHERLANDS BETWEEN 2006 AND 2019

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ABSTRACT

Introduction

Obstetric hemorrhage-related deaths are rare in high income countries. Yet, with increasing incidences of obstetric hemorrhage in these countries, it is of utmost importance to learn lessons from each obstetric hemorrhage-related death to improve maternity care. Our objective was to calculate the obstetric hemorrhage-related maternal mortality ratio (MMR), assess causes of obstetric hemorrhage-related deaths, and identify lessons learned.

Material and Methods

Nationwide mixed-methods prospective case-series with confidential enquiries into maternal deaths due to obstetric hemorrhage in the Netherlands from January 1st, 2006 to December 31st, 2019.

Results

The obstetric hemorrhage-related MMR in the Netherlands in 2006-2019 was 0.7 per 100 000 livebirths, and not statistically significantly different compared to the previous MMR of 1.0 per 100 000 livebirths in 1993-2005 (OR 0.70, 95% CI 0.38 to 1.30). Leading underlying cause of hemorrhage was retained placenta. Early recognition of persistent bleeding, prompt involvement of a senior clinician, and timely management tailored to the cause of hemorrhage with attention for coagulopathy were prominent lessons learned. Also, timely recourse to surgical interventions, including hysterectomy, in case other management options fail to stop bleeding came up as an important lesson in several obstetric hemorrhage-related deaths.

Conclusions

The obstetric hemorrhage-related MMR in the Netherlands in 2006-2019 has not substantially changed compared to the MMR of the previous enquiry in 1993–2005. Although obstetric hemorrhage is commonly encountered by maternity care professionals, it is important to remain vigilant of possible adverse maternal outcome and act upon an ongoing bleeding following birth in a more timely and adequate manner. Our confidential enquiries still led to important lessons learned with clinical advice to professionals as how to improve maternity care and avoid maternal deaths. Drawing lessons from maternal deaths should remain a qualitative and moral imperative.

INTRODUCTION

Successive improvements in maternity care during the 20th century have led to an impressive decline in the overall maternal mortality ratio (MMR) in high-income countries.[1] Nowadays, maternal deaths during pregnancy, childbirth and puerperium have become rare.[2,3] However, the declining death rates in recent decades are not to be taken for granted, and the deaths that do occur remain tragic and are often potentially preventable events.[4]

Despite a declining MMR in most high-income countries, the MMR in the United States of America paradoxically increased in recent years.[5,6] The MMR is an important indicator of the quality of maternity care[7], but in addition to monitoring this quantitative indicator, it is also imperative to draw qualitative lessons from each maternal death. Confidential enquiries can help to define lessons learned and improve the quality of maternity care.[8] Such continuous efforts are necessary to succeed in the reduction of the MMR.[9] Hemorrhage after childbirth has been identified as one of the commonest causes of preventable pregnancy-related death.[4] While there had been a decrease in obstetric hemorrhage-related deaths, these deaths are on the rise again in some high-income countries.[10] A previous confidential enquiry into maternal deaths in the Netherlands showed an unchanged obstetric hemorrhage-related MMR between 1983-1992 and 1993-2005, indicating that the evaluation of maternity care and formulation of lessons learned may help to achieve a reduction in the obstetric hemorrhage-related MMR.[11] Thus, reviewing all obstetric hemorrhage-related maternal deaths remains crucial to improve the quality of maternity care[12,13], particularly so in light of the increasing incidence of obstetric hemorrhage reported in multiple high-income countries, including the Netherlands.[14,15]

The purpose of this study was to systematically investigate all obstetric hemorrhage-related deaths in the Netherlands between 2006-2019 in order to examine the obstetric hemorrhage-related MMR within this time frame, assess causes of obstetric hemorrhage-related maternal deaths, and to identify substandard care factors related to those deaths in order to formulate lessons learned from confidential enquiries that may help to improve the quality of care.

MATERIAL AND METHODS

This was a nationwide mixed-methods prospective case-series in the Netherlands including all obstetric hemorrhage-related maternal deaths reported to the Dutch Audit Committee Maternal Mortality and Morbidity (Auditcomissie Maternal Sterfte en Morbiditeit, AMSM) between January 1st, 2006 and December 31st, 2019.

The AMSM is instituted by the Dutch Society of Obstetrics and Gynaecology (NVOG) and at present consists of eight consultant obstetricians, one obstetric anesthesiologist, one hospital-based midwife, and two residents in O&G.[16] The committee members are authorized by the NVOG to collect and analyze information about maternal deaths in the Netherlands that are reported to the AMSM by medical doctors, general practitioners, and midwives.[16] Since 2016, secure electronic reporting is made possible through the 'Netherlands Obstetric Surveillance System' (NethOSS), which is in line with the general Data Protection Regulation (GDPR). The NethOSS is a national surveillance system of severe maternal morbidity and mortality sending out a monthly email to allocated clinicians in each hospital with a maternity ward which includes a link for online registration. These clinicians are requested to report cases of severe maternal morbidity and mortality, or to declare 'nothing to report'. Once a maternal death has been reported to the AMSM, anonymized complete case file copies are requested to be uploaded to a secure online network that can only be accessed by the AMSM members. The case file copies consist of antenatal charts, surgery reports, radiology reports, laboratory and microbiology tests, autopsy reports, professional correspondence, and local audit reports. Through a confidential enquiry, the AMSM classifies the underlying cause of death according to the ICD-MM, systematically audits the provided care and assesses factors of substandard care and opportunities for improvement of care from which the AMSM formulates lessons learned for each death. The AMSM reports these findings back to the health care professionals in the field in an aggregated manner and directly to the involved caregivers if desired.

Maternal mortality is defined by the World Health Organization as the death of a woman during pregnancy, childbirth, or within 42 days after termination of pregnancy or childbirth.[17] The International Classification of Diseases-Maternal Mortality, tenth revision (ICD-MM), defined underlying cause of death as 'the disease or condition that initiated the morbid chain of events leading to death or circumstances of the accident or violence that produced a fatal injury'.[17] This definition brings into question where the morbid chain of events actually starts.

In the Netherlands, the chain of events is traced back to the primary event.[18] This implies that although a woman may have died due to excessive blood loss, the underlying cause of death might still be classified as preeclampsia, considering that preeclampsia was the primary event that led to clotting dysfunction and excessive obstetric hemorrhage.

Quantitative research

Obstetric hemorrhage was defined as a pregnancy-related bleeding (≥1000mL) following 24 weeks of gestation during pregnancy, childbirth, or up to 6 weeks postpartum. Since we were interested in all obstetric hemorrhage-related deaths, we chose to examine both those cases in which obstetric hemorrhage was classified by the AMSM as the underlying cause of death (defined as the initial event that initiated the chain of events ultimately leading to death), as well as cases where women died due to the complications of hemorrhage at any point in the chain of events, although the initial event starting the chain of events (underlying cause of death) was deemed otherwise by the AMSM. Identifying those cases where women died as a result of excessive bleeding in the chain of events, but the underlying cause of death was deemed otherwise, was done by PR, a resident who had no previous knowledge of these cases, and TA and JMS, both consultant obstetricians who have been members of AMSM for several years. Cases were independently examined and if there was a discrepancy between whether or not to include a woman, her case was brought up to a general AMSM meeting to reach a decision.

