

# Aetiology and treatment of severe postpartum haemorrhage

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## THE 3 ORIGINAL PAPERS ARE

1. Wikkelsø AJ, Edwards HM, Afshari A, Stensballe J, Langhoff-Roos J, Albrechtsen C, Ekelund K, Hanke G, Secher EL, Sharif HF, Pedersen LM, Troelstrup A, Lauenborg J, Mitchell AU, Fuhrmann L, Svare J, Madsen MG, Bødker B, Møller AM, FIB-PPH trial group. Pre-emptive treatment with fibrinogen concentrate for postpartum haemorrhage: randomized controlled trial. *BJA* 2015 Apr;114(4):623-33.
2. Edwards HM, Wikkelsø AJ, Langhoff-Roos J, Afshari A, Møller AM, Lauenborg J, Svare JA, Stensballe J. Massive postpartum transfusion: a multidisciplinary observational study. Submitted.
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## INTRODUCTION

Postpartum haemorrhage (PPH) plays a significant role in maternal morbidity and mortality, and has had an impact on the world for centuries [1,2]. Thousands of women die each year due to PPH, a few of which have given rise to not only cultural and medical innovations, but also shaped the history of the world. The Taj Mahal was built by Mughal emperor Shah Jahan in memory of his wife that died of PPH in 1631 after giving birth to their 14<sup>th</sup> child [3]. Princess Charlotte, daughter of King George IV of England, was in 1817 the only eligible heir to the throne, but died after stillbirth due to 50 hours of labour and PPH, leading to change of reign and the birth of the future Queen Victoria [4]. Last but not least in 1825 the British obstetrician James Blundell was the first

to successfully transfuse human blood. He saved the life of a woman with PPH, by using blood from the woman's husband; later he went on to invent several instruments for transfusion [5–7].

Sadly these innovations do not nearly weigh up the tragedy of a maternal death, and even though maternal deaths worldwide are decreasing [8], PPH has shown an increasing trend over the last few years to an incidence of 3–8% in the developed world [9–11], and is the most common cause of maternal morbidity [12,13]. Therefore, research in prevention and treatment of PPH including recovery measures for women developing life-threatening haemorrhage is needed more than ever [14].

## BACKGROUND

### Postpartum haemorrhage – aetiology and risk factors

PPH is traditionally defined as blood loss  $\geq 500$  ml in the first 24 hours following childbirth, often developing minutes after childbirth, but can also be secondary if occurring after the first 24 hours up to 6 weeks postpartum [15]. For women undergoing caesarean section the cut-off is higher and usually defined as  $\geq 1,000$  ml [16]. However, not all countries or studies agree on these definitions, creating not only confusion but also conflicting results [17]. Further inconsistency is found when it comes to defining severe PPH, where there is variation in not only the cut-off used to define it, but also no uniform agreement of whether to use the term severe, major or moderate PPH [17–20]. Estimation of blood loss can be assessed in many ways depending on the equipment available. Visual estimation is the easiest method, but also the method that is most inaccurate as large quantities of blood loss are often underestimated and small quantities of blood loss overestimated compared to blood collection bags or weighing of drapes ect [1,15,21].

The aetiologies of PPH are classically divided into four different categories, known as the four T's – Tone, Trauma, Tissue, and Thrombin [18]. Tone refers to atony, which is insufficient contraction of the uterus during and after delivery of the placenta, leading to extensive bleeding from the placental bed. Trauma refers mainly to lacerations of the vagina and perineum, graded from first to fourth degree depending on their depth and extent, but can also include vulvar and vaginal haematomas or uterine rupture, all of which will need surgical repair. Tissue refers to retained placenta or fragments of placenta inhibiting contraction of the uterus. Thrombin refers to coagulopathies, that can be defects known prior to childbirth or developed during or after childbirth due to other complications such as amniotic fluid em-

bolism [16,18]. The majority of cases are traditionally attributed to atony [18].

The time from the delivery of the baby to the delivery of the placenta is known as the third stage of labour [22]. The uterus will under normal circumstances contract and expel the placenta within 10 minutes [23–25], efficiently cutting off the blood flow to the placenta [15]. The placenta will in some circumstances need manual removal if it is not delivered spontaneously. If the duration of the third stage of labour exceeds 30 minutes there is an increased risk of PPH [22,26,27]. Recent studies have questioned the 30 minute threshold and have suggested that the risk of PPH is increased after only 15 to 20 minutes [23–25,28,29]. An active management of the third stage of labour has been shown to reduce the risk of PPH. This includes administration of oxytocin (a uterotonic that stimulates contraction of the uterus), controlled cord traction and uterine massage [30]. If the placenta is not delivered spontaneously, several conditions should be considered. The placenta could be detached from the uterine wall but still trapped inside the uterus due to a closed cervix: *an entrapped placenta*; the placenta is not detached but there are no signs of invasive growth in the uterine wall: *an adherent placenta*; or there is abnormal invasive growth into or through the uterine wall: *an abnormal invasive placenta (AIP)* [31,32].

