Recognition and management of persistent postpartum haemorrhage: Time to take timing seriously

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Introduction

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Vignette

A woman gave birth to a healthy son after an uneventful pregnancy. Half an hour later, she had 900 mL of blood loss, with a retained placenta. She was transferred to theatre for manual placenta removal. When she arrived in theatre, 40 min after giving birth, she had 1600 mL of blood loss and was tachycardic with a heart rate 125 bpm. Crystalloids and colloids were infused to maintain circulating blood volume. After removal of the placenta, she had an atonic uterus and persistent bleeding. Bimanual compression was performed, intravenous oxytocin, and later, prostaglandins and tranexamic acid were administered. While the obstetrician repaired a second degree perineal tear, the anaesthetist took a coagulation screen and ordered 2 units of packed red blood cells. Two hours after childbirth, she was taken to the recovery department, with a total blood loss of 3.5L. The clinicians discussed whether plasma transfusion was also indicated, but decided not to transfuse plasma, because the haemorrhage appeared to had stopped. Twenty minutes later she started bleeding again because of uterine atony, and eventually, when she had lost 5.5L of blood, 6h after giving birth, uterine artery embolisation was performed. Rate of bleeding decreased after this procedure, and she was massively transfused. A hysterectomy was performed 18h after childbirth, because of persistent postpartum haemorrhage. She lost more than 10L of blood.

The burden of postpartum haemorrhage

Every day, approximately 830 women die worldwide because of complications in pregnancy, childbirth and postpartum.[1] Obstetric haemorrhage has been the leading cause of maternal deaths for decades, causing more than a quarter of all maternal deaths.[2] In a systematic analysis of the World Health Organisation, postpartum haemorrhage accounted for more than two thirds of maternal deaths.[2]

The LEMMoN study estimated an incidence of 4.5 to 6.1 per 1000 deliveries for *major obstetric haemorrhage* in the time period 2004 to 2006 in the Netherlands, accumulating to more than 800 women with *major obstetric haemorrhage* every year.[3] Few maternal deaths were observed in this nationwide observational study. The good availability of blood products for blood transfusion probably played a pivotal role in preventing death because of postpartum haemorrhage in these women.[3,4]

Nonetheless, severe postpartum haemorrhage accounted for an important proportion of severe acute maternal morbidities such as arterial embolisation, peripartum hysterectomy and admission to the intensive care unit.[3,5]

The treatment algorithm of postpartum haemorrhage consists of three pillars: obstetric interventions to control bleeding, volume resuscitation to maintain circulating blood volume and haemostatic interventions to correct coagulopathy secondary to postpartum haemorrhage.[6,7] From the late 1990s onwards, many resources have been devoted to prevention and correction of coagulopathy during ongoing haemorrhage.

Coagulopathy in major bleeding

During major bleeding, coagulopathy may arise because of the loss, consumption, dilution and dysfunction of coagulation factors and platelets (figure 1). It was first described in patients with major trauma in military and civilian settings.[8] This *trauma-induced coagulopathy* seemed to arise earlier during major haemorrhage than previously thought.[8-10] It was hypothesised that coagulopathy in these patients would be best corrected by a pro-active transfusion strategy consisting of transfusion of packed red blood cells, fresh frozen plasma and platelet concentrates in a ratio of 1:1:1, reconstituting whole blood.[9-11]

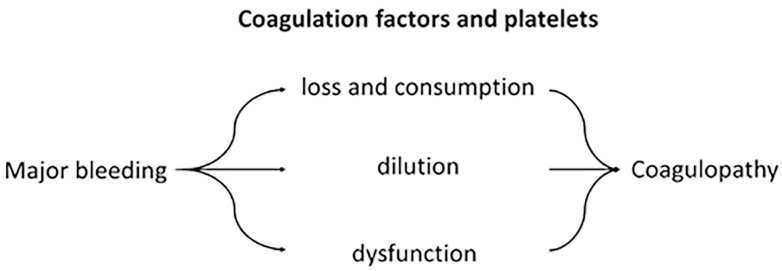

Figure 1. Mechanisms of coagulopathy in patients with major bleeding.

At first, it seemed as if these patients had a better survival after major haemorrhage due to trauma, as compared with patients who were not transfused according to this transfusion strategy.[12-15] However, a few years later, it became apparent that this observed survival benefit could partly be explained by *survival bias*.[16-18] Furthermore, a randomised controlled trial (PROPPR trial) comparing the transfusion strategy

red blood cells: plasma: platelets 1:1:1 versus 2:1:1 in trauma patients with major haemorrhage showed only a better outcome in patients with the former transfusion strategy for death due to exsanguination, but not in overall mortality.[19]

By the time the results of the PROPPR trial became evident, the favourable outcomes observed in the initial reports had already initiated a global change in transfusion practices, both in trauma and in non-trauma patients with major haemorrhage. However, extrapolation of the results in trauma patients to the pregnant population may not be justified because haemostasis in pregnant women is markedly different from haemostasis in the general population: normal pregnancy is a hypercoagulable state because of changes in the coagulation and fibrinolytic systems.[20-23] Thus, diagnosis and treatment of coagulopathy in pregnant women differs from coagulopathy in non-pregnant patients.

