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

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Dacia Henriquez

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Recognition and management of persistent postpartum haemorrhage

Time to take timing seriously

Proefschrift

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Ik heb je zien vechten tegen tijd
Ik heb je zien vechten tegen woorden
Ik heb je zien vechten tegen water
Ik heb je vooral zien vechten tegen je zelf
Maar je stond, je staat en zal altijd staan.

- aanlegvoortalent -

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1

Introduction

Introduction

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]

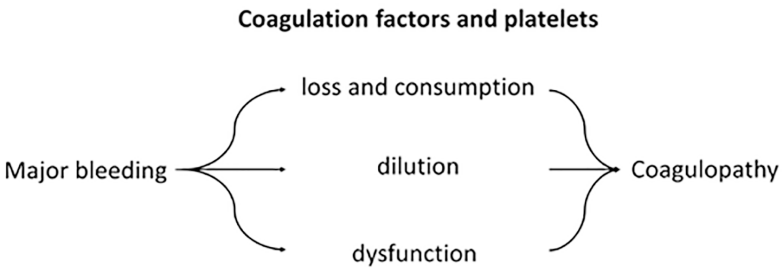

Figure 1. Mechanisms of coagulopathy in patients with major bleeding.

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.

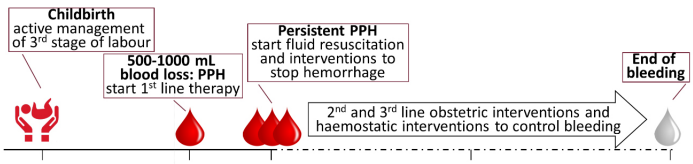

Figure 2. *Persistent postpartum haemorrhage* is defined as postpartum haemorrhage refractory to first-line uterotonic or surgical therapy to control bleeding, depending on the cause of haemorrhage. PPH denotes postpartum haemorrhage.

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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Part 1

Women with postpartum haemorrhage: what issues to resolve?

2

A total blood volume or more transfused during pregnancy or after childbirth: individual patient data from six international population-based observational studies

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(submitted)

Abstract

Background

This study aimed to compare incidence, management and outcomes of women who had been transfused their blood volume or more within 24 hours.

Methods

Combined analysis of individual patient data, prospectively collected in six international population-based studies (France, United Kingdom, Italy, Australia, the Netherlands and Denmark). Massive transfusion in major obstetric haemorrhage was defined as transfusion of eight or more units of red blood cells within 24 hours in a pregnant or postpartum woman. Causes, management and outcomes of women with massive transfusion were compared across countries using descriptive statistics.

Findings

The incidence of massive transfusion was approximately 20 women per 100,000 maternities for The United Kingdom, Australia and Italy; by contrast Denmark, the Netherlands and France had incidences of 82, 66 and 70 per 100,000 maternities, respectively. There was large variation in obstetric and haematological management across countries. Fibrinogen products were used in 87% of women in Australia, while the Netherlands and Italy reported lower use at 35-37% of women. Tranexamic acid was used in 75% of women in the Netherlands, but in less than half of women in the UK and Italy. In all countries, women received large quantities of colloid/crystalloid fluids during resuscitation (>3·5 litres). There was large variation in the use of compression sutures, embolisation and hysterectomy across countries. There was no difference in maternal mortality; however, variable proportions of women had cardiac arrests, renal failure and thrombotic events from 0-16%.

Interpretation

There was considerable variation in the incidence of massive transfusion associated with major obstetric haemorrhage across six high-income countries. There were also large disparities in both transfusion management and obstetric management between these countries. There is a requirement for detailed evaluation of evidence underlying current guidance and cross-country comparison may empower countries to benchmark their clinical care against that of other countries.

Funding:

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Introduction

The most common form of major obstetric haemorrhage (MOH), postpartum haemorrhage (PPH), which occurs in 3-7% of deliveries in high-income settings [1]; and remains a major cause of maternal mortality and morbidity. In France, Italy and the United States, haemorrhage is the leading cause of maternal mortality responsible for 11%, 15% and 14% of maternal deaths, respectively [2-4] and haemorrhage related mortality in the United Kingdom (UK) nearly doubled during the period 2010-12 to 2013-15 [5]. Major obstetric haemorrhage (MOH) is a common reason for admission to intensive care [6].

Management of MOH, often defined pragmatically as transfusion of a total body blood volume (8-10 units of red blood cells) or more within 24 hours of delivery [7-9] and also referred to as massive transfusion, focusses on transfusion and fluid resuscitation, alongside planning for definitive obstetric and surgical interventions [10]. The literature in major haemorrhage caused by trauma has emphasised the importance of damage control resuscitation, including timely transfusion support, early use of coagulation factors and minimising use of crystalloids, all contributing to improved clinical outcomes, although it is unclear how far these protocols should be applied in an obstetric setting [11].

Multiple guidelines to direct transfusion practice in MOH exist and these vary in terms of when blood components should be given and the dose. The reasons for variation in practice are unclear but are likely in part to reflect lack of high-quality data [12,13]. A number of national studies have reported the transfusion management of PPH [14,15], but there has been little comparison reported at a national level, to explore regional variations in practice. As part of an initiative to inform the research agenda, this study was planned to describe and compare the incidence, characteristics, aetiology, management and outcomes of pregnant or postpartum women who have been transfused their total blood volume or more within 24 hours, based on regional or national data collection systems across six countries.

Methods

Study description

This international population-based study of massive transfusion in MOH, used secondary analysis of data from six population-based studies from Australia, Denmark,

France, Italy, the Netherlands and the UK.

Overall description

In each country, data were collected either nationally or from a number of regions on a population basis. A detailed explanation of the methodology for each country can be found in the supplementary section and is summarised in Box 1. In short, these population-based studies collected data, using enhanced systems, from the medical records of the women who met the case definition for each of the respective studies. Danish data were solely based on information entered into the Danish Medical Birth Registry and the Danish Transfusion Database, which included data from all hospitals in Denmark. Four of the included datasets were national except for the Netherlands, France, and Italy. The TeMpOH-1 study in the Netherlands collected data from 75% of national births. Italy collected data from six regions namely Piedmont, Emilia-Romagna, Tuscany, Lazio, Campania and Sicily; these regions represent 49% of births in Italy and the EPIMOMS study in France collected data from six regions: Alsace, Lorraine, Auvergne, Rhone-Alpes, Ile-de-France and Basse-Normandie and these regions represented 18% of national births.

Case definition

Massive transfusion in major obstetric haemorrhage was defined as a receipt of eight or more units of red blood cells within 24 hours in a pregnant or postpartum woman of at least 20 weeks of gestation.

Statistical analysis

Women's characteristics, medical history, haematological features, obstetric and transfusion management and perinatal and maternal outcomes were compared across countries. Normality was assessed using histograms. Normally distributed continuous variables are presented as means with standard deviations and skewed continuous variables are presented as medians with interquartile ranges. The exact binomial distribution was used to estimate confidence intervals for proportions. Statistical hypothesis testing was carried out to test for statistical differences between countries and respective characteristics, management and outcomes of women undergoing massive transfusion. . Descriptive analyses used the following tests where appropriate: Analysis of Variance (ANOVA), Wilcoxon rank-sum test, Kruskal-Wallis test and chi square tests or the Fisher-Freeman-Halton's test. In order to reduce the risk of a type I error a p-value <0·01 was used to indicate statistical significance. Missing data were included as a 'missing' category for categorical variables. Complete

case analysis was used for continuous variables.

Categorisation of aetiology of MOH

France had multiple causes of MOH coded so a primary cause was devised using a hierarchical approach. The primary cause was defined in the following order: first those with abnormal placentation, second women with abruption, third women with trauma and lastly those with atony.

Ethics approval and data sharing agreements

The French data collaborators gained approval from the EPIMOMS steering committee at INSERM, Paris for this analysis. The TeMpOH-1 (the Netherlands) study was approved by the ethics committee of the Leiden University Medical Center and by the institutional review board of each participating hospital; the TeMpOH-1 and ItOSS steering committees approved the study protocol and the data transfer agreement. Approval for the obtained secondary use of Australia data obtained was from the Human Research Ethics Committee, New South Wales, Australia and from Human Research Ethics Committee for individual sites across Australia. Ethics committee approval for the secondary analysis of UK data was not required. The Danish collaborators acquired permission from the Danish Data Protection Agency (J.nr: HGH-2016-066), no permission was required from the Danish Ethics Committee according to Danish law.

Role of the funding source

The funder had no role in the data collection, analysis, interpretation or the writing of the manuscript. They had no decision to publish. SM the corresponding author had full access to the data in the study and the final responsibility for the decision to submit for publication.

Results

Incidence

Denmark reported the highest incidence of massive transfusion at 82 (95% CI: 73-92) women per 100,000 deliveries; followed by the France and the Netherlands with an incidence of approximately 70 per 100,000 deliveries (95% CI: 57-82) and 65 per 100,000 deliveries (95% CI: 56-76), respectively. The UK, Australia and Italy had a similar incidence of massive transfusion at 21 women per 100,000 deliveries; (Table 1). These variable rates are seen despite many similarities in baseline characteristics

of women presenting with PPH, including age and BMI.

Previous medical history and current pregnancy characteristics

Mean age of women with massive transfusion was 32 years (SD ±5·7) and the majority were multiparous (57%) (Table 1). Amongst women with a previous pregnancy, there were differences in the proportion of women with previous caesarean section and a previous postpartum haemorrhage between countries (previous caesarean section: highest in the UK (65%) and lowest in France (45%)).

Amongst cases, there were differences in the proportions of women with multiple pregnancies between countries (Denmark 30% and France 14%, respectively). In addition, the majority of women were delivered by caesarean section in each country (range excluding the Netherlands: 58%-68%), while the Netherlands had the lowest proportion of caesarean deliveries at 42%.

Aetiology of major obstetric haemorrhage

The most common cause of MOH in all countries was atony, with a prevalence ranging from 40% in the UK to 63% in the Netherlands (Supplementary Table 2). The second leading cause was abnormal placentation with a prevalence ranging from 22% in Italy to 32% in Australia. The least common cause was placental abruption with a proportion ranging from 3% in the Netherlands to 9% in the UK.

Transfusion management cross country analysis

Use of blood components varied across countries, Italy had a smaller median use of fresh frozen plasma (FFP) and platelets compared to other countries (Table 2). France had the highest use of FFP with a median of 7 units (IQR: 5-9) compared with the other countries. The inter country difference in use of FFP was statistically significant ($P<0·01$).

Different concentrated sources of fibrinogen were used, the UK and Australia mainly administered cryoprecipitate while France, Italy and the Netherlands used fibrinogen concentrate. The highest proportion of women receiving a fibrinogen product was in Australia (84%), while the Netherlands and Italy had a lowest use (35-37%) compared to the other countries (64%-87%).

Between 13-16% of women received factor VIIa in the Netherlands, Italy and France while the United Kingdom reported the lowest use at 8%, although this difference

was not statistically significant. Use of tranexamic acid (TXA) also varied between countries, the Netherlands used TXA in 75% of women with massive transfusion while it was used in less than a half of women in the UK and Italy, and these differences were statistically significant. The majority of women received either a colloid or crystalloid for fluid resuscitation. Large amounts of colloid and crystalloid fluids were transfused; the median fluid transfusion was between 3.5 and 4.5 litres in Italy, the Netherlands and the UK.

Obstetric management of major obstetric haemorrhage in each country

Medical management of massive haemorrhage due to atony involving the use of ergometrine, oxytocin, prostaglandin and misoprostol ranged from 88% of cases in France to 97% in the UK. The types of drugs that were used was statistically significantly different between each country; oxytocin was more frequently used in the UK and Australia and prostaglandin used more commonly in France and the Netherlands (Table 3).

The use of surgical techniques and interventional radiology also varied between countries. An intrauterine balloon was used in half of all women with massive transfusion except in France where a balloon was only used in a third. Use of arterial embolisation and major vessel ligation was more common in France and the Netherlands (70% and 52 % of women, respectively) compared to the UK and Italy (16% and 4% of women, respectively).

Uterine compression sutures were more commonly used in Australia, France and the UK (35%-24%) compared to the remaining countries (11-14%). In Italy, 74% of women with a massive transfusion had a hysterectomy, compared with less than half of women in the United Kingdom, France, and a third of women in the Netherlands.

Maternal outcomes by country

Overall there were nine maternal deaths which gave a case fatality of 1·5% (95% CI: 0.67-2·7) (Table 4). Nevertheless, maternal mortality was rare across all countries. Fourteen women had a thrombotic event; women in France had about double the proportion of these events compared to the UK and Australia (8% vs. 3-5%, respectively).In addition, France had a higher proportion of renal failure compared to other countries (16% vs. ~1-2%, respectively). Furthermore, France had slightly higher proportion of cardiac arrests compared to other countries (8% vs. ~1-5%). The majority of women were admitted to intensive treatment/care unit (ITU/ICU) in every country.

Discussion

Main findings

This population-based study has shown a five-fold variation in the incidence of massive transfusion across six high-income countries. Despite the same primary evidence being available to clinicians and guideline writers, in each country different obstetric and haematological management is provided for the management of women undergoing transfusion in major obstetric haemorrhage. Although there were no differences in maternal mortality between countries, these numbers are low, and there was evidence of highly variable rates of cardiac arrest, thrombotic events and renal failure. The greatest variation in resuscitation was seen for use of fibrinogen products, tranexamic acid and factor VIIa. Again, there was striking variation in obstetric management including the use of intrauterine balloons, embolisation and hysterectomy between countries.

Findings in context

Incidence

The variation in incidence between countries is likely to be multifactorial. Variations in obstetric management may be a relevant factor. More timely recognition, and control of bleeding may prevent worsening to more severe bleeds (≥8 units), and therefore factors that delay presentation and definitive management need to be explored between countries. National support for robust MOH protocols through appropriate fluid and haematological management may also control the bleeding at earlier stages.

Other factors include variation in risk factors such as the caesarean section rate and rate of multiple pregnancies; for example, a third of the mothers in the Danish massive transfusion cohort had a multiple pregnancy. However, the data collected in each country did not include information about the general obstetric population so there may be other differences in background risks for PPH between countries, which have not been captured. Alternatively, the variation in incidence of massive transfusion may be a reflection of differential transfusion policies.

Transfusion management

Guidelines for the haematological and fluid resuscitation management of haemorrhage vary by country and medical speciality [13]. Consequently, it is not surprising that clinical practice and use of blood components differed by country.

Fibrinogen and cryoprecipitate

Clinicians in the UK and Australia mainly used cryoprecipitate as a source of concentrated fibrinogen while in Italy, France and the Netherlands clinicians only used fibrinogen concentrate. There is a paucity of evidence regarding the efficacy of optimal source and dose of fibrinogen. The recent FIB-PPH trial compared the use of fibrinogen concentrate to placebo in the initial treatment of PPH but the intervention did not reduce the primary outcome of postpartum bleeding [16] and this study explored the efficacy of fibrinogen concentrate among a wide range of cases including non-severe PPH. A comparison of cryoprecipitate to fibrinogen concentrate for both efficacy and safety in pregnant or postpartum women has yet to be undertaken. Whilst the study has focused on sources of concentrated fibrinogen, FFP is also a source of fibrinogen; however there is no evidence in the pregnant population for the most efficacious source of fibrinogen.

Tranexamic acid

At the time of the data collection for this study there was a lack of high quality evidence about the use of TXA in the treatment of obstetric haemorrhage, and there was variation in use. Trials were either too small to detect a statistically significant difference in the primary outcome [17] or did not have the power to examine safety issues of the drug [18]. The findings of the WOMAN trial have now been published and it would be of interest to understand how this trial changes TXA use [19].

Recombinant Factor VIIa

In the majority of countries, current guidelines recommend that factor VIIa should not be given in obstetric haemorrhage [20-22]. A Cochrane review reported no evidence to support the efficacy of Factor VIIa across a range of clinical setting as prophylaxis or therapeutically; but with evidence to indicate an increased risk of thromboembolic events [23]. French guidelines allow for the use of recombinant FVIIa as a "compassionate treatment" to avoid a hysterectomy in nulliparous women or if the vital prognosis is engaged [24]. Overall, despite lack of evidence of benefit alongside risks and high costs, approximately 12% of women across all 6 countries received the pro-haemostatic agent in this international study.

Obstetric management

Previous research has shown that obstetric management of PPH varies internationally [15,25-27]. The findings from this study are consistent with this, as embolisation use was

higher in France and the Netherlands in comparison to the UK. This most likely reflects the availability of the infrastructure required to provide an embolisation service. The intrauterine balloon is the most common second stage management of MOH and its lower use in France most likely reflects high use of embolisation.

This study also showed significant disparity in the use of hysterectomy where three quarters of women had a hysterectomy in Italy while only a third of women did so in the Netherlands and less than a fifth in Denmark. Consistent with previous research, a similar proportion of women in the UK and France had a hysterectomy [15]. With no difference in maternal mortality between countries, this suggests that the future fertility of some of these women could have been saved.

Maternal outcomes

There was no difference in maternal mortality between countries. However, this study may have not been adequately powered to test for this difference in this rare event. A higher number of women with massive transfusion in France had renal failure, cardiac arrest and thrombotic events. The reasons are unclear but higher rates of pro-haemostatic agents were reported. However, EPIMOMS had specific questions on these outcomes within their data collection form, which may have resulted in better ascertainment than the UK, Italy and Australia. Although all studies, excluding Denmark, used the medical notes to complete the data collection form.

Strengths

This study was unique in its ability to compare all women between populations, based on national or regional studies with women who had been transfused at least eight of more units of red blood cells. This study used similar methods to an individual patient data meta-analysis. This methodology allowed the harmonisation of definitions and creation of comparable datasets, which in turn allowed robust comparisons between nations. All countries except for Denmark had tailored data collection forms, which collected detailed information about each woman, and enabled this unique comparison.

Limitation

This analysis should be interpreted in the context of the limitations. Each national study collected slightly different items. To reduce errors due to misclassification all countries had their cases cross-checked against hospital records, other than Denmark,

which was solely based on ICD-10-CM codes

Observational studies examining the association between haematological management and outcomes are prone to confounding by indication i.e. those who received an intervention appear to have worse outcomes [28] and this is reflected in the relationship between the use of blood components and poor outcomes. This analysis was also susceptible to survival bias, as those women who died or had a hysterectomy before they received 8 units of RBC would not have been included in the study population. However, whilst bearing these limitations in mind there are important messages from the findings. Furthermore, there may have been a lack of power to assess difference in maternal mortality between countries.

The findings on patterns of transfsuion and haematological fluid resuscitation are limited by incomplete data for timing. For example, patients who received the same number of units within 24hr may differ according to the acuteness of the bleed i.e. someone who is transfused 8 units within an hour would be clinically very different to a patient who received 8 units over 24 hours.

Conclusion

There was a large variation in the incidence of massive transfusion associated with major obstetric haemorrhage between countries. This was likely to be the result of disparities in timely management of less severe bleeds between countries or differences in transfusion policies. Obstetric management and the use of blood products and haemostatic agents varied substantially. However, despite these variations in management, the rate of maternal mortality was similar. Therefore, there is need for a detailed evaluation of the evidence underlying current guidance, including fibrinogen concentrate and other prothrombotic agents. In addition, this comparison may empower countries to benchmark their clinical care against that of other countries, and provide a challenge to improve current practice, in particular, improved uptake of TXA, immediate use of intrauterine balloons and timely but judicious use of hysterectomy.

Summary

In the absence of high-level evidence, each country has a preferred treatment regime, which may lead to the use of unnecessary costly haematological products, exposure of women to potential adverse effects and radical management such as hysterectomy. With wide variation in obstetric practice, including hysterectomy and embolisation,

significant improvement in the evidence base is required particularly if a women's future fertility could be otherwise preserved. In extreme scenarios there is a delicate balance between saving a women's life and her fertility, however, with a 40% difference in use of hysterectomy between Italy and the Netherlands and no difference in maternal mortality, there must be an examination and comparison of the clinical pathway.

Authors' contribution

SM contributed to study conception, design, co-ordinated the project, data analysis and wrote the first draft of the manuscript. TA interpreted the data, commented on the manuscript. JB was the principal investigator of the TeMpOH-1 project. MPB XXXX with EPIMOMS. CDT was the principal investigator of EPIMOMS. SD was the principal investigator of ITOSS. AM performed the data analysis of the Italian data. HME gained ethical approval for use of Danish data, gained access to the Danish registry, data management of Danish data. AG XXXX with TeMpOH-1, data management of Dutch data. DH set up and conducted the TeMpOH-1 study, and coordinated data management of Dutch data. ZL was responsible for the data management of the Australian data and gained ethical approval for the transfer of Australian data. AS was with EPIMOMS, data management of the French data. ES was the principal investigator of AMOSS. MK was the principal investigator of UKOSS.

All authors interpreted the data and commented on the manuscript.

SS, JK and MK contributed to the study conception, design and supervised the project.

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Research in context

There is a lack of high quality evidence underlying guidelines for the management of obstetric haemorrhage, which has resulted in variation in surgical practices across countries. A number of bi-national analyses have shown that surgical management of severe postpartum haemorrhage varied across countries, with a preference for vessel embolisation in France and the Netherlands and compression sutures in the UK. Furthermore, transfusion management guidelines differ across countries; for example, there are different thresholds for transfusion of blood components and use of haemostatic agents and the type and quantity of product given also differs. It is not clear whether these differences in transfusion guidelines are reflected in clinical practice. In addition, if differences exist in terms of management (surgical and transfusion), whether these difference impact maternal mortality or severe maternal morbidity.

Box 1. Summary of data collection systems and data collected.

Country	Name of system or dataset	Type of system	Date collected
Australia	Australasian Maternity Outcomes Surveillance System (AMOSS). [29]	National obstetric surveillance system. Collected data from hospitals with more than 50 births per year.	One year (July 2014-June 2015)
Denmark	Danish Medical Birth Registry and the Danish Transfusion Database	Routinely collected national data on both birth and transfusions.	Five years (2010-2015)
France	Épidémiologic de la Morbidité Maternelle Sévère study (EPIMOMS) [30]	Prospective Population-based study from all maternity units in 6 regions.	One year (2012-2013)
Italy	Italian Obstetric Surveillance System (ItOSS)	Population-based study from all maternity units in 6 regions in Italy.	Two years (September 2014-August 2016)
The Netherlands	Transfusion strategies in women during Major Obstetric Haemorrhage study (TeMpOH-1) [31]	Collected data from 75% of national births	Two years (January 2011 and January 2013)
United Kingdom	United Kingdom Obstetric Surveillance System (UKOSS) [32]	Obstetric surveillance system which collected data nationally from all consultant-led hospitals.	One year (June 2013- July 2014)

Table 1. Sociodemographic, previous medical history and current pregnancy information in women undergoing massive transfusion for major obstetric haemorrhage.

		UK n=162	Australia n=61	Italy n=99	The Netherlands n=179	France n=126	Denmark n=288	P-value
National denominator		787,105	302,666	458,995	270,101	182,309	349,998	
Incidence per 100,000 maternities		20·6 (17·5-24·0)	20·2 (15·4-25·9)	21·6 (17·5-26·3)	65·5 (80·2-102·1)	69·5 (57·9-82·7)	82·3 (73·1-92·4)	
Age	*Mean (Std)*	33 (5·9)	33 (5·3)	35 (6·0)	32 (5·3)	33 (5·9)	32 (5·30)	<0·001
BMI	*Median (IQR)*	25 (22-29)	25 (21-28)	23 (21-25)	23 (21-26)	24 (21-27)	23 (21-23·3)	<0·001
Previous medical history								
Parity	*Nulliparous*	60 (37·3)	20 (32·8)	48 (48·5)	84 (46·9)	56 (44·8)	176 (44·8)	
	Multiparous	101 (62·7)	41 (67·2)	51 (51·5)	95 (53·1)	69 (55·2)	207 (55·2)	0·185
	Missing	1	0	0	0	1	5	
Previous caesarean section	*None*	35 (34·3)	24 (60)	22 (44·9)	51 (53·7)	38 (55·9)	111 (48·1)	0·023
	Yes	67 (65·7)	16 (40)	27 (55·1)	44 (46·3)	30 (44·1)	101 (51·9)	
	Nulliparous	60	20	48	84	56	176	
	Missing	0	1	2	0	2		
Number of previous caesarean section	*0*	34 (33·7)	25 (61)	15 (36·6)	- -	38 (75·8)	(67·7)	
	1	38 (37·6)	10 (24·4)	16 (39)	- -	21 (16·9)	(19·8)	<0·001
	2+	29 (28·7)	6 (14·6)	10 (24·4)	- -	9 (7·3)	(12·6)	
	Nulliparous	60	20	48	- -	56		
	Missing	1	0	10	- -	2		
Previous postpartum haemorrhage	*None*	78 (76·5)	29 (85·3)	41 (91·1)	86 (91·5)	64 (92·8)	(86·6)	
	Yes	24 (23·5)	5 (14·7)	4 (8·9)	8 (8·5)	5 (7·2)	(13·4)	0·007
	Nulliparous	60	20	48	84	56		
	Missing	0	7	6	1	1		
Current pregnancy								
Hypertension prior to pregnancy or gestational hypertension	*None*	161 (99·4)	59 (96·7)	94 (94·9)	153 (85·5)	124 (99·2)	(94·4)	<0·001
	Yes	1 (0·6)	2 (3·3)	5 (5·1)	26 (14·5)	1 (0·8)	(5·6)	
	Missing	0	0	0	0	1		
Infection in current pregnancy	*No*	161 (99·4)	56 (94·9)	99 (100)	179 (100)	117 (97·5)	(98·9)	0·006*
	Yes	1 (0·6)	3 (5·1)	0 (0)	0 (0)	3 (2·5)	(1·1)	
	Missing	0	2	0	0	6		
Inherited bleeding disorders	*No*	160 (98·8)	55 (98·2)	- -	- -	121 (96·8)		0·602*
	Yes	2 (1·2)	1 (1·8)	- -	- -	4 (3·2)		
	Missing	0	5	-	-	1		
Multiple pregnancy	*No*	155 (95·7)	58 (95·1)	92 (92·9)	167 (93·8)	108 (85·7)	219 (76)	<0·001
	Yes	7 (4·3)	3 (4·9)	7 (7·1)	11 (6·2)	18 (14·3)	69 (24)	
	Missing	0	0	0	1	0	0	
Induced	*None*	103 (65·2)	20 (54·1)	56 (73·7)	117 (65·4)	52 (41·6)	348 (60·5)	<0·001
	Yes	55 (34·8)	17 (45·9)	20 (26·3)	62 (34·6)	73 (58·4)	227 (39·5)	
	Missing	4	24	23	0	1		
Delivery type	*Vaginal delivery*	50 (31·6)	25 (41)	37 (37·4)	104 (58·4)	47 (37·6)	92 (31·9)	<0·001
	Caesarean delivery	108 (68·4)	36 (59)	62 (62·6)	74 (41·6)	78 (62·4)	196 (68·1)	
	N/A Pregnancy loss	4	0	0	1	1	0	

*Used Fisher's exact test·

Table 2. Haematological management by country

Blood products		UK n=162	Australia n=61	Italy n=99	The Netherlands n=179	France n=126	Denmark n=288	P-value
Number of RBC units	*Median (IQR)*				(9-15)	10 (9-12)	11 (8-15)	<0·001
Received Fresh frozen plasma	*n (%)*	162 (100)	59 (96·7)	84 (84·8)	179 (100)	126 (100)	247 (85·8)	<0·001
Fresh frozen plasma	*Median (IQR)*	6 (4-8)	6 (4- 8)	4 (2-8)	6 (4-8)	7 (5- 9)	6 (4-8)	<0·001
Received Platelets	*n (%)*	126 (77·8)	51 (83·6)	40 (40·4)	179 (100)	126 (100)	205 (71·2)	<0·001
Platelets	*Median (IQR)*	1 (1-2)	1 (1- 2)	0 (0-2)	2 (1-3)	1 (1- 3)	2 (0-3)	<0·001
Source of concentrated fibrinogen administered	*No*	58 (35·8)	8 (13·6)	62 (62·6)	116 (64·8)	27 (22·3)	- -	<0·001
	Yes	104 (64·2)	51 (86·4)	37 (37·4)	63 (35·2)	94 (77·7)	- -	
	Missing	0	2	0	0	5	- -	
Fibrinogen concentrate used	*No*	152 (93·8)	54 (100)	62 (62·6)	116 (64·8)	27 (22·3)	- -	<0·001
	Yes	10 (6·2)	0 (0)	37 (37·4)	63 (35·2)	94 (77·7)	- -	
	Missing	0	7	0	0	5	- -	
Cryoprecipitate used	*No*	55 (35·5)	8 (13·6)	- -	- -	- -	- -	0·002
	Yes	100 (64·5)	51 (86·4)	- -	- -	- -	- -	
	Missing	7	2	- -	- -	- -	- -	
Number of units of cryoprecipitate	*Median (IQR)*	2 (0-2)	1 (1- 2)	- -	- -	- -	- -	0·06
Use of cell salvage	*No*	115 (74·2)	46 (85·2)	- -	- -	- -	- -	0·098
	Yes	40 (25·8)	8 (14·8)	- -	- -	- -	- -	
	Missing	7	7	- -	- -	- -	- -	
If Yes, amount transfused (ml)	*Median (IQR)*	1150 (500-1900)	884 (565-1377)	- -	- -	- -	- -	0·92
Recombinant Factor VIIa	*No*	149 (92)	48 (90·6)	86 (86·9)	151 (84·4)	103 (85·1)	- -	0·224
	Yes	13 (8)	5 (9·4)	13 (13·1)	28 (15·6)	18 (14·9)	- -	
	Missing	0	8	0	0	5	- -	
Tranexamic acid	*No*	87 (53·7)	41 (74·5)	57 (57·6)	45 (25·1)	47 (39·2)	- -	<0·001
	Yes	75 (46·3)	14 (25·5)	42 (42·4)	134 (74·9)	73 (60·8)	- -	
	Missing	0	6	0 0	0	6	- -	
Any fluid used during resuscitation	*No*	4 (2·5)	-	0 (0)	0 (0)	0 (0)	- -	<0·001*
	Yes	157 (97·5)	12 (22·2)	55 (100)	167 (100)	108 (100)	- -	
	Missing	1	42	44	12	18	- -	
Total amount (ml)		4000 (3000-6000)		3500 (3000-5000)	4500 (3000-6000)			0·204
Colloid	*Yes*	139 (88·5)	- -	49 (98)	160 (96·4)	87 (82·9)	- -	<0·001
	Missing	5	- -	49	13	21	- -	
If Yes, amount transfused (ml)	*Median (IQR)*	1000 (650-2000)	- -	1000 (500-1500)	1500 (1000-2000)	- -	- -	<0·001
Crystalloid	*Yes*	152 (95)	- -	49 (100)	137 (100)	103 (95·4)	- -	0·025
	Missing	2	- -	50	42	18	- -	
If Yes, amount transfused (ml)	*Median (IQR)*	3000 (1500-4000)	- -	2500 (1700-3500)	2500 (1600-4300)	- -	- -	0·442

*Australia only recorded use of 5 and 25% albumin administration·

Table 3. Obstetric management by country

		UK n=162	Australia n=61	Italy n=99	The Netherlands n=179	France n=126	Denmark n=288	P-value
Medical management								
Syntocinon	*No*	6 (3·7)	7 (11·7)	26 (26·3)	65 (36·3)	47 (39·5)	- -	<0·001
	Yes	156 (96·3)	53 (88·3)	73 (73·7)	114 (63·7)	72 (60·5)	- -	
	Missing		1	0		7	- -	
Ergometrine	*No*	69 (42·6)	32 (56·1)	- -	160 (89·4)	- -	- -	<0·001
	Yes	93 (57·4)	25 (43·9)	- -	19 (10·6)	- -	- -	
	Missing		4				- -	
Prostaglandin	*No*	64 (39·5)	30 (52·6)	49 (49·5)	30 (16·8)	16 (13·6)	- -	<0·001
	Yes	98 (60·5)	27 (47·4)	50 (50·5)	149 (83·2)	102 (86·4)	- -	
	Missing		4	0		8	- -	
Misoprostol	*No*	73 (45·1)	29 (51·8)	- -	117 (65·4)	118 (99·2)	- -	<0·001
	Yes	89 (54·9)	27 (48·2)	- -	62 (34·6)	1 (0·8)	- -	
	Missing		5				- -	
Any utertonic treatment*	*No*	5 (3·1)	3 (5)	21 (21·2)	13 (7·3)	9 (7·5)	- -	<0·001
	Yes	157 (96·9)	57 (95)	78 (78·8)	166 (92·7)	111 (92·5)	- -	
	Missing		1			6	- -	
Surgical management								
Intrauterine balloons	*No*	68 (42)	26 (44·8)	45 (45·5)	77 (43)	88 (72·1)	246 (85·4)	<0·001
	Yes	94 (58)	32 (55·2)	54 (54·5)	102 (57)	34 (27·9)	42 (14·6)	
	Missing	0	3	0	0	4		
Intra-abdominal packing	*No*	147 (90·7)	47 (83·9)	- -	- -	109 (90·1)	- -	0·344
	Yes	15 (9·3)	9 (16·1)	- -	- -	12 (9·9)	- -	
	Missing		5	- -	- -	5	- -	
Embolisaton or ligation	*No*	136 (84)	41 (67·2)	95 (96)	86 (48)	36 (29·5)	286 (99·3)	<0·001
	Yes	26 (16)	20 (32·8)	4 (4)	93 (52)	86 (70·5)	2 (0·7)	
	Missing					4		
Compressive sutures	*No*	123 (75·9)	38 (64·4)	86 (86·9)	154 (86)	90 (73·8)	247 (85·8)	<0·001
	Yes	39 (24·1)	21 (35·6)	13 (13·1)	25 (14)	32 (26·2)	41 (14·2)	
	Missing	0	2	0	0	4		
Hysterectomy	*No*	87 (53·7)	29 (47·5)	26 (26·3)	126 (70·4)	66 (54·5)	223 (77·4)	<0·001
	Yes	75 (46·3)	32 (52·5)	73 (73·7)	53 (29·6)	55 (45·5)	65 (22·6)	
	Missing	- -	- -	- -	- -	5	- -	

* Italian and Danish data include intrauterine packing· The Netherlands: intra-abdominal packing was after hysterectomy·

Table 4. Maternal outcomes by country

Maternal outcome		UK n=162	Australia n=61	Italy n=99	The Netherlands n=179	France n=126	Denmark n=288	P-value
Maternal death	*No*	160 (98·8)	61 (100)	96 (97)	175 (97·8)	123 (97·6)	286 (99·3)	0·37*
	Yes	2 (1·2)	0 (0)	3 (3)	4 (2·2)	3 (2·4)	2 (0·7)	
Cardiac arrest	*No*	154 (95·1)	57 (96·6)	94 (94·9)	- -	116 (92·1)	285 (99)	0·005*
	Yes	8 (4·9)	2 (3·4)	5 (5·1)	- -	10 (7·9)	3 (1)	
	Missing	0	2	0				
Renal failure	*No*	160 (98·8)	58 (98·3)	97 (98)	- -	106 (84·1)	284 (98·6)	<0·001*
	Yes	2 (1·2)	1 (1·7)	2 (2)	- -	20 (15·9)	4 (1·4)	
	Missing		2					
Infection	*No*	157 (96·9)	56 (96·6)	97 (98)	- -	118 (93·7)	- -	0·399*
	Yes	5 (3·1)	2 (3·4)	2 (2)	- -	8 (6·3)	- -	
	Missing	0	3	0		4		
Thrombotic event	*No*	158 (97·5)	57 (96·6)	99 (100)	- -	118 (93·7)	93·7 (287)	<0·001*
	Yes	4 (2·5)	2 (3·4)	0 (0)	- -	8 (6·3)	6·3 (1)	
	Missing	0	2	0	- -			
ITU admission	*No*	30 (18·5)	2 (3·3)	15 (15·3)	32 (17·9)	44 (34·9)	- -	<0·001
	Yes	132 (81·5)	59 (96·7)	83 (84·7)	147 (82·1)	82 (65·1)	- -	

*Fisher's exact

Maternal outcomes: Cardiac arrest: UK included - cardiac arrest, cardiac infection and cardioversion and inotropic support; Italy, Australia and France: cardiac arrest.