AIP has an incidence of approximately 0.2–3 per 1,000 deliveries [33–36]. Depending on the depth of attachment AIP is termed: *placenta accreta* (placenta attached to the myometrium); *placenta increta* (placenta invades the myometrium); or *placenta percreta* (placenta invades through the myometrium) [33,37]. AIP often leads to severe PPH requiring blood transfusions and in more severe cases even the need for hysterectomy, complications that can be minimized if diagnosed before labour [36]. Currently, up to 50% of AIP cases are identified antenatally through ultrasound screening of women with a prior caesarean section and placenta praevia [33,38].

Numerous epidemiological studies have been performed to try and identify women at risk of developing PPH, in the hope of initiating sufficient preventive measures [27,39–41]. Some of the risk factors identified include multiparity, previous caesarean section, hypertensive disorders, macrosomia, previous PPH, induction of labour, augmentation of labour, operative vaginal delivery, caesarean section and placenta praevia [42,43]. Some of the risk factors have a higher risk of PPH than others, but women with high risk or multiple low risks can still have a completely uncomplicated delivery [40]. Furthermore, 22–39% of women that develop PPH have no risk factors, making it extremely difficult to predict which women will in fact develop PPH [9,44–46].

There are a wide range of complications following PPH. Mild cases of PPH can lead to anaemia, fatigue, depression and feelings of separation or anxiety [18,47,48]. In more severe cases the complications are often critical and involve blood transfusions, open surgery, organ failure, treatment in an intensive care unit, thromboembolic complications, hysterectomy and in worst case even death [9,49–51].

### Haemostasis in pregnancy and postpartum

Haemostasis is the process that maintains equilibrium between coagulation and fluidity of blood in damaged blood vessels through the actions of the coagulation cascade, platelets, and fibrinolysis [52,53]. The purpose of the coagulation cascade is to stop bleeding by forming a clot, through a cascade of processes initiated after the exposure of tissue factor primarily after vascular damage [54,55]. The coagulation system is comprised of clotting factors in an inactive state that become activated through a

cascade of processes, and culminates with conversion of large amounts of thrombin from prothrombin. Thrombin converts fibrinogen into fibrin fibres, which together with activated platelets and von Willebrand factor create the blood clot [53,56]. Fibrinogen is a glycoprotein synthesized in the liver and is indispensable in formation of the clot not only through conversion to fibrin fibres but also for platelet aggregation. [57] There are several regulators of the coagulation cascade including the anticoagulation factors: antithrombin, protein C, and protein S that limit the formation of clots in healthy vessels [53,55]. In addition simultaneous activation of fibrinolysis dissolves the clot in a highly regulated process, preventing excessive clot formation [55,56].

During pregnancy blood volume and coagulation increase while anticoagulants and fibrinolysis decrease, all part of the prophylactic measures to prepare for blood loss and placental separation after childbirth [52,55]. This change in haemostasis involves a rise in some of the coagulation factors including prothrombin, fibrinogen, and von Willebrand factor, but also a decrease in platelet count due to haemodilution and presumed consumption at the placental site [52,58,59]. However, this hypercoagulable state in pregnancy leads to an up to six-fold increase in the risk of thromboembolic complications including pulmonary embolisms and deep vein thrombosis [59,60]. Additional increase in coagulation factors including fibrinogen takes place during labour and delivery. Coagulation factors are activated through release of abundant amounts of tissue factor upon placental separation leading to formation of clots. Increased levels of fibrinogen and platelets postpartum are also a result of inflammation [52]. An unimpaired coagulation system will together with sufficient contraction of the uterus result in minimal blood loss after delivery [52,58,59]. However, a high consumption of coagulation factors and platelets in formation of clots at the placental site can potentially lead to depletion if haemorrhage is ongoing [59,61]. Under normal circumstances coagulation factors remain high the first few days after delivery with fibrinolysis rising to normal levels within 1–2 days postpartum and normal coagulation attained within 4–6 weeks postpartum. [52,58]

### Massive haemorrhage and transfusion

Massive haemorrhage is defined as loss of total blood volume within 24 hours, 50% within 3 hours, or a rate of blood loss of 150 ml/min [62]. Blood loss of this quantity can be difficult to assess during an emergency situation, which is why massive haemorrhage can also be defined as haemorrhage requiring massive transfusion of  $\geq 10$  units of red blood cells (RBC) within 24 hours [63]. In obstetrics there is no well-defined consensus for massive haemorrhage, with the terms major and massive PPH being used at random for blood loss of more than 1,000 ml to blood loss of more than 2500 ml [18,64–66].

