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Postpartum hemorrhage: from insight to action

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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 worldwide¹, 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 $\geq 500\text{mL}$ within 24 hours following birth.⁶ The United Kingdom subdivides postpartum bleedings into minor ($\geq 500\text{mL}$), major ($\geq 1000\text{mL}$) and severe ($\geq 2000\text{mL}$)⁷, while the national guidelines from the Netherlands and United States of America define postpartum hemorrhage as $\geq 1000\text{mL}$ 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}

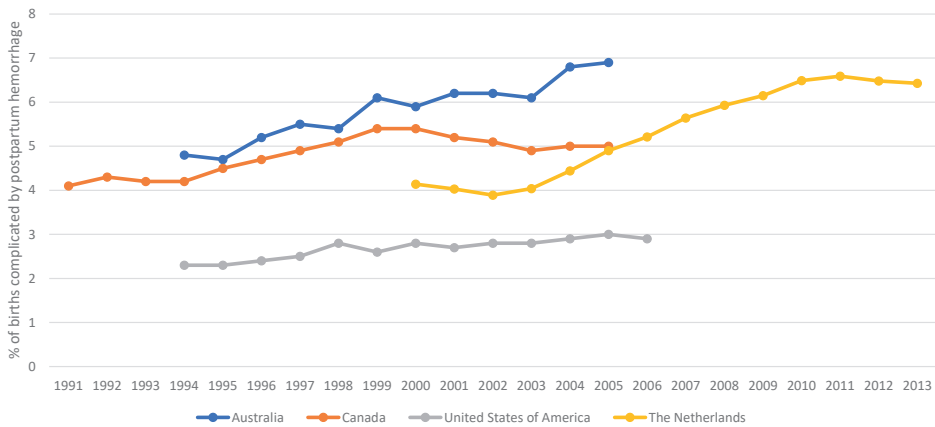


Figure 1. Trends in incidence of postpartum hemorrhage in Australia (defined as ≥ 500 mL after vaginal birth and ≥ 750 mL after cesarean birth), Canada (defined as ≥ 500 mL after vaginal birth and ≥ 1000 mL after cesarean birth), United States of America and the Netherlands (in both settings defined as ≥ 1000 mL 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 (1000-1500 mL), 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 heterogeneous 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 bleeding¹³⁻¹⁵, 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 Netherlands¹¹, 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).

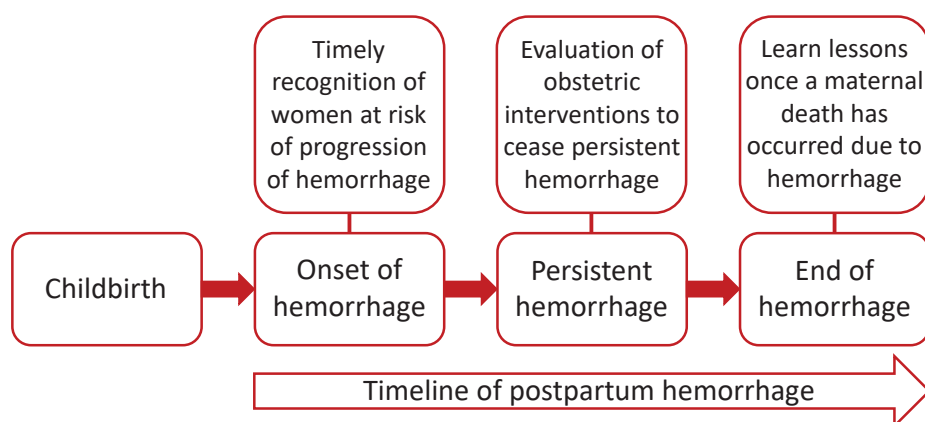


Figure 2. Flowchart of a simplified timeline of postpartum hemorrhage with opportunities to evaluate maternity care at different stages of bleeding in order to reduce the ongoing burden of maternal morbidity and mortality.

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 ($\leq 2\text{g/L}$) 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.

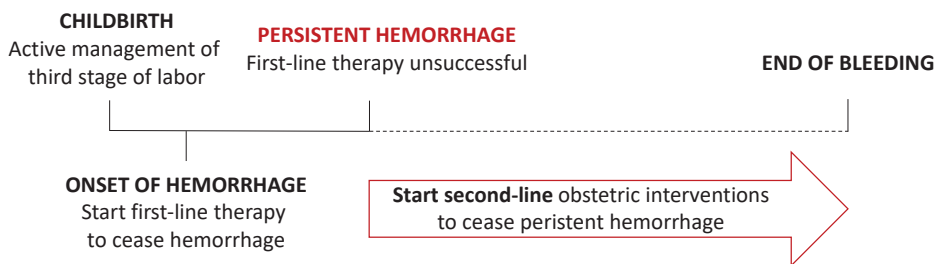


Figure 3. Persistent postpartum hemorrhage is defined as a bleeding refractory to the first-line therapy applied.

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 Netherlands¹¹, 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 was 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 of 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 TeMpoOH-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 TeMpoOH-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 TeMpoOH-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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