Infection: UK: chest infection, septicaemia, septic shock, sepsis, enterococcus infection, necrotising fasciitis, c difficile, abscess, suspected tuberculosis or meningitis, wound infection and wound dehiscence. Australia: sepsis. Italy and France: septicaemia.

Thrombotic: pulmonary embolism, deep venous thrombosis.

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3

Management of postpartum haemorrhage: how to improve maternal outcomes?

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Summary

Postpartum hemorrhage is the leading cause of maternal mortality and severe morbidity. Despite efforts to improve maternal outcomes, management of postpartum hemorrhage still faces at least four challenges, discussed in this review. First, current definitions for severe postpartum hemorrhage hamper early identification of women with high risk of adverse outcome. Adaptations to the definitions and the use of clinical tools such as shock index and early warning systems may facilitate this early identification. Second, surgical and radiological interventions to prevent hysterectomy are not always successful. More knowledge on the influence of patient and bleeding characteristics on the success rates of these interventions is necessary. Scarce data suggest that early timing of intra-uterine balloon tamponade may improve maternal outcomes, whereas early timing of arterial embolization seems to be unrelated to maternal outcomes. Third, fluid resuscitation with crystalloids and colloids is unavoidable in the early phases of postpartum hemorrhage, but may result in dilutional coagulopathy. Effects of different volumes of clear fluids on the occurrence of dilutional coagulopathy and maternal outcomes is unknown. Fourth, a better understanding of diagnosis and correction of coagulopathy during postpartum hemorrhage is needed. Low plasma fibrinogen levels at the start of postpartum hemorrhage predict progression to severe hemorrhage, but standard coagulation screens are time-consuming. A solution may be point-of-care coagulation testing, however, clinical usefulness during postpartum hemorrhage has not been demonstrated. To date, early administration of tranexamic acid is the only hemostatic intervention that was proven to improve outcomes in women with postpartum hemorrhage.

Keywords: blood transfusion, hemostasis, point-of-care testing, postpartum hemorrhage, resuscitation

Introduction

In 2014, the WHO concluded from a systematic analysis that postpartum hemorrhage accounts for almost one fifth of maternal deaths worldwide, ranging from 8% of all maternal deaths in developed regions to 29% in Eastern Asia and 32% in Northern Africa [1]. Incidences of postpartum hemorrhage continue to increase, even in high-resource settings [2-7]. Depending on the definition used, the incidence of postpartum hemorrhage ranges from 3 to 8% of all deliveries [2-4,6].

Main causes of postpartum hemorrhage are uterine atony and placental problems including retained placenta and abnormally invasive placenta. Even though numerous risk factors for postpartum hemorrhage have been identified, it is still an unpredictable obstetric emergency. As a consequence, every woman is considered at risk of developing postpartum hemorrhage following delivery[8].

Quality improvement tools such as triggers, bundles, checklists and protocols in women with postpartum hemorrhage may improve maternal mortality and severe maternal morbidity [9-11]. Introduction of these tools was reported to reduce the use of blood products and improve patient safety in women with postpartum hemorrhage [11]. However, there may be room for improvement in the separate components of these tools. Consequently, optimization of the management of ongoing postpartum hemorrhage still faces numerous challenges

In this article, we review the literature on these controversial issues. We discuss 1) adaptations to postpartum hemorrhage definitions and clinical tools for early identification of women at high risk of adverse outcome, 2) timing of obstetric interventions to stop bleeding, 3) timing of switch from volume resuscitation with clear fluids to transfusion of packed red blood cells and 4) timing of hemostatic interventions to correct coagulopathy in women with severe postpartum hemorrhage.

Improving maternal outcomes: timely recognition of patients with severe postpartum hemorrhage

Definition of severe postpartum hemorrhage

Currently, postpartum hemorrhage and its severity are defined by estimated blood loss within 24 hours following delivery [12]. Cut-off values of 500 and 1000 mL are used for defining postpartum hemorrhage, with the latter mostly used in high-resource settings [13]. However, these cut-off values are relatively poor in identifying women with high risk of severe maternal morbidity and mortality, as only a small proportion of women that reach these cut-off values of blood loss progress to hemorrhage leading to hysterectomy or maternal death.

In a recent Delphi study performed by the International Network of Obstetric Surveillance Systems (INOSS), consensus definitions of several conditions of severe maternal morbidities were developed. The proposed definition for severe primary postpartum hemorrhage was blood loss exceeding 2000 mL and/or the need of transfusion of at least four units of packed red blood cells [14]. This definition enables selection of women with a higher risk of adverse maternal outcome than women with blood loss exceeding 500 or 1000 mL, while facilitating international comparisons of incidences of severe maternal morbidity and mortality as a result of postpartum hemorrhage. In practice, however, this definition excludes the possibility of early identification of women at high risk of adverse maternal outcome, as this definition reflects an intermediary or even end stage of hemorrhage.

Qualitative studies among experienced birth attendants show that severity of hemorrhage not only depends on volume of blood loss, but also on rate of bleeding and physiological response to bleeding [15]. In recognition of these determinants, several guidelines incorporated clinical signs of shock to express physiological response to bleeding in the definition of severe postpartum hemorrhage [16,17]. In addition, an international expert panel proposed to add *response to treatment* as a determinant of severity to the definition of postpartum hemorrhage, and suggested defining severe postpartum hemorrhage as persistent (ongoing) hemorrhage >1000 mL within 24 hours following birth that continues despite the use of initial measures to stop bleeding [8]. Adding *refractoriness to initial measures* to the definition of postpartum hemorrhage has the potential advantage of early identification of women at high risk of adverse maternal outcome by considering women as having a severe hemorrhage

as soon as initial uterotonic treatment fails to stop hemorrhage. Whether or not this adaptation will improve maternal outcomes might become clear in the near future, as this extension has already been implemented in a national guideline (figure 1)[18].

Clinical tools for early recognition of women with severe postpartum hemorrhage

Cardiac output increases during pregnancy due to a physiologic increase in heart rate and blood volume and blood pressure decreases due to lower systemic vascular resistance [19,20]. Cardiac output further increases during labor and delivery, because of a higher preload caused by uterine contractions. After delivery, preload further increases as a result of relief of inferior vena cava compression by the gravid uterus and the return of uterine blood to maternal circulation. As a result, early recognition of a deterioration in clinical condition in women with postpartum hemorrhage is difficult [21].

This early detection of deterioration in clinical condition has gained a lot of interest over the past decades, both in the pregnant and non-pregnant patients. Recent studies examined whether the *shock index* and *early warning systems* can be used to monitor women with postpartum hemorrhage. The *shock index* is the ratio of heart rate to systolic blood pressure. In the non-pregnant population a shock index >1.0, thus a higher heart rate than systolic blood pressure measured at least once in the observation period, has been associated with morbidity and mortality in critically ill patients suffering trauma, sepsis and after surgery [22-25]. A study among 8874 women without postpartum hemorrhage reported a range of 0.5 to 1.1 for the shock index immediately following delivery [26]. Another study among 233 women with postpartum hemorrhage with blood loss exceeding 1500 mL concluded that a shock index ≥1.7 was a predictor of intensive care unit admission, invasive surgical procedures and transfusion of ≥4 units of packed red blood cells, with respective area under the curves 0.75 (95% confidence interval 0.63-0.87), 0.62 (0.45-0.79) and 0.67 (0.58-0.76) [27]. Correspondingly, a secondary analysis of 958 women with hypovolemic shock due to postpartum hemorrhage in low-resource settings showed similar results for a composite maternal outcome for this cut-off value of ≥1.7 for the shock index, area under the curve of 0.76 (0.71-0.81). The composite outcome in this study consisted of maternal death, severe end-organ failure, intensive care unit admission, emergency hysterectomy and transfusion of ≥5 units of packed red blood cells [28].

Early warning scoring systems were also introduced to improve early recognition

of life threatening conditions. These scores are repeatedly calculated based on physiological parameters: heart rate, systolic blood pressure, respiratory rate, temperature and mental state [29]. The principle is that acute deterioration is preceded by subtle changes in these physiological parameters, and that these would be noticed earlier using *early warning scoring systems* than waiting for obvious changes in individual parameters [29,30]. In a systematic review, *early warning systems* were shown to successfully predict mortality in non-pregnant patients in different clinical settings [31]. Another systematic review focused on critically ill patients and concluded that the use of many different *early warning score systems* with different trigger thresholds hampered meta-analysis of conflicting findings [30].

Studies on the use of early warning systems in obstetric populations generally focus on several severe conditions in pregnancy and puerperium simultaneously, including preeclampsia, postpartum hemorrhage and sepsis. A retrospective study among 702 obstetric patients, in a low-resource setting, admitted to the intensive care unit showed an area under the curve for maternal death for high early warning scores of 0.84 (0.75-0.92) [32] . Similarly, several other obstetric early warning systems also showed to be able to differentiate well between women with and without an adverse outcome [33-36]. Maternal outcomes were also reported to improve after introduction of a Maternal Early Warning Trigger tool, as compared to before introduction of the tool. In this study, hysterectomy rates decreased from 0.94/1000 to 0.63/1000 deliveries [37].

To conclude, adding *refractoriness to initial measures* to definitions of severe postpartum hemorrhage may warrant early identification of women at high risk of adverse outcome. Clinical tools as *shock index* and *early warning scores* seem to have a good ability to predict adverse outcomes in women with postpartum hemorrhage. Further studies to quantify the added clinical value with respect to preventing adverse outcomes are to be awaited.

Improving maternal outcomes: obstetric interventions to stop bleeding

Initial measures to stop bleeding depend on the primary cause of hemorrhage. In case of uterine atony, the uterus is massaged as soon as uterine atony is diagnosed, and uterotonic agents are administered. The first-choice uterotonic agent is oxytocin, but if unavailable, misoprostol or ergot alkaloids are recommended [12,38]. If postpartum hemorrhage occurs with the placenta still in utero, manual removal of the placenta is performed. If the placenta has already been delivered, examination of the uterine

cavity under anesthesia to exclude placental remnants should be considered. However, when postpartum hemorrhage proves to be refractory to these initial measures to stop bleeding, guidelines prostaglandins as second-line uterotonic agents for treatment of uterine atony [16,18,39]. Bimanual uterine compression is recommended as a temporizing measure awaiting definitive uterotonic, surgical or radiological interventions to stop bleeding [12]. Surgical and radiological interventions to stop bleeding include intrauterine balloon tamponade, arterial embolization, arterial ligation and uterine compression sutures (brace sutures). If bleeding persists despite these interventions, hysterectomy should be performed.

Hysterectomy to avoid maternal death should be performed "sooner rather than later", according to the Royal College of Obstetricians & Gynaecologists (RCOG)[16]. Intrauterine balloon tamponade, arterial embolization, arterial ligation and uterine compression sutures have all been reported to be effective in stopping hemorrhage and preventing hysterectomy [40-51]. Yet, if unsuccessful, these interventions may also delay hysterectomy, especially because they are performed with low frequency, and thus, experience with these techniques may be insufficient.

When it comes to these interventions to avoid hysterectomy in women with severe postpartum hemorrhage two important issues on the appropriate timing of hysterectomy need to be resolved. First, we need to be able to recognize situations in which hysterectomy will be needed anyway. If surgical and radiological interventions fail most of the time in women with already high volumes of blood loss, high bleeding rates or who are hemodynamically unstable at moment of employment of these interventions, perhaps treating physicians should immediately perform the hysterectomy [52-54].

Second, we would argue for more insight into the interaction between the timing of the surgical and radiological and interventions and their success rates. Early employment of these interventions could minimize delay in hysterectomy in women in whom the bleeding proves refractory to these interventions. A study among 420 women with estimated blood loss >500 mL after vaginal delivery and >1000 mL after cesarean delivery assessed the effect of timing of uterine balloon tamponade and uterine artery embolization on maternal morbidity including hysterectomy and intensive care unit admission [55]. Timing of intervention was expressed as a function of estimated blood loss at the moment of employment of the intervention, and early timing of balloon tamponade (n=48) was associated with improved maternal

outcomes. For early timing of arterial embolization (n=20), this association was not shown. Larger studies are needed to know whether these findings are robust, and whether earlier surgical and radiological interventions to stop bleeding result in a reduction in adverse maternal outcomes.

In conclusion, a better understanding of the influence of patient and bleeding characteristics and timing of interventions on the success rates of surgical and radiological interventions to stop bleeding is necessary to improve outcomes of women with postpartum hemorrhage.

Improving maternal outcomes: timing of switch from resuscitation with clear fluids to transfusion of blood products

Fluid resuscitation should start as soon as the severity of postpartum hemorrhage becomes evident, to maintain circulating blood volume and preserve tissue oxygenation [8]. The first stage of fluid resuscitation consists of administration of crystalloids and colloids, and in case of ongoing hemorrhage, this stage is followed by the second stage consisting of transfusion of blood products.

In addition to abovementioned goals of resuscitation, blood products are also administered to support hemostasis and correct coagulopathy. Transfusion of plasma provides deficient coagulation factors, and packed red blood cells may also support primary hemostasis through different mechanisms. Red blood cells in the center of the vessel lumen may increase platelet concentrations near the endothelium [56]. Theoretically this so-called margination of platelets might support primary hemostasis, but this has not been supported by quantitative evidence. In addition, red blood cells may enhance platelet reactivity [57,58], support shear-induced platelet aggregation [59] and support thrombin generation by exposing procoagulant phospholipids [60-62].

Fluid resuscitation with high volumes of crystalloids and colloids, induces dilution of clotting factors and platelets, causing dilutional coagulopathy and thus aggravating hemorrhage [63]. In women with severe postpartum hemorrhage it has never been assessed, nonetheless, which volumes of clear fluids cause dilutional coagulopathy, nor whether dilutional coagulopathy contributes to adverse maternal outcome. A study examining varying degrees of hemodilution in healthy volunteers showed both in vitro and in vivo that hemodilution with normal saline decreased concentrations of coagulation and antifibrinolytic factors (α2-antiplasmin and thrombin-activatable fibrinolysis inhibitor (TAFI)), and decreased thrombin generation [64,65]. Impaired

thrombin generation was also confirmed in bleeding patients with dilutional coagulopathy during major surgery, concomitant with impaired fibrin clot formation [66]. In these patients, volume of crystalloids, colloids, but also red blood cells, exceeded 5L.

Moreover, colloid fluids have been associated with impairment of different aspects of coagulation. Colloid fluids like hydroxyethyl starches, dextrans and gelatins have been associated with impaired platelet function, inhibition of fibrin polymerization and increase of fibrinolysis, and may lead to decreased levels of von Willebrand factor [65,67]. Clinically relevant effects of colloid fluids on coagulation in non-pregnant patients seem to arise when larger volumes are administered [67]. Effects of administration of colloid fluids on adverse maternal outcome in women with postpartum hemorrhage are unknown.

The RCOG guideline on prevention and management of postpartum hemorrhage recommends a maximum volume of clear fluids of 3.5L before start of blood transfusion, comprising up to 2L crystalloids and 1.5L colloids [16]. This advice was based on consensus from a Working Party of Haemostasis and Thrombosis Task Force [68]. However, thus far there is insufficient quantitative evidence to support this hypothesis. As a consequence, it is uncertain which volumes and combination of clear fluids increase the risk of adverse maternal outcome in women with postpartum hemorrhage.

Summarizing, resuscitation with clear fluids in women with postpartum hemorrhage is generally unavoidable because of the unpredictability of postpartum hemorrhage. However, switching to transfusion of blood products when these are available would probably reinforce hemostasis and thus be beneficial for women with ongoing postpartum hemorrhage.

Improving maternal outcomes: timing of hemostatic interventions to correct coagulopathy

Diagnosis of coagulopathy in women with postpartum hemorrhage

Pregnancy is a hypercoagulable state due to changes in the coagulation system throughout the pregnancy (figure 2) [69-72]. The majority of procoagulant factors increase, while the level of protein S as endogenous anticoagulant and fibrinolytic activity decrease. The most marked increases in procoagulants seem to occur in

concentrations of factor VII, factor VIII, von Willebrand factor and fibrinogen [72]. Fibrinogen concentration increases to approximately twice the non-pregnant values at term, with levels between 4 and 6 g/L [71]. The physiologic increase in plasma volume in pregnancy may also cause a mild thrombocytopenia [73]. Altogether, haemostatic changes of pregnancy lead to a slightly shortened prothrombin time (PT) and activated partial thromboplastin time (APTT), within the range of non-pregnant reference values [69,71,73].

A woman with ongoing postpartum hemorrhage may develop coagulopathy due to loss, dilution and consumption of platelets and clotting factors. All factors involved in coagulation may become deficient, procoagulant and anti-coagulant proteins, as well as fibrinolytic and antifibrinolytic proteins [66]. Impairment of hemostasis may also occur because of disseminated intravascular coagulation [64]. Risk factors for developing disseminated intravascular coagulation are placental abruption, preeclampsia with HELLP syndrome, and amniotic fluid embolism [64].

The monitoring of coagulation in women with severe postpartum hemorrhage is subject of debate. Conventional hemostasis assays such as the PT and APTT tests are considered unsuitable because of an inability to detect specific changes in coagulation, a disregard of large parts of coagulation (i.e. platelet function and fibrinolysis) and long turn-around times [74]. Studies that assessed the changes in PT and APTT during postpartum hemorrhage reported values within non-pregnant reference values during postpartum hemorrhage, even with high volumes of blood loss [75,76]. Among 356 women with postpartum hemorrhage PT and aPTT measured at 1-1.5L blood loss were not associated with progression to blood loss >2.5L [77].

Data on changes in platelet counts and function during postpartum hemorrhage are scarce. Available studies report minimal decreases of platelet counts during postpartum hemorrhage, and platelet counts measured in women with blood loss between 1 and 1.5L seem not to be associated with progression to higher volumes of blood loss [78,79].

Several observational studies reported a plasma fibrinogen level measured early during postpartum hemorrhage to be predictive of progression to more severe bleeding and invasive procedures in women with postpartum hemorrhage [75,77,79-81]. Positive predictive value of a fibrinogen level ≤2g/L for progression to severe bleeding was reported to be 100%, whilst negative predictive value of fibrinogen >4 g/L was 79%

[79]. Reported odds ratios for fibrinogen <2 g/L for progression to severe hemorrhage were 12.0 (95% confidence interval 2.6-56.1) and for fibrinogen between 2 and 3 g/L 1.9 (1.2-3.1) [80]. A point-of-care test to measure fibrinogen within a few minutes or seconds might be a promising monitoring tool for women with severe postpartum hemorrhage.

Since obtaining results of standard coagulation screens are time-consuming, coagulation monitoring with point-of-care tests is increasingly used in women with severe postpartum hemorrhage to detect coagulopathy and guide hemostatic interventions. However, the clinical usefulness of thromboelastography and thromboelastometry in women with postpartum hemorrhage has not been established [74]. As with the standard coagulation screens, thromboelastography and thromboelastometry values are different from the non-pregnant population due to the prohemostatic changes of pregnancy [63,74]. Several observational studies reported reference values for these point-of-care tests in pregnancy and the peripartum period, confirming the increased coagulability with faster initiation of coagulation and decreased fibrinolysis [82-84]. The next steps to be undertaken to eventually determine the clinical usefulness of these point-of-care tests in women with postpartum hemorrhage are 1) investigation of the changes in the measured values during postpartum hemorrhage and whether these measured values reflect impaired coagulation, as compared with standard coagulation assays, 2) investigation of appropriate interventions to correct these changes and 3) investigation of effects of the use of these tests in treatment algorithms for postpartum hemorrhage on clinically relevant maternal outcomes [85].

Overall, there seem to be minimal changes in PT, aPTT and platelet counts during postpartum hemorrhage, and only low plasma fibrinogen concentrations seem associated with progression to larger bleeds. Clinical usefulness of thromboelastography and thromboelastometry in women with postpartum hemorrhage is yet to be determined.

Correction of coagulopathy: early timing of fresh frozen plasma

Early timing of fresh frozen plasma, expressed as a high fresh frozen plasma to packed red blood cells ratio, seemed to reduce mortality in (non-pregnant) trauma patients in observational studies. Despite concerns about high risk of bias in these studies, massive transfusion protocols incorporating high ratio plasma and platelets to red blood cells were widely implemented in many different clinical settings with major

hemorrhage. A randomized clinical trial among 680 trauma patients with major bleeding receiving either a plasma:platelets:red blood cells ratio of 1:1:1 or ratio 1:1:2 showed no statistically significant difference in 24 hours and 30 days mortality with risk differences -4.2% (95% confidence interval -9.6 to 1.1) and -3.7% (-10.2 to 2.7) [86]. Death from exsanguination, a secondary outcome, was significantly decreased in patients that received a high ratio as compared with a low ratio, difference -5.4% (-10.4 tot -0.5).

In women with postpartum hemorrhage, studies on early timing of plasma to correct coagulopathy and improve maternal outcomes are limited. An observational before-and-after study among 142 women with severe postpartum hemorrhage, defined as postpartum hemorrhage requiring the second-line prostaglandin analogue sulprostone and packed red blood cells transfusion within six hours following delivery, compared fresh frozen plasma to red blood cells ratio of >0.5 with ratio ≤0.5 on advanced interventional procedures [87]. To account for confounding by indication, propensity score matching was performed for the 41 women who received plasma. In this study, a low fresh frozen plasma to red blood cells ratio was associated with more advanced interventions, odds ratio 1.3 (1.1-1.5), suggesting a beneficial effect of administering plasma early during the course of postpartum hemorrhage [87].

High ratios of plasma to red blood cells in women with postpartum hemorrhage were also studied within massive transfusion protocols. These massive transfusion packs were part of an obstetric hemorrhage protocol that included a whole series of other changes in management [11]. The combination of changes in management seemed to reduce blood product use in these women, but the ratios of blood products in the designated “obstetrics hemorrhage pack” were based on evidence from trauma-related hemorrhage. Future studies need to address the comparison of different transfusion protocols for postpartum hemorrhage.

Interestingly, in a recent observational study among 605 women with postpartum hemorrhage exceeding 1L of blood loss fresh frozen plasma was administered when thromboelastometry showed signs of fibrinogen deficiency (Fibtem A5 ≤15 mm)[88]. The women who did not reach Fibtem A5 below 15 mm did not develop clinically significant hemostatic impairment, defined as continued bleeding and laboratory hemostatic failure (PT or aPTT >1.5 times the midpoint of the normal range or fibrinogen <2 g/L).

Concluding, whether early administration of plasma during the course of

postpartum hemorrhage improves maternal outcomes is still unclear.

Correction of coagulopathy: early timing of tranexamic acid

The effect of early administration of the antifibrinolytic agent tranexamic acid on maternal mortality and hysterectomy, as compared with placebo, has recently been assessed in the WOMAN trial, an international randomized controlled trial among 20060 women with postpartum hemorrhage [89]. Postpartum hemorrhage was defined as 500 or 1000 mL depending on the mode of delivery, or blood loss causing hemodynamic instability. In this study all-cause mortality and composite outcome consisting of all-cause mortality and hysterectomy did not differ between women treated with tranexamic acid or placebo, corresponding risk ratios 1.02 (0.88-1.07) and 0.97 (0.87-1.09). Compared with placebo, death due to bleeding was significantly reduced in women treated with tranexamic acid, risk ratio 0.81 (0.65-1.00), and when administered within three hours following birth 0.69 (0.52-0.91). Importantly, administration of tranexamic acid was not associated with an increased risk of venous thromboembolism.

Generalizability of the results of the WOMAN trial has been questioned, as almost all study participants (97%) were recruited in low-resource settings with high maternal mortality ratios [90-92]. Effect of adding tranexamic acid to treatment algorithms in high-resource settings, with advanced uterotonic, surgical and radiological interventions and transfusion of blood products available, on severe maternal morbidity and mortality remains unclear. A randomized controlled trial in a high-resource setting among 144 women with postpartum hemorrhage >800 mL following delivery compared the effect of high-dose tranexamic acid versus no tranexamic acid at moment of diagnosis of postpartum hemorrhage on total blood loss and invasive interventions to stop bleeding [93]. Tranexamic acid reduced median additional blood loss from moment of diagnosis of postpartum hemorrhage till end of bleeding slightly from 221 (interquartile range 105 to 564) to 173 mL (59 to 377) (p-value 0.04), and there was no difference in advanced interventions to stop bleeding. Similarly, a before-and-after observational study in a high-resource setting including 289 women with hemorrhage ≥500 mL following delivery, did not show a decrease in mean estimated blood loss after incorporating tranexamic acid in the treatment algorithm [94]. Additionally, early administration of tranexamic acid did not reduce adverse maternal outcome in a cohort study among 1260 women in the Netherlands with postpartum hemorrhage >1L and refractory to first-line obstetric interventions, odds ratio 0.9 (95% confidence interval 0.7-1.3) [95].

In women with postpartum hemorrhage, early tranexamic acid seems to reduce the risk of maternal death due to exsanguination, with a favorable safety profile. However, the effect on maternal outcome in women with postpartum hemorrhage in high-resource settings may be limited. Future studies need to establish whether and when tranexamic acid improves clinical outcomes of women with postpartum hemorrhage.

Correction of coagulopathy: early timing of fibrinogen concentrate

Two randomized controlled trials investigated the effect of fibrinogen concentrate on maternal outcome. In the first trial, including 249 women with severe postpartum hemorrhage (after vaginal delivery >0.5L blood loss with retained placenta or >1L blood loss and intended manual exploration of the uterus, or >1L blood loss after caesarean delivery), pre-emptive treatment with 2g fibrinogen concentrate did not reduce the need for packed red blood cell transfusion or secondary outcomes, as compared with placebo [96]. At inclusion mean blood loss was 1459 mL (standard deviation 476 mL) and mean plasma fibrinogen level was 4.5 g/L (standard deviation 1.2). In the second trial, that randomized 55 women to fibrinogen concentrate or placebo, fibrinogen concentrate was administered in case the Fibtem A5-value, the thromboelastometry surrogate measure of plasma fibrinogen level, was below 15 mm [97]. This cut-off value for Fibtem was chosen after a preceding observational study among 365 women with postpartum hemorrhage (1-1.5L) indicating a predictive role of low Fibtem values for development of severe hemorrhage [77]. Median blood loss at time of study medication infusion was 1950 mL (interquartile range 1500-2285) and median fibrinogen level 2.5 g/L. In this trial administration of fibrinogen concentrate did not reduce the number of transfused blood components.

There are some published data on the use of algorithms to guide treatment of postpartum hemorrhage using thromboelastography and thromboelastometry. A before-and-after observational study with Rotem-guided fibrinogen concentrate administration reported a lower blood components use as compared with administration of fresh frozen plasma in major hemorrhage transfusion packs [98]. The study included 93 women with ongoing postpartum hemorrhage (>1500 ml) and coagulopathy defined as Fibtem A5 <12mm.

Thus, administration of fibrinogen concentrate to women with ongoing postpartum hemorrhage and fibrinogen level above 2g/L does not seem associated with better

maternal outcomes. Trials with fibrinogen administration in women with postpartum hemorrhage and plasma fibrinogen levels below 2g/L might demonstrate an effect on maternal outcomes. Before performing these trials, we need a test that provides fast and accurate estimates of a woman's fibrinogen concentration.

Correction of coagulopathy: recombinant activated factor VII

Following an abundance of case series, only one randomized controlled trial has been published on administration of recombinant activated factor VII in women with postpartum hemorrhage for correction of coagulopathy [99]. In this open-label trial 84 women with severe postpartum hemorrhage (>1.5L) refractory to the uterotonic agent sulprostone were randomized to a single dose of recombinant activated factor VII (60 ug/kg) or standard care. Randomization occurred one hour after onset of sulprostone, and outcomes were the need of advanced surgical or radiological intervention after randomization. Early administration of recombinant factor VII was associated with a reduction in advanced interventions to stop bleeding, relative risk 0.56 (0.42-0.76). However, information bias could have influenced the study results, as there was no allocation concealment in the study. Venous thromboembolism occurred in 5% of women who received recombinant activated factor VII, and did not occur in the women who underwent standard care. In a meta-analysis including only randomized controlled trials among non-obstetric bleeding patients this hemostatic agent was associated with arterial thromboembolism with odds ratio 1.7 (1.2-2.4), but not with venous thromboembolism (odds ratio 0.9 (0.7-1.2)) [100].

Correction of coagulopathy: prothrombin complex concentrate

To date, comparative studies on administration of prothrombin complex concentrate in women with postpartum hemorrhage have not been published. A randomized controlled trial comparing prothrombin complex concentrate and fibrinogen concentrate with fresh frozen plasma (NCT01910675) did not get permission from the appropriate Medical Ethical Committee, because it was not feasible to get proper informed consent from these acute, severely ill patients (personal communication).

Conclusion

In the optimization of management of postpartum hemorrhage we are still facing several challenges. Early recognition of women at high risk of adverse outcomes because of postpartum hemorrhage may be achieved by adaptations to the definition of severe postpartum hemorrhage and the use of clinical tools such as *shock index* and

early warning scores.

Optimization of timing of surgical, radiological and hemostatic interventions in these women to stop bleeding and timing of switch from resuscitation with clear fluids to transfusion of blood products is of utmost importance to reach the goal of improving maternal outcomes. However, well-designed studies on obstetric interventions to stop bleeding are scarce and results from studies on hemostatic interventions to stop hemorrhage in these women show conflicting results. Broadening our understanding of the interaction of individual patient characteristics with these interventions will enable us to improve management and outcomes of women with severe postpartum hemorrhage.

Addendum

D.D.C.A. Henriquez collected literature and wrote the first draft of the manuscript. All authors were involved in interpretation of data and revision of the manuscript.

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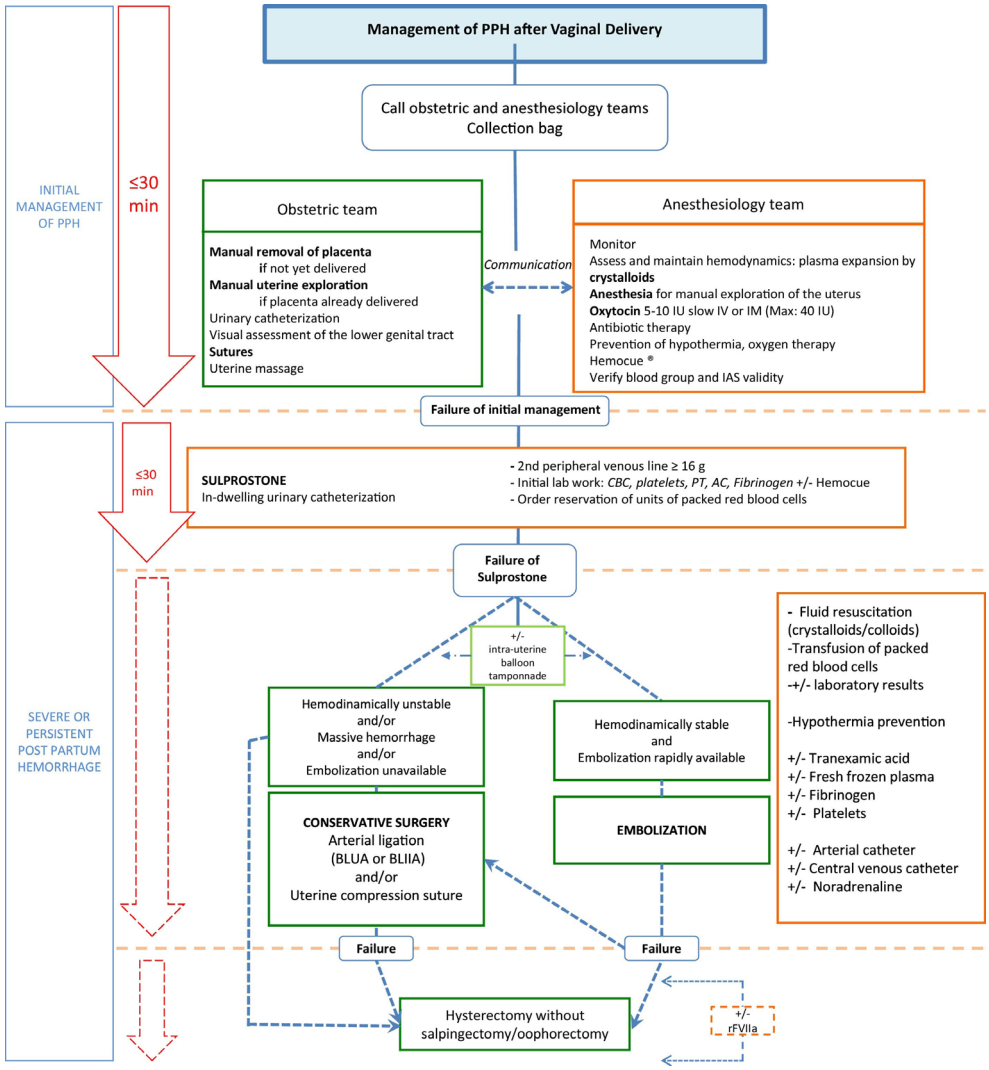

Figure 1. Algorithm from French guideline for management of postpartum hemorrhage after vaginal delivery, with definition of severe postpartum hemorrhage as postpartum hemorrhage refractory to initial measures to stop bleeding. PPH, postpartum hemorrhage; IV, intravenous; IM, intramuscular; IU, international unit; IAS, irregular antibody screening; CBC, complete blood count; PT, prothrombin time; ACT, activated clotting time; BLUA, bilateral ligation of uterine arteries; BLIIA, bilateral ligation of internal iliac arteries; rFVIIa, recombinant activated Factor VII. Adapted from Sentilhes et al. [18]

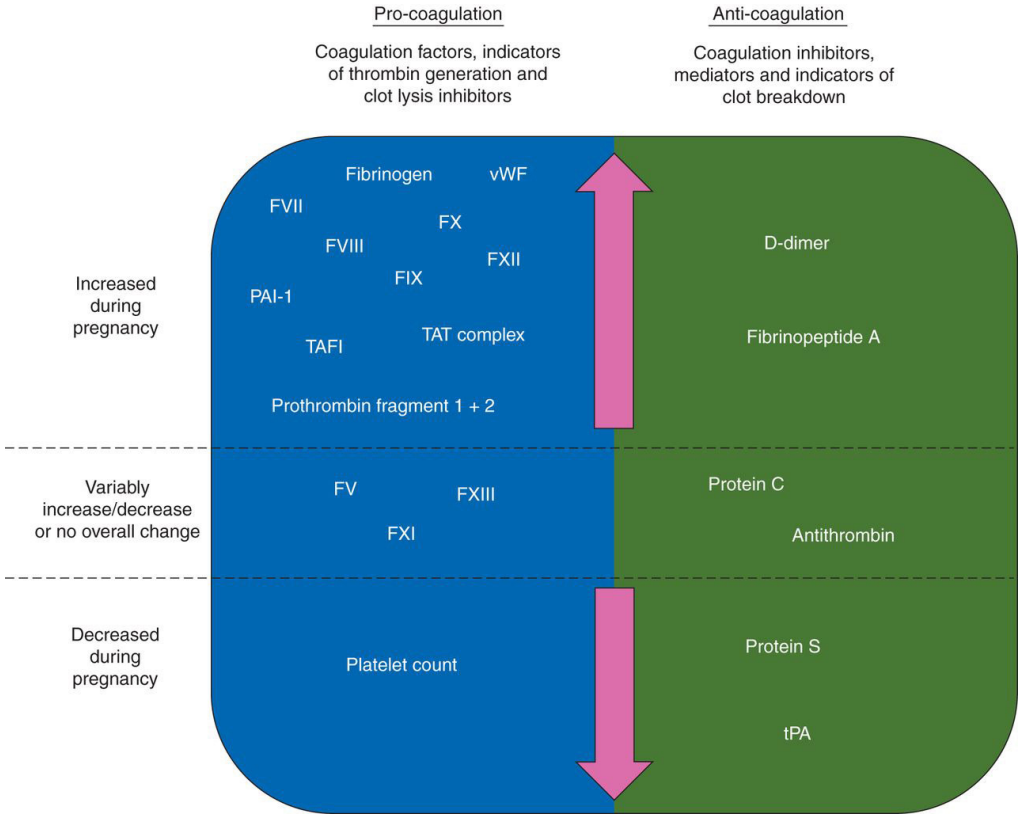

Figure 2. Hemostatic changes during normal pregnancy. The overall increase in pro-coagulant factors results in a hypercoagulable state which increases throughout pregnancy. Increases and decreases are relative to non-pregnancy. Positioning of factors is not indicative of the precise level of increase or decrease. FV, Factor V; FVII, Factor VII; FVIII, Factor VIII; FIX, Factor IX; FX, Factor X; FXI, Factor XI; FXII, Factor XII; FXIII, Factor XIII; PAI-1, plasminogen activator inhibitor 1; TAFI, thrombin activatible fibrinolysis inhibitor; TAT complex, thrombin-antithrombin complex; tPA, tissue plasminogen activator; vWF, von Willebrand factor. Solomon et al. [70]

PART 2

Women with postpartum haemorrhage: who is at risk of adverse outcome?