Furthermore, we classified 'obstetric hemorrhage' as the underlying cause of death in women who died due to excessive bleeding as a complication of cesarean section. This classification is in accordance with the classification system used by the ICD-MM[17]. In a previous report on maternal mortality in the Netherlands between 1993-2005, the underlying cause of death in a woman who died due to excessive hemorrhage as a complication of cesarean section was classified as 'complication of cesarean section'.[11] In order to pursue international uniformity regarding the classification of underlying cause of death, whilst still being able to compare our results to those presented for the Netherlands in the previous time frame of 1993-2005, we reclassified all deaths due to excessive bleeding as a complication of cesarean section for that previous time frame as 'obstetric hemorrhage' instead of 'complication of cesarean section'.[11]

We calculated the obstetric hemorrhage-related MMR for the time frame 2006-2019, with and without those cases where women died due to excessive blood loss within the chain of events, but with an underlying cause of death deemed

otherwise. The number of livebirths in the Netherlands between 2006-2019 was obtained from Statistics Netherlands, which is the governmental authority that collects vital perinatal statistics.[19] Odds ratio's (OR) with 95% confidence intervals (CI) were calculated to compare the MMR due to obstetric hemorrhage with hemorrhage as underlying cause of death in the Netherlands between the time frames 1993-2005 and 2006-2019.[11] Maternal deaths were cross-checked with the maternal mortality data from Statistics Netherlands up to 2011. Thereafter, cross-check was no longer facilitated by Statistics Netherlands due to alleged privacy issues. However, to ensure completeness of reporting to AMSM, a cross-check with the TeMpOH-1 study (*Transfusion strategies in women during Major Obstetric Hemorrhage*) was performed. The TeMpOH-1 study was a nationwide retrospective cohort study into major obstetric hemorrhage, specifically in 61 hospitals in the Netherlands (71% of all the hospitals in the country at the time with a maternity ward), that collected data from women who received 4 units of packed red blood cells or any transfusion of fresh frozen plasma or platelets in addition to packed cells because of obstetric hemorrhage (≥1000mL) between January 1, 2011 and January 1, 2013.[20] The numerator to calculate the obstetric hemorrhage-related MMR in the Netherlands in the time frame 2006-2019 also included women who died because of obstetric hemorrhage who were identified from the TeMpOH-1 study but were not reported to the AMSM. Statistical analyzes were performed with IBM SPSS Statistics (version 22.0, IBM Corp, Armon, NY, USA).

Qualitative research

All obstetric hemorrhage-related deaths reported to the AMSM in 2006-2019 were critically reviewed by the entire AMSM in order to identify substandard care factors and formulate lessons learned. Each woman's care is thus systematically reviewed by all AMSM members and evaluated against relevant national guidelines.[21-25] Substandard care was defined as all factors that might have contributed to the chain of events leading to death.[26] Substandard care could be 1) patient related, 2) primary maternity care related (care provided by community midwives or general practitioners), or 3) secondary and tertiary care related (care provided by obstetricians or other medical doctors and hospital-based midwives). This classification system is in accordance with that of two previous national assessments of maternal mortality in the Netherlands.[11,26] Lessons learned were formulated from substandard care factors identified by the AMSM. De-identified case histories are given to illustrate specific lessons learned.

Ethical approval

Ethical approval for this study was waived, considering that the AMSM was mandated by the NVOG to collect and analyze maternal deaths, and that ethical approval is not required in the Netherlands for performing confidential enquiries with anonymized data. The TeMpOH-1 study was approved by the Ethical Committee of Leiden University Medical Center (P12.273; 31 January 2013) and by the institutional review board of each of the participating hospital. The TeMpOH-1 study was registered in the Netherlands Trial Register (Trial NL3909; 17 July 2013).

RESULTS

A total of 27 obstetric hemorrhage-related maternal deaths were identified in the Netherlands between January 1, 2006 and December 31, 2019. Of these deaths, 24 (89%) were reported directly to the AMSM. The other 3 (11%) obstetric hemorrhage-related maternal deaths were identified after a cross-check with the TeMpOH-1. In 17 women (63%, N=17/27, including the 3 deaths that were identified from the TeMpOH-1), obstetric hemorrhage was considered as the underlying cause of death. Ten women (37%, N=10/27) died due to the complications of obstetric hemorrhage within the chain of events with a different underlying cause of death.

The MMR of obstetric hemorrhage as underlying cause of death in the Netherlands between 2006-2019 was 0.7 per 100 000 live births (17/2.473.951) and was not statistically significantly different compared to the MMR of 1.0 per 100 000 live births (25/2.557.208) in the Netherlands in 1993-2005 (OR 0.70, 95% CI 0.38-1.30).[26] The overall obstetric hemorrhage-related MMR (including cases where women died because of hemorrhage in the chain of events but with a different underlying cause of death) in 2006-2019 was 1.1 per 100 000 live births (27/2.473.951).

Maternal and pregnancy-related characteristics are presented in Table 1. Nine women (34%, N=9/27) were booked as having a 'high-risk' pregnancy upon the first antenatal visit, with maternity care provided by an obstetrician. Eighteen women (66%, N=18/27) started out with a 'low-risk' pregnancy with care provided by a primary care midwife. Of these 18 women, 10 (56%) were referred to obstetrician-led care during pregnancy, five (28%) during labor, and three (16%) following childbirth. Four women (15%, N=4/27) were at home at the start of the lethal event, of whom two had already given birth and two had perimortem cesarean section. Out of the three women in total who underwent a perimortem cesarean section in this study (including the two women who were at home), two had obstetric hemorrhage prior to the cardiorespiratory arrest that led to a perimortem cesarean section. One had hemorrhage after perimortem cesarean section and successful resuscitation. All other women had hemorrhage following vaginal birth, or during or after cesarean section.

Causes of obstetric hemorrhage-related deaths are presented in Table 2 and subdivided into causes where obstetric hemorrhage was the underlying cause of death and causes where women died because of obstetric hemorrhage in the chain of events but with a different underlying cause of death. Commonest cause

for obstetric hemorrhage as underlying cause of death was retained placenta (N=5/17). Amniotic fluid embolism was the commonest cause in women with hemorrhage in the chain of events leading to death (N=6/10). Thirteen women (48%, N=13/27) had intrauterine balloon tamponade, 4 (15%, N=4/27) had uterine artery embolization, and 8 (30%, N=8/27) a hysterectomy. Sixteen out of 27 women (59%) died the same day, 9 (34%) within one week, and 2 (7%) within two weeks following hemorrhage.

Confidential enquiries were only available for the women reported to the AMSM (N=24). Assessment of maternity care identified substandard care factors in 18 women. In 6 women no substandard care factors were identified. Most of these substandard care factors were secondary or tertiary care related (Table 3), with the majority related to inadequate management (75%, N=18/24), or delayed diagnosis (42%, N=10/24). Lessons learned with regard to improving maternity care derived from these substandard care factors are in 'Box 1', along with de-identified case histories to illustrate specific situations.