Because data on management of coagulopathy in women with severe postpartum haemorrhage is either scarce or inconclusive, there is a wide variation in recommendations from (inter)national guidelines and expert panels when it comes to transfusion indications, the use of massive transfusion protocols and the use of haemostatic agents to prevent and correct coagulopathy.[6,24,25] The haemostatic management of a woman with severe postpartum haemorrhage in the Netherlands is different from a women in a similar clinical condition in the UK, and from a woman in the US, Canada or Australia.

TeMpOH-studies

The TeMpOH-studies (*Transfusion strategies in women during Major Obstetric Haemorrhage*) were initiated by the Center for Clinical Transfusion Research (Sanquin/ LUMC Leiden) and the Departments of Clinical Epidemiology and Obstetrics of the Leiden University Medical Center. The studies were designed to address knowledge gaps in haemostatic impairment in women with postpartum haemorrhage and the haemostatic management of women with severe postpartum haemorrhage.

The TeMpOH-1 study is a nationwide, retrospective cohort study with the primary objective to determine whether the early start of plasma transfusion is associated with less adverse maternal outcomes in women with severe postpartum haemorrhage, as compared with no early start of plasma transfusion. Sixty-one out of the 86 Dutch hospitals (71%) with an obstetric care unit in 2012 participated in

this study, and we included 1391 consecutive women who, within 24 hours after childbirth, received at least four units of packed red blood cells or a multicomponent blood transfusion because of severe postpartum haemorrhage. For the purpose of this study, we reconstructed the course of postpartum haemorrhage for every woman who fulfilled the TeMpOH-1 inclusion criteria, including the timing of every obstetric and haemostatic intervention. We defined severe postpartum haemorrhage in the TeMpOH-1 study as *persistent postpartum haemorrhage*: postpartum haemorrhage exceeding 1 litres of blood loss within 24 hours following childbirth, that continued despite initial measures to control bleeding (figure 2).[6]

The TeMpOH-2 study is a multicentre prospective cohort study set up to describe the changes in haemostatic parameters in women during postpartum haemorrhage, and to examine the association between haemostasis parameters and adverse maternal outcome. The main objective of the TeMpOH-3 study, also a nationwide observational study, is to determine whether or not severe postpartum haemorrhage could be prevented by the placement of balloon catheters in the uterine arteries prior to caesarean section in women with suspected placenta accreta spectrum disorder.

The articles in this thesis are derived from the TeMpOH-1 study.

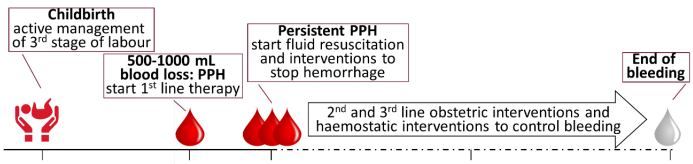

Figure 2. *Persistent postpartum haemorrhage* is defined as postpartum haemorrhage refractory to first-line uterotonic or surgical therapy to control bleeding, depending on the cause of haemorrhage. PPH denotes postpartum haemorrhage.

Outline of this thesis

The three central questions of this thesis concern the recognition and management of women with severe postpartum haemorrhage. We specifically address the timing of recognition of women with high risk of adverse outcome, and the timing of obstetric and haemostatic interventions to stop bleeding in these women.

Part I. What issues to resolve?

Chapter 2 is a cross-country comparison of the management of major obstetric haemorrhage performed within the International Network of Obstetric Surveillance Systems. The results are derived from population-based studies in six different high-resource countries: Australia, Denmark, France, Italy, the Netherlands and the United Kingdom. **Chapter 3** of this thesis is a review on the management of postpartum haemorrhage, focussing on the controversies regarding the early recognition of women with severe postpartum haemorrhage, the timing of obstetric interventions to stop bleeding, the timing of switch from fluid resuscitation with crystalloids and colloids to transfusion of packed red blood cells and the haemostatic interventions to correct coagulopathy in women with severe postpartum haemorrhage.

Part II. Who is at risk of adverse outcome?

Chapter 4 is a plea for redefining severe postpartum haemorrhage. We describe the clinical characteristics and outcomes of women with severe postpartum haemorrhage captured by the definition *persistent postpartum haemorrhage*, based on refractoriness to first-line treatment to control bleeding, compared with current definitions of severe postpartum haemorrhage based on estimated blood loss or units of packed red blood cells transfused. In **chapter 5** we focus on outcomes of women with persistent postpartum haemorrhage and concurrent hypertensive disorders of pregnancy, as this specific group of women has a particularly high risk of severe postpartum haemorrhage.

Part III. When and what to transfuse?

In **chapter 6** we determine the association between the volume of crystalloids and colloids administered prior to transfusion of packed red blood cells for volume resuscitation in women with persistent postpartum haemorrhage and outcomes of these women. **Chapter 7** addresses the timing of plasma transfusion and adverse maternal outcome of women with persistent postpartum haemorrhage. A time-dependent propensity score-matched analysis was performed to account for time-dependent confounding in this study. We discuss the risk of this specific bias in **chapter 8**, a commentary on an article that aimed to determine whether early administration of tranexamic acid in women with severe postpartum haemorrhage reduces the risk of adverse outcome in these women.

Finally, **chapter 9** summarises the main findings of the research articles in this thesis, and discusses the validity of our study results.

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