4

Clinical characteristics and outcomes of women captured by extending the definition of severe postpartum haemorrhage with 'refractoriness to treatment': a cohort study

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Abstract

Background The absence of a uniform and clinically relevant definition of severe postpartum haemorrhage hampers comparative studies and optimization of clinical management. The concept of persistent postpartum haemorrhage, based on refractoriness to initial first-line treatment, was proposed as an alternative to common definitions that are either based on estimations of blood loss or transfused units of packed red blood cells (RBC). We compared characteristics and outcomes of women with severe postpartum haemorrhage captured by these three types of definitions.

Methods In this large retrospective cohort study in sixty-one hospitals in the Netherlands we included 1391 consecutive women with postpartum haemorrhage who received either ≥4 units of RBC or a multicomponent transfusion. Clinical characteristics and outcomes of women with severe postpartum haemorrhage defined as persistent postpartum haemorrhage were compared to definitions based on estimated blood loss or transfused units of RBC within 24 hours following birth. Adverse maternal outcome was a composite of maternal mortality, hysterectomy, arterial embolisation and intensive care unit admission.

Results 1260 out of 1391 women (90.6%) with postpartum haemorrhage fulfilled the definition of persistent postpartum haemorrhage. The majority, 820/1260 (65.1%), fulfilled this definition within one hour following birth, compared to 819/1391 (58.7%) applying the definition of ≥1L blood loss and 37/845 (4.4%) applying the definition of ≥4 units of RBC. The definition persistent postpartum haemorrhage captured 430/471 adverse maternal outcomes (91.3%), compared to 471/471 (100%) for ≥1L blood loss and 383/471 (81.3%) for ≥4 units of RBC. Persistent postpartum haemorrhage did not capture all adverse outcomes because of missing data on timing of initial, first-line treatment.

Conclusion The definition persistent postpartum haemorrhage identified women with severe postpartum haemorrhage at an early stage of haemorrhage, unlike definitions based on blood transfusion. It also captured a large majority of adverse maternal outcomes, almost as large as the definition of ≥1L blood loss, which is commonly applied as a definition of postpartum haemorrhage rather than severe haemorrhage.

Trial registration Netherlands Trial Register, identifier: NTR4079

Keywords

Definition, maternal morbidity, maternal mortality, postpartum haemorrhage

Background

Postpartum haemorrhage is a common obstetric emergency, complicating 3-8% of all births.[1-6] Severe postpartum haemorrhage accounts for more than a quarter of all maternal deaths worldwide,[7] and is the leading cause of severe maternal morbidity in high-resource countries.[4,5,8-10] Consequently, prevention and optimization of its management continue to receive considerable attention.

Optimization of management of postpartum haemorrhage, however, is currently hampered by the use of many different definitions of severe postpartum haemorrhage. Commonly used definitions of postpartum haemorrhage and its severity are based on estimations of blood loss or the need of transfusion of packed red blood cells (RBC) within 24 hours following birth.[11-19] Severity of postpartum haemorrhage, however, depends not only on volume, but also on the rate of blood loss, physiological response to bleeding and response to treatment.[11,20,21] Such characteristics of bleeding are important determinants of clinical management during the dynamic process of ongoing haemorrhage.[20] The need for transfusion on the other hand, reflects an intermediary state during ongoing bleeding or the end stage of haemorrhage, and is therefore unsuitable when it comes to decisions regarding when to start more aggressive interventions to prevent adverse maternal outcome in women with severe postpartum haemorrhage.

Because of these shortcomings, a panel of experts on postpartum haemorrhage proposed to define severe postpartum haemorrhage not only according to the volume of blood loss, but also to failure to respond to initial, first-line measures to control bleeding. An important advantage of this definition, which they named *persistent postpartum haemorrhage*[11], is that it can be universally applied in low-, middle- and high-income settings, since the initial, first-line uterotonic and surgical measures to stop bleeding are commonly performed across all regions. This includes regions dealing with lack of blood for transfusion, where many women who suffer from severe haemorrhage would not be included if case definitions based on the number of transfusions given would be applied.[17] Furthermore, '*refractoriness to treatment*' is a clear-cut moment during haemorrhage that may allow for differentiation between women who will stop bleeding soon, and those with ongoing haemorrhage who are at increased risk of adverse maternal outcome.

In order to gain knowledge on the case-mix of women captured by *persistent*

postpartum haemorrhage as a definition of severe postpartum haemorrhage, we aimed to describe clinical characteristics and outcomes of women selected by this definition, as compared to definitions based on estimations of blood loss and transfused RBC.

Methods

Population

The current analysis was performed as part of the TeMpOH-1 study, a cohort study in the Netherlands on Transfusion strategies in women with Major Obstetric Haemorrhage in which 61 out of 86 hospitals (71%) participated. In the TeMpOH-1 study, we included consecutive women who, from January 1st, 2011, to January 1st, 2013, received either ≥4 units of RBC or a multicomponent blood transfusion within 24 hours following birth because of postpartum haemorrhage exceeding 1000 mL of blood loss. A multicomponent blood transfusion was defined as blood transfusion consisting of a combination of RBC and fresh frozen plasma and/or platelet concentrates. Women were retrospectively selected from transfusion databases and birth registries of participating hospitals.

Data collection

Detailed information concerning pregnancy, birth and the course of bleeding was gathered from routinely documented medical information. Comprehensive chart reviews were uniformly performed by well-trained medical students and research nurses. At the end of data collection, the first author and two data managers checked all data for completeness and inconsistencies, and whenever necessary, on-site chart review was repeated.

Collected data included age, ethnicity, weight, height, comorbidity, mode of birth, primary cause of haemorrhage, consecutive estimates of blood loss and timing of estimations, blood pressure and heart rate throughout the haemorrhage and timing of measurements, volume of clear fluids for fluid resuscitation and timing of administration, timing of all obstetric and haemostatic interventions to control bleeding, timing of administration of every unit of RBC, fresh frozen plasma and platelets.

Outcomes

We followed women from onset of childbirth until cessation of bleeding postpartum or death, and in this manner reconstructed the course of every included woman

with postpartum haemorrhage. Primary outcome was adverse maternal outcome, a composite of maternal mortality and severe maternal morbidity, with the latter defined as postpartum arterial embolisation, hysterectomy or intensive care unit admission. Secondary outcomes were total blood loss, time from birth until cessation of bleeding or death, total number of units of RBC transfused and time from birth till transfusion of first unit of RBC.

Persistent postpartum haemorrhage

Persistent postpartum haemorrhage was defined as ongoing postpartum haemorrhage of at least 1000 mL within 24 hours following birth, refractory to initial, first-line treatment to stop bleeding.[11] Initial, first-line treatment depended on the primary cause of postpartum haemorrhage. Postpartum haemorrhage caused by uterine atony, retained placenta, genital tract trauma, placenta previa or placental abruption was considered persistent if bleeding continued despite uterine massage, oxytocin, misoprostol, methylergometrine, suturing of tears, and manual removal of placenta or placental remnants. Women with abnormally invasive placenta as primary cause of postpartum haemorrhage, a surgical cause (including uterine rupture) or a pre-existent coagulation disorder (congenital or acquired) were regarded as having persistent postpartum haemorrhage irrespective of initial first-line treatment, since these complex haemorrhages require a series of obstetric and haemostatic measures to control bleeding.

Blood loss, bleeding rate and signs of haemorrhagic shock at time of inclusion

In the Netherlands, volume of blood loss during postpartum haemorrhage is determined by weighing gauzes, cloths and surgical swabs and by measurements using suction canisters. We linearly interpolated volume of blood loss between consecutive estimations of blood loss throughout bleeding, by using all recorded estimations of blood loss and timing of measurements from onset until cessation of bleeding. Cessation of bleeding was defined as the time of the last estimation of blood loss recorded in the medical files or the time of the last obstetric intervention to stop bleeding. Bleeding rate was calculated by dividing blood loss between two consecutive estimations by the time interval in between. At least one measurement of systolic blood pressure ≤90 mmHg and/or a heart rate ≥120 beats per minute from start of haemorrhage till time of inclusion were considered signs of haemorrhagic shock.[22]

Statistical analysis

We summarized clinical characteristics and outcomes of women captured by the definition *persistent postpartum haemorrhage* and of women captured by different cut-offs for estimated blood loss and for transfused units of RBC within 24 hours following birth. Cut-offs used for estimations of blood loss were: ≥1000 mL, ≥1500 mL, ≥2000 mL and ≥2500 mL. Cut-offs for the number of transfused units of RBC were: ≥4 units, ≥6 units, ≥8 units and ≥10 units.

For every one of these nine definitions, we determined bleeding characteristics of all women who complied with the definition of interest. Bleeding characteristics were calculated at the time of satisfying the criteria for each of the definitions. For example, in case of estimation of volume of blood loss, we calculated all bleeding characteristics at the moment the women's blood loss reached the predefined cut-off value. Bleeding characteristics included time from birth to time of inclusion (<1h, ≥1 to 2h, ≥2h), cause of haemorrhage (uterine atony/retained placenta/abnormally invasive placenta/placenta previa/placental abruption/surgical cause/pre-existent coagulation disorder), volume of blood loss at moment of inclusion (<1L, ≥1 to 2L, ≥2L), bleeding rate at moment of inclusion (<1L/h, ≥1 to 2L/h, ≥2L/h), signs of haemorrhagic shock at moment of inclusion (no/yes), and units of transfused RBC at moment of satisfying the criteria for the definition (no/yes).

We also determined the occurrence of adverse maternal outcome for women captured by all definitions of severe postpartum haemorrhage. Lastly, we calculated for all definitions median blood loss, time from birth till end of bleeding, median number of transfused units of RBC and time from birth until transfusion of first unit of RBC.

Results

A total of 1391 women with postpartum haemorrhage out of 270,101 births met the TeMpOH-1 inclusion criteria (5.1 per 1000 births). *Persistent postpartum haemorrhage* was observed in 1260 women (90.6%) (figure 1). A total of 1344 out of 1391 women (96.6%) reached a minimal volume of blood loss of 1500 mL following birth, 1252 (90.0%) ≥2000 mL and 1050 (75.5%) ≥2500 mL of blood loss within 24 hours following birth (figure 1). At least four units of RBC were transfused within 24 hours following birth in 845/1391 women (60.7%), ≥6 units in 325/1391 women (23.4%), ≥8 units in 176/1391 women (12.7%) and ≥10 units in 115/1391 women (8.3%). Please note that

women who received six or more units of RBC also met the criteria for inclusion in the previous category (≥4 units of RBC), and so on.

Time from birth to moment of meeting the criteria for *persistent postpartum haemorrhage* was less than one hour in 820 out of 1260 women (65.1%). At the moment of meeting these criteria, 673 women (53.4%) had bled less than 1L (tables 1 and 2). When defining severe postpartum haemorrhage based on estimated blood loss, time from birth to the moment she reached 1L of blood loss was less than one hour in 819 out of 1391 women (58.7%). With the number of transfused units of RBC within 24 hours following birth as definition, time from birth to moment of transfusion of four units of RBC was less than one hour in 37 out of 845 women (4.4%).

Mode of birth for women meeting the criteria for *persistent postpartum haemorrhage* was vaginal in 967 out of 1260 women (76.7%), comparable to women captured by all definitions based on estimated blood loss and transfusion of RBC up to a minimum of 4 units. A total of 62 out of 126 women (49.2%) captured by the definition ≥10 units of RBC had a vaginal birth. Cause of haemorrhage showed similar distributions for women categorized according to all definitions, with uterine atony as main cause of haemorrhage. With definitions based on the number of units transfused RBC within 24 hours following birth the proportion of abnormally invasive placenta, surgical causes and congenital or acquired coagulation disorders increased slightly with increasing number of transfused units.

Adverse maternal outcome occurred in 471 out of 1391 women (33.9%) in our study. In the 1260 women meeting the criteria for *persistent postpartum haemorrhage* we observed 430 of these 471 women with adverse outcome (91.3%). The 41 women with adverse maternal outcome not captured by the definition *persistent postpartum haemorrhage* all had missing data on timing of initial first-line measures to stop bleeding, and therefore could not be classified as having had *persistent postpartum haemorrhage* or not. Because of this, nine women with hysterectomies and eight with arterial embolisations were 'missed' with this definition (table 3).

The definition ≥1L of blood loss within 24 hours following birth captured all 471 adverse outcomes and in women with ≥2.5L blood loss 417 of these 471 outcomes (88.5%) were captured. One woman who was not captured by the latter definition died. She had postpartum haemorrhage with blood loss of 1.5L due to uterine atony, but also suffered from cerebral haemorrhage as a result of eclampsia. Two women

with hysterectomies (1x abnormally invasive placenta and 1x uterine atony) and five with embolisations (4x uterine atony and 1x surgical cause) were not captured by the definition of ≥2.5L blood loss within 24 hours following birth, partly because of uncertain total blood loss after postpartum haemorrhage.

A total of 383 out of 471 adverse outcomes (81.3%) were captured by the definition transfusion of ≥4 units of RBC within 24 hours following birth and 113 out of 471 adverse outcomes (24.0%) in women with ≥10 units of RBC transfused. Among the 88 women with adverse outcome not captured by the definition ≥4 units of RBC within 24 hours following birth were five women with hysterectomies (4x abnormally invasive placenta and 1x placenta praevia) and 14 with arterial embolisations (1x abnormally invasive placenta and 1x surgical cause).

Median total blood loss was 3.0L (interquartile range, IQR 2.5-4.0) in women with *persistent postpartum haemorrhage*, similar to women with up to 2000 mL of blood loss at moment of inclusion (table 4). Women with ≥2500 mL had median blood loss of 3.5L (IQR 3.0-4.2). Number of transfused RBCs did not differ between definition *persistent postpartum haemorrhage* and all definitions based on estimated blood loss. With increasing units of RBC transfused median total blood loss increased from 3.4L (IQR 2.5-4.5) to 7.0L (IQR 5.3-9.1) and median units transfused increased from 5 (IQR 4-7) to 13 (IQR 11-17).

Discussion

Main findings

A large proportion of women who fulfilled the definition *persistent postpartum haemorrhage* was captured at an early stage of haemorrhage (within one hour after birth), and this definition captured a high proportion of adverse maternal outcomes (91.3%). Women with this definition for severe postpartum haemorrhage had similar clinical characteristics and maternal outcomes compared to women who fulfilled the definition of severe postpartum haemorrhage up to 2000 mL of blood loss.

Strengths and limitations

To the best of our knowledge, this is the first study in a large, consecutive cohort of women with postpartum haemorrhage that compared clinical characteristics and outcomes of women captured by different definitions of severe postpartum haemorrhage. Data

were collected retrospectively, and we were able to reconstruct the course of every woman with postpartum haemorrhage without loss to follow-up. Previously, many authors discussed the use of different definitions, and experts proposed various new or adapted definitions of severe postpartum haemorrhage.[11,14,15,19,21,23,24] This study provides insight into variations in bleeding characteristics and maternal outcomes depending on the definition used.

However, our study population comprised only women with postpartum haemorrhage who received 4 or more units of RBC or a multicomponent blood transfusion within 24 hours following birth, and our results cannot be generalized to all women who satisfy the criteria for *persistent postpartum haemorrhage*. The effects on clinical practice of extending the definition of severe postpartum haemorrhage with '*refractoriness to treatment*' will need to be addressed in studies among all women meeting the criteria of *persistent postpartum haemorrhage*. In the updated version of the French guideline on postpartum haemorrhage, the definition *persistent postpartum haemorrhage* and failure of initial first-line management has been incorporated. [25] This guideline provides an opportunity to further analyse the consequences of implementing this definition in practice.

Another limitation are the 131 women (9.4%) women in our cohort with missing information regarding the exact time at which the initial first-line measure to stop bleeding was employed. This excluded the possibility of classifying all women according to the criteria for *persistent postpartum haemorrhage*, and consequently, 41 women (8.7%) with adverse maternal outcome had to be excluded. In daily clinical practice, these women would have been classified correctly by using this definition, as in daily clinical practice physicians will always have this information at their disposal.

Interpretation

One of the most striking findings of our study is that the use of the definition *persistent postpartum haemorrhage* seems to allow for early identification of women with severe bleeding and therefore early identification of women at risk of adverse maternal outcome. Recent studies on timing of interventions in women with postpartum haemorrhage have shown improvements in maternal outcome with early start of treatment.[26,27] Early identification of women with high risk of adverse maternal outcome would facilitate this, ultimately leading to a reduction in severe maternal morbidity and mortality. The fact that the definition *persistent postpartum*

haemorrhage allows for earlier inclusion is an advantage over definitions based on estimated blood loss, since early inclusion would also allow for more robust prospective data collection during the course of haemorrhage.

The definition *persistent postpartum haemorrhage* captured more than 90% women with adverse maternal outcome because of severe postpartum haemorrhage. This proportion was comparable to the proportions of the definitions based on estimated blood loss within 24 hours following birth. Definitions based on transfusions of RBC yielded a selection of women with exceptionally high rates of adverse maternal outcome. However, the definition ≥4 units of RBC within 24 hours following birth excluded 88 women (18.7%) with adverse maternal outcome, considerably higher than with the definition *persistent postpartum haemorrhage* and all definitions based on estimated blood loss. An explanation for this finding would be that a proportion of women with severe postpartum haemorrhage will undergo invasive procedures to stop bleeding before they may have reached four or more units of RBC transfused. This survival bias was previously also encountered in studies on massive transfusion in non-pregnant patients with major haemorrhage after trauma.[28,29] The fact that for all women with adverse outcomes missed by the definition, data essential for classification were absent from the medical records, underlines the requirement for adequate record keeping that the definition *persistent postpartum haemorrhage* needs. Implementing this definition may in this way contribute to improved documentation.

An observational study among pregnant and non-pregnant patients with massive transfusion because of major haemorrhage of different aetiologies also concluded that definitions of major haemorrhage based on massive transfusion are prone to exclude a substantial proportion of critically bleeding patients. The definition transfusion of ≥5 units of RBC within a 4-hour period excluded 77 out of 542 patients (14.2%) with major haemorrhage.[30]

The experts in a recent Delphi process led by the International Network of Obstetric Survey Systems needed seven rounds to reach consensus on a definition of severe postpartum haemorrhage, reaching a rate of agreement of 75%.[19] This underlines the fact that it is rather challenging to accommodate the variety in opinion into one definition, and at the same time the need to explore new definitions or adaptations to existing definitions of severe postpartum haemorrhage.[11,14,15,20,21] The definition *persistent postpartum haemorrhage* is internationally applicable and relies on basic interventions to control postpartum haemorrhage.[11,17] However, before its

implementation as the standard to identify severe haemorrhage in clinical practice, audit, surveillance and research we will need to validate and test this definition also in other cohorts and different settings.

Conclusion

The definition *persistent postpartum haemorrhage* identified women with severe postpartum haemorrhage at an early stage of haemorrhage and captured a large proportion of adverse maternal outcomes. Clinical characteristics and outcomes of women included in this definition were comparable to those of women selected by definitions based on estimated blood loss up to 2L within 24 hours following birth, but not to definitions based on the number of units of RBC transfused. Whether or not extending the definition of severe postpartum haemorrhage with '*refractoriness to treatment*' will lead to early identification of women at high risk of adverse outcome, early start of treatment and improvement of outcomes needs to be clarified in future studies.

Abbreviations

RBC: packed red blood cells

Declarations

Ethics Approval and consent to participate

The study was approved by the medical research ethics committee of the Leiden University Medical Center (P12.273) and by the institutional review board of each study centre (supplement). A waiver for informed consent from the individual patients was granted by the medical research ethics committee. All data were anonymized before being received by the research team. The study was registered in the Netherlands Trial Register (NTR4079).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

TA and JR are on the editorial board of BMC Pregnancy and Childbirth. All other authors declare that they have no competing interests.

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None.

Authors' contributions

DH, KB, JZ, JR and JB were responsible for study concept and design. DH monitored data collection for the whole trial, wrote the statistical analysis plan, cleaned and analysed the data. SS and RC collected data. DH and JB drafted and revised the paper. AG, KB, TA, JZ and JR critically reviewed the manuscript and approved the final version. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1. Bleeding characteristics at time of inclusion of women with persistent postpartum haemorrhage, as compared with women with different cut-off values for estimations of blood loss within 24 hours following birth. Women with higher volumes of blood loss are included in the cohorts starting with lower volumes of blood loss.

Bleeding characteristic	Persistent postpartum haemorrhage (N=1260)	Blood loss ≥1000 ml (N = 1391)	Blood loss ≥1500 ml (N =1344)	Blood loss ≥2000 ml (N =1252)	Blood loss ≥2500 ml (N =1050)
Time from birth till inclusion of patients – no. (%)					
<1 hour	820 (65.1)	819 (58.7)	553 (41.1)	309 (24.7)	160 (15.2)
≥1-2 hours	251 (19.9)	318 (22.9)	385 (28.6)	419 (33.5)	341 (32.5)
≥2 hours	189 (15.0)	257 (18.5)	406 (30.2)	524 (41.9)	549 (52.3)
Mode of birth					
Vaginal	967 (76.7)	1032 (74.2)	1002 (74.6)	945 (75.5)	792 (75.4)
Caesarean	285 (22.6)	351 (25.2)	3354 (24.9)	301 (24.0)	253 (24.1)
Unknown	8 (0.6)	8 (0.6)	7 (0.5)	6 (0.5)	5 (0.5)
Cause of haemorrhage – no. (%)					
Uterine atony	805 (63.9)	901 (64.8)	874 (65.0)	824 (65.8)	685 (65.2)
Retained placenta	219 (17.4)	231 (16.6)	227 (16.9)	207 (16.5)	172 (16.4)
Abnormally invasive placenta	113 (9.0)	113 (8.1)	107 (8.0)	100 (8.0)	89 (8.5)
Placenta previa	12 (1.0)	19 (1.4)	19 (1.4)	18 (1.4)	17 (1.6)
Placental abruption	12 (1.0)	28 (2.0)	24 (1.8)	18 (1.4)	16 (1.5)
Surgical cause	92 (7.3)	92 (6.6)	87 (6.5)	81 (6.5)	69 (6.6)
Pre-existent coagulation disorder	7 (0.6)	7 (0.5)	6 (0.4)	4 (0.3)	2 (0.2)
Bleeding rate – no. (%)					
<1L/hr.	457 (36.3)	496 (35.7)	508 (37.8)	499 (39.9)	432 (41.1)
≥1-2L/hr.	316 (25.1)	332 (23.9)	315 (23.4)	302 (24.1)	266 (25.3)
≥2L/hr.	481 (38.2)	552 (39.7)	513 (38.2)	445 (35.5)	349 (33.2)
Unknown	6 (0.5)	11 (0.8)	8 (0.6)	6 (0.5)	3 (0.3)
Signs of haemorrhagic shock – no. (%)					
No	344 (27.3)	416 (29.9)	385 (28.6)	295 (23.6)	190 (18.1)
Yes	580 (46.0)	488 (35.1)	693 (51.6)	811 (64.8)	782 (74.5)
Unknown	336 (26.7)	487 (35.0)	266 (19.8)	146 (11.7)	78 (7.4)
Packed red blood cells transfused – no. (%)					
No	1196 (94.9)	1271 (91.4)	1145 (85.2)	888 (70.9)	536 (51.0)
Yes	64 (5.1)	120 (8.6)	199 (14.8)	364 (29.1)	514 (49.0)

Table 2. Bleeding characteristics at time of inclusion of women with persistent postpartum haemorrhage, as compared with women with different cut-off values for transfused units of packed red blood cells (RBC) within 24 hours following birth. Women with higher numbers of RBCs are included in cohorts of women with fewer units transfused.

Bleeding characteristic	Persistent postpartum haemorrhage (N=1260)	≥4 units RBC (N =845)	≥6 units RBC (N =325)	≥8 units RBC (N =176)	≥10 units RBC (N =115)
Time from birth till inclusion of patients – no. (%)					
<1 hour	820 (65.1)	37 (4.4)	9 (2.8)	4 (2.3)	2 (1.7)
≥1-2 hours	251 (19.9)	96 (11.4)	41 (12.6)	11 (6.3)	3 (2.6)
≥2 hours	189 (15.0)	712 (84.3)	275 (84.6)	161 (91.5)	110 (95.7)
Unknown	-	-	-	1 (0.5)	-
Mode of birth					
Vaginal	967 (76.7)	612 (72.4)	207 (63.7)	100 (56.8)	62 (53.9)
Caesarean	285 (22.6)	228 (27.0)	116 (35.7)	75 (42.6)	53 (46.1)
Unknown	8 (0.6)	5 (0.6)	2 (0.6)	1 (0.6)	-
Cause of haemorrhage – no. (%)					
Uterine atony	805 (63.9)	539 (63.8)	214 (65.8)	107 (60.8)	66 (57.4)
Retained placenta	219 (17.4)	135 (16.0)	29 (8.9)	18 (10.2)	13 (11.3)
Abnormally invasive placenta	113 (9.0)	71 (8.4)	26 (8.0)	17 (9.7)	13 (11.3)
Placenta previa	12 (1.0)	13 (1.5)	6 (1.8)	4 (2.3)	3 (2.6)
Placental abruption	12 (1.0)	18 (2.1)	11 (3.4)	5 (2.8)	1 (0.9)
Surgical cause	92 (7.3)	66 (7.8)	36 (11.1)	22 (12.5)	16 (13.9)
Pre-existent coagulation disorder	7 (0.6)	3 (0.4)	3 (0.9)	3 (1.7)	3 (2.6)
Blood loss – no. (%)					
<1L	673 (53.4)	7 (0.8)	1 (0.3)	1 (0.6)	-
≥1-2L	407 (32.3)	82 (9.7)	15 (4.6)	3 (1.7)	2 (1.7)
≥2L	180 (14.3)	756 (89.5)	309 (95.1)	172 (97.7)	113 (98.3)
Bleeding rate – no. (%)					
<1L/hr.	457 (36.3)	689 (81.5)	24 (74.2)	127 (72.2)	80 (69.6)
≥1-2L/hr.	316 (25.1)	100 (11.8)	56 (17.2)	34 (19.3)	21 (18.3)
≥2L/hr.	481 (38.2)	41 (4.9)	23 (7.1)	12 (6.8)	12 (10.4)
Unknown	6 (0.5)	15 (1.8)	5 (1.5)	3 (1.7)	2 (1.7)
Signs of haemorrhagic shock – no. (%)					
No	344 (27.3)	85 (10.1)	23 (7.1)	9 (5.1)	6 (5.2)
Yes	580 (46.0)	722 (85.4)	288 (88.6)	159 (90.3)	104 (90.4)
Unknown	336 (26.7)	38 (4.5)	14 (4.3)	8 (4.5)	5 (4.3)

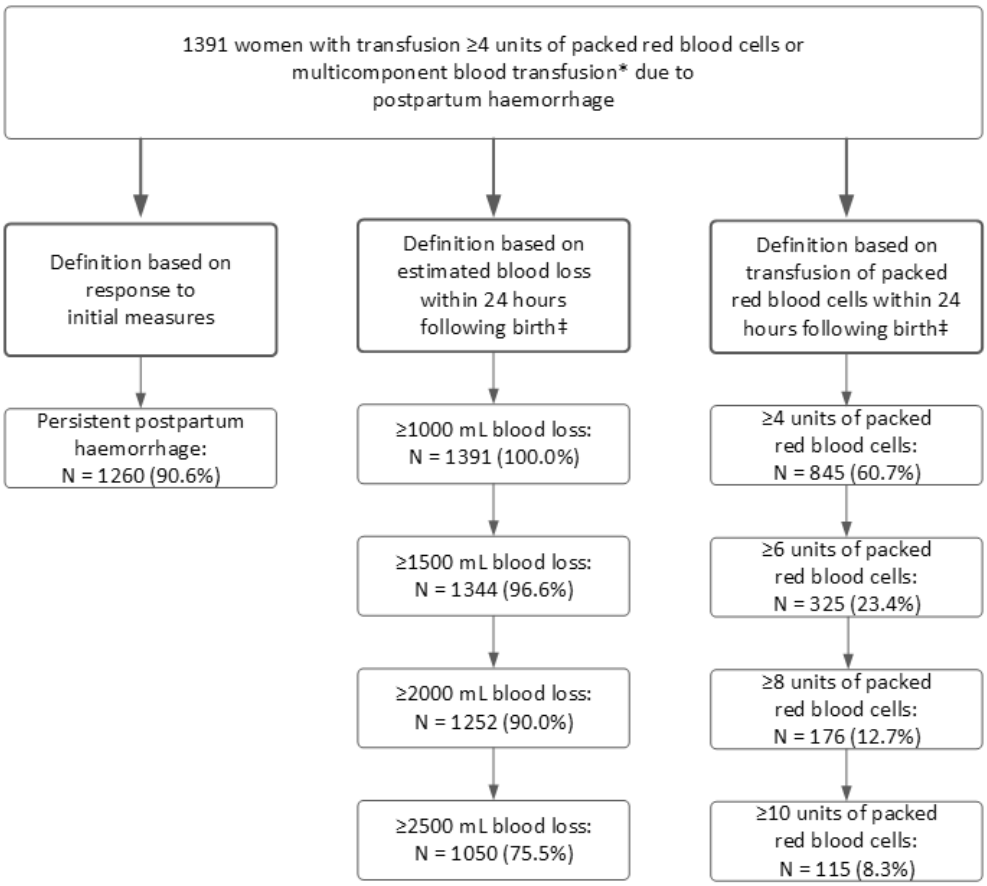
Table 3. Adverse maternal outcome in women with persistent postpartum haemorrhage, compared with women with different cut-off values for estimations of blood loss and transfused packed red blood cells within 24 hours following birth.

Definition based on	Maternal death	Hysterectomy	Arterial embolisation	Admission on intensive care unit	Composite adverse maternal outcome
			number of patients (%)		
Persistent postpartum haemorrhage (N=1260)	7 (0.6)	64 (5.1)	165 (13.1)	362 (28.7)	430 (34.1)
Estimated blood loss					
≥1000 mL (N=1391)	7 (0.5)	73 (5.2)	173 (12.4)	399 (28.7)	471 (33.9)
≥1500 mL (N=1344)	7 (0.5)	73 (5.4)	171 (12.7)	388 (28.9)	459 (34.2)
≥2000 mL (N=1252)	6 (0.5)	73 (5.8)	171 (13.7)	372 (29.7)	443 (35.4)
≥2500 mL (N=1050)	6 (0.6)	71 (6.8)	168 (16.0)	348 (33.1)	417 (39.7)
Transfusion of packed red blood cells					
≥4 units (N=845)	7 (0.8)	68 (8.0)	159 (18.8)	321 (38.0)	383 (45.3)
≥6 units (N=325)	5 (1.5)	62 (19.1)	125 (38.5)	215 (66.2)	258 (79.4)
≥8 units (N=176)	4 (2.3)	54 (30.7)	84 (47.7)	146 (83.0)	165 (93.8)
≥10 units (N=115)	3 (2.6)	44 (38.3)	64 (55.7)	101 (87.8)	113 (98.3)

Table 4. Total blood loss and total units of transfused packed red blood cells in women with persistent postpartum haemorrhage, compared with women with different cut-off values for estimations of blood loss and transfused packed red blood cells (RBC) within 24 hours following birth.