Table 1. Maternal and pregnancy-related characteristics of women who died because of obstetric hemorrhage in the Netherlands between 2006-2019

	N=27	(%)
Maternal age, years		
20-29	6	(22)
30-39	18	(66)
≥40	3	(11)
Body mass index, kg/m^2		
18.5 to 24.9	11	(41)
25.0 to 29.9	3	(11)
≥30	5	(18)
Missing	8	(30)
Ethnic background		
Dutch native	15	(55)
European	1	(4)
African	4	(15)
Asian	4	(15)
Missing	3	(11)
Parity		
Nulliparous	12	(44)
Parous	15	(66)
Initial antenatal care		
Primary midwife-led care	18	(66)
Obstetrician-led care	9	(34)
Multiple pregnancy	0	(0)
Prior cesarean section	5	(18)
Prior obstetric bleeding	0	(0)
Gestational age, weeks		
24+0 to 31+6	1	(4)
32+0 to 36+6	5	(18)
≥37 weeks	21	(78)
Mode of birth		
Vaginal	6	(22)
Instrumental	10	(37)
Cesarean section	11	(41)
Scheduled	*1*	*(9)*
Non-scheduled	*7*	*(64)*
Perimortem	*3*	*(27)*

Table 2. Initial causes of obstetric hemorrhage-related deaths in the Netherlands between 2006-2019

	N (%) (N=17)	MMR (Live Births=2.473.951)
Obstetric hemorrhage considered as the underlying cause of death		
Uterine atony	3 (18)	0.12
Retained placenta	5 (29)	0.20
Remnant of placental tissue	3 (18)	0.12
Cesarean section related	4 (23)	0.16
Ruptured interstitial pregnancy	1 (6)	0.04
Spontaneous splenic rupture	1 (6)	0.04
	N (%) (N=10)	MMR (Live Births=2.473.951)
Causes with obstetric hemorrhage in the chain of events leading to death		
Amniotic fluid embolism	6 (60)	0.24
Pre-eclampsia	2 (20)	0.08
Septic shock	2 (20)	0.08

Table 3. Number of identified substandard care factors in the 24 obstetric hemorrhage-related maternal deaths that were reported to the AMSM in the Netherlands between 2006 and 2019*

	N
Patient related	
Delay in consulting a doctor	1
Refusing medical treatment	1
Communication difficulties	1
Primary obstetric care related[1]	
Inadequate antenatal visit	1
Delay in referral to hospital	1
Delay in diagnosis	2
Secondary or tertiary care related[2]	
Delay in diagnosis	10
Inadequate management	18
Communication difficulties between obstetricians and other specialists	2
Failure to stabilize before transport	2

* Multiple substandard care factors could be identified per maternal death

[1] Care provided by community midwives and/or general practitioners

[2] Care provided by obstetricians and/or other medical specialists

Box 1. Lessons learned from the confidential enquiries of obstetric hemorrhage-related deaths reported to the AMSM in the Netherlands between 2006-2019

COMMUNICATION

- Use a structured format of communication so that as little information as possible is lost, e.g. through the communication tool SBAR (Situation–Background–Assessment–Recommendation).
- Effective communication between members of a multidisciplinary team is essential during acute severe hemorrhage. Caregivers should inform each other of the current clinical situation and emphasize their findings that deserve prompt medical reaction.

"A woman gave birth to her second child in the hospital and had a retained placenta. When she was transferred to the operating room, both the consultant obstetrician and anesthesiologist were not notified of the additional 1 liter blood loss before transportation and clinical signs of shock. After manual removal of the placenta, the woman deteriorated quickly, and blood products were not yet available considering that both clinicians in charge did not anticipate such a rapid decline. Despite swift recourse to invasive interventions to cease hemorrhage, she died from multiorgan failure the following week."

TRAINING

- Multidisciplinary obstetric hemorrhage simulation training sessions, preferably on a local and national level, may help to ensure that clinical caregivers are appropriately trained for care during the course of bleeding, barriers in care are identified and cleared so that facilities are properly equipped to handle obstetric hemorrhage, and may improve communication and collaboration between multidisciplinary team members during acute and severe obstetric bleedings.

ANTENATAL CARE

- Maternity caregivers should make an effort to overcome language barriers and invest time in creating health literacy (the ability to find, understand, and use information and services to inform health-related decisions and actions)[27] among women seeking care.
- Women who refuse transfusion of blood products should have pre-conception or antenatal counseling by experienced professionals, including the anesthesiologist and hematologist. Clinical caregivers must explain possible risks and consequences of refusing blood products, and a multidisciplinary plan should be in place to ensure optimal care during hemorrhage.

"A non-native woman with poor Dutch and English skills who had recently moved to the Netherlands had a spontaneous onset of labor. Her midwife advised her by phone to come to the hospital. Because of the language barrier, the woman arrived at the wrong hospital (one without a maternity ward) and gave birth under guidance of an ER doctor. She had massive bleeding due to uterine atony and was transported to another hospital where an obstetrician and operating room stood prepared upon arrival. A peripartum hysterectomy was performed to cease bleeding. She died of a cardiac arrest on the ICU."

PREVENTION & TIMELY RECOGNITION

- Implement risk assessment tools to identify women at risk of obstetric hemorrhage, such as those proposed by the Safe Motherhood Initiative of the American College of Obstetricians and Gynecologists.[28,29] Women with an estimated high risk of obstetric hemorrhage should have venous access early during labor with blood sampling for hemoglobin testing and crossmatching. Emphasis should be on active management of the third stage of labor.
- Timely recognition of persistent bleeding is crucial to prevent a delay in referral and medical response. Keep track of total blood loss and be aware of clinical signs of hypovolemia, such as tachycardia and hypotension, which indicate that a woman may have lost more blood than expected. Hypotension is often a late sign and should be acted upon immediately.
- Implement obstetric warning scores for early detection of imminently deteriorating women to trigger prompt medical evaluation, especially during postoperative care. Be aware that the bleeding might be concealed, and be alerted by non-specific complaints. A reduced level of consciousness or collapse is a red flag.
- Immediate recourse to a manual removal of the placenta(l) (remnant) is warranted once a retained placenta is diagnosed or a placental remnant is suspected. Delay (especially >1 hour) can result in more blood loss. Close monitoring of vital signs is also essential as blood can accumulate in the uterus and may lead to abrupt deterioration of a woman.

"An obese woman gave birth in hospital whilst intravenous access had not been established during labor. Following birth, the clinician in charge sutured multiple extensively bleeding vaginal lacerations. Total blood loss was estimated at 550mL despite signs of tachycardia and hypotension indicating that actual total blood loss might have been higher. Ten minutes later she collapsed and fundal expression revealed concealed hemorrhage loss inside the uterus. Vasoconstriction made it difficult to establish venous access at this point. The woman was taken to the operating room and hemoglobin level at that time was 3.22 g/dL (2.0 mmol/L). Bleeding was stopped with intrauterine balloon tamponade. Cardiorespiratory support was withdrawn when it became clear that she had lost all cortical functions."

COORDINATION & TIMELY MANAGEMENT

- In case of persistent bleeding, a senior clinician must be notified and a massive obstetric hemorrhage protocol should be activated, while recording clinical events and parameters (volume of blood loss, vital signs, and administration of medication, fluids and/or blood products).
- At least one senior clinician must coordinate management of persistent bleeding and maintain situational awareness. Assigning this task to a clinician will provide leadership and direction to the team in an acute setting, while this clinician keeps an overview of the situation.
- Manage obstetric hemorrhage timely and appropriately with administration of uterotonics and tranexamic acid. Early fluid resuscitation is essential to maintain adequate circulating volume and tissue perfusion.
- Prompt access to uterotonic agents on the maternity ward and operating room is crucial and having an 'emergency' trolley with medications and (laminated) instruction cards for acute settings may prevent delay in adequate management.
- Resort to surgical interventions sooner rather than later when hemorrhage does not cease despite the administration of uterotonics and additional conservative interventions, such as uterine massage and bimanual compression of the uterus.
- Proceed to hysterectomy when other invasive interventions are unsuccessful. Resort to peripartum hysterectomy should be expedited when blood products are refused or when there has been a delay in diagnosis with a woman in extremis.

"Following cesarean section because of breech presentation, a woman's hemoglobin level dropped and abdominal ultrasound examination revealed free fluid intra-abdominally. Transient postoperative bleeding was suspected and the woman was given blood products. Later that day her clinical condition deteriorated and she presented with abdominal swelling accompanied by oliguria. There was no senior clinician that coordinated care, and lack of leadership prevented exploratory laparotomy. The woman was transferred to the ICU where abdominal paracentesis revealed bloody ascites. She had a cardiac arrest and following resuscitation a laparotomy revealed 5L of hemorrhagic ascites without apparent bleeding focus. Due to progressive acute respiratory distress syndrome a transition to end-of-life care was decided."

BLOOD PRODUCTS & COAGULOPATHY

- Repeat hemoglobin measurements during ongoing bleeding. One hemoglobin test result taken during the early phases of hemorrhage should neither be reassuring nor used to guide or withhold blood products when bleeding is ongoing.
- When bleeding is severe and ongoing, a massive transfusion protocol should be activated with an appropriate fixed-ratio (packed cells : plasma : platelets) transfusion strategy that may help to ensure timely correction of blood volume and coagulopathy.
- Coagulation must be monitored by observing clot formation and screening for coagulation parameters. Coagulation factors may be administered when coagulopathy is suspected or relevant changes in coagulation parameters are detected.
- Be aware of hemostatic impairment when bleeding is persistent or when there has been a delay in diagnosis. Timely recognition of coagulopathy may prevent delay in hemostatic interventions.

"After removal of a placental remnant, the consultant-obstetrician noted excessive bleeding without clot formation and advised the anesthesiologist to administer packed cells that were not cross-matched and fresh frozen plasma. The anesthesiologist deemed otherwise based on a hemoglobin level of 9.18 g/dL (5.7 mmol/L) at induction of anesthesia with vital signs being with normal ranges following administration of phenylephrine IV. No blood products were administered, and a coagulation screening was initially not performed, despite the fact that the woman had already lost 4 liters of blood. Later, coagulation tests appeared abnormal. The obstetrician failed to control the bleeding, and cardiac arrest followed after intrauterine balloon tamponade with administration of sulprostone. A hysterectomy was performed after successful resuscitation. Loss of cortical functions and multiorgan failure led to cessation of medical support."

DISSEMINATED INTRAVASCULAR COAGULATION

- Be vigilant of disseminated intravascular coagulation-related hemorrhage that may arise in women with amniotic fluid embolism, sepsis and preeclampsia. It is important to be aware and correct coagulopathy at an early stage during hemorrhage.
- Amniotic fluid embolism is a rare, life-threatening complication during or shortly after childbirth, characterized by an unexplained sudden (cardiovascular) collapse followed by disseminated intravascular coagulopathy if a woman survived the initial event. Timely consideration of the diagnosis with supportive therapy and rapid correction of coagulopathy is essential to avert adverse outcome.[30]

"A woman had labor induced and received epidural analgesia. Shortly after her membranes had ruptured spontaneously, she had a cardiovascular collapse and CPR was initiated. During resuscitation it turned out that she already had full dilation and a successful instrumental vaginal birth was performed. She then developed disseminated intravascular coagulopathy followed by persistent hemorrhage, which had not been anticipated. There was no overall assessment of blood loss and insufficient replacement of clear fluids soon after resuscitation. Correction of coagulopathy was not initiated. Bleeding ceased after intrauterine balloon tamponade and radiological uterine artery embolization. She did not recover and supportive care was withdrawn on the ICU."

REFERRAL TO (ANOTHER) HOSPITAL

- Obstetric hemorrhage may occur after return of circulation following peri-mortem cesarean section. If an out-of-hospital resuscitation is successful, compress or close the uterus and abdomen before transportation to hospital.
- Stabilize hemodynamically unstable women before transport to another hospital.

"A woman collapsed at home and was found in a puddle of blood by the medical response team on site. Perimortem cesarean section was performed during resuscitation followed by spontaneous circulation. The placenta was not removed and the uterus was not closed before transportation. Upon arrival at the hospital, the woman was pronounced dead due to complete exsanguination from uterine blood loss."

DISCUSSION

The MMR of obstetric hemorrhage as underlying cause of death in the Netherlands was 0.7 per 100 000 live births in 2006-2019, which was similar to the MMR in 1993-2005.[11] The overall obstetric hemorrhage-related MMR (including women who died to hemorrhage in the chain of events, but with a different underlying cause of death) in 2006-2019 was 1.1 per 100 000 live births. Commonest cause of hemorrhage as the underlying cause of death was retained placenta. Amniotic fluid embolism was the commonest underlying cause with hemorrhage in the chain of events. Our confidential enquiries provide clear lessons learned with emphasis on timely recognition and management of persistent bleeding with attention for coagulation. These lessons learned have led to clear advice on how to improve maternity care in order to reduce the obstetric hemorrhage-related MMR in the Netherlands in the following years.

Main strength of this study was that we prospectively collected obstetric hemorrhage-related maternal deaths over a 14-year period through a national surveillance system. Furthermore, we adapted the definition of obstetric hemorrhage as underlying cause of death as proposed by the ICD-MM.[17] Using this uniform definition enabled us to compare our findings with other international studies on obstetric hemorrhage-related maternal deaths. Through systematic confidential enquiries based on actual medical records, we were able to identify improvable care factors and formulate lessons learned. Nevertheless, the ability of cross-checking with Statistics Netherlands stopped in 2012.[19] A cross-check with the TeMpOH-1 study revealed an additional 3 deaths due to obstetric hemorrhage between 2011-2013 that were not reported to the AMSM. This implies that the MMR of obstetric hemorrhage in the Netherlands in 2006-2019 is possibly higher and our findings are an underestimation of the actual problem. This affirms the importance of reliable national pregnancy-related mortality surveillance and thus we hope to reestablish the possibility to cross-check with Statistic Netherlands. Nevertheless, since 2016, NethOSS sends out a monthly email to allocated clinicians in all hospitals with a maternity ward in order to report cases of severe maternal morbidity and mortality, or to declare 'nothing to report'. This secure electronic way of reporting with the option to declare 'nothing to report' will help to ascertain validity of this registration system and will lead to a reliable national pregnancy-related mortality surveillance system in the Netherlands.

While the overall MMR in the Netherlands between 2006-2018 decreased by 50% compared to 1993-2005, the obstetric hemorrhage as underlying cause of death-related MMR remained relatively low and stable.[26] Nevertheless, our MMR 0.7 per

100 000 live births was comparable to the obstetric hemorrhage-related MMR of France (0.9 in 2013-2015)[31], Spain (0.82 in 1999-2015) [32], and the United Kingdom (which varied between 0.34-0.78 in the time frame 2009-2017).[33] The United States (1.74 in 2016-2017)[10] and Italy (1.92 in 2006-2012)[34] reported obstetric hemorrhage-related MMRs that were considerably higher. It is also of note that the United Kingdom and France reported maternal deaths due to uterine rupture, uterine inversion, placental abruption, placenta previa and abnormally invasive placenta, all causes that are associated with severe obstetric hemorrhage, while none of the deaths in the Netherlands were related to one of these causes.[31,33] It is difficult to point out a clear explanation for this difference, and it would require comparisons with near miss cases. However, this finding emphasizes to remain vigilant of possible adverse outcome in all obstetric hemorrhage causes. The majority of our lessons learned are similar to those contained in the annual reports of 'Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK (MBRRACE-UK)', a national program of work investigating maternal deaths in the United Kingdom and Ireland.[33,35,36] These MBRRACE-UK reports also stress the importance of early recognition of bleeding and activating a massive obstetric hemorrhage protocol with one clinician taking a 'helicopter view' to coordinate all aspects of care, while clear communication within the whole team is crucial and invasive interventions should be applied sooner rather than later.[33,35,36] Furthermore, a report from nine maternal mortality review committees in the United States with data ranging from 2008-2017 identified similar improvable care factors (i.e. delay in diagnosis, inadequate management, and lack of coordination or communication) and stated that 70% of these obstetric hemorrhage-related deaths were preventable.[30] It indicates that multiple high-income countries are facing similar problems and may learn from each other's recommendations in order to save women's lives during obstetric hemorrhage.