Definition based on	Total blood loss (L)	Time from birth till end of bleeding (hours)	Total units of transfused RBCs	Time from birth till transfusion of first RBC-unit (hours)
		median (interquartile range)		
Persistent postpartum haemorrhage (N=1260)	3.0 (2.5-4.0)	3.4 (2.1-5.9)	4 (3-6)	2.5 (1.6-4.2)
Estimated blood loss				
≥1000 mL (N=1391)	3.0 (2.5-4.0)	3.3 (2.0-5.8)	4 (3-6)	2.5 (1.5-4.2)
≥1500 mL (N=1344)	3.0 (2.5-4.0)	3.3 (2.0-5.8)	4 (3-6)	2.5 (1.5-4.2)
≥2000 mL (N=1252)	3.0 (2.5-4.0)	3.4 (2.1-5.9)	4 (3-6)	2.4 (1.5-4.1)
≥2500 mL (N=1050)	3.5 (3.0-4.2)	3.6 (2.1-6.1)	4 (3-6)	2.3 (1.5-3.8)
Transfusion of packed red blood cells				
≥4 units (N=845)	3.5 (2.7-4.5)	3.8 (2.2-6.4)	5 (4-7)	2.3 (1.4-3.7)
≥6 units (N=325)	4.8 (3.6-6.5)	6.5 (3.1-8.6)	8 (6-12)	2.0 (1.0-3.3)
≥8 units (N=176)	6.0 (4.5-8.0)	6.1 (4.1-12.0)	11 (9-15)	1.9 (0.8-3.3)
≥10 units (N=115)	7.0 (5.1-9.8)	6.9 (4.4-12.8)	13 (11-18)	1.8 (0.7-3.0)

Figure 1. Number of women meeting the criteria for persistent postpartum haemorrhage as definition of severe postpartum haemorrhage, and women captured by definitions of severe postpartum haemorrhage based on estimated blood loss and number of transfused units of packed red blood cells within 24 hours following birth.



* A multicomponent blood transfusion was defined as blood transfusion consisting of a combination of RBC and fresh frozen plasma and/or platelet concentrates.

‡ Women who bled ≥1500 ml also fulfilled the definition ≥1000 ml and were also included in this previous category, and so on. Similarly, women who received ≥6 units of RBC also met the criteria for inclusion in the previous category (≥4 units of RBC), etc.

5

Hypertensive disorders of pregnancy and outcomes of persistent postpartum haemorrhage: a cohort study

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Abstract

Background Hypertensive disorders of pregnancy have been associated with postpartum hemorrhage, but it is unclear whether women with persistent postpartum hemorrhage and concurrent hypertensive disorders of pregnancy are also at increased risk of adverse maternal outcome associated with severe bleeding. The objective was to assess whether women with persistent postpartum hemorrhage and concurrent hypertensive disorders of pregnancy are at increased risk of maternal mortality, arterial embolization or hysterectomy to stop bleeding, as compared with women with persistent postpartum hemorrhage without concurrent hypertensive disorders of pregnancy.

Methods From a Dutch cohort of women with postpartum hemorrhage that received either ≥4 units of red blood cells or a multicomponent transfusion, we selected women with persistent postpartum hemorrhage. Persistent postpartum hemorrhage was defined as hemorrhage refractory to initial measures to stop bleeding. Adverse maternal outcome was a composite of maternal mortality, and arterial embolization or hysterectomy to stop bleeding. Associations were adjusted for patient and bleeding characteristics in multivariable analysis.

Results Out of 1260 women with persistent postpartum haemorrhage, 63 had concurrent chronic or gestational hypertension (5.0%) and 127 preeclampsia (10.1%). Adverse maternal outcomes occurred in 180 women (16.8%) with persistent postpartum haemorrhage without hypertensive disorders, in 5 women (7.9%) with concurrent hypertension and in 28 women (22.0%) with concurrent preeclampsia. Adjusted odds ratios were 0.3 (95% confidence interval 0.1-0.8) for women with hypertension and 1.8 (1.1-3.0) for women with preeclampsia.

Conclusion Our findings show an increased risk of haemorrhage-related adverse maternal outcome in women with persistent postpartum haemorrhage and concurrent preeclampsia, as compared with women without hypertensive disorders of pregnancy. This increased risk was not found for women with concurrent chronic or gestational hypertension.

Trial registration

Netherlands Trial Registry, http://www.trialregister.nl, identifier NTR4079.

Keywords

Adverse maternal outcome, postpartum hemorrhage, preeclampsia, maternal morbidity

Background

Obstetric haemorrhage poses a significant burden on women's health by being the principal cause of severe maternal morbidity and maternal mortality worldwide. It accounts for 27% of all maternal deaths, with severe postpartum haemorrhage as its main component. [1,2]

Interestingly, hypertensive disorders of pregnancy, the second most common cause of maternal death and severe maternal morbidity, [1,2] have been identified as one of many risk factors for postpartum haemorrhage. Women with hypertensive disorders of pregnancy have been reported to have a 1.5-5 fold increased risk of postpartum haemorrhage when compared to women without hypertensive disorders. [3-11]

Mechanisms for this interaction are not fully understood, [7,11,12] in line with uncertainties in the pathogenesis of in particular preeclampsia. Angiogenic factors of the vascular endothelial growth factor family (VEGF) in maternal circulation may be a common pathway in the development of both preeclampsia and postpartum haemorrhage. In preeclampsia, placental soluble fms-like tyrosine kinase 1 (sFlt-1) and other antiangiogenic factors seem to be upregulated, antagonising angiogenic factors VEGF and placenta growth factor (PlGF). [13-16] Angiogenesis on its turn, is thought to be closely related to the hemostatic system and activation of clotting. [17,18] In addition, impaired coagulation may also be induced by HELLP syndrome, placental abruption and disseminated intravascular coagulation, known complications of severe preeclampsia, [19,20] thereby increasing the risk of excessive bleeding after delivery.

While the association between hypertensive disorders of pregnancy and postpartum haemorrhage emphasises the importance of active management of the third stage of labour to prevent postpartum haemorrhage especially in women with concurrent hypertensive disorders of pregnancy, the implication of this association for management of postpartum haemorrhage in these women is unclear. Issues to be resolved are whether or not the course of postpartum

haemorrhage in women with concurrent hypertensive disorders is more severe than in women without hypertensive disorders, and if so, whether and how the management of postpartum haemorrhage in these women should differ from women without concurrent hypertensive disorders of pregnancy in order to prevent adverse maternal outcomes.

We set out to assess whether women with persistent postpartum haemorrhage and concurrent hypertensive disorders of pregnancy are at increased risk of maternal mortality, arterial embolisation or hysterectomy to stop bleeding, as compared with women with persistent postpartum haemorrhage without concurrent hypertensive disorders of pregnancy.

Methods

Patients

For the present study, we used data from the TeMpOH-1 study, a retrospective cohort study in the Netherlands on transfusion strategies in women with major obstetric haemorrhage comprising consecutive women from 61 Dutch hospitals who, from 1 January 2011 to 1 January 2013, received either ≥4 units of red blood cells or a multicomponent blood transfusion within 24 hours following delivery because of postpartum haemorrhage (≥1000 mL blood loss). Patients were selected from transfusion databases and birth registries of participating hospitals.

From this cohort, we selected women with persistent postpartum haemorrhage. We defined persistent postpartum haemorrhage as ongoing postpartum haemorrhage within 24 hours following delivery exceeding 1000 mL of blood loss, that continued in spite of initial measures to stop bleeding.[21] Initial measures depended on primary cause of haemorrhage, and included uterine massage, oxytocin, misoprostol, methylergometrine, manual placenta removal and removal of placental remnants in case of uterine atony, retained placenta, genital tract trauma, placenta praevia or placental abruption as primary cause of postpartum haemorrhage. Women with an abnormally invasive placenta as

primary cause of postpartum haemorrhage, a surgical cause (including uterine rupture) or a congenital or acquired coagulation disorder were regarded as having persistent postpartum haemorrhage irrespective of the firstly applied therapy, as these complex haemorrhage s require a series of therapeutic measures to control bleeding.

Approval and a waiver of informed consent was obtained from the Medical Ethics Research Committee of Leiden University Medical Center (reference number P12.273), and from the institutional review board of each study center. The study was registered in the Netherlands Trial Register (NTR4079).

Data collection

We collected detailed information concerning pregnancy, delivery and the course of bleeding from routinely documented medical information of selected patients. Comprehensive chart reviews were uniformly performed by well-trained medical students and research nurses. At the end of data collection, the first author and two data managers checked all data for completeness and inconsistencies, and whenever necessary, on-site chart review was repeated.

Collected data included maternal and pregnancy characteristics, bleeding characteristics and all interventions during the course of haemorrhage to stop bleeding. Maternal characteristics included age, ethnicity, weight, height, comorbidity, and pregnancy characteristics included parity, gestational age, type and severity of hypertensive disorder of pregnancy, medication because of hypertensive disorder, mode of delivery and primary cause of postpartum haemorrhage. Bleeding characteristics included blood loss, bleeding rate and signs of haemorrhagic shock at the moment of diagnosis of persistent (ongoing) haemorrhage, volume of clear fluids for volume resuscitation, and all uterotonic, surgical, radiological and hemostatic interventions to stop bleeding.

Outcomes

Women were followed up until end of bleeding. Adverse maternal outcome was a composite of maternal mortality, arterial embolisation and hysterectomy

to stop bleeding. Secondary outcomes were total blood loss, number of units of packed red blood cells transfused and admission to intensive care unit.

Hypertensive disorders of pregnancy

Hypertensive disorders of pregnancy included chronic hypertension, gestational hypertension and preeclampsia, and were defined according to the International Society for the Study of Hypertension in Pregnancy (ISSHP) [22]. Hypertension was defined as blood pressure ≥140/90 mmHg, measured on two separate occasions. Chronic hypertension was defined as hypertension occurring before pregnancy or before 20 weeks of gestation. Gestational hypertension was defined as de novo blood pressure ≥140/90 mmHg occurring for the first time after 20 weeks of gestation. Preeclampsia was defined as gestational hypertension with proteinuria ≥300 mg/24h and/or clinical signs and symptoms of preeclampsia, or chronic hypertension with de novo proteinuria ≥300 mg/24h or clinical signs and symptoms of preeclampsia after 20 weeks of gestation (superimposed preeclampsia) [22,23].

Bleeding characteristics at time of diagnosis of persistent postpartum haemorrhage

In the Netherlands, volume of blood loss during postpartum haemorrhage is determined by weighing of gauzes, cloths and surgical swabs and measured with suction canisters. Estimation of the volume of blood loss at time of diagnosis of persistent postpartum haemorrhage was performed by linearly interpolating blood loss from time of delivery until end of bleeding, using available consecutive estimations of blood loss during haemorrhage. Haemorrhage was considered ongoing until the last estimation of blood loss of last obstetric intervention to stop bleeding.

Bleeding rate at time of diagnosis of persistent postpartum haemorrhage was calculated by dividing total blood loss up till that moment by the time interval from delivery till diagnosis of persistent postpartum haemorrhage. For patients with abnormally invasive placenta, surgical cause or coagulation disorder as primary cause of postpartum haemorrhage, baseline bleeding rate was assessed 5 minutes after diagnosis of persistent postpartum haemorrhage, as persistent postpartum haemorrhage was diagnosed at time of delivery for

these patients.

At least one measurement of systolic blood pressure ≤90 mmHg and/ or a heart rate ≥120 beats per minute from time of delivery to diagnosis of persistent postpartum haemorrhage were considered signs of haemorrhagic shock up till moment of diagnosis of postpartum haemorrhage [24].

Statistical analysis

The association of concurrent chronic or gestational hypertension and of preeclampsia with maternal mortality, arterial embolisation and hysterectomy to stop bleeding in women with persistent postpartum haemorrhage was modelled using logistic regression models. We adjusted these associations in multivariable models for the following predefined confounders: age (categories: <35 years / ≥35 years), ethnicity (Caucasian / other), parity (0 / ≥1), gestational age (< 37 weeks / ≥37 weeks), mode of delivery (vaginal / caesarean), cause of haemorrhage (uterine atony/retained placenta/ other), total volume of clear fluids for resuscitation (<4L / ≥4L), blood loss at moment of diagnosis of persistent postpartum haemorrhage (<1L, ≥1 to 2L, ≥2L), bleeding rate at moment of diagnosis of persistent postpartum haemorrhage (<1L/h, ≥1 to 2L/h, ≥2L/h) and signs of haemorrhagic shock at moment of diagnosis of persistent postpartum haemorrhage (no / yes). In case of missing values in confounding variables, we estimated these values by using multiple imputation techniques. In the imputation models we included confounding variables, outcome measures and variables associated with missing variables [25,26].

Results

Out of 1391 women with postpartum haemorrhage meeting the TeMpOH-1 inclusion criteria, we identified 1260 women as having persistent postpartum haemorrhage (figure 1). A total of 63 women (5.0%) with persistent postpartum haemorrhage had concurrent chronic or gestational hypertension and 127 women (10.1%) had been diagnosed with preeclampsia (table 1). Median age of included women was 32 years (interquartile range, IQR 28-35), most women were of Caucasian ethnicity (N = 903, 71.7%), and 657 women (52.1%) were

nulliparous. Delivery before 37 weeks of gestation was seen in 162 women (12.9%), and the mode of delivery was predominantly vaginal (N = 967, 76.7%). More women with persistent postpartum haemorrhage and concurrent hypertensive disorders of pregnancy were nulliparous (67.9 versus 49.3%) and delivered before gestational age 37 weeks (27.4 versus 10.3%). Postpartum haemorrhage was caused by uterine atony in 805 women (63.9%), and at moment of diagnosis of persistent postpartum haemorrhage median blood loss and bleeding rate was similar between women with and without hypertensive disorders of pregnancy (table 2). Signs of haemorrhagic shock at moment of diagnosis of persistent postpartum haemorrhage were present in 434 women (34.4%) and median volume of crystalloids and colloids for resuscitation was 3.0L (IQR 2.5-4.4L).

Adverse maternal outcome was seen in 213 women (16.9%): 7 maternal deaths (0.6%), 165 arterial embolisations (13.1%) and 64 hysterectomies (5.1%) (table 3). Arterial embolisation was performed in one woman (0.1%) who died due to postpartum haemorrhage, and hysterectomy in 3 women (0.2%) prior to death. In 19 women (1.5%) hysterectomy was necessary after arterial embolisation. A total of 180 adverse maternal outcomes (16.8%) occurred in women with persistent postpartum haemorrhage without concurrent hypertensive disorders of pregnancy, 5 (7.9%) in women with concurrent chronic or gestational hypertension and 28 (22.0%) in women with concurrent preeclampsia (table 3). Compared with women with persistent postpartum haemorrhage without hypertensive disorders, women with concurrent chronic or gestational hypertension did not have increased odds for adverse maternal outcomes (adjusted odds ratio 0.3 (95% confidence interval (CI) 0.1-0.8)), whereas women with concurrent preeclampsia did have significantly higher odds of adverse maternal outcomes (1.8 (1.1-3.0)). Women with preeclampsia were also more often admitted to the intensive care unit (adjusted odds ratio 1.9 (1.3-3.0)). Total blood loss and number of transfused units of packed red blood cells did not differ between women with and without hypertensive disorders of pregnancy.

Discussion

Main findings

In this nationwide cohort study comparing maternal outcomes in 1260 women with persistent postpartum haemorrhage with and without hypertensive disorders of pregnancy, concurrent preeclampsia was associated with more haemorrhage-related adverse maternal outcomes when compared with women without concurrent hypertensive disorders of pregnancy. In contrast, this risk of adverse maternal outcomes was relatively lower in women with persistent postpartum haemorrhage and concurrent chronic or gestational hypertension.

Strengths and Limitations

We carefully reconstructed the course of every postpartum haemorrhage in this large observational study. Therefore, there were no losses to follow up and primary outcome after haemorrhage was known for every woman who experienced postpartum haemorrhage.

A limitation of our study was the study population, that comprised a selection of women with severe haemorrhage and thus high risk of severe maternal morbidity. Our results are therefore only applicable to women with severe postpartum haemorrhage. Nonetheless, for this specific group of women, our findings indicate that concurrent preeclampsia contributes significantly to the risk of adverse maternal outcome, possibly because of altered coagulation.

The observation that women with concurrent chronic or gestational hypertension had fewer advanced procedures to stop bleeding than women without concurrent hypertension is somewhat counterintuitive but can be explained as follows. Our study comprises women with severe postpartum haemorrhage. Each of the included women inherently has a number of risk factors that caused the haemorrhage. The women who did not have chronic or gestational hypertension as risk factors probably had other, more serious risk factors, explaining the observed relatively higher number of advanced procedures to stop bleeding.

Additionally, we had a proportion of 25-30% of missing values in the confounding variables haemorrhagic shock and volume resuscitation in all three groups of women in our analyses, due to the retrospective design of our study. For multivariable analysis, we imputed these missing values rather than excluding these women, avoiding selection bias that would be introduced by exclusion of women due to missing values. However, we cannot rule out residual confounding due to these missing values.

Interpretation

Several studies reported on hypertensive disorders of pregnancy as a risk factor for developing postpartum haemorrhage [3-11]. The LEMMoN study, a preceding, nationwide cohort study on severe maternal morbidity in the Netherlands in the period 2004-2006, identified concurrent preeclampsia in 11.2% of women with major obstetric haemorrhage [27], comparable to the 10.1% of women with persistent postpartum haemorrhage and concurrent preeclampsia in this study. An Australian population-based study showed an increased risk of severe maternal morbidity in women with postpartum haemorrhage and hypertension, with odds ratio 1.3 (95% confidence interval 1.2-1.4) [28]. The association between adverse outcome in women with severe postpartum haemorrhage and concurrent preeclampsia was also described in a cohort study in Finland, that calculated a 6.9-fold increased risk (95% confidence interval 4.4-10.7) of severe maternal complications [29]. Our study not only confirms the association between severe postpartum haemorrhage with concurrent hypertensive disorders of pregnancy and advanced procedures to stop bleeding, but it also clearly shows that this association is fully explained by concurrent preeclampsia, and not concurrent chronic or gestational hypertension. In addition, we found this association in women with concurrent preeclampsia, despite a remarkably lower rate of hysterectomies in these women compared with women without hypertensive disorders of pregnancy. An explanation for this lower rate would be a more aggressive management of women with severe haemorrhage and concurrent preeclampsia.

The similar total blood loss and total units of transfused packed red blood

cells between women with severe postpartum haemorrhage with and women without concurrent hypertensive disorders also suggest a more aggressive treatment of women with preeclampsia. Women with preeclampsia have a relatively small circulating blood volume [30], and thus, are able to tolerate smaller volumes of blood loss than women without preeclampsia. As a result, arterial embolisations may be performed relatively early in the course of postpartum haemorrhage in women with preeclampsia than in women without preeclampsia, to avoid further deterioration in clinical condition.

Associations between concurrent preeclampsia and haemorrhage-related adverse maternal outcome in women with persistent postpartum haemorrhage, may also be explained by alterations in angiogenic factors in maternal circulation and by impaired coagulation caused by complications of severe preeclampsia. As upregulation of placental sFLT-1 is also seen in pregnancies complicated by intra-uterine growth restriction and small for gestational age infants [31,32], pro-active management of haemorrhage to avoid adverse maternal outcome might be advisable not only in women with concurrent preeclampsia, but perhaps in all women with disturbed placental function.

Over the last decades, much effort has been put into early timing of haemostatic interventions to stop bleeding in women with severe postpartum haemorrhage. Apart from tranexamic acid, effects on clinically relevant maternal outcomes have been disappointing or inconclusive[33-36]. In view of our results, personalised haemostatic interventions need further study especially in women with concurrent preeclampsia, because of their high risk of haemostatic impairment.

Conclusion

In conclusion, our findings show a significantly higher risk of adverse maternal outcome in women with persistent postpartum haemorrhage and concurrent preeclampsia, as compared with women without hypertensive disorders of pregnancy. This increase in risk was not seen in women with concurrent chronic or gestational hypertension. Therefore, particularly in women with

preeclampsia who develop severe postpartum haemorrhage, complications of bleeding should be anticipated and haemorrhage should be managed proactively to prevent severe maternal morbidity and mortality.

Declarations

Ethics Approval

The study was approved by the research ethics committee of the Leiden University Medical Center, Leiden, the Netherlands (reference number P12.273) on 31 January 2013. A waiver for informed consent was granted, and all data were anonymised before being received by the research team.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests.

Funding

None.

Authors' contributions

DH, KB, JZ, JR and JB were responsible for study concept and design. DH monitored data collection for the whole trial, wrote the statistical analysis plan, cleaned and analysed the data. RG collected data and helped development of the data collection tool. DH and JB drafted and revised the paper. RG, KB, JL, JZ and JR critically reviewed the manuscript and approved the final version. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1. Pregnancy characteristics of women with persistent postpartum haemorrhage according to the presence or absence of hypertensive disorders of pregnancy

Pregnancy characteristics	Women without concurrent hypertensive disorders of pregnancy (N = 1070)	Women with concurrent chronic or gestational hypertension (N = 63)	Women with concurrent preeclampsia (N = 127)
Age – no. (%)			
< 35 years	776 (72.5)	43 (68.3)	90 (70.9)
≥ 35 years	293 (27.4)	20 (31.7)	37 (29.1)
Unknown	1 (0.1)	-	-
Ethnicity – no. (%)			
Caucasian	756 (70.7)	54 (85.7)	93 (73.2)
Other/unknown	314 (29.3)	9 (14.3)	34 (26.8)
Nulliparous – no. (%)	528 (49.3)	39 (61.9)	90 (70.9)
Gestational age – no. (%)			
<32 weeks	33 (3.1)	-	6 (4.7)
≥32- <37 weeks	77 (7.2)	4 (6.3)	42 (33.1)
≥37 weeks	952 (89.0)	59 (93.7)	79 (62.2)
Unknown	8 (0.7)	-	-
Location of delivery – no. (%)			
University hospital	136 (12.7)	12 (19.0)	31 (24.4)
Non-university hospital	770 (72.0)	49 (77.8)	93 (73.2)
Home birth	161 (15.0)	2 (3.2)	2 (1.6)
Unknown	3 (0.3)	-	1 (0.8)
Mode of delivery – no. (%)			
Vaginal	828 (77.4)	47 (74.6)	92 (72.4)
Caesarean	235 (22.0)	16 (25.4)	34 (26.8)
Unknown	7 (0.7)	-	1 (0.8)

Table 2. Bleeding characteristics of women *at moment of diagnosing* persistent postpartum haemorrhage according to the presence or absence of hypertensive disorders of pregnancy

Bleeding characteristics	Women without concurrent hypertensive disorders of pregnancy (N = 1070)	Women with concurrent chronic or gestational hypertension (N = 63)	Women with concurrent preeclampsia (N = 127)
Cause of haemorrhage – no. (%)			
Uterine atony	673 (62.9)	45 (71.4)	87 (68.5)
Retained placenta	190 (17.8)	11 (17.5)	18 (14.2)
Abnormally invasive placenta	99 (9.3)	2 (2.3)	12 (9.4)
Placenta Praevia	12 (1.1)	-	-
Placental abruption	10 (0.9)	-	2 (1.6)
Surgical bleeding	82 (7.7)	5 (7.9)	5 (3.9)
Pre-existent coagulation disorder	4 (0.4)	-	3 (2.4)
Blood loss – no. (%)			
<1L	583 (54.5)	39 (61.9)	61 (48.0)
≥1-2L	339 (31.7)	17 (27.0)	46 (36.2)
≥2L	145 (13.6)	7 (11.1)	20 (15.7)
Unknown	3 (0.3)	-	-
Bleeding rate – no. (%)			
<1L/hr.	470 (43.9)	24 (38.1)	62 (48.8)
≥1-2L/hr.	269 (25.1)	16 (25.4)	24 (18.9)
≥2L/hr.	327 (30.6)	23 (36.5)	41 (32.3)
Unknown	4 (0.4)	-	-
Signs of haemorrhagic shock – no. (%)			
No	358 (33.5)	22 (34.9)	54 (42.5)
Yes	371 (34.7)	23 (36.5)	38 (29.9)
Unknown	341 (31.9)	18 (28.6)	35 (27.6)
Volume of clear fluids for resuscitation – no. (%)			
<4L	498 (46.5)	21 (33.3)	66 (52.0)
≥4L	283 (26.4)	24 (38.1)	26 (20.5)
Unknown	289 (27.0)	18 (28.6)	35 (27.6)

Table 3. Maternal outcomes in women with persistent postpartum haemorrhage			
Outcome	**Women without concurrent hypertensive disorders of pregnancy**	**Women with concurrent chronic or gestational hypertension**	**Women with concurrent preeclampsia**
	(N = 1070)†	**(N = 63)**	**(N = 127)**
Adverse maternal outcome* – no. (%)	180 (16.8)	5 (7.9)	28 (22.0)
Arterial embolisation	136 (12.7)	3 (4.8)	26 (20.5)
Hysterectomy	62 (5.8)	1 (1.6)	1 (0.8)
Maternal death	4 (0.4)	1 (1.6)	2 (1.6)
Crude odds ratio	**1**	**0.4 (0.2-1.1)**	**1.4 (0.9-2.2)**
Adjusted odds ratio‡	**1**	**0.3 (0.1-0.8)**	**1.8 (1.1-3.0)**
Secondary outcomes			
Total blood loss – median (IQR)	3.0 (2.5-4.0)	3.0 (2.5-4.0)	3.0 (2.2-4.0)
Units of red blood cells transfused – median (IQR)	4 (3-6)	4 (3-5)	4 (3-6)
Admission on intensive care unit – no. (%)	298 (27.9)	14 (22.2)	50 (39.4)

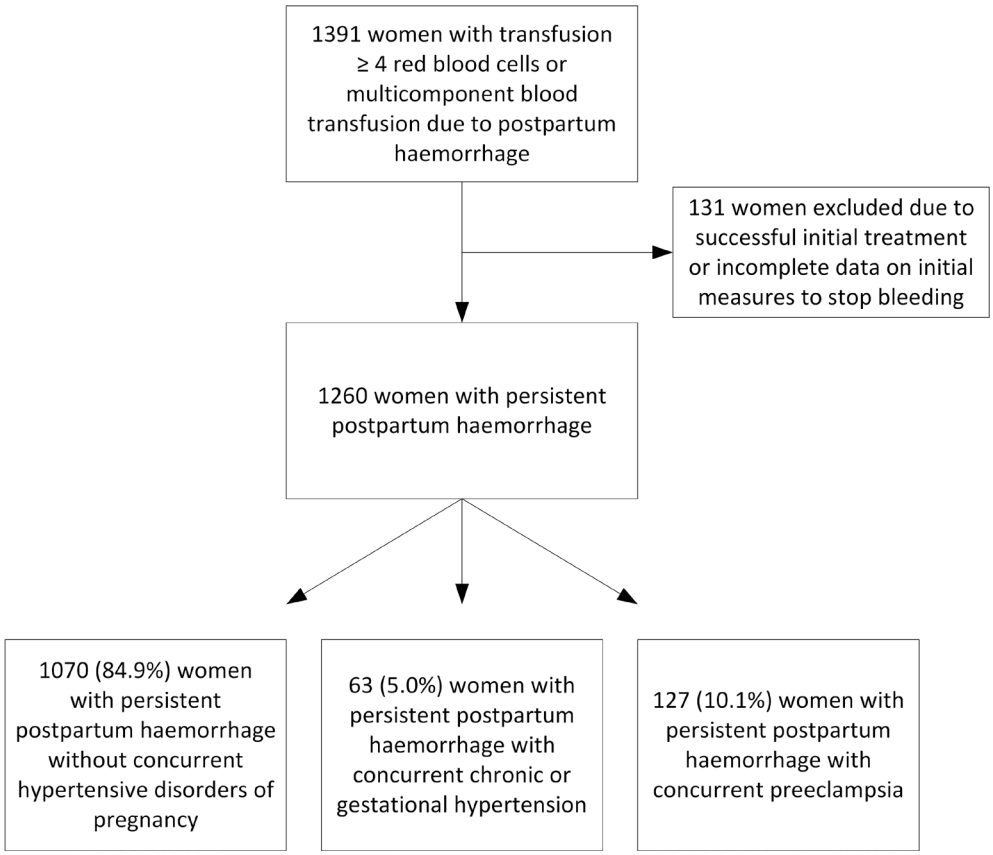
CI denotes confidence interval, IQR denotes interquartile range.

*Multiple endpoints per patient possible.

†Reference category.

‡ Adjusted for: age (<35 / ≥35 years), ethnicity (Caucasian / other), parity (0 / ≥1), gestational age (<37 / ≥37 weeks), mode of delivery (vaginal / caesarean), cause of haemorrhage (uterine atony / retained placenta / other), volume of clear fluids for resuscitation (< 4 / ≥4L), at moment of diagnosis of persistent postpartum haemorrhage: blood loss (<1L / ≥1-2L / ≥2L), bleeding rate (<1L/h. / ≥1-2L/h. / ≥2L/h.), signs of haemorrhagic shock (no / yes).

Figure 1. Flow chart of women with persistent postpartum haemorrhage without concurrent hypertensive disorder of pregnancy, with concurrent chronic or gestational hypertension and with concurrent preeclampsia.



Part 3

Women with postpartum haemorrhage: when and what to transfuse?

6

Fluid resuscitation during persistent postpartum haemorrhage and maternal outcome: a nationwide cohort study

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Abstract

Objective To determine the association between increasing volumes of crystalloids and colloids administered before transfusion of packed red blood cells in women with persistent postpartum haemorrhage and adverse maternal outcomes.

Study Design Retrospective cohort study in the Netherlands. Women with persistent postpartum haemorrhage and known clear fluids volume for resuscitation were included. Women who received ≤2L of clear fluids were the reference group. We determined the effect of every additional litre of clear fluids on total blood loss, severe maternal morbidity and mortality. Results were adjusted for patient and bleeding characteristics.

Results Of the 883 included women, 199 received ≤2L of clear fluids. Median blood loss for the reference group was 2.9L (interquartile range 2.2 to 3.4). Adjusted mean difference in blood loss compared with the reference group was 0.2L (95% confidence interval -0.1 to 0.5) for women in the >2 to ≤3L, 0.4L (0.1 to 0.7) for the >3 to ≤4L category, 0.6L (0.5 to 0.7) for the >4 to ≤5L category, and 1.9L (1.5 to 2.3) for the >5 to ≤7L category. Adjusted odds ratios for adverse maternal outcomes were 1.0 (0.7 to 1.6), 1.2 (0.8 to 1.9), 1.8 (1.1 to 3.1) and 4.4 (2.6 to 7.5) for women in the 2 to ≤3L category, >3 to ≤4L, >4 to ≤5L, and >5 to ≤7L volume categories respectively. Results were similar in strata of different severities of bleeding.

Conclusion Clear fluids volume >4L was independently associated with adverse maternal outcome in women with persistent postpartum haemorrhage.

Key words Blood transfusion, crystalloid solutions, colloids, postpartum haemorrhage, resuscitation

Introduction

Almost 20% of maternal deaths worldwide are due to postpartum haemorrhage, the leading cause of maternal death and morbidity.[1,2] Following childbirth, women are at risk of postpartum haemorrhage, and when postpartum haemorrhage is refractory to first-line therapy, it may deteriorate to severe haemorrhage.[3] Management of postpartum haemorrhage consists of obstetric and haemostatic interventions to stop bleeding, and fluid resuscitation to prevent and treat haemorrhagic shock.[3]

During fluid resuscitation, infusion of crystalloids and colloids precedes transfusion of red blood cells. Red-cell transfusion during ongoing haemorrhage not only maintains circulating blood volume and tissue oxygenation, but may also support haemostasis by improving coagulation.[4-10] Obviously, red-cell transfusions are also associated with adverse effects including transfusion reactions and transfusion-related acute lung injury.[11,12] And, fluid resuscitation with crystalloids and colloids may worsen maternal outcomes by causing dilution of clotting factors and platelets.[13-15] Moreover, colloid fluids have been associated with dysfunction of clotting factors.[16-20] The effects of fluid resuscitation on patient outcomes have been studied in patients with major trauma or surgery, but not in women with postpartum haemorrhage.[18,21-25]

Because of the potential adverse effects of both red-cell transfusion and fluid resuscitation with crystalloids and colloids, timing of switch from fluid resuscitation to resuscitation with packed red blood cells in women with severe postpartum haemorrhage should be carefully balanced. Nonetheless, it is unknown which volumes of crystalloids and colloids potentially worsen maternal outcomes, and therefore, justify switching to red-cell transfusion.

We set out to describe the association between increasing volumes of clear fluids administered before transfusion of packed red blood cells in women with severe postpartum haemorrhage and adverse maternal outcomes.

Materials and Methods

Patients

We used the TeMpOH-1 (*Transfusion strategies in women during Major Obstetric Haemorrhage*) study, a nationwide, retrospective cohort study on transfusion strategies in women with major obstetric haemorrhage in the Netherlands. The cohort comprised consecutive women from 61 hospitals who, from 1 January 2011 to 1 January 2013, received either ≥4 units of red blood cells or a multicomponent blood transfusion within 24 hours following birth because of postpartum haemorrhage (≥1000 mL blood loss). Women were selected from transfusion databases and birth registries of participating hospitals. For the present analysis we selected all women with *persistent postpartum haemorrhage*.[3,26]

Persistent postpartum haemorrhage was defined as postpartum haemorrhage refractory to first-line measures to control bleeding.[3] This definition is a pragmatic definition of severe postpartum haemorrhage that considers haemorrhage as severe as soon as initial measures fail to stop haemorrhage. With this definition we selected only women with ongoing postpartum haemorrhage, irresponsive to initial therapy. First-line therapies were uterine massage, continuous intravenous oxytocin, misoprostol, methylergometrine, manual placenta removal and inspection of genital tract and uterine cavity as first-line therapy in case of uterine atony, retained placenta, genital tract trauma, placenta previa or placental abruption as primary cause of postpartum haemorrhage. If a woman had multiple causes of postpartum haemorrhage, three authors (DH, KB, JvdB) determined primary cause by carefully reviewing the haemorrhage and discussion until consensus. Women with clinically abnormally invasive placenta as primary cause of postpartum haemorrhage, a surgical cause (including uterine rupture) or a congenital or acquired coagulation disorder were regarded as having persistent postpartum haemorrhage irrespective of the firstly applied therapy, as these complex haemorrhages require a series of therapeutic measures to control bleeding.

Women with unknown total volume of resuscitation fluids and women in

whom fluid resuscitation with clear fluids was started after a red-cell transfusion were excluded.

Approval and a waiver of informed consent was obtained from the Medical Ethics Research Committee of the Leiden University Medical Center (P12.273), and from the institutional review board of each study centre. The study was registered in the Netherlands Trial Registry (NTR 4079).

Data collection

In the Netherlands, the course and management of obstetric emergencies are carefully recorded in medical files facilitating reconstruction of obstetric emergencies for different purposes. Detailed information concerning pregnancy, birth and course of bleeding was gathered retrospectively from routinely collected medical information. Comprehensive chart reviews were performed by well-trained medical students and research nurses. We checked all data for completeness and inconsistencies, and whenever necessary, on-site chart review was repeated.

Data included mode of birth, primary cause of haemorrhage, total volume crystalloids and colloids and time of administration, consecutive estimates of blood loss and time of estimations, blood pressure and heart rate and time of measurements, time of transfusions and time of obstetric and haemostatic interventions to control bleeding.

Outcomes

Women were followed until end of bleeding. Outcome parameters were total blood loss and adverse maternal outcome. Adverse maternal outcome was a composite of maternal mortality and severe maternal morbidity, with the latter defined as hysterectomy, arterial embolisation, or intensive care unit admission.

Clear fluids

Volume of clear fluids consisted of total volume of crystalloids and total volume of colloids administered prior to transfusion of red cells. During the study period, both crystalloid and colloid fluids were used in the Netherlands as resuscitation fluids in women with postpartum haemorrhage, at the treating physician's discretion.

We categorized women into predefined groups according to volume of clear fluids. Women who received ≤2L of clear fluids formed the reference category, and we determined the effect of every additional litre of clear fluids on maternal outcome: >2 to ≤3L of clear fluids, >3 to ≤4L, >4 to ≤5L, and, >5 to ≤7L. We excluded women with total volume of clear fluids > 7L.

Baseline blood loss, bleeding rate and signs of haemorrhagic shock

As the first obstetric intervention to control bleeding generally occurs simultaneously with the start of fluid resuscitation we defined *baseline* as the moment of diagnosis of *persistent postpartum haemorrhage* (figure S1).[3] Depending on the patients' and bleeding characteristics, this first obstetric intervention is usually employed between 500 and 1000 mL of blood loss. For women with abnormally invasive placenta, surgical cause or coagulation disorder as primary cause of postpartum haemorrhage, baseline was set at time of birth.

To enable adjustment for *severity of haemorrhage* we quantified three variables at baseline: volume of blood loss, rate of bleeding and presence of haemorrhagic shock. Volume of blood loss during postpartum haemorrhage had been measured regularly during haemorrhage by weighing all gauzes, cloths and surgical swabs and suction into canisters. We estimated volume of blood loss at baseline with linear interpolations between observed volumes of blood loss. Rate of bleeding at baseline was calculated by dividing the volume of blood loss between the two nearest observed measurements by the time between those measurements. Haemorrhagic shock was considered present with one measurement of systolic blood pressure ≤90 mmHg and/or a heart rate ≥120 bpm birth.[27]

Statistical analyses

We used regression analyses to quantify the association between volume of clear fluids and total blood loss, maternal mortality and severe maternal morbidity. Multivariable models adjusted for the predefined potential confounders preeclampsia (yes/no), mode of birth (vaginal/caesarean), primary cause of haemorrhage (categories: uterine atony, retained placenta, abnormally invasive placenta, other), baseline blood loss (categories: <1.0L, ≥1.0 to <2.0L, ≥2.0L), baseline bleeding rate (<1.0 L/hr., ≥1 to <2L/hr., ≥2 L/hr.), and signs of haemorrhagic shock at baseline (yes/no).

Missing data in confounding variables were imputed using multiple imputation to minimize the risk of bias because of these missing data.[28] We included confounding variables, outcome parameters and parameters associated with the missing variables as predictive variables in the imputation models.

To assess whether our findings were robust we performed the following sensitivity analyses: analyses with categorization of women in quintiles of clear fluids volume, analyses among women with high volumes of blood loss, high bleeding rates and with signs of haemorrhagic shock present at baseline, analyses after excluding women in whom the need of red blood cells transfusion could have been predicted prior to onset of haemorrhage (i.e. women with abnormally invasive placenta), and analyses after excluding women that were treated with neuraxial blockade during labour, as in the Netherlands vascular loading with crystalloids prior to neuraxial blockade is common practice. For all sensitivity analyses we adjusted for the same confounding variables as in the main analyses.

Results

Patients

We assessed 270,101 deliveries during the study period. A total of 1391 women (0.51%) received a transfusion of at least four units of packed red blood cells or a multicomponent blood transfusion, and 1260 (0.47%) women were classified

as having persistent postpartum haemorrhage (figure 1). A total of 377 women were excluded due to incomplete data on volume of crystalloids and colloids (n = 340), start of administration of clear fluids after start of packed red blood cells transfusion (n = 10), or clear fluids volume > 7L (n = 27).

All 883 women received a combination of crystalloids and colloids for resuscitation. Median volume of crystalloids was 2.0L (interquartile range, IQR 1.0 to 3.0), and of colloids 1.0L (1.0 to 1.5).

Baseline characteristics of the women are depicted in table 1. Pregnancy was complicated by preeclampsia in 13.6% of women, 20.6% of women underwent a caesarean section, and postpartum haemorrhage was predominantly caused by uterine atony (58.8%). At baseline, median blood loss and bleeding rate were 0.9L (0.2 to 1.6) and 1.2 L/hr. (0.6 to 2.4) (table 2). Signs of haemorrhagic shock at baseline were present in 32.1% of women, with missing data in 219 women (24.8%). Median time from baseline until the first red-cell transfusion was 100 minutes (50-170), similarly distributed across all clear fluids volume categories (table 2).

Baseline characteristics of women excluded due to incomplete data on clear fluids volume were similar to characteristics of included women (tables S1 to S2).

Total blood loss

Median blood loss for all women was 3.0L (IQR 2.5 to 4.0L), and for women that received ≤2L of clear fluids 2.9L (2.2 to 3.4). Adjusted mean difference in blood loss compared with the reference group was +0.2L (CI -0.1 to 0.5) for women in the >2 to ≤3L category, +0.4L (0.1 to 0.7) for the >3 to ≤4L category, +0.6L (0.5 to 0.7) for the >4 to ≤5L category, and +1.9L (1.5 to 2.3) for the highest volume of clear fluids category (table 3).

Adverse maternal outcome

Four maternal deaths were observed in the 883 women. Arterial embolization was performed in 109 women (12.3%), and hysterectomy in 36 women (4.1%). Admission to an intensive care unit was necessary in 239 women (27.1%).

Adverse maternal outcome occurred in 32.5% of the study population (n=287).

Table 3 presents the association between volumes of clear fluids, consisting of crystalloid and colloid fluids, and adverse maternal outcome. Women who received >4L of crystalloids and colloids suffered more adverse maternal outcomes than women in the reference group. Odds ratios (OR) for adverse maternal outcome after adjustment for confounding were for women in the >2 to ≤3L clear fluids category 1.0 (CI 0.7 to 1.6), for the >3 to ≤4L clear fluids category 1.2 (0.8 to 1.9), for the >4 to ≤5L clear fluids category 1.8 (1.1 to 3.1) and for the >5 to ≤7L clear fluids category 4.4 (2.6 to 7.5)(figure 2).

Sensitivity analyses

Sensitivity analyses showed similar adjusted mean differences in blood loss from the reference group and similar odds ratios for adverse maternal outcome (tables S3 to S12).

Comment

Principal findings

In this multicentre cohort study among 883 consecutive women with persistent postpartum haemorrhage, resuscitation with >4L clear fluids was associated with subsequent bleeding and accompanying adverse maternal outcome. This association was observed within all strata of severity of bleeding.

Current knowledge

The Royal College of Obstetricians and Gynaecologists recommends crystalloids and colloids up to 3.5L before start of blood transfusion.[29] Thus far, this recommendation was based on expert opinion and not supported by clinical quantitative evidence.

To the best of our knowledge this is the first study reporting on the association between high volumes of clear fluids and subsequent adverse maternal outcome among women with severe postpartum haemorrhage. Previous studies showed that haemodilution can lead to impaired thrombin generation and fibrin clot formation, which has been called dilutional coagulopathy.[14-16]

The effects of volumes of fluid resuscitation have been studied in non-pregnant trauma patients with massive haemorrhage. Results of these studies are conflicting, and consequently, there is no consensus for trauma patients.[24,25,30] Fluid volumes of 20L were administered, fluid resuscitation was guided by systolic blood pressures and haematocrit levels, and pregnancy was generally an exclusion criterion. A recent observational study compared crystalloid resuscitation <2L in 1282 trauma patients with uncontrolled haemorrhage with crystalloid resuscitation ≥2L in 289 patients.[31] Adjusted mortality was almost 2-fold higher in the high-volume patients compared with the low-volume patients. The alterations in coagulation due to pregnancy hamper translation of the results of these studies to postpartum haemorrhage.

Strengths and limitations

In this large cohort of consecutive women with persistent postpartum haemorrhage, we included women at risk of haemodilution due to resuscitation with clear fluids. To achieve this we defined persistent postpartum haemorrhage as recently proposed by an international expert panel.[3] This enabled identification of women truly at risk of progression from mild to severe haemorrhage, morbidity and mortality. Refractoriness to first-line therapy is also a clear and recognizable transition point in management of women with postpartum haemorrhage, and thus, findings of this study have direct clinical relevance for the management of women with postpartum haemorrhage.

We carefully adjusted our results for confounding. One of the most important confounders in research on management of postpartum haemorrhage is severity of haemorrhage. We adjusted for cause of haemorrhage, blood loss, bleeding rate and signs of haemorrhagic shock at baseline as proxies for severity of haemorrhage. Yet, we cannot rule out residual confounding. However, given that sensitivity analyses among women in the worst clinical condition at start of fluid resuscitation showed similar results, we feel confident to infer that resuscitation with >4L clear fluids before start of red cell transfusion does not seem to be beneficial for these women. In contrast, it may worsen clinical outcome of women with persistent postpartum haemorrhage. Moreover, red-

cell transfusions were initiated in similar timeframes across all five clear fluids volume categories, indicating similar severity of postpartum haemorrhage between groups at baseline.

Colloid fluids are expected to have a different effect on maternal outcomes because of their additional association with impaired coagulation.[16,17] Unfortunately, stratification based on type of clear fluid was not possible in our study.

To optimise adjustment for confounding we aimed to collect sequential information on blood loss and vital signs at relevant time points during ongoing postpartum haemorrhage, and cautiously reconstructed the course of bleeding in every woman. Loss to follow up did not occur because information from start till end of bleeding was available for all women, including all interventions and outcomes. As expected, we had missing data on signs of haemorrhagic shock in almost 25% of women, distributed across all categories of clear fluids volume. These missing values were imputed by using all available data on blood pressures and heart rates throughout the bleeds. It has been shown that multiple imputation is a better solution than complete case analysis in case of missing data.[32]

In the Netherlands, there is a 24/7 availability of arterial embolisation in most hospitals, and this intervention is performed before resorting to hysterectomy. This may explain our relatively high embolisation and low hysterectomy rate.

Clinical implications

Our findings suggest that fluid resuscitation with clear fluids becomes clinically relevant in women with persistent postpartum haemorrhage when clear fluids volume exceeds 4L, within all strata of severity of bleeding. Consequently, clinicians should switch to red-cell transfusion before reaching this 4L limit of clear fluids in women with ongoing postpartum haemorrhage, in order to prevent adverse maternal outcome associated with high clear fluids volume.

Authors' contributions

DH, KB, JZ, JR, JJZ and JvdB were responsible for study concept and design. DH monitored data collection for the whole trial, wrote the statistical analysis plan, cleaned and analysed the data. RM collected data and helped development of the data collection tool. DH and JvdB drafted and revised the paper. KB, JZ, JR and JJZ critically reviewed the manuscript and approved the final version. All authors had full access to the data and take responsibility for the integrity of the data and the accuracy of the data analyses.

Data statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Role of the funding source

None.

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Table 1. Demographic and pregnancy characteristics of included women with persistent postpartum haemorrhage

Characteristic	Clear fluids volume ≤2L* (N = 199)	Clear fluids volume >2 to ≤3L (N = 262)	Clear fluids volume >3 to ≤4L (N = 211)	Clear fluids volume >4 to ≤5L (N = 106)	Clear fluids volume >5 to ≤7L (N = 105)
Age – no. (%)					
< 35 years	142 (71.4)	197 (75.2)	161 (76.3)	77 (72.6)	78 (74.3)
≥ 35 years	56 (28.1)	65 (24.8)	50 (23.7)	29 (27.4)	27 (25.7)
Unknown	1 (0.5)	-	-	-	-
Ethnicity – no. (%)					
Caucasian	143 (71.9)	178 (67.9)	151 (71.6)	83 (78.3)	82 (78.1)
Other/unknown	56 (28.1)	84 (32.1)	60 (28.4)	23 (21.7)	23 (21.9)
BMI – no. (%)					
<25 kg/m^2	101 (51.8)	136 (51.9)	132 (62.6)	57 (53.8)	56 (53.3)
≥25 to 30 kg/m^2	34 (17.1)	51 (19.5)	31 (14.7)	19 (17.9)	21 (20.0)
≥30 kg/m^2	17 (8.5)	23 (8.8)	20 (9.5)	12 (11.3)	12 (11.4)
Unknown	45 (22.6)	52 (19.8)	28 (13.3)	18 (17.0)	16 (15.2)
Preeclampsia – no. (%)	27 (13.6)	29 (11.1)	15 (7.1)	6 (5.7)	14 (13.3)
Mode of birth – no. (%)					
Vaginal	156 (78.4)	209 (79.8)	175 (82.9)	82 (77.4)	75 (71.4)
Caesarean	41 (20.6)	52 (19.8)	34 (16.1)	23 (21.7)	30 (28.6)
Unknown	2 (1.0)	1 (0.4)	2 (0.9)	1 (0.9)	-
Cause of haemorrhage – no. (%)					
Uterine atony	117 (58.8)	171 (65.3)	144 (68.2)	72 (67.9)	83 (79.0)
Retained placenta	43 (21.6)	49 (18.7)	31 (14.7)	17 (16.0)	7 (6.7)
Abnormally invasive placenta	30 (15.1)	24 (9.2)	17 (8.1)	7 (6.6)	6 (5.7)
Surgical	5 (2.5)	15 (5.7)	17 (8.1)	7 (6.6)	8 (7.6)
Other†	4 (2.0)	3 (1.1)	2 (0.9)	3 (2.8)	1 (1.0)

*Reference category. † Includes placenta previa, placental abruption and congenital or acquired coagulation disorders.

Table 2: Bleeding characteristics at time of diagnosis of persistent postpartum haemorrhage and details of fluid resuscitation

Characteristic	Clear fluids volume ≤2L* (N = 199)	Clear fluids volume >2 to ≤3L (N = 262)	Clear fluids volume >3 to ≤4L (N = 211)	Clear fluids volume >4 to ≤5L (N = 106)	Clear fluids volume >5 to ≤7L (N = 105)
Blood loss at baseline† – no. (%)					
< 1.0L	108 (54.3)	145 (55.3)	108 (51.2)	59 (55.7)	56 (53.3)
≥1.0 to <2.0L	66 (33.2)	77 (29.4)	79 (37.4)	30 (28.3)	34 (32.4)
≥2.0L	22 (11.1)	40 (15.3)	24 (11.4)	17 (16.0)	15 (14.3)
Unknown	3 (1.5)	-	-	-	-
Bleeding rate at baseline† – no. (%)					
< 1.0 L/hr.	86 (43.2)	123 (46.9)	81 (38.4)	43 (40.6)	41 (39.0)
≥1.0 to <2.0 L/hr.	55 (27.6)	60 (22.9)	56 (26.5)	21 (19.8)	28 (26.7)
≥ 2.0 L/hr.	55 (27.6)	79 (30.2)	74 (35.1)	42 (39.6)	36 (34.3)
Unknown	3 (1.5)	-	-	-	-
Signs of haemorrhagic shock at baseline† – no. (%)					
No	82 (41.2)	121 (46.2)	95 (45.0)	36 (34.0)	49 (46.7)
Yes	57 (28.6)	79 (30.2)	66 (31.3)	43 (40.6)	36 (34.3)
Unknown	60 (30.2)	62 (23.7)	50 (23.7)	27 (25.5)	20 (19.0)
Type of clear fluid – L, median (interquartile range)					
Crystalloids	1.0 (0.5-1.0)	1.5 (1.5-2.0)	2.5 (2.0-3.0)	3.0 (3.0-3.5)	4.0 (4.0-4.5)
Colloids	1.0 (0.5-1.0)	1.0 (1.0-1.5)	1.5 (1.0-1.5)	1.5 (1.0-1.5)	1.5 (1.5-2.0)
Time from baseline until first unit of red blood cells - no (%)					
< 1 hour	50 (25.1)	75 (28.2)	56 (26.5)	32 (30.2)	40 (38.1)
≥1 to <3 hours	91 (45.7)	124 (47.3)	109 (51.7)	53 (50.0)	47 (44.8)
≥3 hours	51 (25.6)	64 (24.4)	44 (20.9)	20 (18.9)	19 (17.1)
Unknown	7 (3.5)	-	2 (0.9)	1 (0.9)	-

*Reference category. † Baseline was defined as time of diagnosis of persistent postpartum haemorrhage.

Table 3. Total blood loss and maternal outcomes					
Outcome	**Clear fluids volume ≤2L (N = 199)**	**Clear fluids volume >2 to ≤3L (N = 262)**	**Clear fluids volume >3 to ≤4L (N = 211)**	**Clear fluids volume >4 to ≤5L (N = 106)**	**Clear fluids volume >5 to ≤7L (N = 105)**
Median total blood loss (IQR) – L	2.9 (2.2 to 3.4)	3.0 (2.3 to 3.5)	3.0 (2.5 to 4.0)	3.4 (2.7 to 4.0)	4.0 (3.5 to 5.2)
Mean difference from reference group (95% CI)	ref.	0.2 (-0.1 to 0.5)	0.4 (0.1 to 0.8)	0.6 (0.2 to 1.0)	2.0 (1.6 to 2.4)
Adjusted mean difference from reference group (95% CI)*	ref.	0.2 (-0.1 to 0.5)	0.4 (0.1 to 0.7)	0.6 (0.5 to 0.7)	1.9 (1.5 to 2.3)
Adverse maternal outcome – no. (%)†	52 (26.1)	69 (26.3)	61 (28.9)	41 (38.7)	64 (61.0)
Maternal mortality – no. (%)	1 (0.5)	1 (0.4)	-	-	2 (1.9)
Hysterectomy – no. (%)	3 (1.5)	7 (2.7)	9 (4.3)	4 (3.8)	13 (12.4)
Arterial embolization – no. (%)	17 (8.5)	24 (9.2)	23 (10.9)	14 (13.2)	31 (29.5)
ICU-admission – no. (%)	46 (23.1)	55 (21.0)	51 (24.2)	35 (33.0)	52 (49.5)
Crude OR (95% CI)	1	1.0 (0.7 to 1.5)	1.2 (0.7 to 1.8)	1.8 (1.1 to 2.9)	4.4 (2.7 to 7.3)
Adjusted OR (95% CI)*	1	1.0 (0.7 to 1.6)	1.2 (0.8 to 1.9)	1.8 (1.1 to 3.1)	4.4 (2.6 to 7.5)
Summary of sensitivity analyses in women with the most severe haemorrhages$^{\phi}$					
Baseline blood loss ≥ 1L (N = 404)	N = 88	N = 117	N = 103	N = 47	N = 49
Crude OR (95% CI)*	1	1.0 (0.6 to 1.6)	1.2 (0.8 to 1.9)	1.7 (1.0 to 2.9)	4.7 (2.8 to 8.1)
Adjusted OR (95% CI)*	1	0.8 (0.4 to 1.5)	1.2 (0.6 to 2.4)	1.4 (0.6 to 3.3)	3.9 (1.8 to 8.5)
Baseline bleeding rate ≥ 1L/hr. (N = 506)	N = 110	N = 139	N = 130	N = 63	N = 64
Crude OR (95% CI)*	1	1.3 (0.7 to 2.3)	1.3 (0.7 to 2.3)	3.0 (1.6 to 5.9)	5.4 (2.8 to 10.5)
Adjusted OR (95% CI)*	1	1.3 (0.7 to 2.4)	1.4 (0.8 to 2.6)	3.1 (1.5 to 6.2)	5.9 (2.8 to 12.1)
Signs of haemorrhagic shock present at baseline (N=281)	N = 57	N = 79	N = 66	N = 43	N = 36
Crude OR (95% CI)*	1	0.9 (0.4 to 1.9)	1.2 (0.5 to 2.5)	2.2 (0.9 to 5.0)	5.7 (2.3 to 14.2)
Adjusted OR (95% CI)*	1	1.0 (0.4 to 2.2)	1.2 (0.5 to 2.7)	2.2 (0.9 to 5.4)	5.8 (2.2 to 15.7)

IQR denotes interquartile range; 95% CI denotes 95% confidence interval; ICU denotes intensive care unit; OR denotes odds ratio.

*Adjusted for: preeclampsia (yes/no), mode of birth (vaginal/caesarean), primary cause of haemorrhage (uterine atony, retained placenta, abnormally invasive placenta, or other), blood loss at baseline (<1.0L, ≥1.0 to <2.0L, ≥2.0L), bleeding rate at baseline (<1 L/hr., ≥1 to <2 L/hr., ≥2 L/hr.), signs of haemorrhagic shock at baseline (yes/no).

† Multiple endpoints per patient possible. $^{\phi}$ Full results shown in tables S7-S10

Figure 1. Overview of included women and clear fluids volume categories.
RBC denotes packed red blood cells, PPH denotes postpartum haemorrhage.

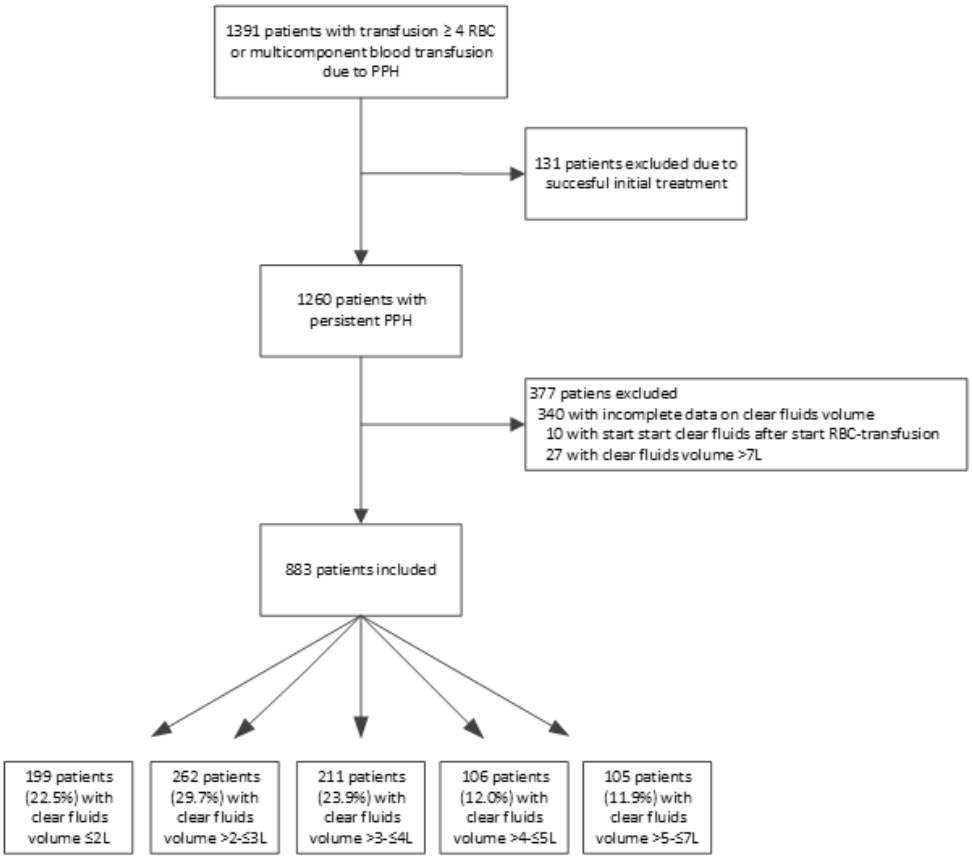
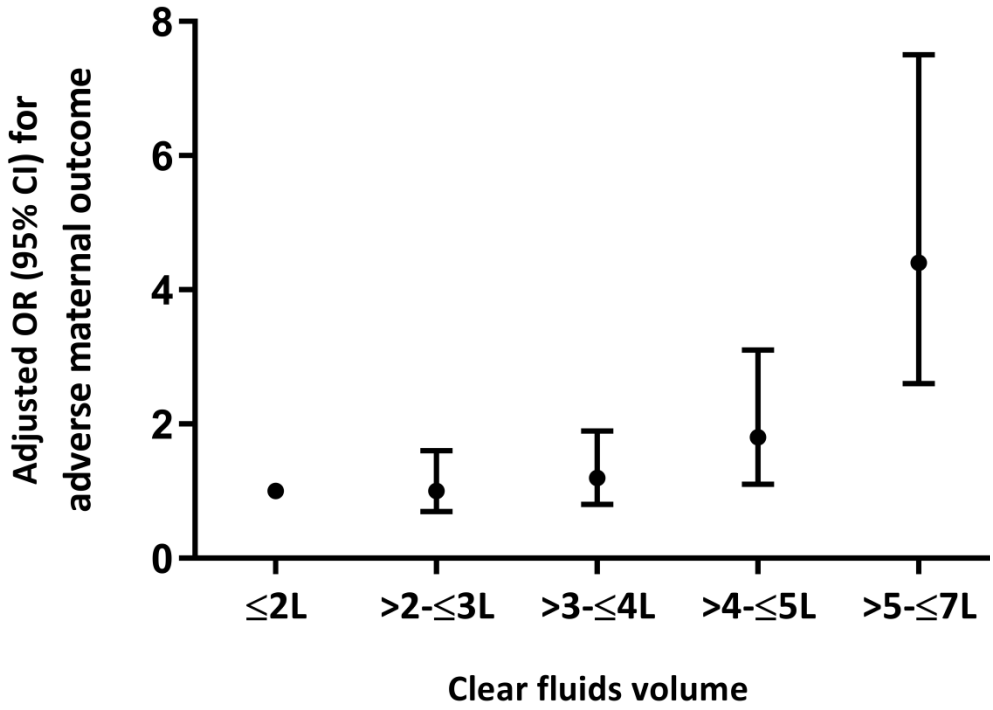


Figure 2. Adjusted odd ratios for adverse maternal outcome plotted against clear fluids volume categories.

Adjustments for preeclampsia, mode of birth, primary cause of haemorrhage, baseline blood loss, bleeding rate and signs of haemorrhagic shock. OR denotes odds ratio, CI denotes confidence interval.

*Reference category



Supplement Chapter 6

Fluid resuscitation during persistent postpartum haemorrhage and maternal outcome: a nationwide cohort study

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Figure S1. Definition of persistent postpartum haemorrhage and study baseline. Persistent postpartum haemorrhage is defined as postpartum haemorrhage refractory to first-line uterotonic or surgical therapy to control bleeding, depending on primary cause of haemorrhage. Time of diagnosis of persistent postpartum haemorrhage is regarded as study baseline. PPH denotes postpartum haemorrhage.

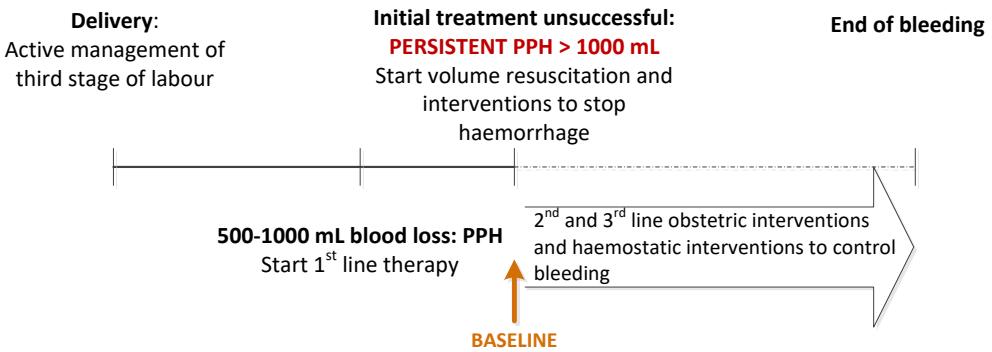

Table S1. Demographic and pregnancy characteristics of patients excluded due to incomplete data on clear fluids volume, compared to included patients

Characteristic	Included patients with persistent PPH (N = 883)	Excluded patients with persistent PPH (N = 377)
Age – no. (%)		
< 35 years	655 (74.2)	254 (67.4)
≥ 35 years	227 (25.7)	123 (32.6)
Unknown	1 (0.1)	-
Ethnicity – no. (%)		
Caucasian	637 (72.1)	266 (70.6)
Other/unknown	246 (27.9)	111 (29.4)
BMI – no. (%)		
<25 kg/m^2	484 (54.8)	201 (53.3)
≥25 to 30 kg/m^2	156 (17.7)	66 (17.5)
≥30 kg/m^2	84 (9.5)	32 (8.5)
Unknown	159 (18.0)	78 (20.7)
Preeclampsia – no. (%)	91 (10.3)	36 (9.5)
Mode of delivery – no. (%)		
Vaginal	697 (78.9)	270 (71.6)
Caesarean	180 (20.4)	105 (27.9)
Unknown	6 (0.7)	2 (0.5)
Cause of haemorrhage – no. (%)		
Uterine atony	587 (66.5)	218 (57.8)
Retained placenta	147 (16.6)	72 (19.1)
Abnormally invasive placenta	84 (9.5)	29 (7.7)
Surgical	52 (5.9)	40 (10.6)
Other†	13 (1.5)	18 (4.8)

PPH: postpartum haemorrhage.

† Includes placenta previa, placental abruption and congenital or acquired coagulation disorders.

Table S2. Bleeding characteristics of patients excluded due to incomplete data on clear fluids volume, compared to included patients

Characteristic	Included patients with persistent PPH (N = 883)	Excluded patients with persistent PPH (N = 377)
Blood loss at baseline* – no. (%)		
< 1.0L	476 (53.9)	207 (54.9)
≥1.0 to <2.0L	286 (32.4)	116 (30.8)
≥2.0L	118 (13.4)	54 (14.3)
Unknown	3 (0.3)	-
Bleeding rate at baseline* – no. (%)		
< 1.0 L/hr.	374 (42.4)	182 (48.3)
≥1.0 to <2.0 L/hr.	220 (24.9)	89 (23.6)
≥ 2.0 L/hr.	286 (32.4)	105 (27.9)
Unknown	3 (0.3)	1 (0.3)
Signs of haemorrhagic shock at baseline* – no. (%)		
No	328 (37.1)	119 (31.6)
Yes	337 (38.2)	115 (30.5)
Unknown	218 (24.7)	143 (37.9)
Type of clear fluid – median (interquartile range)		
Crystalloids	2.0 (1.0-3.0)	Unknown
Colloids	1.0 (1.0-1.5)	Unknown
Time from baseline till first unit of red blood cells (hrs.)		
< 1 hour	252 (28.5)	128 (34.0)
1 to 3 hours	424 (48.0)	131 (34.7)
≥3 hours	197 (22.3)	98 (26.0)
Unknown	10 (1.1)	20 (5.3)

PPH: postpartum haemorrhage.

* Baseline was defined as time of diagnosis of persistent postpartum haemorrhage.

Table S3. Demographic and pregnancy characteristics of included women with persistent postpartum haemorrhage, with patients categorized into quintiles of clear fluids volume

Characteristic	Clear fluids volume ≤2L* (N = 199)	Clear fluids volume >2 to ≤3L (N = 262)	Clear fluids volume >3 to ≤3.5L (N = 103)	Clear fluids volume >3.5 to ≤4.5L (N = 178)	Clear fluids volume > 4.5L (N = 168)
Age – no. (%)					
< 35 years	142 (71.4)	197 (75.2)	80 (77.7)	137 (77.0)	117 (69.6)
≥ 35 years	56 (28.1)	65 (24.8)	23 (22.3)	41 (23.0)	51 (30.4)
Unknown	1 (0.5)	-	-	-	-
Ethnicity – no. (%)					
Caucasian	143 (71.9)	178 (67.9)	75 (72.8)	130 (73.0)	133 (79.2)
Other/unknown	56 (28.1)	84 (32.1)	28 (27.2)	48 (27.0)	35 (20.8)
BMI – no. (%)					
<25 kg/m^2	103 (51.8)	136 (51.9)	61 (59.2)	107 (60.1)	95 (56.5)
≥25 to <30 kg/m^2	34 (17.1)	51 (19.5)	18 (17.5)	25 (14.0)	33 (19.6)
≥30 kg/m^2	17 (8.5)	23 (8.8)	10 (9.7)	18 (10.1)	19 (11.3)
Unknown	45 (22.6)	52 (19.8)	14 (13.6)	28 (15.7)	21 (12.5)
Preeclampsia – no. (%)	27 (13.6)	29 (11.1)	8 (7.8)	12 (6.7)	15 (8.9)
Mode of delivery – no. (%)					
Vaginal	156 (78.4)	209 (79.8)	86 (83.5)	149 (83.7)	111 (66.1)
Caesarean	41 (20.6)	52 (19.8)	16 (15.5)	27 (15.2)	57 (33.9)
Unknown	2 (1.0)	1 (0.4)	1 (1.0)	2 (1.1)	-
Cause of haemorrhage – no. (%)					
Uterine atony	117 (58.8)	171 (65.3)	69 (67.0)	124 (69.7)	119 (70.8)
Retained placenta	43 (21.6)	49 (18.7)	17 (16.5)	27 (15.2)	17 (10.1)
Abnormally invasive placenta	30 (15.1)	24 (9.2)	8 (7.8)	12 (6.7)	12 (7.1)
Surgical	5 (2.5)	15 (5.7)	8 (7.8)	12 (6.7)	17 (10.1)
Other†	4 (2.0)	3 (1.1)	1 (1.0)	3 (1.7)	3 (1.8)

*Reference category. † Includes placenta previa, placental abruption and congenital or acquired coagulation disorders.

Table S4. Bleeding characteristics at time of diagnosis of persistent postpartum haemorrhage and details of fluid resuscitation, with patients categorized into quintiles of clear fluids volume

Characteristic	Clear fluids volume ≤2L* (N = 199)	Clear fluids volume >2 to ≤3L (N = 262)	Clear fluids volume >3 to ≤3.5L (N = 103)	Clear fluids volume >3.5 to 4.5L (N = 178)	Clear fluids volume > 4.5L (N = 168)
Blood loss at baseline† – no. (%)					
< 1.0L	108 (54.3)	145 (55.3)	55 (53.4)	89 (50.0)	95 (56.5)
≥1.0 to <2.0L	66 (33.2)	77 (29.4)	38 (36.9)	63 (35.4)	46 (27.4)
≥2.0L	22 (11.1)	40 (15.3)	10 (9.7)	26 (14.6)	28 (16.7)
Unknown	3 (1.5)	-	-	-	-
Bleeding rate at baseline† – no. (%)					
< 1.0 L/hr.	86 (43.2)	123 (46.9)	45 (43.7)	63 (35.4)	66 (39.3)
≥1.0 to <2.0 L/hr.	55 (27.6)	60 (22.9)	24 (23.3)	46 (25.8)	43 (25.6)
≥ 2.0 L/hr.	55 (27.6)	79 (30.2)	34 (33.0)	69 (38.8)	59 (35.1)
Unknown	3 (1.5)	-	-	-	-
Signs of haemorrhagic shock at baseline† – no. (%)					
No	82 (41.2)	121 (46.2)	44 (42.7)	72 (40.4)	75 (44.6)
Yes	57 (28.6)	79 (30.2)	34 (33.0)	62 (34.8)	62 (36.9)
Unknown	60 (30.2)	62 (23.7)	25 (24.3)	44 (24.7)	31 (18.5)
Type of clear fluid – median (interquartile range)					
Crystalloids	1.0 (0.5-1.0)	1.5 (1.5-2.0)	2.0 (2.0-2.5)	3.0 (2.5-3.0)	4.0 (3.5-5.0)
Colloids	1.0 (0.5-1.0)	1.0 (1.0-1.5)	1.5 (1.0-1.5)	1.5 (1.0-1.5)	1.5 (1.5-2.0)
Time from baseline till first unit of red blood cells (hrs.)					
< 1 hour	50 (25.1)	74 (28.2)	26 (25.2)	51 (28.7)	63 (37.5)
1 to 3 hours	91 (45.7)	124 (47.3)	53 (51.5)	90 (50.6)	79 (47.0)
≥3 hours	51 (25.6)	64 (24.4)	24 (23.3)	34 (19.1)	26 (15.5)
Unknown	7 (3.5)	-	-	3 (1.7)	-

PPH: postpartum haemorrhage.