Our lessons learned create awareness and provide clinical caregivers tools to improve maternity care during obstetric hemorrhage. Timely recognition and management of hemorrhage and vigilance for concealed hemorrhage and the development of coagulopathy remains of utmost importance. Appointing a clinical care coordinator is essential as several women died due to a lack of coordination and absence of a clear plan. As 19/29 women died with their uterus preserved, a decision to perform a hysterectomy may be taken more readily, especially in women in extremis or refusing blood products. Caregivers need to be aware of the risk of severe obstetric hemorrhage with amniotic fluid embolism, sepsis and preeclampsia and correct coagulopathy promptly. Considering that 66% of the women started out with a 'low-risk' pregnancy without risk factors should

assert clinical caregivers to remain vigilant of possible severe hemorrhage, and stimulate an active management of the third stage of labor. Finally, we endorse multidisciplinary team training, both at a local and national level, to be prepared for obstetric hemorrhage and improve communication and collaboration between caregivers during acute settings.

Our findings show that there are still multiple opportunities to improve maternity care during the course of obstetric hemorrhage in order to avert maternal deaths. This should encourage performing confidential enquiries in other countries to evaluate maternity care and identify improvable care factors that may avoid maternal deaths because of obstetric hemorrhage. It has been acknowledged that a comprehensive maternal mortality surveillance system with confidential enquiries and the engagement of community participation so that lessons learned are widely disseminated lead to a reduction in maternal deaths.[8] The United Kingdom has demonstrated commitment to reviewing maternal deaths and formulating lessons learned through the MBRRACE-UK program.[33] This program provides a framework for how national surveillance of maternal deaths may be applied in order to improve quality of maternity care.[33] We applaud the efforts to implement a similar program in the United States, i.e. 'Enhancing Reviews and Surveillance to Eliminate Maternal Mortality' (ERASE MM) with standardized collection of data on maternal deaths through the 'Maternal Mortality Review Information Application' (MMRIA).[37] Maternal deaths because of obstetric hemorrhage are rare in the Netherlands, and general lessons learned for specific obstetric-related maternal deaths are not yet reported back to clinical caregivers Implementing a recurring (e.g. 5-year) cycle in which data on maternal deaths due to obstetric hemorrhage are shared and trended over time allows for more robust comparisons and evaluation of previously formulated lessons learned that may be published among clinical caregivers. Implementing a recurring obstetric hemorrhage-related theme-based cycle with confidential enquiries into deaths to repeatedly evaluate maternity care and formulate lessons learned should be encouraged across all settings.

CONCLUSION

The obstetric hemorrhage-related MMR remained relatively low and stable in the Netherlands between the time frames 1993–2005 and 2006–2019. Nevertheless, it remains imperative to evaluate maternity care during obstetric hemorrhage in order to learn and avoid maternal deaths. Our lessons learned that were identified from confidential enquiries have led to clear advice on how to improve maternity care in order to reduce the obstetric hemorrhage MMR in the Netherlands in the following years. Implementing a recurring obstetric hemorrhage-related theme-based cycle of confidential enquiries into maternal deaths to repeatedly evaluate maternity care and formulate lessons learned should be encouraged across all settings.

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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.

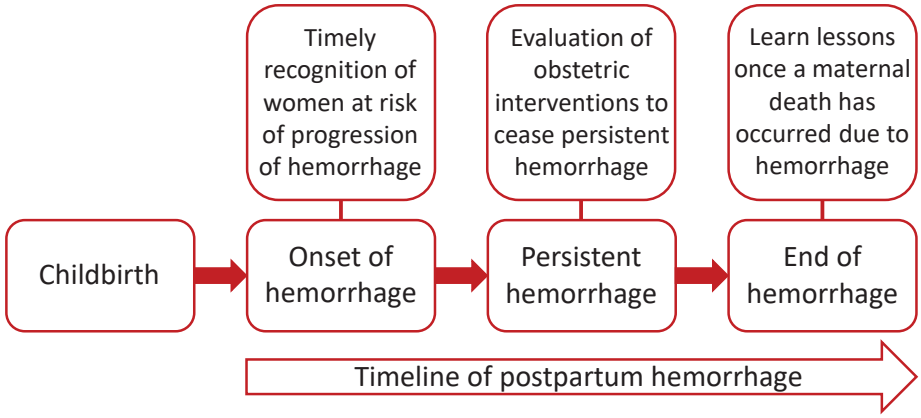

Figure 1. Flowchart of a simplified timeline of postpartum hemorrhage with opportunities to evaluate maternity care at different stages of bleeding in order to reduce the ongoing burden of maternal morbidity and mortality

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.

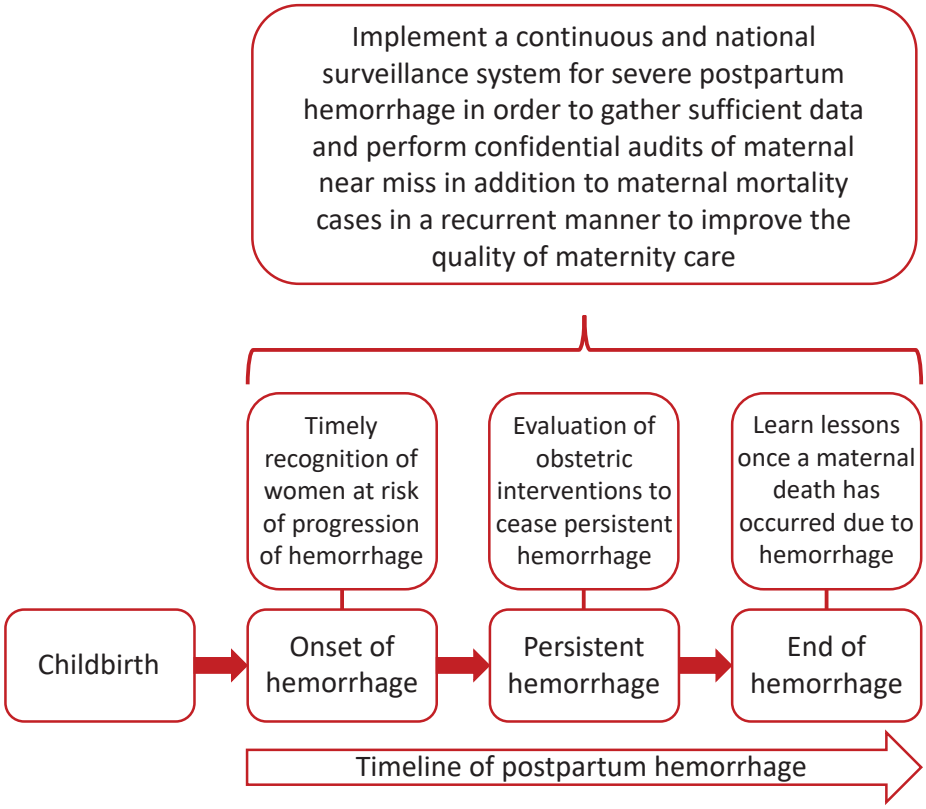

Figure 2. Flowchart of a simplified illustration of the timeline of postpartum hemorrhage that combines the opportunities to evaluate maternity care at different stages of bleeding and the increasing need for national surveillance of severe postpartum hemorrhage to evaluate these opportunities and perform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

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CHAPTER 8

SUMMARY
NEDERLANDSE SAMENVATTING

SUMMARY

In this thesis we focused on gaining insight into severe postpartum hemorrhage associated with severe maternal outcome and aimed to evaluate maternity care at different stages of bleeding in the course of postpartum hemorrhage. In **Part I** we investigated women in need of massive blood transfusion because of postpartum hemorrhage in order to improve our understanding of postpartum hemorrhage associated with severe maternal outcome and to compare management strategies and maternal outcome between different settings. In **Part II** we evaluated maternity care at different stages of bleeding following childbirth, i.e.: onset of hemorrhage (timely recognition of women at risk of progression of hemorrhage), persistent hemorrhage (evaluation of obstetric interventions to cease persistent hemorrhage), and end of hemorrhage (learn lessons once a maternal death from obstetric hemorrhage has occurred).