*Reference category. † Baseline was defined as time of diagnosis of persistent PPH.

Table S5. Total blood loss and maternal outcomes, with patients categorized in quintiles of clear fluids volume					
Outcome	**Clear fluids volume ≤2L**	**Clear fluids volume >2 to ≤3L**	**Clear fluids volume >3 to ≤3.5L**	**Clear fluids volume >3.5 to ≤4.5L**	**Clear fluids volume > 4.5L**
	(N = 199)	**(N = 262)**	**(N = 103)**	**(N = 178)**	**(N = 168)**
Median total blood loss (IQR) – L	2.9 (2.2 to 3.4)	3.0 (2.3 to 3.5)	3.0 (2.5 to 3.9)	3.0 (2.5 to 4.0)	4.0 (3.5 to 6.0)
Mean difference from reference group (95% CI)	ref.	0.2 (-0.2 to 0.5)	0.4 (-0.1 to 0.9)	0.5 (0 to 0.9)	2.3 (1.8 to 2.7)
Adjusted mean difference from reference group (95% CI)*	ref.	0.2 (-0.2 to 0.5)	0.4 (0 to 0.9)	0.4 (0 to 0.8)	2.1 (1.7 to 2.5)
Adverse maternal outcome – no. (%)†	52 (26.1)	69 (26.3)	30 (29.1)	59 (33.1)	100 (59.5)
Maternal mortality – no. (%)	1 (0.5)	1 (0.4)	-	-	3 (1.8)
Hysterectomy – no. (%)	3 (1.5)	7 (2.7)	6 (5.8)	4 (2.2)	25 (14.9)
Arterial embolisation – no. (%)	17 (8.5)	24 (9.2)	14 (13.6)	20 (11.2)	45 (26.8)
ICU-admission – no. (%)	46 (23.1)	55 (21.0)	23 (22.3)	51 (28.7)	82 (48.8)
Crude OR (95% CI)	1	1.0 (0.7 to 1.5)	1.2 (0.7 to 2.0)	1.4 (0.9 to 2.2)	4.2 (2.7 to 6.5)
Adjusted OR (95% CI)*	1	1.0 (0.7 to 1.6)	1.2 (0.7 to 2.1)	1.5 (0.9 to 2.4)	4.0 (2.5 to 6.4)

IQR: interquartile range; 95% CI: 95% confidence interval; ICU: intensive care unit; OR: odds ratio

*Adjusted for: preeclampsia (yes/no), mode of delivery (vaginal/caesarean), primary cause of haemorrhage (uterine atony, retained placenta, abnormally invasive placenta or other), blood loss at baseline (<1.0L, ≥1.0 to <2.0L, ≥2.0L), bleeding rate at baseline (<1 L/hr., ≥1 to <2 L/hr., ≥2 L/hr.), signs of haemorrhagic shock (yes/no).

† Multiple endpoints per patient possible.

Table S6. Sensitivity analysis with the highest clear fluids volume category as reference category					
Outcome	**Clear fluids volume ≤2L**	**Clear fluids volume >2 to ≤3L**	**Clear fluids volume >3 to ≤4L**	**Clear fluids volume >4 to ≤5L**	**Clear fluids volume >5 to ≤7L**
	(N = 199)	**(N= 262)**	**(N= 211)**	**(N= 106)**	**(N= 105)**
Median total blood loss (IQR) – L	2.9 (2.2 to 3.4)	3.0 (2.3 to 3.5)	3.0 (2.5 to 4.0)	3.4 (2.7 to 4.0)	4.0 (3.5 to 5.2)
Mean difference from reference group (95% CI)	-2.0 (-2.4 to -1.6)	-1.4 (-1.9 to -0.9)	-1.6 (-2.0 to -1.2)	-1.8 (-2.2 to -1.4)	ref.
Adjusted mean difference from reference group (95% CI)*	-1.9 (-2.3 to -1.5)	-1.8 (-2.2 to -1.4)	-1.5 (-1.9 to -1.1)	-1.4 (-1.8 to -0.9)	ref.
Adverse maternal outcome – no. (%)†	52 (26.1)	69 (26.3)	61 (28.9)	41 (38.7)	64 (61.0)
Maternal mortality – no. (%)	1 (0.5)	1 (0.4)	-	-	2 (1.9)
Hysterectomy – no. (%)	3 (1.5)	7 (2.7)	9 (4.3)	4 (3.8)	13 (12.4)
Arterial embolisation – no. (%)	17 (8.5)	24 (9.2)	23 (10.9)	14 (13.2)	31 (29.5)
ICU-admission – no. (%)	46 (23.1)	55 (21.0)	51 (24.2)	35 (33.0)	52 (49.5)
Crude OR (95% CI)	0.2 (0.1 to 0.4)	0.2 (0.1 to 0.4)	0.3 (0.2 to 0.4)	0.4 (0.2 to 0.7)	1
Adjusted OR (95% CI)*	0.2 (0.1 to 0.4)	0.2 (0.1 to 0.4)	0.3 (0.2 to 0.5)	0.4 (0.2 to 0.7)	1

IQR: interquartile range; 95% CI: 95% confidence interval; ICU: intensive care unit; OR: odds ratio

*Adjusted for: preeclampsia (yes/no), mode of delivery (vaginal/caesarean), primary cause of haemorrhage (uterine atony, retained placenta, abnormally invasive placenta or other), blood loss at baseline (<1.0L, ≥1.0 to <2.0L, ≥2.0L), bleeding rate at baseline (<1 L/hr., ≥1 to <2 L/hr., ≥2 L/hr.), signs of haemorrhagic shock (yes/no).

† Multiple endpoints per patient possible.

Table S7: Summary of sensitivity analyses in patients with the most severe haemorrhages: blood loss ≥ 1L, bleeding rate ≥ 1L/hr., and signs of haemorrhagic shock present at time of diagnosis of persistent PPH. Complete results of sensitivity analyses provided in Tables S8 to S10.

Outcome	Clear fluids volume ≤2L	Clear fluids volume >2 to ≤3L	Clear fluids volume >3 to ≤4L	Clear fluids volume >4 to ≤5L	Clear fluids volume >5 to ≤7L
Patients with baseline blood loss ≥ 1L (N = 404)	88	117	103	47	49
Median total blood loss (IQR) – L	3.0 (2.5 to 3.5)	3.0 (2.5 to 3.5)	3.0 (2.5 to 4.0)	3.5 (3.0 to 4.0)	4.0 (3.1 to 4.8)
Adjusted mean difference from reference group (95% CI)*	ref.	0 (-0.5 to 0.5)	0.5 (0 to 1.1)	0.8 (0.1 to 1.4)	1.8 (1.1 to 2.5)
Adverse maternal outcome – no. (%)†					
Adjusted OR (95% CI)*	22 (25.0)	26 (22.2)	29 (28.2)	15 (31.9)	28 (57.1)
	1	0.8 (0.4 to 1.5)	1.2 (0.6 to 2.4)	1.4 (0.6 to 3.3)	3.9 (1.8 to 8.5)
Patients with baseline bleeding rate ≥ 1L/hr. (N = 506)	110	139	130	63	64
Median total blood loss (IQR) – L	3.0 (2.5 to 3.5)	3.0 (2.5 to 4.0)	3.0 (2.5 to 4.0)	3.5 (3.0 to 4.0)	4.3 (3.5 to 6.0)
Adjusted mean difference from reference group (95% CI)*	ref.	0.3 (-0.2 to 0.7)	0.5 (0 to 0.9)	0.7 (0.1 to 1.3)	2.1 (1.5 to 2.6)
Adverse maternal outcome – no. (%)†					
Adjusted OR (95% CI)*	26 (23.6)	39 (28.1)	37 (28.5)	30 (47.6)	40 (62.5)
	1	1.3 (0.7 to 2.4)	1.4 (0.8 to 2.6)	3.1 (1.5 to 6.2)	5.9 (2.8 to 12.1)
Patients with signs of haemorrhagic shock present at baseline (N = 281)	57	79	66	43	36
Median total blood loss (IQR) – L	3.0 (2.5 to 3.5)	3.0 (2.4 to 4.0)	3.0 (2.5 to 4.0)	3.5 (2.5 to 4.0)	4.0 (3.0 to 5.9)
Adjusted mean difference from reference group (95% CI)*	ref.	0.3 (-0.1 to 0.6)	0.3 (-0.5 to 1.0)	0.4 (-0.1 to 1.0)	1.9 (1.4 to 2.3)
Adverse maternal outcome – no. (%)†	17 (29.8)	21 (26.6)	21 (31.8)	20 (46.5)	25 (69.4)
Adjusted OR (95% CI)*	1	1.0 (0.4 to 2.2)	1.2 (0.5 to 2.7)	2.2 (0.9 to 5.2)	5.8 (2.2 to 15.7)

IQR: interquartile range; 95% CI: 95% confidence interval; ICU: intensive care unit; OR: odds ratio

*Adjusted for: preeclampsia (yes/no), mode of delivery (vaginal/caesarean), primary cause of haemorrhage (uterine atony, retained placenta, abnormally invasive placenta, surgical cause or other), blood loss at baseline (<1.0L, ≥1.0 to <2.0L, ≥2.0L), bleeding rate at baseline (<1 L/hr., ≥1 to <2 L/hr., ≥2 L/hr.), signs of haemorrhagic shock (yes/no).

† Multiple endpoints per patient possible.

Table S8. Sensitivity analysis of only patients with baseline blood loss ≥ 1L					
Outcome	**Clear fluids volume ≤2L**	**Clear fluids volume >2 to ≤3L**	**Clear fluids volume >3 to ≤4L**	**Clear fluids volume >4 to ≤5L**	**Clear fluids volume >5 to ≤7L**
	(N = 88)	**(N= 77)**	**(N= 103)**	**(N= 47)**	**(N= 49)**
Median total blood loss (IQR) – L	2.9 (2.3 to 3.3)	3.0 (2.3 to 3.5)	3.0 (2.5 to 4.0)	3.2 (2.6 to 4.0)	4.0 (3.5 to 5.0)
Mean difference from reference group (95% CI)	ref.	0.1 (-0.2 to 0.5)	0.4 (0.1 to 0.8)	0.5 (0.1 to 0.9)	2.0 (1.5 to 2.4)
Adjusted mean difference from reference group (95% CI)*	ref.	0.1 (-0.2 to 0.5)	0.4 (0 to 0.7)	0.5 (0.1 to 0.9)	1.9 (1.5 to 2.3)
Adverse maternal outcome – no. (%)†	41 (24.8)	57 (24.3)	55 (28.6)	34 (35.4)	60 (61.2)
Maternal mortality – no. (%)	1 (0.6)	1 (0.4)	-	-	2 (2.0)
Hysterectomy – no. (%)	1 (0.6)	3 (1.3)	7 (3.6)	1 (1.0)	9 (9.2)
Arterial embolisation – no. (%)	16 (9.7)	20 (8.5)	14 (13.7)	4 (8.5)	13 (26.0)
ICU-admission – no. (%)	35 (21.2)	46 (19.6)	21 (10.9)	14 (14.6)	30 (30.6)
Crude OR (95% CI)	1	1.0 (0.6 to 1.6)	1.2 (0.8 to 1.9)	1.7 (1.0 to 2.9)	4.7 (2.8 to 8.1)
Adjusted OR (95% CI)*	1	1.0 (0.6 to 1.5)	1.2 (0.7 to 2.0)	1.6 (0.9 to 2.9)	4.3 (2.5 to 7.6)

IQR: interquartile range; 95% CI: 95% confidence interval; ICU: intensive care unit; OR: odds ratio

*Adjusted for: preeclampsia (yes/no), mode of delivery (vaginal/caesarean), primary cause of haemorrhage (uterine atony, retained placenta, abnormally invasive placenta or other), blood loss at baseline (<1.0L, ≥1.0 to <2.0L, ≥2.0L), bleeding rate at baseline (<1 L/hr., ≥1 to <2 L/hr., ≥2 L/hr.), signs of haemorrhagic shock (yes/no).

† Multiple endpoints per patient possible.

Table S9. Sensitivity analysis of only patients with baseline bleeding rate ≥ 1L/hr.					
Outcome	**Clear fluids volume ≤2L**	**Clear fluids volume >2 to ≤3L**	**Clear fluids volume >3 to ≤4L**	**Clear fluids volume >4 to ≤5L**	**Clear fluids volume >5 to ≤7L**
	(N = 110)	**(N= 139)**	**(N= 130)**	**(N= 63)**	**(N= 64)**
Median total blood loss (IQR) – L	3.0 (2.5 to 3.5)	3.0 (2.5 to 4.0)	3.0 (2.5 to 4.0)	3.5 (3.0 to 4.0)	4.3 (3.5 to 6.0)
Mean difference from reference group (95% CI)	ref.	0.3 (-0.2 to 0.7)	0.4 (-0.1 to 0.9)	0.8 (0.2 to 1.3)	2.1 (1.5 to 2.7)
Adjusted mean difference from reference group (95% CI)*	ref.	0.3 (-0.2 to 0.7)	0.5 (0 to 0.9)	0.7 (0.1 to 1.3)	2.1 (1.5 to 2.6)
Adverse maternal outcome – no. (%)†	2 (23.6)	39 (28.1)	37 (28.5)	30 (47.6)	40 (62.5)
Maternal mortality – no. (%)	1 (0.9)	1 (0.7)	-	-	1 (1.6)
Hysterectomy – no. (%)	2 (1.8)	7 (5.0)	6 (4.6)	3 (4.8)	8 (12.5)
Arterial embolisation – no. (%)	4 (3.6)	14 (10.1)	12 (9.2)	11 (17.5)	18 (28.1)
ICU-admission – no. (%)	26 (23.6)	29 (20.9)	33 (25.4)	25 (39.7)	35 (54.7)
Crude OR (95% CI)	1	1.3 (0.7 to 2.3)	1.3 (0.7 to 2.3)	3.0 (1.6 to 5.9)	5.4 (2.8 to 10.5)
Adjusted OR (95% CI)*	1	1.3 (0.7 to 2.4)	1.4 (0.8 to 2.6)	3.1 (1.5 to 6.2)	5.9 (2.8 to 12.1)

IQR: interquartile range; 95% CI: 95% confidence interval; ICU: intensive care unit; OR: odds ratio

*Adjusted for: preeclampsia (yes/no), mode of delivery (vaginal/caesarean), primary cause of haemorrhage (uterine atony, retained placenta, abnormally invasive placenta or other), blood loss at baseline (<1.0L, ≥1.0 to <2.0L, ≥2.0L), bleeding rate at baseline (<1 L/hr., ≥1 to <2 L/hr., ≥2 L/hr.), signs of haemorrhagic shock (yes/no).

† Multiple endpoints per patient possible.

Table S10. Sensitivity analyses of only patients with signs of haemorrhagic shock at baseline					
Outcome	**Clear fluids volume ≤2L**	**Clear fluids volume >2 to ≤3L**	**Clear fluids volume >3 to ≤4L**	**Clear fluids volume >4 to ≤5L**	**Clear fluids volume >5 to ≤7L**
	(N = 57)	**(N= 79)**	**(N= 66)**	**(N= 43)**	**(N= 36)**
Median total blood loss (IQR) – L	3.0 (2.5 to 3.5)	3.0 (2.4 to 4.0)	3.0 (2.5 to 4.0)	3.5 (2.5 to 4.0)	4.0 (3.0 to 5.9)
Mean difference from reference group (95% CI)	ref.	0.3 (-0.4 to 1.1)	0.4 (-0.4 to 1.1)	0.6 (-0.2 to 1.5)	1.9 (1.1 to 2.8)
Adjusted mean difference from reference group (95% CI)*	ref.	0.3 (-0.4 to 1.0)	0.3 (-0.4 to 1.0)	0.5 (-0.3 to 1.2)	1.9 (1.0 to 2.7)
Adverse maternal outcome – no. (%)†	16 (28.6)	21 (26.6)	21 (31.8)	20 (46.5)	25 (69.4)
Maternal mortality – no. (%)	-	1 (1.3)	-	-	1 (2.8)
Hysterectomy – no. (%)	2 (3.6)	4 (5.1)	4 (6.1)	1 (2.3)	4 (11.1)
Arterial embolisation – no. (%)	4 (7.1)	8 (10.1)	7 (10.6)	5 (11.6)	10 (27.8)
ICU-admission – no. (%)	15 (26.8)	15 (19.0)	17 (25.8)	19 (44.2)	19 (52.8)
Crude OR (95% CI)	1	0.9 (0.4 to 1.9)	1.2 (0.5 to 2.5)	2.2 (0.9 to 5.0)	5.7 (2.3 to 14.2)
Adjusted OR (95% CI)*	1	1.0 (0.4 to 2.2)	1.2 (0.5 to 2.7)	2.2 (0.9 to 5.4)	5.8 (2.2 to 15.7)

IQR: interquartile range; 95% CI: 95% confidence interval; ICU: intensive care unit; OR: odds ratio

*Adjusted for: preeclampsia (yes/no), mode of delivery (vaginal/caesarean), primary cause of haemorrhage (uterine atony, retained placenta, abnormally invasive placenta or other), blood loss at baseline (<1.0L, ≥1.0 to <2.0L, ≥2.0L), bleeding rate at baseline (<1 L/hr., ≥1 to <2 L/hr., ≥2 L/hr.), signs of haemorrhagic shock (yes/no).

† Multiple endpoints per patient possible.

Table S11. Sensitivity analysis of only patients with need for RBC-transfusion not predictable prior to start of haemorrhage

Outcome	Clear fluids volume ≤2L (N = 165)	Clear fluids volume >2 to ≤3L (N= 235)	Clear fluids volume >3 to ≤4L (N= 192)	Clear fluids volume >4 to ≤5L (N= 96)	Clear fluids volume >5 to ≤7L (N= 98)
Median total blood loss (IQR) – L	2.9 (2.3 to 3.3)	3.0 (2.3 to 3.5)	3.0 (2.5 to 4.0)	3.2 (2.6 to 4.0)	4.0 (3.5 to 5.0)
Mean difference from reference group (95% CI)	ref.	0.1 (-0.2 to 0.5)	0.4 (0.1 to 0.8)	0.5 (0.1 to 1.0)	2.0 (1.5 to 2.4)
Adjusted mean difference from reference group (95% CI)*	ref.	0.1 (-0.2 to 0.5)	0.4 (0 to 0.7)	0.5 (0.1 to 0.9)	1.9 (1.5 to 2.3)
Adverse maternal outcome – no. (%)†	41 (24.8)	57 (24.3)	55 (28.6)	34 (35.4)	60 (61.2)
Maternal mortality – no. (%)	1 (0.6)	1 (0.4)	-	-	2 (2.0)
Hysterectomy – no. (%)	1 (0.6)	3 (1.3)	7 (3.6)	1 (1.0)	9 (9.2)
Arterial embolisation – no. (%)	16 (9.7)	20 (8.5)	21 (10.9)	14 (14.6)	30 (30.6)
ICU-admission – no. (%)	35 (21.2)	46 (19.6)	48 (25.0)	29 (30.2)	49 (50.0)
Crude OR (95% CI)	1	1.0 (0.6 to 1.6)	1.2 (0.8 to 1.9)	1.7 (1.0 to 2.9)	4.7 (2.8 to 8.1)
Adjusted OR (95% CI)*	1	1.0 (0.6 to 1.5)	1.2 (0.7 to 2.0)	1.6 (0.9 to 2.9)	4.3 (2.5 to 7.6)

RBC: red blood cells; IQR: interquartile range; 95% CI: 95% confidence interval; ICU: intensive care unit; OR: odds ratio

*Adjusted for: preeclampsia (yes/no), mode of delivery (vaginal/caesarean), primary cause of haemorrhage (uterine atony, retained placenta, abnormally invasive placenta or other), blood loss at baseline (<1.0L, ≥1.0 to <2.0L, ≥2.0L), bleeding rate at baseline (<1 L/hr., ≥1 to <2 L/hr., ≥2 L/hr.), signs of haemorrhagic shock (yes/no).

† Multiple endpoints per patient possible.

Table S12. Sensitivity analysis of only patients without neuroaxial blockade during labour.					
Outcome	**Clear fluids volume ≤2L**	**Clear fluids volume >2 to ≤3L**	**Clear fluids volume >3 to ≤4L**	**Clear fluids volume >4 to ≤5L**	**Clear fluids volume >5 to ≤7L**
	(N = 127)	**(N = 164)**	**(N = 137)**	**(N = 60)**	**(N = 58)**
Median total blood loss (IQR) – L	2.8 (2.1 to 3.0)	3.0 (2.3 to 3.5)	3.0 (2.5 to 3.5)	3.2 (2.6 to 4.0)	4.0 (3.5 to 5.4)
Mean difference from reference group (95% CI)	ref.	0.2 (-0.2 to 0.5)	0.4 (0 to 0.8)	0.6 (0.1 to 1.0)	2.2 (1.8 to 2.7)
Adjusted mean difference from reference group (95% CI)*	ref.	0.2 (-0.2 to 0.6)	0.4 (0 to 0.8)	0.5 (0.1 to 1.0)	2.2 (1.7 to 2.7)
Adverse maternal outcome – no. (%)†	23 (18.1)	34 (20.7)	36 (26.3)	19 (31.7)	35 (60.3)
Maternal mortality – no. (%)	-	1 (0.6)	-	-	2 (3.4)
Hysterectomy – no. (%)	1 (0.8)	1 (0.6)	2 (1.5)	1 (1.7)	7 (12.1)
Arterial embolisation – no. (%)	10 (7.9)	11 (6.7)	15 (10.9)	8 (13.3)	21 (36.2)
ICU-admission – no. (%)	20 (15.7)	26 (15.9)	29 (21.2)	15 (25.0)	25 (43.1)
Crude OR (95% CI)	1	1.2 (0.7 to 2.1)	1.6 (0.9 to 2.9)	2.1 (1.0 to 4.2)	6.9 (3.4 to 13.8)
Adjusted OR (95% CI)*	1	1.1 (0.6 to 2.1)	1.7 (0.9 to 3.1)	1.9 (0.9 to 4.1)	6.7 (3.2 to 13.8)

IQR: interquartile range; 95% CI: 95% confidence interval; ICU: intensive care unit; OR: odds ratio

*Adjusted for: preeclampsia (yes/no), mode of delivery (vaginal/caesarean), primary cause of haemorrhage (uterine atony, retained placenta, abnormally invasive placenta or other), blood loss at baseline (<1.0L, ≥1.0 to <2.0L, ≥2.0L), bleeding rate at baseline (<1 L/hr., ≥1 to <2 L/hr., ≥2 L/hr.), signs of haemorrhagic shock (yes/no).

† Multiple endpoints per patient possible.

7

Association of timing of plasma transfusion with adverse maternal outcomes in women with persistent postpartum hemorrhage

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Abstract

Importance Early plasma transfusion for women with severe postpartum hemorrhage (PPH) is recommended to prevent coagulopathy. However, there is no comparative, quantitative evidence on the association of early plasma transfusion with maternal outcomes.

Objective To compare the incidence of adverse maternal outcomes among women who received plasma during the first 60 minutes of persistent PPH vs women who did not receive plasma for similarly severe persistent PPH.

Design, setting, participants This multicenter cohort study used a consecutive sample of women with persistent PPH, defined as PPH refractory to first-line measures to control bleeding, between January 1, 2011, and January 1, 2013. Time-dependent propensity score-matching was used to select women who received plasma during their first 60 minutes of persistent PPH and match each of them with a woman who had shown the same severity and received the same treatment for PPH but who had not received plasma at the moment of matching. Transfusions were not guided by coagulation tests. Statistical analysis was performed from June 2018 to June 2019.

Exposure Transfusion of plasma during the first 60 minutes of persistent PPH vs no or later plasma transfusion.

Main outcomes and measures Incidence of adverse maternal outcomes, defined as a composite of death, hysterectomy, or arterial embolization.

Results This study included 1216 women (mean [SD] age, 31.6 [5.0] years) with persistent PPH, of whom 932 (76.6%) delivered vaginally and 780 (64.1%) had PPH caused by uterine atony. Seven women (0.6%) died because of PPH; 62 women (5.1%) had a hysterectomy and 159 women (13.1%) had arterial embolizations. Among women who received plasma during the first 60 minutes of persistent PPH, 114 women could be matched with a comparable woman who had not received plasma at the moment of matching. The incidence of adverse maternal outcomes was similar between the women, with adverse outcomes recorded in 24 women (21.2%) who received early plasma transfusion and 23 women (19.9%) who did not receive early plasma transfusion (odds ratio, 1.09; 95% CI, 0.57-2.09). Results of sensitivity analyses were comparable to the primary results.

Conclusion and Relevance In this cohort study, initiation of plasma transfusion during the first 60 minutes of persistent PPH was not associated with adverse maternal outcome, compared with no or later plasma transfusion, independent of severity of PPH.

Introduction

Obstetric hemorrhage accounts for 27% of all maternal deaths.[1] In high-resource settings maternal death due to postpartum hemorrhage (PPH) has become uncommon, but PPH remains an important cause of severe maternal morbidity.[2-7]

Women with persistent PPH are at risk of developing coagulopathy due to depletion of coagulation factors and platelets.[8-12] Coagulopathy can eventually lead to worse maternal outcomes. Timely transfusion of plasma may prevent coagulopathy and thereby improve maternal outcomes.

Results from a 2015 study[13] among patients with trauma suggest that formulaic plasma transfusion, comprising a fixed ratio of fresh frozen plasma to red blood cells (RBCs), is associated with better outcomes. Whether such transfusion strategies are also associated with better outcomes among women with persistent PPH is not clear. Some studies have suggested that early and aggressive plasma transfusion has a positive association with outcomes in women with PPH.[14-19] However, a 2017[20] study suggested that women with persistent PPH have better outcomes when plasma transfusion is postponed or even avoided. Uncertainty about the outcomes associated with plasma transfusion among women with persistent PPH can lead to significant variation in clinical practice. This variation in practice, along with careful documentation of confounding factors, enables the use of routinely collected clinical data to compare outcomes among women treated according to different treatment strategies.

The aim of this study was to assess whether early plasma transfusion is associated with improved maternal outcomes in women with persistent PPH. Our hypothesis was that initiation of plasma transfusion during the first 60 minutes of persistent PPH would be associated with fewer adverse maternal outcomes, defined as maternal death, hysterectomy or arterial embolization, compared with women who received no or later plasma transfusion.

Methods

Approval was obtained from the Medical Ethics Research Committee of the Leiden University Medical Center and from the institutional review board of each study center, and a waiver of informed consent was granted because the study used deidentified data. The study was registered in the Netherlands Trial Register[21], and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Study design and population

The *Transfusion strategies in women during Major Obstetric Haemorrhage* (TeMpOH-1) study[21] is a multicenter, retrospective cohort study in the Netherlands that included consecutive women who had received either 4 or more units of RBCs or a multicomponent blood transfusion within 24 hours after giving birth because of severe PPH (ie, ≥1000 mL blood loss) from January 1, 2011, to January 1, 2013. A multicomponent blood transfusion was defined as transfusion of at least one unit of packed RBCs in combination with fresh frozen plasma or platelet concentrates. We selected women from transfusion databases and birth registries in 61 participating hospitals.

From this cohort, we identified women with persistent PPH, defined as PPH with at least 1000 mL of blood loss refractory to first-line interventions to control bleeding.[8,22] First-line interventions depended on the cause of bleeding, as previously described (eTable 1 in the Supplement).[23] We regarded the time of initiation of the first-line intervention to stop PPH as the moment of diagnosis of persistent PPH, under the assumption that refractoriness to first-line treatment would become evident shortly after initiation of this therapy. Women were followed up from onset until cessation of PPH.

We excluded women with unknown timing of initiation of plasma transfusion. We also excluded women with initiation of plasma transfusion for any reason other than correcting coagulopathy secondary to PPH (ie, comorbidity).

Data collection

Trained medical students and research nurses uniformly performed comprehensive health record reviews. From routinely collected medical information, we reconstructed the treatment course of every woman with PPH. We checked all data for completeness and inconsistencies and repeated on-site health record review as necessary.

Data included comorbidity, mode of birth, primary cause of hemorrhage, consecutive estimates of blood loss and time of estimations, blood pressure and heart rate and time of measurements, volume of crystalloids and colloids for fluid resuscitation, time of transfusions of packed RBCs, plasma and platelets, and time of obstetric, radiological and hemostatic interventions to stop bleeding.

Fresh frozen plasma transfusion

Women with plasma transfusions received 1 or more units of fresh frozen plasma during the treatment of persistent PPH. Transfusion of plasma was not guided by coagulation tests. The time to plasma transfusion was defined as the interval between the moment of diagnosis of persistent PPH and administration of the first unit of plasma.

Previous studies on hemostatic interventions to correct coagulopathy in pregnant and non-pregnant patients with major hemorrhage showed beneficial associations of these interventions when initiated early after the start of hemorrhage, specifically within 3 hours.[24,25] Therefore, we examined the association of plasma transfusion during the first 60 minutes of persistent PPH with maternal outcomes.

Outcome

The outcome was the incidence of adverse maternal outcomes defined as a composite of death, hysterectomy or arterial embolization to control bleeding. The end of bleeding was defined as the time of the final recorded measurement of blood loss or the time of the last obstetric intervention to stop bleeding.

In the Netherlands, uterine or internal iliac artery embolization is performed before resorting to hysterectomy, if the woman's hemodynamic condition is stable enough to perform this procedure. During our study, 83.6% of the hospitals had this treatment modality 24 hours per day, 7 days per week, and 92.5% of our study population gave birth in 1 of these hospitals. If a hospital does not have this treatment modality available, it is common practice to transfer the woman with PPH to a nearby hospital with embolization facilities. Embolization has almost completely substituted ligation of uterine or internal iliac arteries in the Netherlands, and in our study, ligation of arteries was performed in 0.8% of women with persistent PPH.

Statistical analyses

Women with more severe PPH are more likely to receive early plasma transfusion, which confounds the association of early plasma transfusion with maternal outcomes. We used time-dependent propensity score matching to ensure that the contrasted groups were similar in terms of severity of hemorrhage and other treatments for PPH.[26-31] First, we calculated the predicted probability to receive early plasma transfusion for all women in the cohort. Second, we selected pairs of women with the same probability for receiving plasma transfusion. These pairs consisted of one woman who received early plasma transfusion and another woman who did not. Third, we compared the matched groups.

Propensity scores

The propensity score reflects the estimated probability of initiation of plasma transfusion in women with persistent PPH, given the observed characteristics of the women at the time of initiation of plasma transfusion.[28,29] We calculated a propensity score for every woman with persistent PPH by using a multivariable Cox proportional hazards model. The outcome variable in this model was time to plasma transfusion, and the linear predictor at any given minute from diagnosing persistent PPH was used as the propensity score. In women with initiation of plasma transfusion before diagnosing persistent PPH (ie, women with placental abruption), we considered the time of diagnosing persistent PPH

as the time of initiating plasma transfusion as.

We included baseline and time-dependent covariates associated with initiation of plasma transfusion and maternal outcome in a Cox model to calculate propensity scores. Selection of these potentially confounding variables was based on clinical reasoning and prior knowledge.[7,8,32-36] The baseline covariates were: mode of birth (ie, vaginal or cesarean), cause of hemorrhage (ie, uterine atony, retained placenta, abnormally invasive placenta, or other), preeclampsia (yes or no) and volume of crystalloids and colloids for fluid resuscitation (continuous variable). We included the following time-dependent variables: estimated volume of blood loss (continuous variable), bleeding rate (continuous variable), hemorrhagic shock (yes or no), oxytocin infusion (yes or no), misoprostol (yes or no), ergometrine (yes or no), the prostaglandin E2 analogue sulprostone (yes or no), manual removal of placenta (yes or no), exploration of uterine cavity and genital tract under anesthesia (yes or no), intra-uterine balloon tamponade (yes or no), tranexamic acid (yes or no), fibrinogen concentrate (yes or no), recombinant factor VIIa (yes or no), packed red blood cells transfusion (ie, 0, 1, 2, 3, or ≥4 units) and platelet transfusion (yes or no). Additional information on handling of the time-dependent covariates in statistical analyses is provided in eTable 2 in the Supplement.

Matching

We applied a 1:1 nearest-neighbor risk-set matching algorithm on the propensity score without replacement, with a maximum caliper width of 0.1 of the SD of the logit of the propensity score.[37-40] In this way, we sequentially matched every woman with persistent PPH in whom plasma transfusion was initiated at any given time point (0-60 minutes after diagnosis of persistent PPH) to a woman with similar propensity score in whom plasma transfusion was not initiated before or at that same time point (figure 1). In this matched counterpart, plasma transfusion may have been initiated at a later time point during PPH. After cessation of PPH or after reaching an endpoint (ie, arterial embolization, hysterectomy or death), a woman was no longer considered 'at risk' for plasma transfusion for correction of coagulopathy during ongoing

hemorrhage.

Missing covariate data were imputed by using multiple imputation.[41-43] We included all confounding variables, outcome variables and parameters associated with the missing variables as predictive variables in the imputation models, and generated ten imputed data sets. We tested our Cox model for non-proportional hazards by adding interactions with time.

In each imputed dataset, we estimated the propensity score for initiation of plasma transfusion for each woman with persistent PPH. We performed a time-dependent propensity score matching within each of these imputed data sets, and then we pooled the effect estimates by averaging them according to Rubin's rule.[44-46]

After matching, we performed a check of the balance between the confounding variables to ensure our propensity score model was specified correctly. To this end, we calculated the standardized differences in the confounding variables between the women with plasma transfusion during the first 60 minutes of persistent PPH and the women with no or later plasma transfusion in our matched cohort.[47-50] Absolute standardized differences less than 10% are generally considered a good balance of the observed confounding variables.[28,51,52]

Main and sensitivity analyses

We used logistic regression to assess the adjusted association of plasma transfusion during the first 60 minutes of persistent PPH with adverse maternal outcomes; the composite maternal outcome was the dependent variable and plasma transfusion (ie, early versus no or later transfusion) was the independent variable. We used robust SEs to calculate 95% CIs.

We performed several sensitivity analyses to assess the robustness of our results and to assess whether our effect estimate was influenced by women with plasma at a later time point in our comparison group. First, we performed sensitivity analyses with initiation of plasma transfusion during the first 120 and

180 minutes of persistent PPH, because a potential beneficial effect of correction of coagulopathy has been previously described within the first 3 hours after the onset of hemorrhage in obstetric and non-obstetric populations.[24,25]

Second, we performed sensitivity analyses by excluding pairs of women with a crossover of the woman initially without plasma to treatment with plasma shortly after matching. These analyses were performed with a restriction of 15, 30, 45 and 60 minutes on the time interval of switching from no plasma to plasma treatment. For example, if a woman treated with plasma at 50 minutes was matched to a women without plasma until 50 minutes but with initiation of plasma at 64 minutes, we excluded this pair in the sensitivity analysis for no crossover within 15 minutes.

Third, we performed sensitivity analyses by excluding pairs of women with a crossover of the woman initially without plasma to treatment with plasma while still being within the first 60 minutes of persistent PPH. An example: if a woman treated with plasma at 30 minutes was matched to a woman without plasma at 30 minutes but with initiation of plasma at 55 minutes, we excluded the pair from this sensitivity analysis.

Results

Population

The cohort included 1391 women with PPH who received 4 or more units of packed RBCs or a multicomponent blood transfusion within 24 hours after giving birth (figure 2). Of these women, we classified 1260 (90.6%) as having persistent PPH. We excluded 43 women with persistent PPH because of unknown time of initiation of plasma transfusion, and one woman in whom plasma transfusion had been started before birth because of leukemia instead of obstetric hemorrhage. Our final cohort included 1216 women (mean [SD] age, 31.6 [5.0] years). Seven women (0.6%) died because of PPH, 62 women (5.1%) had a hysterectomy and 159 women (13.1%) had arterial embolizations.

A total of 598 women (49.2%) received plasma during ongoing PPH. Among

women in the no or later plasma transfusion group, 618 women (57.1%) did not receive plasma and 465 women (42.9%) received plasma at a later time after matching. Median (interquartile range [IQR]) time to initiation of plasma transfusion was 105 (65-196) minutes. Overall, plasma transfusion was initiated during the first 60 minutes of persistent PPH in 133 women (10.9%), during the first 120 minutes in 338 women (27.8%) and during the first 180 minutes in 433 women (35.6%).

Baseline and time-dependent characteristics of women with early plasma transfusion vs no or later plasma transfusion are presented in table 1. We imputed missing data on volume of fluid resuscitation (16.0%) and hemorrhagic shock at moment of diagnosing persistent PPH (34.9%). For this latter time-dependent confounding variable, more data (ie, measured blood pressures and heart rates) became available for an increasing proportion of women with progression of the PPH.

And adverse maternal outcome was observed in 30 women (22.6%) with plasma transfusion during the first 60 minutes of persistent PPH and in 175 women (16.2%) with no or later plasma transfusions (odds ratio, 1.51; 95% CI, 0.98-2.34) (table 2).

Time-dependent propensity score-matched population

The number of matched pairs of women with plasma transfusion during the first 60 minutes and women with no or later plasma transfusion fluctuated across the 10 imputed datasets. We found a pooled average of 114 matches of women with plasma transfusion during the first 60 minutes and women with no plasma or plasma transfusion at a later time during persistent PPH. Nineteen women with plasma transfusion during the first 60 minutes had no match on propensity score (table 1). Median (IQR) time to plasma transfusion in women with plasma transfusion during the first 60 minutes was 40 minutes (IQR 16-50). Of their matched counterparts, 47 women (41.2%) did not receive plasma during PPH and 67 women (58.8%) received plasma at a later time during PPH, with a median (IQR) time to plasma transfusion 66 minutes (47-90) in these 67 women.

Across the 10 imputed datasets, we included a pooled average 29 women twice in this matched cohort: first as a woman with no or later plasma transfusion, and later as a woman with plasma transfusion during the first 60 minutes.

Outcomes in adjusted analyses

The distribution of baseline and time-dependent covariates in the matched cohort were well balanced between women with plasma transfusion during the first 60 minutes and women with no or later plasma transfusion (figure 3 and table 2). In the matched cohort, we observed a pooled average of 24 adverse maternal outcomes (21.2%) in women with plasma transfusion within 60 minutes vs 23 adverse maternal outcomes (19.9%) in women with no or later plasma transfusion (odds ratio, 1.09; 95% CI, 0.57-2.09).

Sensitivity analyses

Unadjusted and adjusted sensitivity analyses in women with plasma transfusion within 120 minutes and within 180 minutes vs no or later plasma transfusion within these intervals yielded similar results as the primary analysis (table 2) (eTable 3 and eTable 4 in the Supplement). In the sensitivity analyses excluding pairs of women in which a woman crossed over from no or later plasma to plasma transfusion 15, 30, 45 or 60 minutes after matching, we also found effect estimates comparable to our main analysis (eTable 5). In the sensitivity analysis excluding 29 pairs of women because of crossover from no or later plasma to plasma transfusion during the first 60 minutes of persistent PPH, the odds ratio was 0.94 (95% CI, 0.43-2.06) for the remaining pairs of women.

Discussion

In this multicenter, time-dependent propensity score-matched cohort of women with persistent PPH, empirical, early plasma transfusion was not associated with better maternal outcomes compared with women who received no or later plasma transfusion. Similar results were observed in all sensitivity analyses.

Early plasma transfusion is believed to improve maternal outcomes because

it could prevent or treat coagulopathy occurring among women treated for persistent PPH. Studies evaluating the effect of plasma transfusion on outcomes of women with severe PPH are scarce, to our knowledge. Contrary to our findings, a single-center observational study[15] among 142 women with severe PPH reported a decreased rate of advanced interventions with a high ratio of fresh frozen plasma to packed RBCs.[15] In that study, only 41 women received plasma in the management of PPH. Similarly, high ratios of fresh frozen plasma to packed RBCs have been reported to improve maternal outcomes when incorporated within PPH protocols, but whether this improvement could be attributed to the transfusion strategy or to other parts of the protocol is unclear.[17,18]

The observed absence of an effect of early plasma transfusion on maternal outcomes among women with persistent PPH may have several explanations. First, there may have been too few women who developed significant coagulopathy and therefore there was no need to treat or prevent it. This explanation is consistent with findings from studies among women with severe PPH in whom fibrinogen concentrate was administered early during hemorrhage to prevent and correct coagulopathy.[53,54] In these studies, most women had not developed coagulopathy at the time of administration of fibrinogen, and outcomes did not improve. Yet, in the TeMpOH-1 study cohort, 26% of women eventually reached a fibrinogen level of less than 2g/L, and 5% of women reached this level after losing less than 2L of blood,[55] which suggests that the absence of coagulopathy in our cohort is not explanation for our findings.

Second, plasma might not be effective in preventing or treating coagulopathy in women with persistent PPH, or the dose of plasma may have been too low to show a difference. It is conceivable that personalized supplementation of factor concentrates will be a better strategy to prevent adverse outcomes among women with PPH.

Third, 42.9% of the women in the control group were eventually also treated with plasma. Some of these women received plasma relatively shortly after the

moment at which they had been matched to their rapidly treated counterpart. If such later plasma was as effective as early administration of plasma, that could explain the observed absence of association of early plasma transfusion with outcomes. Yet, sensitivity analysis among matched pairs without this problem showed similar results, suggesting that this is also did not explain our findings.

Limitations

Our findings had some limitations and should be interpreted with caution, as they may also be explained by residual confounding. Women with more severe PPH are more likely to be rapidly treated with plasma than women with less severe hemorrhages. Time-dependent propensity score matching permitted us to balance all measured prognostic factors at any time during PPH, but this technique does not account for the distribution of unknown or unmeasured confounders. Yet, the professionals treating the women with severe PPH in our cohort carefully documented all parameters that are generally considered relevant with respect to the severity and treatment of PPH, to our knowledge. We could not think of any other parameters that might explain the observed absence of association. In addition, our findings may also be explained by random error. The confidence interval around the point estimate covers values between 0.57 and 2.09, suggesting that there may be a protective or harmful association of early plasma transfusion with maternal outcomes, in line with the findings of previous studies.[15-20]

A strength of our study was the use of persistent PPH, an intuitive and pragmatic definition of severe PPH with easy translation to daily clinical practice, to select women for this analysis.[8,22,36] In the Netherlands, clinical parameters and the times of interventions are carefully recorded during obstetric emergencies. Thus, we were able to make a detailed reconstruction of the course of PPH and we had no loss to follow up. In addition, extensive sensitivity analyses showed consistent results.

Conclusion

This cohort study found that among women with persistent PPH, empirical early plasma transfusion was not associated with less maternal deaths, hysterectomies and arterial embolizations compared with no or later plasma transfusion. Results were carefully adjusted for severity of PPH and time-dependent confounding, but residual confounding cannot be ruled out because of the observational nature of the study design.

Our findings do not suggest that plasma transfusion has no place in the treatment of women with severe PPH. Rather, our study underlines the importance of developing tools to diagnose coagulopathy during persistent PPH. These tools may enable individualization of treatment of women with persistent PPH by identifying women who develop coagulopathy during persistent PPH.

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Dacia Henriquez and Camila Caram-Deelder had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1. Characteristics of women with *persistent postpartum hemorrhage* in the total cohort and the propensity score matched cohort according to plasma transfusion strategy

Numbers of pairs in the propensity matched cohort are pooled averages after multiple imputation.

Characteristic	Women, No. (%)				
	Overall cohort		**Propensity score matched cohort**		
	Characteristics at moment of diagnosing persistent postpartum hemorrhage		*Characteristics at moment of matching*		
	No or later plasma transfusion[d] (n = 1083)	**Plasma transfusion within 60 minutes (n = 133)**	**No or later plasma transfusion[d,e] (n = 114)**	**Plasma transfusion within 60 minutes [e,f] (n = 114)**	**Standardized difference after propensity score matching (%)**
Mode of birth					2.9
Vaginal	846 (78.1)	86 (64.7)	82 (72.0)	76 (66.7)	
Cesarean	231 (21.3)	47 (35.3)	32 (28.0)	38 (33.3)	
Unknown	6 (0.6)	-	-	-	
Cause of hemorrhage[a]					
Uterine atony	701 (64.7)	79 (59.4)	70 (60.9)	69 (60.8)	reference
Retained placenta	188 (17.4)	24 (18.0)	24 (20.9)	20 (17.4)	0.8
Abnormally invasive placenta	93 (8.6)	12 (9.0)	7 (6.3)	11 (9.6)	0.6
Other[b]	101 (9.3)	18 (13.5)	14 (11.9)	14 (12.2)	5.4
Preeclampsia	107 (9.9)	19 (14.3)	9 (7.9)	17 (15.1)	3.1
Fluid resuscitation with crystalloids and colloids[c]					2.0
≤2L	266 (24.6)	32 (24.1)	27 (23.7)	33 (28.8)	
>2 to ≤4L	438 (40.4)	46 (34.6)	61 (53.2)	55 (48.5)	
>4L	211 (19.5)	29 (21.8)	26 (23.1)	26 (22.7)	
Unknown	168 (15.5)	26 (19.5)	-	-	
Volume of blood loss[c]					1.6
≤1L	605 (55.9)	43 (32.3)	8 (7.4)	2 (1.8)	
>1 to ≤2L	349 (32.2)	45 (33.8)	34 (29.5)	35 (30.3)	
>2L	129 (11.9)	45 (33.8)	72 (63.1)	78 (68.0)	

Table 1, *continued*. Characteristics of women with *persistent postpartum hemorrhage* in the total cohort and the propensity score matched cohort according to plasma transfusion strategy. Numbers of pairs in the propensity matched cohort are pooled averages after multiple imputation.

	Women, No. (%)				
	Overall cohort		Propensity score matched cohort		
	Characteristics at moment of diagnosing persistent postpartum hemorrhage		*Characteristics at moment of matching*		
Characteristic	No or later plasma transfusion[d] (n = 1083)	Plasma transfusion within 60 minutes (n = 133)	No or later plasma transfusion[d,e] (n = 114)	Plasma transfusion within 60 minutes[e,f] (n = 114)	Standardized difference after propensity score matching (%)
Bleeding rate[c]					4.0
≤1L/h.	576 (53.2)	64 (48.1)	57 (49.8)	44 (38.4)	
>1 to ≤2L/h.	231 (21.3)	33 (24.8)	33 (28.5)	44 (38.3)	
>2L/h.	276 (25.5)	36 (27.1)	25 (21.6)	27 (23.3)	
Hemorrhagic shock					9.5
No	378 (34.9)	56 (42.1)	47 (41.5)	59 (51.4)	
Yes	303 (28.0)	55 (41.4)	67 (58.5)	56 (48.6)	
Unknown	402 (37.1)	22 (16.5)	-	-	
Obstetric interventions					
Oxytocin infusion	422 (39.0)	34 (25.6)	45 (39.1)	53 (46.1)	1.3
Misoprostol	153 (14.1)	12 (9.0)	21 (18.7)	19 (16.6)	6.9
Ergometrine	23 (2.1)	1 (0.8)	11 (9.5)	4 (3.4)	2.6
Sulprostone	59 (5.4)	35 (26.3)	62 (54.3)	60 (52.5)	5.1
Manual removal of placenta	160 (14.8)	37 (27.8)	43 (37.2)	41 (35.5)	5.7
Exploration of uterine cavity and genital tract	77 (7.1)	28 (21.1)	57 (49.6)	57 (50.3)	7.6
Intra-uterine balloon tamponade (Bakri)	8 (0.7)	1 (0.8)	18 (15.3)	21 (18.2)	3.2
Hemostatic interventions					
Tranexamic acid	19 (1.8)	17 (12.8)	39 (34.1)	39 (33.8)	2.0
Fibrinogen concentrate	5 (0.5)	2 (1.2)	4 (3.1)	5 (4.4)	2.5
Recombinant factor VIIa	-	-	-	-	-

Table 1, continued. Characteristics of women with *persistent postpartum hemorrhage* in the total cohort and the propensity score matched cohort according to plasma transfusion strategy. Numbers of pairs in the propensity matched cohort are pooled averages after multiple imputation.

	Women, No. (%)				
	Overall cohort		**Propensity score matched cohort**		
	Characteristics at moment of diagnosing persistent postpartum hemorrhage		*Characteristics at moment of matching*		
Characteristic	**No or later plasma transfusion[d] (n = 1083)**	**Plasma transfusion within 60 minutes (n = 133)**	**No or later plasma transfusion[d,e] (n = 114)**	**Plasma transfusion within 60 minutes[e,f] (n = 114)**	**Standardized difference after propensity score matching (%)**
Transfusion[a]					
Packed red blood cells					
0	1050 (97.0)	97 (72.9)	25 (21.9)	26 (22.8)	reference
1	14 (1.3)	12 (9.0)	20 (17.8)	23 (20.1)	5.8
2	11 (1.0)	13 (9.8)	41 (35.8)	36 (31.2)	5.1
3	4 (0.4)	3 (2.3)	14 (12.5)	19 (16.5)	4.6
≥4	4 (0.4)	8 (6.0)	14 (12.0)	11 (9.5)	9.4
Platelets					0.7
≥1	2 (0.2)	4 (3.0)	2 (1.5)	4 (3.5)	

[a]Covariate entered as a categorical variable in the propensity score model, with the first category as reference category. [b]includes genital tract trauma, placenta previa, placental abruption and congenital or acquired coagulation disorders. [c]Covariate entered as a continuous variable in the propensity score model. [d]'No or later plasma transfusion' includes women with no plasma transfusion and women with plasma transfusion at a later time point during hemorrage. [e]The proportion of women who have ondergone a time-dependent intervention increases during the course of postpartum hemorrhage, as an increasing amount of interventions will be performed in a single woman until cessation of the hemorrhage.[f]Numbers of women and proportions are averages derived from 10 imputed databases, and numbers of women were rounded to the nearest integer. Therefore, they may exceed the 'total' number of women or a proportion of 1, and the same number of women may correspond to different proportions.

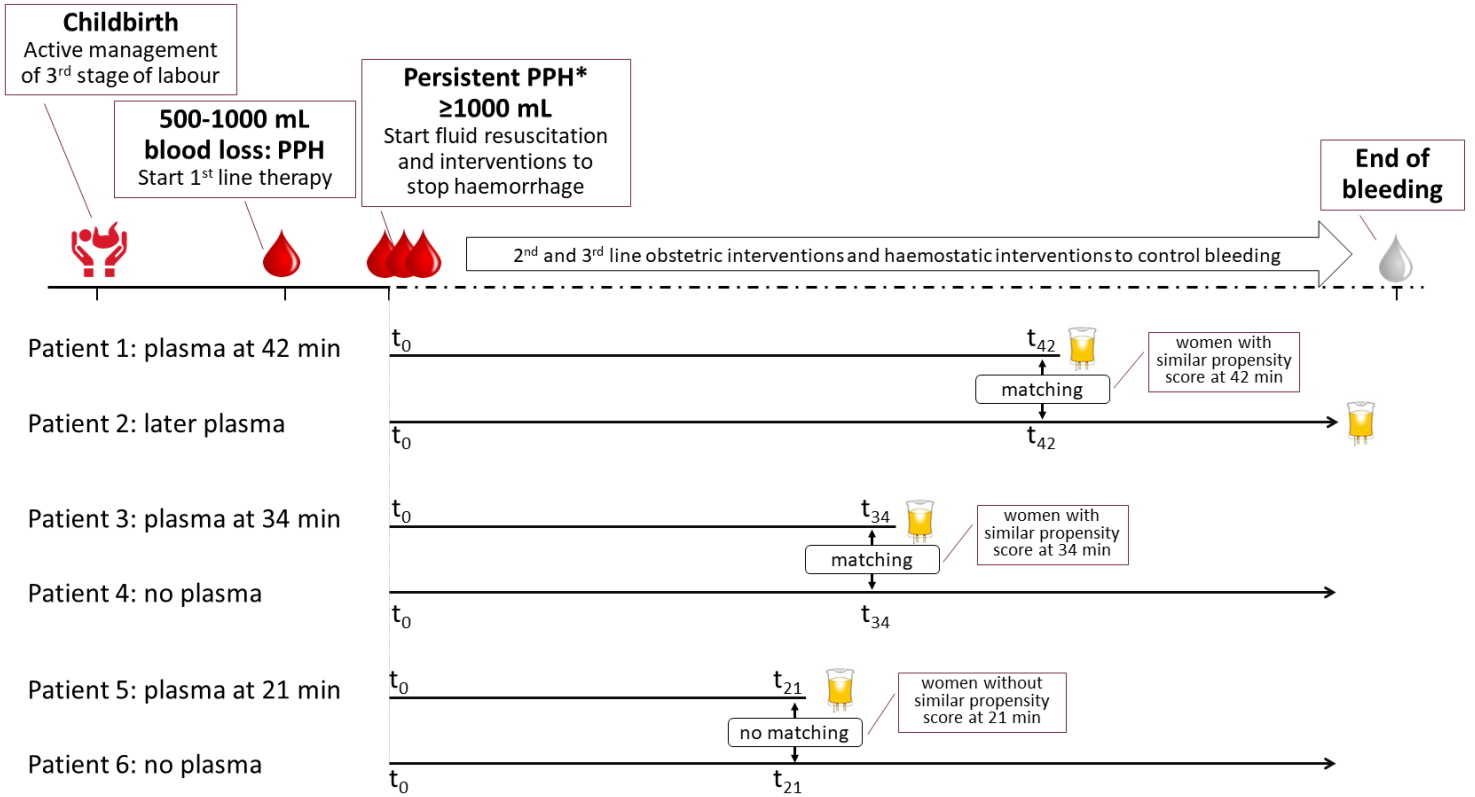
Table 2. Outcomes of women with *persistent postpartum hemorrhage in the total cohort and the propensity matched cohort according to plasma transfusion strategy.*

Numbers of pairs in the propensity matched cohort are pooled averages after multiple imputation.

	No. of women with outcome/total women (%)					
	Unadjusted analyses			Propensity score matched analyses[a]		
Outcome	No plasma transfusion within *x* minutes[b]	Plasma transfusion within *x* minutes	OR (95% CI)	No plasma transfusion within *x* minutes[b,c]	Plasma transfusion within *x* minutes[b]	OR (95% CI)
Main analysis: no or later plasma versus plasma transfusion within 60 minutes						
Composite outcome	175/1083 (16.2)	30/133 (22.6)	1.51 (0.98-2.34)	23/114 (19.9)	24/114 (21.2)	1.09 (0.57-2.09)
Mortality	5/1083 (0.5)	2/133 (1.5)		2/114 (1.3)	2/114 (1.8)	
Hysterectomy	50/1083 (4.6)	12/133 (9.0)		10/114 (8.3)	10/114 (8.9)	
Arterial embolization	137/1083 (12.7)	22/133 (16.5)		16/114 (13.9)	18/114 (15.8)	
Sensitivity analysis: no or later plasma versus plasma transfusion within 120 minutes						
Composite outcome	128/878 (14.6)	77/338 (22.8)	1.73 (1.26-2.37)	59/283 (21.0)	59/283 (21.0)	1.00 (0.67-1.51)
Mortality	3/878 (0.3)	4/338 (1.2)		2/283 (0.8)	4/283 (1.4)	
Hysterectomy	37/878 (4.2)	25/338 (7.4)		19/283 (6.7)	20/283 (7.2)	
Arterial embolization	99/878 (11.3)	60/338 (17.8)		47/283 (16.5)	45/283 (15.9)	
Sensitivity analysis: no or later plasma versus plasma transfusion within 180 minutes						
Composite outcome	95/783 (12.1)	110/433 (25.4)	2.47 (1.82-3.35)	80/348 (23.0)	77/348 (22.2)	0.96 (0.67-1.37)
Mortality	3/783 (0.4)	4/433 (0.9)		4/348 (1.0)	4/348 (1.1)	
Hysterectomy	28/783 (3.6)	34/433 (7.9)		23/348 (6.5)	27/348 (7.7)	
Arterial embolization	73/783 (9.3)	86/433 (19.9)		64/348 (18.5)	58/348 (16.6)	

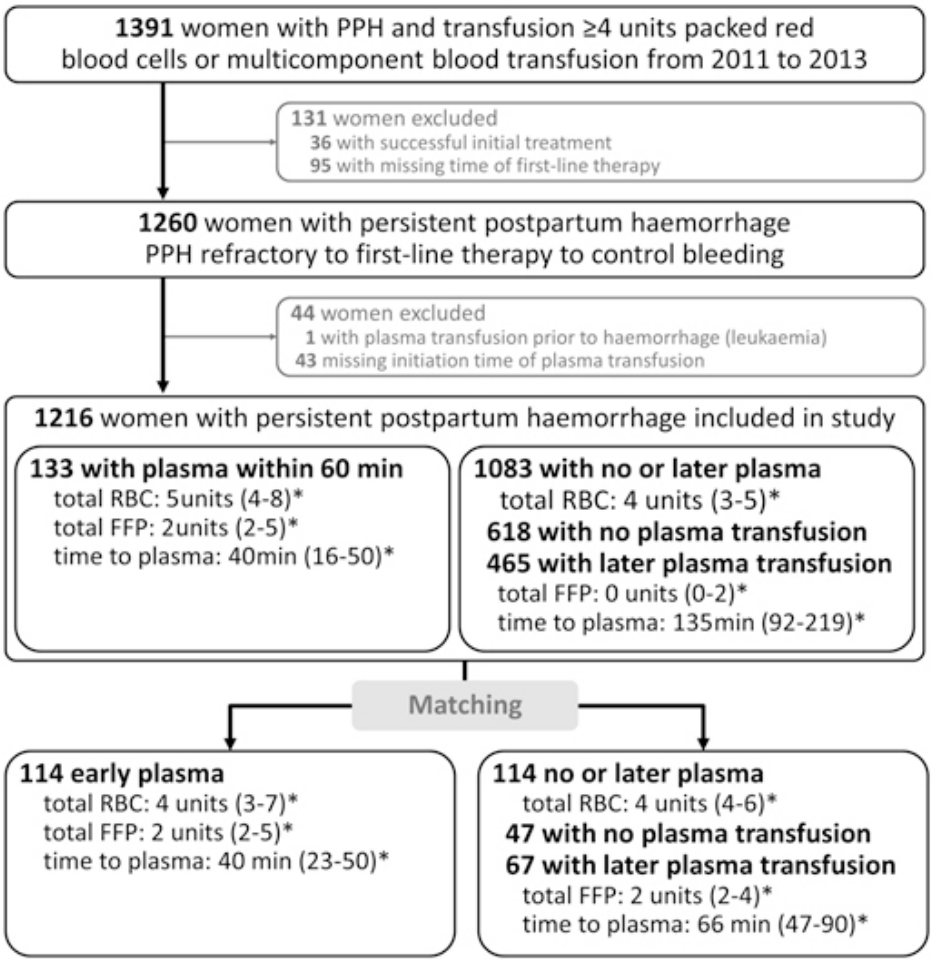
[a] Adjusted for all variables included in the propensity score, as shown in tables 1 and S1. [b]'No plasma transfusion' includes women without plasma transfusion and women with plasma transfusion at a later time point during hemorrage. [c]Numbers of women and proportions are averages derived from 10 imputed databases, and numbers of women were rounded to the nearest integer. Therefore, they may exceed the 'total' number of women or a proportion of 1, and the same number of women may correspond to different proportions.

Figure 1. Time-dependent propensity score matching of women with persistent postpartum hemorrhage. Women with plasma transfusion within 60 minutes after diagnosing persistent postpartum hemorrhage were matched to women with no or later plasma transfusion. Propensity score is the probability of plasma transfusion at a specific time point, given the woman's observed characteristics at that time point.



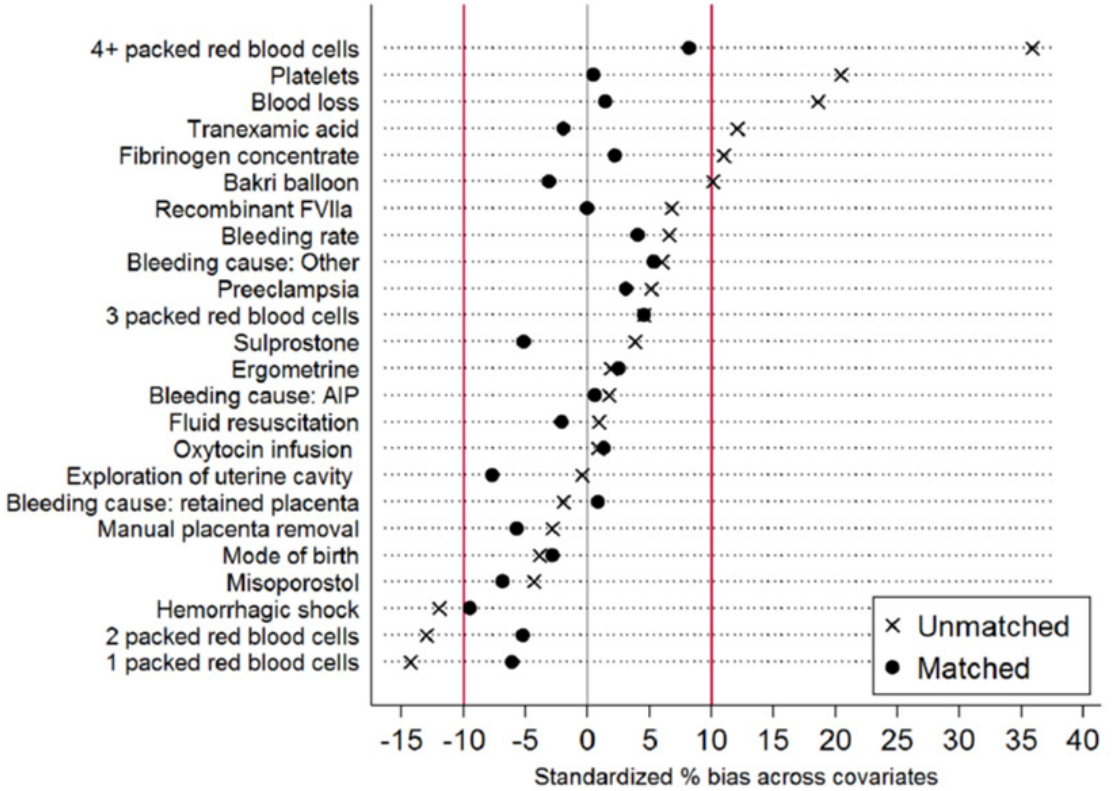
*Postpartum hemorrhage

Figure 2. Derivation of study population



PPH: postpartum hemorrhage, RBC: packed red blood cells, FFP: fresh frozen plasma
*numbers are medians with interquartile ranges

Figure 3. Balance of covariate values after time-dependent propensity score matching of women with persistent postpartum hemorrhage. Women with plasma transfusion within 60 minutes were matched to women with no or later plasma transfusion following diagnosing persistent postpartum hemorrhage.



Supplement Chapter 7

Association of timing of plasma transfusion with adverse maternal outcomes in women with persistent postpartum hemorrhage

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Supplementary content

eTable 1. First-line interventions to control bleeding depending on primary cause of PPH.

eTable 2. Handling of time-dependent covariates included in the propensity score model.

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eTable 4. Sensitivity analysis '180 minutes': characteristics of women with persistent PPH.

eTable 5. Sensitivity analyses excluding pairs of women with cross-overs from no or later plasma to plasma shortly after matching.

eTable 1. First-line interventions to control bleeding depending on primary cause of postpartum hemorrhage. The intervention that was employed first was regarded as the first-line intervention to stop bleeding.

Primary cause of postpartum hemorrhage	First-line interventions to stop bleeding
Uterine atony	Uterine massage and uterotonic agents (oxytocin, misoprostol, methylergometrine)
Retained placenta or placental remnants	Manual removal of placenta, exploration of uterine cavity and uterotonic agents
Trauma of birth canal	Surgical repair and uterotonic agents
Surgical cause during/after cesarean birth	Surgical repair and uterotonic agents
Placental abruption	Cesarean section and uterotonic agents
Placenta previa	Cesarean section and uterotonic agents
Placenta accreta spectrum	Surgical interventions and uterotonic agents
Congenital coagulation disorder or anticoagulant use	Combination of interventions depending on preexistent coagulation disorder

eTable 2. Handling of time-dependent covariates included in the propensity score model.

Variable	Handling in statistical analyses
Volume of blood loss	Volume of blood loss during postpartum hemorrhage was estimated regularly by weighing all gauzes, cloths and surgical swabs and suction into canisters. We performed linear interpolations between the observed volumes of blood loss to determine the volume of blood loss at any given time during postpartum hemorrhage. This variable was entered as a continuous variable in the propensity score model.
Bleeding rate	Rate of bleeding was calculated by dividing the volume of blood loss between the two nearest observed measurements by the time between those measurements. The calculated value was carried forward between these two measurements of blood loss volume to determine the bleeding rate at any given time during hemorrhage. This variable was entered as a continuous variable in the propensity score model.
Hemorrhagic shock	Hemorrhagic shock was considered present with at least one measurement of systolic blood pressure ≤90 mmHg and/or heart rate ≥120 bpm during postpartum hemorrhage. Values were carried forward between measurements of vital parameters to determine whether a woman had experienced hemorrhagic shock at any given time during postpartum hemorrhage. In women with missing vital parameters' values we imputed values every 5 minutes and carried forward between these values. This variable was entered as a dichotomous variable in the propensity score model.
Obstetric interventions: oxytocin infusion, misoprostol, ergometrine, sulprostone, manual removal of placenta, exploration of uterine cavity, intra-uterine balloon tamponade	The value of every obstetric intervention was 'no' until employment of the intervention. From the time of employment onwards the value was 'yes'. These variables were entered as dichotomous variables in the propensity score model.
Hemostatic interventions: tranexamic acid, fibrinogen concentrate, recombinant factor VIIa	The value of every hemostatic intervention was 'no' until employment of the intervention. From the time of employment onwards the value was 'yes'. These variables were entered as dichotomous variables in the propensity score model.
Transfusion: packed red blood cells, platelets	Transfusion of packed red blood cells or platelets was '0' until transfusion of the first unit of these blood products. From the time of transfusion of the first unit the value '1' was carried forward until the time of transfusion of the second unit, and so forth. These variables were entered as categorical variables in the propensity score model.

eTable 3. Sensitivity analyses '120 minutes': characteristics of women with *persistent postpartum hemorrhage*.

Characteristic	Women, No. (%)				
	Overall cohort		Propensity score matched cohort		
	Characteristics at moment of diagnosing persistent postpartum hemorrhage		*Characteristics at moment of matching*		
	No or later plasma transfusion[d] (n = 878)	Plasma transfusion within 120 minutes (n = 338)	No or later plasma transfusion[d,e] (n = 283)	Plasma transfusion within 120 minutes[e,f] (n = 283)	Standardized difference after propensity score matching (%)
Mode of birth					2.9
Vaginal	676 (77.0)	256 (75.7)	219 (77.2)	215 (76.1)	
Cesarean	197 (22.4)	81 (24.0)	64 (22.8)	68 (23.9)	
Unknown	5 (0.6)	1 (0.3)	-	-	
Cause of hemorrhage[a]					
Uterine atony	563 (64.1)	217 (64.2)	186 (65.8)	181 (64.1)	reference
Retained placenta	154 (17.5)	58 (17.2)	51 (17.8)	50 (17.7)	0.8
Abnormally invasive placenta	82 (9.3)	23 (6.8)	21 (7.5)	19 (6.7)	0.6
Other[b]	79 (9.0)	40 (11.8)	25 (8.9)	33 (11.5)	5.4
Preeclampsia	87 (9.9)	39 (11.5)	27 (9.6)	29 (10.4)	3.1
Fluid resuscitation with crystalloids and colloids[c]					2.0
≤2L	229 (26.1)	69 (20.4)	70 (24.7)	70 (24.9)	
>2 to ≤4L	358 (40.8)	126 (37.3)	149 (52.7)	140 (49.6)	
>4L	156 (17.8)	84 (24.9)	64 (22.5)	72 (25.5)	
Unknown	135 (15.4)	59 (17.5)	-	-	

eTable 3, *continued*. Sensitivity analyses '120 minutes': characteristics of women with *persistent postpartum hemorrhage*.