Part I: Massive blood transfusion in relation to postpartum hemorrhage

In **chapter 2** and **chapter 3** we addressed the incidence, causes, management and outcome of women who had received a so called 'massive blood transfusion' (i.e. ≥8 units of packed red blood cells transfused within 24h following birth) because of postpartum hemorrhage in the Netherlands within the time frames 2004–2006 and 2011–2012 using two nationwide population-based cohort studies. We showed that postpartum hemorrhage with massive blood transfusion was associated with high rates of severe maternal outcome. Although we observed a decreasing incidence between both time frames, the incidence of women who received massive blood transfusion after birth in the Netherlands remained significantly higher than that of some other settings with similar healthcare systems and resources. Furthermore, we observed considerable variation in the obstetric and hematologic management between different settings. Our study results showed the importance of nationwide studies into severe postpartum hemorrhage and the urgent need to evaluate and compare the management strategies to deduce a best practice to manage these severe obstetric-related bleedings and improve maternal outcome. Evidence-based uniform management guidelines are essential.

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

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

In **chapter 4** we evaluated the implementation of ROTEM® FIBTEM A5 as part of standard clinical care during the onset of postpartum hemorrhage and its ability to identify women at risk of progression to severe postpartum hemorrhage (composite endpoint of a total blood loss >2000mL, transfusion of ≥4 units of packed red blood cells, and/or need for an invasive intervention to stop the bleeding). Our results showed that the point-of care test FIBTEM A5 lacks the capability to discriminate between women with and without progression to severe postpartum hemorrhage when routinely measured between 800–1500mL of blood loss after childbirth. Furthermore, FIBTEM A5 values were only moderately correlated with fibrinogen concentrations, for which ROTEM® FIBTEM is a surrogate measure. Although we found no evidence to support the implementation of ROTEM® FIBTEM A5 as part of standard clinical care during the onset of bleeding, targeted use might still be useful to identify women at risk of progression and to withhold blood products and surpass formulaic transfusion protocols.

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) by constructing a propensity score matched-cohort. We showed that initial management by intrauterine balloon tamponade has the potential to cease bleeding and obviate the need for uterine artery embolization in a majority of women without an increased risk of peripartum hysterectomy or maternal mortality. Furthermore, we demonstrated no significant differences in total blood loss or units of packed red blood cells transfused. Two-thirds of the women within our propensity score-matched cohort with an estimated blood loss of 1000-7000mL can be spared an additional intervention when intrauterine balloon tamponade is used as the intervention of first choice during the course of persistent postpartum hemorrhage. However, because of the small sample size of 50 women in each intervention arm, our propensity score-matched cohort was underpowered to demonstrate equivalence. Nevertheless, our study design could be used as a useful framework for future comparative research during persistent postpartum hemorrhage where a randomized controlled trial is not likely to be feasible.

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

Chapter 6 contains a nationwide mixed-methods prospective case-series of maternal deaths due to obstetric hemorrhage in the Netherlands that were reported to the Dutch Maternal Mortality and Severe Morbidity Audit Committee in 2006–2019. We demonstrated that the obstetric hemorrhage-related maternal mortality ratio (MMR) in the Netherlands in 2006–2019 was low. However, the obstetric hemorrhage-related MMR remained comparable to the previous enquiry in the Netherlands in 1993–2005. Our confidential enquiries brought to light important lessons learned to improve the quality of maternity care during obstetric-related bleedings, avoid maternal deaths and reduce the obstetric hemorrhage-related MMR in the Netherlands in the following years. Our study findings indicate that continuous efforts are necessary to improve maternal safety. We argue for the implementation of a recurring obstetric hemorrhage-related theme-based cycle of confidential enquiries into maternal deaths to repeatedly evaluate care and formulate lessons learned to improve maternal outcome.

Chapter 7 contains the general discussion in which we demonstrate that postpartum hemorrhage is and remains a topic that requires attention to improve maternity care and maternal safety. However, to further improve maternity care and maternal outcome during severe blood loss after childbirth we pledge for a necessary 'next step' in which the occurrence and management of severe postpartum hemorrhage is continuously monitored, evaluated and improved. In order to do so our attention should be focused on:

- Developing an international consensus definition of severe postpartum hemorrhage to enable within- and cross-country comparison in search for optimal management strategies and best maternal outcome
- Establish a continuous and systematically registration system for severe postpartum hemorrhage on a nationwide scale in order to gather and evaluate data over time
- Performing maternal near miss audits of severe postpartum hemorrhage in addition to maternal mortality reports because of obstetric hemorrhage in order to identify opportunities to further improve the quality of maternity care

SAMENVATTING

Postpartum hemorragie is het verliezen van overmatig bloedverlies na de bevalling en is een van de belangrijkste oorzaken van maternale morbiditeit en mortaliteit wereldwijd. Het belang van gedegen onderzoek naar postpartum hemorragie wordt benadrukt door de toenemende incidentie van postpartum hemorragie in meerdere hoge inkomenslanden. Om deze reden ligt de focus van dit proefschrift op het inzicht verkrijgen van ernstige postpartum hemorragie in Nederland welke geassocieerd is met ernstige maternale morbiditeit en mortaliteit, en richt zich daarnaast op het evalueren van de obstetrische zorg op verschillende momenten tijdens overmatig bloedverlies na de bevalling. **Deel 1** van dit proefschrift omvat ons onderzoek naar vrouwen die ruim zijn getransfundeerd met bloedproducten bestaande uit rode bloedcellen (d.w.z. massale bloedtransfusie) vanwege postpartum hemorragie om op die manier inzicht te krijgen in ernstig bloedverlies na de bevalling welke geassocieerd is met ernstige maternale morbiditeit en mortaliteit en om de verscheidene behandelstrategieën te kunnen vergelijken tussen verschillende settingen. In **Deel 2** van dit proefschrift evalueren we obstetrische zorg tijdens verschillende momenten gedurende postpartum hemorragie: tijdens de aanvang van het bloedverlies (vroegtijdige herkenning van vrouwen met een verhoogd risico op progressie naar ernstiger bloedverlies), tijdens aanhoudend bloedverlies (door evaluatie van obstetrische interventies om aanhoudend bloedverlies te stoppen), en aan het einde van het bloedverlies (door lessen te trekken uit een maternale sterfte ten gevolge van obstetrisch bloedverlies).

Deel I: Postpartum hemorragie geassocieerd met massale bloedtransfusie

In **hoofdstuk 2** en **hoofdstuk 3** onderzochten we de incidentie, oorzaken, behandelingen en uitkomsten van vrouwen die een zogenoemde massale bloedtransfusie (gedefinieerd als ≥8 zakjes met erytrocyten binnen 24 uur na de bevalling) hadden gekregen vanwege postpartum hemorragie binnen Nederland in de tijdsperiodes van 2004-2006 en 2011-2012 door gebruik te maken van twee grote landelijke multicenter cohortstudies, de LEMMoN en de TeMpOH-1 studie. We lieten zien dat postpartum bloedingen waarbij een massale bloedtransfusie werd gegeven geassocieerd zijn met een aanzienlijk hoog risico op ernstige maternale uitkomst. Hoewel de incidentie tussen beide tijdsperiodes afnam was de incidentie van vrouwen die een massale bloedtransfusie na de bevalling hadden gekregen in Nederland nog aanzienlijk hoger dan andere settingen met vergelijkbare zorgstelsels en beschikbaarheid tot dezelfde medische

hulpmiddelen. Daarnaast zagen we een groot verschil in de obstetrische en hematologische behandelstrategieën tussen deze verschillende settingen. Onze resultaten benadrukken het belang van deze nationale studies naar ernstige postpartum hemorragie en de noodzaak tot verdere evaluatie en vergelijking van behandelstrategieën tussen verschillende settingen om zo tot een beste behandelstrategie te komen voor ernstig postpartum bloedverlies. Evidence-based uniforme richtlijnen zijn essentieel om zo de maternale uitkomst te doen verbeteren.

Deel II: Evaluatie van obstetrische zorg tijdens en na postpartum hemorragie

Aanvang van bloedverlies: vroegtijdige herkenning van progressie naar ernstig bloedverlies

In **hoofdstuk 4** presenteren we een prospectieve studie waarin we de voorspellende waarde van ROTEM® FIBTEM A5 voor progressie naar ernstige postpartum hemorragie (gedefinieerd als een totaal bloedverlies >2000mL, transfusie van ≥4 zakjes erytrocyten, en/of noodzaak tot een invasieve interventie) beoordelen wanneer deze test wordt afgenomen tussen de 800 en 1500mL bloedverlies na de bevalling. Onze resultaten lieten zien dat ROTEM® FIBTEM A5 niet in staat was om onderscheid te maken tussen vrouwen met en zonder progressie naar ernstige postpartum hemorragie. Daarnaast waren de FIBTEM A5 waardes slechts matig gecorreleerd aan de tegelijk bepaalde Clauss fibrinogeen concentraties waarvoor ROTEM® FIBTEM eigenlijk een surrogaat bepaling hoort te zijn. Hoewel er geen bewijs werd gevonden om FIBTEM A5 te implementeren als standaard bepaling tijdens aanvang van bloedverlies zou ROTEM® FIBTEM mogelijk wel van toegevoegde waarde zijn in een specifieke patiëntenpopulatie om vrouwen met progressie naar ernstiger bloedverlies te kunnen identificeren of om onnodige toediening van bepaalde bloedproducten tegen te gaan wanneer deze vooralsnog niet zijn geïndiceerd.

Aanhoudend bloedverlies: evaluatie van obstetrische interventies om de bloeding te stoppen

Persisterende postpartum hemorragie is gedefinieerd als persisterend bloedverlies ondanks het toepassen van initieel noodzakelijke medicatie of handelingen die nodig worden geacht bij de desbetreffende oorzaak van het bloedverlies. In het geval van persisterend bloedverlies kunnen verschillende interventies worden toegepast, maar welke de voorkeur heeft boven de ander is veelal nog onduidelijk. In **hoofdstuk 5** vergelijken we de uitkomsten van vrouwen die vanwege een persisterende postpartum hemorragie aanvankelijk werden behandeld met intra-uteriene ballon tamponade of door middel van embolisatie van de toevoerende vaten naar de

baarmoeder. Door het construeren van een *propensity score matched-cohort* konden we deze twee interventie groepen met elkaar te vergelijken en onze bevindingen lieten zien dat een initiële behandeling met intra-uteriene ballon tamponade de potentie heeft om bloedverlies te doen stoppen en de noodzaak tot een embolisatie bij de meeste vrouwen kan voorkomen zonder verhoogd risico op een hysterectomie of maternale sterfte. Daarnaast zagen we ook geen verschil in de totale hoeveelheid bloedverlies en het aantal getransfundeerde zakjes met erytrocyten tussen beide interventiegroepen. Een intra-uteriene ballon lijkt dus een geschikte interventie als eerste maatregel tijdens een persisterende postpartum hemorragie. Hoewel onze kleine studiepopulatie tot grote betrouwbaarheidsintervallen leidden dient onze studie-opzet wel als een geschikt voorbeeld voor eventueel toekomstig vergelijkend onderzoek naar obstetrische interventies wanneer een gerandomiseerde studie niet haalbaar wordt geacht.

Einde bloedverlies: lessen trekken uit maternale sterfte ten gevolge van obstetrisch bloedverlies

Hoofdstuk 6 bestaat uit een zowel kwantitatief als kwalitatief landelijke casestudie naar alle maternale sterfte ten gevolge van obstetrisch bloedverlies in Nederland die tussen 2006 en 2019 zijn gemeld aan de Auditcommissie Maternale Sterfte en Morbiditeit van de Nederlandse Vereniging van Obstetrie en Gynaecologie. In deze casestudie laten we zien dat de maternale mortaliteitsratio (MMR) van obstetrisch bloedverlies in Nederland tussen 2006 en 2019 laag was, maar nog steeds vergelijkbaar met de MMR van de vorige tijdsperiode tussen 1993 en 2005. Onze vertrouwelijke audits naar de gerapporteerde sterfte ten gevolge van obstetrisch bloedverlies tussen 2006 en 2019 leidden tot een meerdere aanbevelingen hoe we de zorg in zulke ernstige bloedingen alsnog kunnen verbeteren zodat we moedersterfte ten gevolge van obstetrisch bloedverlies in de toekomst kunnen voorkomen en de MMR in de komende jaren kunnen reduceren. Deze resultaten geven aan dat voortdurende inspanningen nodig zijn om de kwaliteit van de zorg te verbeteren en de veiligheid van moeders tijdens de bevalling zo nog meer te kunnen waarborgen. Wij pleiten voor de implementatie van een terugkerende cyclus van vertrouwelijke audits naar obstetrisch bloeding-gerelateerde maternale sterfte om zo herhaaldelijk de zorg te kunnen evalueren en waar nodig aanbevelingen te kunnen doen.

Hoofdstuk 7 bevat de algemene discussie waarin we laten zien dat postpartum hemorragie een obstetrische complicatie is die onze aandacht vereist om zo de zorg te kunnen verbeteren en de veiligheid van moeders tijdens ernstig bloedverlies verder te kunnen waarborgen. Om dit te kunnen bewerkstellingen pleiten we

voor een noodzakelijke 'next step' waarbij we de incidentie en behandeling van ernstige postpartum hemorragie continue blijven monitoren, evalueren en verbeteren. Resultaten in dit proefschrift moedigen verder aan tot:

- Ontwikkelen van een internationaal geaccepteerde definitie van ernstige postpartum hemorragie zodat het mogelijk is om behandelstrategieën en maternale uitkomsten tussen verschillende settingen te vergelijken om zo op zoek te gaan naar de meest optimale management strategieën leidend tot de beste maternale uitkomst
- Opzetten van een landelijk systeem voor continue en systematische registratie van ernstige postpartum hemorragie om zo gegevens in de loop van de tijd te kunnen verzamelen en te evalueren
- Uitvoeren van *maternal near miss* audits van ernstige postpartum hemorragie als aanvulling op de vertrouwelijke audits naar maternale sterfte wegens obstetrische bloedingen om zo nog meer mogelijkheden te kunnen identificeren om de kwaliteit van onze obstetrische zorg verder te kunnen verbeteren

PART IV

APPENDICES

LIST OF PUBLICATIONS

ABOUT THE AUTHOR

DANKWOORD

SAFE MOTHERHOOD SERIES

APPENDIX

LIST OF PUBLICATIONS

IN THIS THESIS:

1. **Ramler PI**, van den Akker T, Henriquez DDCA, Zwart JJ, van Roosmalen J. Incidence, management and outcome of women requiring massive transfusion after childbirth in the Netherlands: a secondary analysis of a nationwide cohort study between 2004 and 2006. BMC Pregnancy and Childbirth. 2017;17(1):197.