Characteristic	Women, No. (%)				
	Overall cohort		Propensity score matched cohort		
	Characteristics at moment of diagnosing persistent postpartum hemorrhage		*Characteristics at moment of matching*		
	No or later plasma transfusion[d] (n = 878)	Plasma transfusion within 120 minutes (n = 338)	No or later plasma transfusion[d,e] (n = 283)	Plasma transfusion within 120 minutes[e,f] (n = 283)	Standardized difference after propensity score matching (%)
Volume of blood loss[c]					1.6
≤1L	500 (56.9)	148 (43.8)	12 (4.3)	6 (2.1)	
>1 to ≤2L	274 (31.2)	120 (35.5)	65 (23.0)	61 (21.4)	
>2L	104 (11.8)	70 (20.7)	206 (72.8)	216 (76.5)	
Bleeding rate[c]					4.0
≤1L/h.	484 (55.1)	156 (46.2)	168 (59.5)	156 (55.1)	
>1 to ≤2L/h.	186 (21.2)	78 (23.1)	77 (27.1)	90 (31.7)	
>2L/h.	208 (23.7)	104 (30.8)	38 (13.4)	38 (13.3)	
Hemorrhagic shock					9.5
No	314 (35.8)	120 (35.5)	128 (45.2)	137 (48.3)	
Yes	240 (27.3)	118 (34.9)	155 (54.8)	146 (51.7)	
Unknown	324 (36.9)	100 (29.6)	-	-	
Obstetric interventions					
Oxytocin infusion	330 (37.6)	126 (37.3)	156 (55.0)	159 (56.1)	1.3
Misoprostol	125 (14.2)	40 (11.8)	84 (29.7)	72 (25.5)	6.9
Ergometrine	16 (1.8)	8 (2.4)	23 (8.1)	22 (7.9)	2.6
Sulprostone	43 (4.9)	51 (15.1)	171 (60.6)	160 (56.7)	5.1
Manual removal of placenta	138 (15.7)	59 (17.5)	107 (37.7)	105 (36.9)	5.7
Exploration of uterine cavity and genital tract	60 (6.8)	45 (13.3)	162 (57.3)	155 (54.6)	7.6

eTable 3, *continued*. Sensitivity analyses '120 minutes': characteristics of women with *persistent postpartum hemorrhage*

Characteristic	Women, No. (%)				
	Overall cohort		Propensity score matched cohort		
	Characteristics at moment of diagnosing persistent postpartum hemorrhage		*Characteristics at moment of matching*		
	No or later plasma transfusion (n = 878)[d]	Plasma transfusion within 120 minutes (n = 338)	No or later plasma transfusion[d,e] (n = 283)	Plasma transfusion within 120 minutes[e,f] (n = 283)	Standardized difference after propensity score matching (%)
Intra-uterine balloon tamponade (Bakri)	6 (0.7)	3 (0.9)	70 (24.6)	59 (20.8)	3.2
Hemostatic interventions					
Tranexamic acid	16 (1.8)	20 (5.9)	102 (36.0)	99 (35.1)	2.0
Fibrinogen concentrate	2 (0.2)	5 (1.5)	9 (3.1)	12 (4.1)	2.5
Recombinant factor VIIa	-	-	-	-	-
Transfusion[a]					
Packed red blood cells					
0	851 (96.9)	296 (87.6)	51 (18.2)	52 (18.4)	reference
1	10 (1.1)	16 (4.7)	55 (19.5)	49 (17.3)	5.8
2	10 (1.1)	14 (4.1)	115 (40.7)	106 (37.5)	5.1
3	4 (0.5)	3 (0.9)	33 (11.7)	38 (13.5)	4.6
≥4	3 (0.3)	9 (2.7)	28 (10.0)	38 (13.4)	9.4
Platelets					0.7
≥1	2 (0.2)	4 (1.2)	7 (2.4)	7 (2.6)	

[a]Covariate entered as a categorical variable in the propensity score model, with the first category as reference category. [b]includes genital tract trauma, placenta previa, placental abruption and congenital or acquired coagulation disorders. [c]Covariate entered as a continuous variable in the propensity score model. [d]'No or later plasma transfusion' includes women with no plasma transfusion and women with plasma transfusion at a later time point during hemorrage. [e]The proportion of women who have ondergone a time-dependent intervention increases during the course of postpartum hemorrhage, as an increasing amount of interventions will be performed in a single woman until cessation of the hemorrhage.[f]Numbers of women and proportions are averages derived from 10 imputed databases, and numbers of women were rounded to the nearest integer. Therefore, they may exceed the 'total' number of women or a proportion of 1, and the same number of women may correspond to different proportions.

eTable 4. Sensitivity analyses '180 minutes': characteristics of women with *persistent postpartum hemorrhage*

Characteristic	Women, No. (%)				
	Overall cohort		Propensity score matched cohort		
	Characteristics at moment of diagnosing persistent postpartum hemorrhage		*Characteristics at moment of matching*		
	No or later plasma transfusion[d] (n = 783)	Plasma transfusion within 180 minutes (n = 433)	No or later plasma transfusion[d,e] (n = 348)	Plasma transfusion within 180 minutes[e,f] (n = 348)	Standardized difference after propensity score matching (%)
Mode of birth					2.9
Vaginal	604 (77.1)	328 (75.8)	270 (77.6)	266 (76.4)	
Cesarean	174 (22.2)	104 (24.0)	78 (22.4)	82 (23.6)	
Unknown	5 (0.6)	1 (0.2)	-	-	
Cause of hemorrhage[a]					
Uterine atony	497 (63.5)	283 (65.4)	233 (66.9)	226 (64.8)	reference
Retained placenta	143 (18.3)	69 (15.9)	58 (16.6)	59 (17.0)	0.8
Abnormally invasive placenta	68 (8.7)	37 (8.5)	28 (8.1)	29 (8.2)	0.6
Other[b]	75 (9.6)	44 (10.2)	29 (8.4)	35 (10.0)	5.4
Preeclampsia	77 (9.8)	49 (11.3)	34 (9.7)	37 (10.7)	3.1
Fluid resuscitation with crystalloids and colloids[c]					2.0
≤2L	210 (26.8)	88 (20.3)	82 (23.5)	87 (25.0)	
>2 to ≤4L	312 (39.8)	172 (39.7)	178 (51.0)	177 (50.7)	
>4L	136 (17.4)	104 (24.0)	89 (25.5)	85 (24.3)	
Unknown	125 (16.0)	69 (15.9)	-	-	

eTable 4, *continued*. Sensitivity analyses '180 minutes': characteristics of women with *persistent postpartum hemorrhage*

Characteristic	Women, No. (%)				
	Overall cohort		Propensity score matched cohort		
	Characteristics at moment of diagnosing persistent postpartum hemorrhage		*Characteristics at moment of matching*		
	No or later plasma transfusion[d] (n = 783)	Plasma transfusion within 180 minutes (n = 433)	No or later plasma transfusion[d,e] (n = 348)	Plasma transfusion within 180 minutes[e,f] (n = 348)	Standardized difference after propensity score matching (%)
Volume of blood loss[c]					1.6
≤1L	436 (55.7)	212 (49.0)	13 (3.7)	60 (1.7)	
>1 to ≤2L	251 (32.1)	143 (33.0)	74 (21.2)	74 (21.4)	
>2L	96 (12.3)	78 (18.0)	262 (75.1)	268 (76.9)	
Bleeding rate[c]					4.0
≤1L/h.	435 (55.6)	205 (47.3)	215 (61.6)	210 (60.2)	
>1 to ≤2L/h.	167 (21.3)	97 (22.4)	91 (26.0)	101 (29.1)	
>2L/h.	181 (23.1)	131 (30.3)	43 (12.4)	38 (10.8)	
Hemorrhagic shock					9.5
No	285 (36.4)	149 (34.4)	159 (45.5)	175 (50.3)	
Yes	217 (27.7)	141 (32.6)	190 (54.5)	173 (49.7)	
Unknown	281 (35.9)	143 (33.0)	-	-	
Obstetric interventions					
Oxytocin infusion	296 (37.8)	160 (37.0)	199 (57.1)	201 (57.7)	1.3
Misoprostol	107 (13.7)	58 (13.4)	112 (32.2)	101 (29.0)	6.9
Ergometrine	14 (1.8)	10 (2.3)	26 (7.6)	29 (8.3)	2.6
Sulprostone	36 (4.6)	58 (13.4)	217 (62.3)	209 (59.9)	5.1
Manual removal of placenta	134 (17.1)	63 (14.5)	129 (36.9)	119 (34.2)	5.7
Exploration of uterine cavity and genital tract	57 (7.3)	48 (11.1)	204 (58.4)	190 (54.6)	7.6

eTable 4, *continued*. Sensitivity analyses '180 minutes': characteristics of women with *persistent postpartum hemorrhage*

Characteristic	Women, No. (%)				
	Overall cohort		Propensity score matched cohort		
	Characteristics at moment of diagnosing persistent postpartum hemorrhage		*Characteristics at moment of matching*		
	No or later plasma transfusion[d]	Plasma transfusion within 180 minutes	No or later plasma transfusion[d,e]	Plasma transfusion within 180 minutes[e,f]	Standardized difference after propensity score matching (%)
	(n = 783)	(n = 433)	(n = 348)	(n = 348)	
Intra-uterine balloon tamponade (Bakri)	5 (0.6)	4 (0.9)	79 (22.6)	74 (21.3)	3.2
Hemostatic interventions					
Tranexamic acid	15 (1.9)	21 (4.8)	121 (34.8)	118 (33.8)	2.0
Fibrinogen concentrate	2 (0.3)	5 (1.2)	10 (2.9)	12 (3.4)	2.5
Recombinant factor VIIa	-	-	-	-	-
Transfusion[a]					
Packed red blood cells					
0	758 (96.8)	389 (89.8)	59 (17.0)	60 (17.2)	reference
1	10 (1.3)	16 (3.7)	69 (19.7)	61 (17.4)	5.8
2	9 (1.1)	15 (3.5)	142 (40.7)	133 (38.2)	5.1
3	3 (0.4)	4 (0.9)	43 (12.3)	48 (13.9)	4.6
≥4	3 (0.4)	9 (2.1)	36 (10.3)	47 (13.3)	9.4
Platelets					0.7
≥1	1 (0.1)	5 (1.2)	9 (2.6)	9 (2.7)	

[a]Covariate entered as a categorical variable in the propensity score model, with the first category as reference category. [b]includes genital tract trauma, placenta previa, placental abruption and congenital or acquired coagulation disorders. [c]Covariate entered as a continuous variable in the propensity score model. [d]'No or later plasma transfusion' includes women with no plasma transfusion and women with plasma transfusion at a later time point during hemorrage. [e]The proportion of women who have ondergone a time-dependent intervention increases during the course of postpartum hemorrhage, as an increasing amount of interventions will be performed in a single woman until cessation of the hemorrhage.[f]Numbers of women and proportions are averages derived from 10 imputed databases, and numbers of women were rounded to the nearest integer. Therefore, they may exceed the 'total' number of women or a proportion of 1, and the same number of women may correspond to different proportions.

eTable 5. Sensitivity analyses excluding pairs of women with cross-over from no plasma to plasma shortly after matching.

Restriction on cross-over time interval	Average number of pairs of women	OR (95% confidence interval)
Main analysis	114	1.09 (0.57-2.09)
No cross-over within 15 min after matching	96	1.07 (0.51-2.23)
No cross-over within 30 min after matching	79	1.09 (0.47-2.53)
No cross-over within 45 min after matching	65	1.06 (0.41-2.73)
No cross-over within 60 min after matching	59	1.13 (0.42-3.04)

8

The best timing of tranexamic acid administration for bleeding after trauma or childbirth remains to be established

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Haemorrhage is worldwide the leading cause of maternal death[1] and an important cause of death after trauma.[2] Antifibrinolytic drugs inhibit the lysis of a fibrin clot and are, therefore, used to stop or prevent haemorrhage. Intravenous administration of tranexamic acid has been shown to reduce the risk of death due to haemorrhage after trauma[3] and the risk of death due to postpartum haemorrhage.[4] Previous analyses have suggested that tranexamic acid needs to be administered early after the start of haemorrhage, because effects of delayed administration might be absent or even harmful for patients suffering life-threatening bleeding.[3,4] A recent systematic review and meta-analysis was set up to quantify the effect of treatment delay on the effectiveness of antifibrinolytics.[5]

This individual patient-level data meta-analysis included randomized placebo-controlled trials (RCT) with more than 1000 patients with traumatic or postpartum haemorrhage. The primary measure of treatment benefit was absence of death from bleeding. “Treatment delay” was defined as the interval between bleeding onset and start of tranexamic acid treatment, or, if not available, as interval between birth and randomisation. The association between “treatment delay” and treatment effect was examined in logistic regression models with adjustment for the confounders age and systolic blood pressure, and with and without various interaction terms for treatment and “treatment delay”, for treatment and study, for “treatment delay” and study. The protocol was registered with PROSPERO. The review clearly stated the question being addressed, the search strategy, study selection, assessment of study quality, data extraction and synthesis and it adhered to the recognised protocols for systematic reviews and meta-analysis from The Cochrane Collaboration and PRISMA.

Two RCTs were analysed: the CRASH2 trial reporting on 20 211 bleeding trauma patients,[3] and the WOMAN trial reporting on 20 060 women with postpartum haemorrhage.[4] Any cause of death and death due to haemorrhage occurred in 15.2% and 5.3% in the CRASH2 and 2.4% and 1.7% in the WOMAN trial. The numbers needed to treat to prevent one death due to haemorrhage

were 125 and 250 for patients with trauma and postpartum haemorrhage respectively. The odds for absence of death due to bleeding among patients treated with tranexamic acid compared to placebo was 1.7 among patients who had received tranexamic acid during the first hour of bleeding, and it was lower among patients who had been treated later.

Unfortunately, this analysis does not address the question whether tranexamic acid should be administered soon after the start of the bleeding or whether its administration might as well be postponed. What these findings do describe, is the effect of treatment among patients who were treated early, and the effect of treatment among patients who were treated later. However, the effect of late treatment among patients who were treated early, and vice versa, the effect of early treatment among patients who were treated late were not studied.

Patients who were treated early with tranexamic acid may have differed for several reasons from those who were treated late. Reasons for postponing randomization (and administration of tranexamic acid) may have been: less severe bleeding, or conversely, more severe bleeding and thus no time to include into trial, the clinical impression that the bleeding is about to stop or that haemorrhage can be stopped with other interventions than tranexamic acid. All these time-dependent factors influence the time-dependent effects of treatment, and, therefore, also the findings.

The authors attempted to correct for this time-dependent confounding by adjustments for age and blood pressure at inclusion. But in a bleeding patient, severity of bleeding and its proxies such as systolic blood pressure change constantly. So, adjustment for severity of bleeding only at baseline does not suffice; the results are biased by time-dependent confounding. A future study could randomize patients to different treatment delays in a multi-arm trial, or carefully measure and adjust for time-dependent confounders.[6,7]

Implications for practice

It is tempting to conclude from these findings that all patients with severe

acute haemorrhage need to be treated as soon as possible after the start of the haemorrhage, and that treatment three hours after the start of bleeding should be avoided, but this conclusion is not supported by these findings. These findings show that the effect of tranexamic acid differs in subgroups of patients who were treated at different times after the start of bleeding. Future research should examine the underlying clinical characteristics that determine whether and when a patient with severe bleeding would benefit from treatment with tranexamic acid.

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Summary and General discussion

Summary

The three central questions of this thesis concerned the recognition and management of women with severe postpartum haemorrhage. We specifically addressed 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.

I. Women with postpartum haemorrhage: what issues to resolve?

Within the International Network for Obstetric Surveillance Systems, we performed a cross-country comparison of management and outcomes of women with severe postpartum haemorrhage in 6 high-resource countries. This comparison showed similar causes of postpartum haemorrhage among women with at least 8 units of packed red blood cells transfused, but revealed striking differences in both obstetric and haemostatic management. Case fatality rate between the countries did not differ, but there was up to 40% difference in hysterectomy rates and a 5-fold variation in the incidence of massive transfusion. In our review on how to improve maternal outcomes, we identified four opportunities for improvement of the management of women with postpartum haemorrhage: 1) definitions of severe postpartum haemorrhage and their use to recognise clinical deterioration in women with severe postpartum haemorrhage along with timely recognition of women at risk of adverse outcomes, 2) the timing of obstetric interventions to stop bleeding, 3) the timing of switch from fluid resuscitation with crystalloids and colloids to transfusion of packed red blood cells, and 4) the diagnosis of coagulopathy during ongoing postpartum haemorrhage and the timing of haemostatic interventions to stop bleeding.

II. Women with postpartum haemorrhage: who is at risk of adverse outcome?

Within the TeMpOH-1 study population, we compared the clinical characteristics and outcomes of women captured by the definition *persistent postpartum haemorrhage* with those of women captured by the most common definitions of severe postpartum haemorrhage based on volumes of blood loss and transfusion criteria. This definition identified women at an early stage of haemorrhage, comparable with definitions based on volume of blood loss. It also captured a large majority of adverse maternal outcomes, contrary to definitions based on transfusion criteria. Because women with hypertensive disorders of pregnancy have a high risk of postpartum haemorrhage compared with women without hypertensive disorders, we wondered whether

outcomes of women with persistent postpartum haemorrhage and concurrent hypertensive disorders of pregnancy would be worse than the outcomes of women with persistent postpartum haemorrhage who did not have concurrent hypertension. Women with concurrent preeclampsia experienced more haemorrhage-related adverse outcomes than women without concurrent hypertensive disorders of pregnancy, odds ratio 1.8 (95% confidence interval 1.1-3.0).

III. Women with postpartum haemorrhage: when and what to transfuse?

Finally, in this thesis we also addressed the timing of switch from fluid resuscitation with crystalloids and colloids to transfusion of packed red blood cells and the timing of initiation of plasma transfusion in women with persistent postpartum haemorrhage. Fluid resuscitation with more than 4L crystalloids and colloids was associated with more adverse maternal outcomes as compared with fluid resuscitation with ≤2L clear fluids, after adjustment for severity of haemorrhage. In our time-dependent propensity score-matched analysis, plasma transfusion within 60 minutes after diagnosing persistent postpartum haemorrhage was not associated with better maternal outcomes as compared with no or later start of plasma transfusion, adjusted odds ratio 1.09 (95% confidence interval 0.57-2.08). This cohort study was specifically designed to address the confounding-by-indication inherently associated with research questions on timing of initiation of treatment. Addressing this risk of bias remains challenging in the field of haemostatic interventions to manage postpartum haemorrhage, as outlined in our commentary on a secondary analysis of a recent large randomised controlled trial (the WOMAN trial) evaluating the timing of administration of tranexamic acid in women with postpartum haemorrhage. In this commentary we describe the time-dependent confounding that the authors did not adjust for, and as a consequence, the conclusion that delay in administration of tranexamic acid in bleeding patients reduces its effectiveness was not justified.

General discussion

Inferences of the results of the TeMpOH-1 study call for some methodological considerations. After discussing these, we discuss lessons learnt about the occurrence and management of coagulopathy in women with severe postpartum haemorrhage.

Study population

Our aim was to collect data from women with a high probability of developing coagulopathy secondary to postpartum haemorrhage and adverse maternal outcome (i.e. arterial embolisation, hysterectomy and death), to determine whether early start of plasma transfusion to correct coagulopathy would reduce maternal mortality and severe maternal morbidity. Therefore, we selected consecutive women with postpartum haemorrhage who received a) 4 or more units of packed red blood cells within 24 hours following birth, or b) a multicomponent blood transfusion: transfusion of fresh frozen plasma and/or platelets alongside red blood cells transfusion within 24 hours following birth. This selection led to a cohort of women with severe postpartum haemorrhage with a median total blood loss of 3L and adverse maternal outcome in one third of our study population.

Alternatively, we could have included either all women with postpartum haemorrhage with or without blood transfusion, or all women with postpartum haemorrhage and transfusion of at least one unit of packed red blood cells in our study. However, with these inclusion criteria the feasibility of the TeMpOH-1 study would have been at stake, because of an incidence of postpartum haemorrhage of approximately 6.5% of all births in the Netherlands,[1] but a much lower incidence of blood transfusion and adverse maternal outcome in the Netherlands, respectively <1.0% and 0.5% of all births.[1,2] Our study results are only generalizable to women with the most severe postpartum haemorrhages, but in daily clinical practice, these are the women for whom we consider haemostatic interventions to correct coagulopathy and improve outcome.

Quality of data

A common misconception about retrospective studies is that the quality of the data is inferior to the quality of data from prospective studies. Yet, the quality of the study data depends on the risk of bias due to misclassification (information bias) and selection (selection bias). Both biases may occur more frequently in retrospective studies, but that does not justify the conclusion that retrospective studies are inferior to prospective studies. If there is low risk of information and selection bias, retrospective studies are as good as, or may also be better than prospective studies, and often less time-consuming and less costly. From a societal perspective, resources should not be wasted on unjustifiably long data collection, if data are available from other, reliable sources.

Data documentation in the hospitals that participated in the TeMpOH-1 study was very accurate. We were therefore able to reconstruct the course of every women with postpartum haemorrhage by collecting detailed information about all vital parameters, measurements of blood loss and all interventions in combination with the time of the measurements and interventions. We thoroughly examined the medical files, and whenever necessary, we repeated this process. Some data were missing, particularly vital parameters in women with very severe haemorrhages and also in women with initially mild haemorrhages. To minimize possible bias due to missing data we imputed these missing values.[3]

The excellent infrastructure and regulations for storing medical information in the Netherlands[4] may have played a pivotal role in these reconstructions and the quality of our data. The collected data represent daily Dutch obstetric practise. Our experiences should encourage future researchers to perform retrospective studies of routinely collected medical information, whenever this design fits the research question, as it may be an efficient design with relatively low costs. Additionally, informed consent procedures are known to be difficult and sometimes presumed not to be ethical in acute, medical situations, posing a significant challenge in designing and conducting prospective studies, either

observational or randomized, in this field.[5-13]

Dealing with time-dependent confounding

The primary objective of the TeMpOH-1 study was to determine whether early start of transfusion of fresh frozen plasma improves maternal outcomes, as compared with no early start of plasma transfusion. The most straightforward design to answer this research question would have been a randomised controlled trial. We set out to mimic a randomised controlled trial by using propensity score methods to analyse routinely collected medical information during the course of postpartum haemorrhage.[14]

A propensity score reflects the patient's probability of receiving a specific treatment for a condition, given the observed characteristics of the patient at a certain timepoint during treatment.[15-18] These observed characteristics, in combination with unobserved characteristics, may be associated with both the given treatment as with the patient's outcome after treatment.[16-18] Because of this risk of bias, adjustment for confounding is required to estimate the effect of the assigned treatment on the outcome.[19,20] Propensity scores may be used in different ways to adjust for confounding: by stratifying on the propensity score, by including the propensity score as covariate in a multivariable regression model, by matching on the propensity score and by weighting the propensity score.[17,18]

An important advantage of using propensity scores to answer our research question is the possibility to not only address confounding at baseline, but also confounding during treatment,[21-25] as a woman's characteristics change constantly during the course of postpartum haemorrhage. However, adjustment for this time-dependent confounding is more complex than the traditional epidemiologic methods to adjust for confounding, and experience with these newer methods is still limited.

Previously, weighting of propensity scores, also referred to as inverse probability weighting (IPW) of the propensity score, was applied to emulate a randomised controlled trial when dealing with time-dependent confounding.[26]

We also intended to weight our time-dependent propensity scores, but in our analyses, some observations led to very large weights. On the one hand, these observations were in women with postpartum haemorrhage in a very critical condition, who did not receive plasma at all, or relatively late when compared with women in a similar critical condition. On the other hand, these observations were also in women with seemingly mild haemorrhages who were treated with plasma relatively early during haemorrhage. Because of these extremes on the spectrum of postpartum haemorrhage, our models yielded unstable weights, and consequently, we decided not to proceed with these analyses. Instead, we chose to match on the time-dependent propensity scores. In this way, the observations of women on the extremes on the spectrum of postpartum haemorrhage had a more reliable influence on the study results.

Our experiences with addressing time-dependent confounding in women with severe postpartum haemorrhage bring new questions to light for these newer epidemiologic methods: do certain methods only work when working within a narrow bandwidth of observations, when there are no outliers? And do certain methods only work for analysing specific types of clinical situations, i.e. for emergency situations but not for non-acute settings, and vice versa? Although different epidemiologic methods to deal with time-dependent confounding seem to result in similar treatment effect estimates,[27] different methods may have different interpretations.[28] It would be desirable to expand our experiences with these methods especially in studies performed in acute clinical situations as life-threatening haemorrhage, to understand the possibilities and limitations of these methods better.

Residual confounding

The severity of haemorrhage is one of the most important confounding variables in observational studies on the management of postpartum haemorrhage.[29-32] We used the variables volume of blood loss, bleeding rate and haemorrhagic shock at any given timepoint during haemorrhage as proxies for the severity of haemorrhage. However, adjustment for confounding in observational studies is only possible for known and measured confounding variables. Although

we couldn't think of any other confounding variables in the TeMpOH-1 study, there may well have been other confounding variables, either unknown or unmeasured, that we could not adjust for in our analyses. Residual confounding can never be ruled out and study results should be interpreted with this possibility in mind.

Coagulopathy in women with persistent postpartum haemorrhage: lessons learnt

The idea of early onset of coagulopathy due to depletion, loss and dilution of platelets and coagulation factors in women with postpartum haemorrhage arose after studies demonstrating these mechanisms in non-pregnant, bleeding patients.[33-35] From current knowledge from studies in women with postpartum haemorrhage we can state that early onset of coagulopathy in this population is a rare event, but some women do develop coagulopathy early during haemorrhage[36-38] However, we do not know:

1) which women have a high risk of developing this coagulopathy;

2) at what moment during bleeding the risk of developing this coagulopathy is the highest;

3) which coagulation tests diagnose this coagulopathy the best;

4) which women will benefit from haemostatic interventions;

5) which haemostatic interventions will improve outcome in these women; and,

6) at what moment does administration of these haemostatic agents improve maternal outcome.

Obviously, it will take some time to deepen our understanding of coagulopathy in women with persistent postpartum haemorrhage. For the time being, it is reassuring that coagulopathy seems to be a rare event in this population. This implies that as clinicians, we should keep our focus on resolving obstetric complications with appropriate obstetric interventions, to

prevent adverse maternal outcome in most women with severe postpartum haemorrhage. Prevention of dilutional coagulopathy may be achieved with a restrictive fluid resuscitation strategy,[39,40] and when postpartum haemorrhage proves to be refractory to first-line measures to stop bleeding, switching to transfusion of packed red blood cells when these become available will probably be beneficial for haemostasis.[41] There is insufficient evidence for early treatment of coagulopathy with plasma transfusion[42,43] and fibrinogen concentrate.[37,44] Women with severe postpartum haemorrhage may benefit from early treatment with tranexamic acid, but the size of the effect may be limited.[45-48]

Where do we go from here?

Coagulopathy may worsen prognosis of women with postpartum haemorrhage. When it comes to haemostatic interventions in women with severe postpartum haemorrhage, the ideal treatment algorithm would be to treat only the women who develop coagulopathy during postpartum haemorrhage with these agents, at the moment when they develop this coagulopathy, with the haemostatic agent that is best suitable for the specific haemostatic impairment encountered at that moment: personalised medicine.

Within large observational studies we can study specific characteristics of the few women in whom coagulopathy is diagnosed, and at what moment during bleeding this coagulopathy arises. Within the TeMpOH-studies we have already attempted to answer some of these questions, but there are still myriad knowledge gaps.

Subsequently, a randomised controlled trial will be needed to determine whether targeted haemostatic therapy will improve outcomes in women with severe postpartum haemorrhage. In this trial, preferably cluster-randomized with a run-in period for both treatment arms, we should compare women with persistent haemorrhage receiving 'standard' obstetric management with women with persistent haemorrhage receiving 'standard' obstetric management extended with an algorithm for diagnosing and correction of coagulopathy. This algorithm should include sequential coagulation testing, with rapid results, and whenever coagulopathy is diagnosed, the specific haemostatic impairment should dictate which haemostatic agent should be administered: plasma, tranexamic acid or fibrinogen concentrate.

The design of such a trial would be rather challenging though, with the low incidence of coagulopathy in women with postpartum haemorrhage and informed consent issues. In order to increase the feasibility of this trial, we therefore call for international collaboration to design and perform this trial.

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Appendices

Dutch summary

In dit proefschrift zijn drie vragen over het herkennen en behandelen van vrouwen met ernstige fluxus postpartum centraal gesteld. De focus van deze drie vragen was in het bijzonder het tijdig herkennen van de vrouw met hoog risico op een slechte uitkomst ten gevolge van fluxus postpartum, en het tijdig toepassen van obstetrische en haemostatische interventies om het bloedverlies te stoppen.

I. Vrouwen met fluxus postpartum: welke problemen dienen nog te worden opgelost?

Binnen het internationale samenwerkingsverband *International Network for Obstetric Surveillance Systems* (INOSS) hebben we de behandeling en uitkomsten vergeleken van vrouwen met een ernstige fluxus postpartum in zes verschillende landen met hoge inkomens. In deze vergelijking hebben we gezien dat vrouwen die in deze landen een transfusie van ten minste 8 eenheden erytrocytenconcentraat hebben gekregen vergelijkbare oorzaken van de fluxus postpartum hadden, maar dat de behandeling grote verschillen vertoonde in de obstetrische en haemostatische interventies. Het risico op overlijden ten gevolge van fluxus postpartum was gelijk in deze landen, maar tussen de landen werd tot 40% verschil gezien in het aantal uterusextirpaties en een vijfvoudige variatie in de incidentie van massale transfusie.

In onze review met als onderwerp het verbeteren van de maternale uitkomsten hebben we vier domeinen geïdentificeerd om deze uitkomsten te verbeteren: 1) definities van ernstige fluxus postpartum en het gebruik hiervan voor het tijdig herkennen van vrouwen met een ernstige fluxus postpartum, en het tijdig onderkennen van een achteruitgang in de klinische situatie van deze vrouwen, 2) de timing van obstetrische interventies om het bloeden te stoppen, 3) het moment voor switchen van volumeresuscitatie met kristalloïden en colloïden naar transfusie van erytrocytenconcentraten, en 4) het stellen van de diagnose “coagulopathie” tijdens een doorgaande fluxus postpartum en de timing van haemostatische interventies om het bloeden te stoppen.

II. Vrouwen met fluxus postpartum: wie heeft een verhoogd risico op een slechte uitkomst?

In de groep vrouwen die geïncludeerd zijn in de TeMpOH-1 studie, hebben we de klinische karakteristieken en uitkomsten van vrouwen vergeleken die voldeden aan de criteria van verschillende definities van ernstige fluxus postpartum: vrouwen die voldeden aan de definitie *persistent postpartum haemorrhage* werden vergeleken met vrouwen die voldeden aan definities gebaseerd op de hoeveelheid bloedverlies en aan

definities gebaseerd op aantallen getransfundeerde eenheden erytrocytentransfusie. Met de definitie *persistent postpartum haemorrhage* werden vrouwen vroeg tijdens de fluxus geïdentificeerd, vergelijkbaar met vrouwen geïdentificeerd met de definities gebaseerd op de hoeveelheid bloedverlies. Met deze definitie werd ook het grootste gedeelte van de vrouwen met slechte uitkomsten ten gevolge van de fluxus geïdentificeerd, in tegenstelling tot de definities gebaseerd op transfusiecriteria.

Omdat vrouwen met hypertensieve aandoeningen van de zwangerschap een hoog risico hebben op een fluxus postpartum vergeleken met vrouwen zonder hypertensieve aandoeningen, hebben we geanalyseerd of de uitkomsten van vrouwen met *persistent postpartum haemorrhage* én een hypertensieve aandoening als co-morbiditeit slechter zouden zijn dan uitkomsten van vrouwen met *persistent postpartum haemorrhage* zonder hypertensieve aandoeningen. Vrouwen met preëclampsie bleken een verhoogd risico te hebben op ernstige uitkomsten ten gevolge van de bloeding, vergeleken met vrouwen zonder hypertensieve aandoeningen van de zwangerschap.

III. Vrouwen met fluxus postpartum: wanneer en welke bloedproducten transfunderen?

In dit proefschrift hebben we ook gekeken naar de timing van het switchen van volumeresuscitatie met kristalloïde en colloïde vloeistoffen naar erytrocytentransfusie, en naar de timing van plasmatransfusie om maternale uitkomsten te verbeteren. Na het corrigeren voor de ernst van de bloeding, bleek volumeresuscitatie met meer dan 4 liter kristalloïden en colloïden geassocieerd met een slechte maternale uitkomst, vergeleken met volumeresuscitatie met 2 liter of minder van deze vloeistoffen. In onze analyse van vrouwen met *persistent postpartum haemorrhage* gematched op tijdsafhankelijke propensity scores, was plasmatransfusie gestart binnen 60 minuten na het stellen van de diagnose *persistent postpartum haemorrhage* niet geassocieerd met verbeterde maternale uitkomsten vergeleken met geen of een latere start van plasmatransfusie. Onze cohortstudie hebben we specifiek opgezet om ook te kunnen corrigeren voor de *confounding-by-indication* bias inherent verbonden met vraagstukken rondom de timing van behandeling. Dat dit risico op bias een uitdagend probleem blijft voor wetenschappelijk onderzoek naar haemostatische interventies bij vrouwen met fluxus postpartum, hebben we laten zien in ons commentaar op de secundaire analyse van een grote, gerandomiseerde trial bij vrouwen met fluxus postpartum. In deze analyse naar de timing van tranexaminezuur bij deze vrouwen hebben de auteurs niet gecorrigeerd voor tijdsafhankelijke confounding, met als

gevolg dat hun conclusie niet onderbouwd wordt door de resultaten verkregen uit de uitgevoerde analyses.

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List of publications

This thesis

McCall SJ, **Henriquez DDCA**, McKinnon Edwards H, Van den Akker T, Van der Bom JG, Bonnet MP, Deneux-Tharaux C, Donati S, Gillissen A, Kurinczuk JJ, Li Z, Maraschini A, Seco A, Sullivan E, Stanworth S, Knight M on behalf of the INOSS collaboration. A total blood volume or more transfused during pregnancy or after childbirth: individual patient data from six international population-based observational studies. *Submitted.*

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Dacia Henriquez was born on the 25th of September, 1981, in Curaçao. She attended the secondary school Maria Immaculata Lyceum in Willemstad, Curaçao, and graduated cum laude in 1999. She moved to Leiden, the Netherlands, for her medical training at the Leiden University Medical Center, and from 2006 to 2009, she worked as a medical doctor at the Department of Obstetrics & Gynaecology of the Medical Center Haaglanden in The Hague. In 2009 she started the Residency Program Obstetrics & Gynaecology in the Medical Center Haaglanden (Dr. M.J. Kagie) and Leiden University Medical Center (Prof. Dr. J.M.M. van Lith). She discontinued her residency in 2012 to work on her PhD project at the Center for Clinical Transfusion Research (Sanquin Research Leiden) and the LUMC Department of Clinical Epidemiology and Department of Obstetrics & Gynaecology (Prof. Dr. J.G. van der Bom and Prof. Dr. K.W.M. Bloemenkamp). During her PhD program, she set up and coordinated the nationwide *Transfusion strategies in women with Major Postpartum Haemorrhage* (TeMpOH-1) study, and she supervised the scientific internship of ten medical students. She was also closely involved in the conduction of the TeMpOH-2 study and supervised the TeMpOH-3 study. From 2015 to 2019, she continued her clinical training in Obstetrics & Gynaecology at the Leiden University Medical Center and the HagaZiekenhuis in The Hague (Dr. B.W.J. Hellebrekers). After her residency she worked as an Obstetrician at the Spaarne Gasthuis in Haarlem & Hoofddorp. In January 2021, she will start a fellowship in Maternal Fetal Medicine at the Amsterdam University Medical Center.

Dacia is married to Dinomar and they live with their three children Emme (2012), Marcus (2016) and Maxime (2020) in The Hague.