2. **Ramler PI**, van den Akker T, Henriquez DDCA, Zwart JJ, van Roosmalen J, van Lith JMM, van der Bom JG. Women receiving massive transfusion due to postpartum hemorrhage: a comparison over time between two nationwide cohort studies. Acta Obstet Gynecol Scand. 2019;98(60):795-804.

3. **Ramler PI**, Gillissen A, Henriquez DDCA, Caram-Deelder, Markovski AA, de Maat PMP, Duvekot JJ, Eikenboom JCJ, Bloemenkamp KWM, van Lith JMM, van den Akker T, van der Bom JG. Clinical value of early viscoelastometric point-of-care testing during postpartum hemorrhage for the prediction of severity of bleeding: a multicenter prospective cohort study in the Netherlands. Acta Obstet Gynecol Scand. 2021;100(9):1656-1664.

4. **Ramler PI**, Henriquez DDCA, van den Akker T, Caram-Deelder C, Groenwold RHH, Bloemenkamp KWM, van Roosmalen J, van Lith JMM, van der Bom JG. Comparison of outcome between intrauterine balloon tamponade and uterine artery embolization in the management of persistent postpartum hemorrhage: a propensity score-matched cohort study. Acta Obstet Gynecol Scand. 2019;98(11):1473-1482.

5. **Ramler PI**, Beenakkers ICM, Bloemenkamp KWM, van der Bom JG, Braams-Lisman BAM, Cornette JMJ, Kallianidis AF, Kuppens SMI, Rietveld AL, Schaap TP, Schutte JM, Stekelenburg J, Zwart JJ, van den Akker T. Nationwide confidential enquiries into maternal deaths because of obstetric hemorrhage in the Netherlands between 2006 and 2019. Acta Obstet Gynecol Scand. 2022;101(4):450-460.

OTHER PUBLICATIONS:

6. Tahitu M, **Ramler PI**, Gillissen A, Caram-Deelder C, Henriquez DDCA, de Maat MPM, Duvekot JJ, Eikenboom JCJ, Bloemenkamp KWM, van den Akker T, van der Bom JG. Clinical value of early assessment of hyperfibrinolysis by rotational thromboelastometry during postpartum hemorrhage for the prediction of severity of bleeding: a multicenter prospective cohort study in the Netherlands. Acta Obstet Gynecol Scand. 2022;101(1):145-152.

CHAPTER IN EDITED BOOK

1. **Ramler PI**, van den Akker T. Chapter 23 (pages 341-351): Maternal Complications in Multifetal Pregnancy. In: Twin and Higher-order Pregnancies. Springer, Cham. DOI: https://doi.org/10.1007/978-3-030-47652-6.

APPENDIX

ABOUT THE AUTHOR

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Paul Ramler was born on March 28, 1992 in Alkmaar and lived together with his parents (Hans and Pieternella) and his sister (Nine) in Heiloo. He graduated from secondary school at the Jac. P. Thijsse College in Castricum in 2010, and moved to Leiden to study medicine at the Leiden University Medical Center. In 2016 he attained his medical degree and started to work as a physician (ANIOS) at the department of Obstetrics and Gynecology at the Haaglanden Medisch Centrum in Den Haag (Marjolein Kagie). In 2017 he was given the opportunity to conduct his first medical research under supervision of professor Jos van Roosmalen that formed the basis of this thesis with professor Anske van der Bom, professor Thomas van den Akker and professor Jan van Lith as his doctoral supervisors. For a period of 8 months Paul worked in 2018 as a full time researcher at the Center for Clinical Transfusion Research of Sanquin Research in Leiden. He supervised the scientific internship of medical (delta) and biomedical sciences students. In 2021 he started his residency in Obstetrics and Gynecology at the HagaZiekenhuis in Den Haag (Hanneke Feitsma) and is currently continuing his residency at the Leiden University Medical Center in Leiden (Marieke Sueters). Paul lives together with Beau van Heusden, and they are expecting their first child.

APPENDIX

DANKWOORD

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APPENDIX

SAFE MOTHERHOOD SERIES

SAFE MOTHERHOOD SERIES

The Dutch Working Party 'International Safe Motherhood and Reproductive Health' aims to contribute to improvement of the reproductive health status of women around the globe, in particular by collaborating with local health workers (http://www.safemotherhood.nl). The Working Party is part of both the Dutch Society of Obstetrics and Gynaecology (NVOG) and the Dutch Society for International Health and Tropical Medicine (NVTG). The activities that are undertaken under the umbrella of the Working Party can be grouped into four pillars: education, patient care, research and advocacy.

Research activities are undertaken by (medical) students, Medical Doctors International Health and Tropical Medicine and many others. Some research activities develop into PhD-trajectories. PhD- candidates all over the world, Dutch and non-Dutch, work on finding locally acceptable and achievable ways to improve the quality of maternal health services, supervised by different members of the Working Party. Professor Jos van Roosmalen initiated the Safe Motherhood Series, which started in 1995.

THE SAFE MOTHERHOOD SERIES

- The role of oral (methyl)ergometrin in the prevention of postpartum haemorrhage. (**Akosua de Groot**), Radboud UMC, Nijmegen, the Netherlands, 1995
- Perinatal assessment in rural Tanzania. (**Gijs Walraven**), Radboud UMC, Nijmegen, the Netherlands, 1995
- Confidential enquiries into Maternal Deaths in the Netherlands, 1983- 1992. (**Nico Schuitemaker**), UMC Leiden, the Netherlands, 1998
- Confidential enquiries into Maternal Deaths in Surinam. (**Ashok Mungra**), UMC Leiden, the Netherlands, 1999
- Reproductive health matters in rural Ghana. (**Diederike Geelhoed**), UMC Leiden, the Netherlands, 2003
- Vaginal birth after caesarean section in Zimbabwe and The Netherlands (**Wilbert Spaans**), AMC Amsterdam, the Netherlands, 2004
- Safe Motherhood and Health systems research: Health care seeking behaviour and utilization of health services in Kalabo District (**Jelle Stekelenburg**), VU Amsterdam, the Netherlands, 2004
- Enhancing survival of mothers and their newborns in Tanzania (**Godfrey Mbaruku**), Karolinska Institute, Stockholm, Sweden, 2005
- Beyond the numbers: confidential enquiries into maternal deaths in Accra-Ghana (**Afisah Yakubu Zakariah, Accra, Ghana**), Vrije Universiteit Brussel, Belgium, 2008
- Severe maternal morbidity in the Netherlands: the LEMMoN study (**Joost Zwart**), UMC Leiden, the Netherlands, 2009
- Obstetric audit in Namibia and the Netherlands (**Jeroen van Dillen**), VU Amsterdam, the Netherlands, 2009
- Confidential enquiries into maternal deaths in the Netherlands 1993- 2005 (**Joke Schutte**), VU Amsterdam, the Netherlands, 2010
- Delay in Safe Motherhood (**Luc van Lonkhuijzen**), UMC Groningen, the Netherlands, 2011
- Medical Mirrors: Maternal care in a Malawian district (**Thomas van den Akker**), VU University Medical Centre, Amsterdam, the Netherlands, 2012
- Leading change in the maternal health care system in Tanzania: application of operations research (**Angelo Nyamtema, Ifakara**, Tanzania), VU Amsterdam, the Netherlands, 2012
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