Massive haemorrhage following trauma, surgery or childbirth may lead to coagulopathy – a state of impaired haemostasis. In all three circumstances the abundant release of tissue factor leads to activation of the coagulation cascade and consequent consumption of coagulation factors and platelets [54,67]. The simultaneous systemic hypoperfusion causes hypothermia and acidosis, inhibiting coagulation and activating anticoagulation factors and fibrinolysis, which complicate coagulation further [63,67]. At the same time transfusion with RBCs, crystalloids or colloids are given in an effort to re-establish perfusion causing additional dilutional coagulopathy. The combination of consumptive and dilutional coagulopathy, acidosis and hypothermia, known as the lethal triad will result in further haemorrhage [54,67,68]. Therefore, treatment involving not only volume resus-

citation and surgical control of haemorrhage, but also correction of coagulopathy is necessary [68,69].

Fibrinogen is the first coagulation factor known to drop to critical levels during massive haemorrhage, and as the normal level of fibrinogen is 2.0-4.5 g/L in healthy adults, low levels are difficult to substitute with FFP alone, where the concentration is 1-3 g/L [57,70]. Additional substitution is, however, possible through cryoprecipitate and fibrinogen concentrate. Cryoprecipitate contains high concentrations of fibrinogen (approximately 15 g/L), von Willebrand factor and other coagulation factors. However, cross matching and thawing is necessary before administration. Fibrinogen concentrate on the other hand only contains fibrinogen (15-20 g/L), and comes as a powder that only requires dissolving in sterile water before administration [57,71].

Identifying patients with low levels of specific coagulation factors is possible through conventional laboratory testing. However, these tests can be time consuming and they do not assess the general functionality of coagulation, which is why point-of-care viscoelastic assays are being used more and more. These assays can be performed bedside and give an assessment of clot formation and fibrinolysis, thereby providing vital information on the development of coagulopathy [63,72]. Prevention and treatment of coagulopathy in patients with massive haemorrhage is also possible with early transfusion of RBCs, FFP and PLTs. Furthermore, studies from both trauma and non-trauma have shown a reduction in mortality when a fixed ratio of 1:1:1 of PLTs, FFP and RBCs is used during massive haemorrhage [73-75].

Due to the high risks associated with blood transfusions, all strategies that can reduce blood transfusions are essential. Today the risk of transmission of infection through blood transfusions is low; instead the risks are related to non-infectious reactions including haemolytic, allergic, and immunological reactions that occur in approximately 1% of all transfusions [76-78]. Transfusion related acute lung injury (TRALI) is an immunological reaction and the leading cause of transfusion related morbidity and mortality with an incidence of 0.08-15% [76]. TRALI evolves within 6 hours of transfusion and is mainly associated with plasma transfusions. Symptoms include dyspnoea, hypoxaemia and hypotension due to pulmonary oedema and up to 70% will need respiratory support [76]. Additional complications are seen in patients requiring massive transfusions, including metabolic complications due to haemolysis and high levels of citrate, and transfusion associated circulatory overload [63].

### **Severe postpartum haemorrhage – prevention and treatment**

Active management of the third stage of labour and removal of a retained placenta can reduce the risk of PPH. Further preventive measures include minimizing avoidable risk factors or giving additional uterotonics to high risk women [14,18,79]. Once PPH has developed treatment options relate to the cause of haemorrhage: uterotonics for atony, surgical repair of lacerations, removal of retained tissue, and correction of diagnosed coagulopathy [18]. However, progression in severity is not always avoidable, and has therefore led to increased focus on early warning signs and treatment of severe PPH. Risk factors associated with progression to a more severe PPH include instrumental delivery, augmentation of labour, multiple pregnancy, polyhydramnios and hypertensive disorders [39,80]. As these risk factors are not always preventable or directly treatable, recent studies have tried to identify more specific predictors of severity related to coagulopathy.

The main focus has been on fibrinogen since Charbit et al in 2007 showed that a fibrinogen concentration  $\leq 2$  g/L was 100%

predictive of severe PPH [81]. The study included 128 women with PPH of which 50 (39%) developed severe PPH (defined as haemoglobin decrease  $\geq 4$  g/dl, transfusion of  $\geq 4$  RBCs, embolization, arterial ligation, hysterectomy or death). Women were enrolled if they had PPH requiring IV prostaglandin infusion (uterotonics). A fibrinogen level of  $\leq 2$  g/L at enrolment was identified in 11 of the 50 women (22%) that developed severe PPH. A number of other studies have confirmed the association between low levels of fibrinogen and blood loss in PPH [20,82,83]. However, association is not always the same as causation. The results from Charbit et al have therefore led to recent studies investigating the impact of fibrinogen substitution on development of a more severe PPH [84-86]. However as the normal level of fibrinogen at delivery is higher than in the non-pregnant woman (3.5-6.5 g/L vs. 2.0-4.5g/L), the exact threshold for intervention is unclear [58,70,87].

Intensive treatment and care becomes the main focus once PPH has progressed, involving a close collaboration between obstetricians, gynaecologists, anaesthetists and sometimes also coagulation experts. Atony is mainly treated with additional uterotonics, but other causes of PPH should be considered if haemorrhage is refractory to first-line uterotonics [30,88]. Further treatment of all causes of ongoing PPH mainly takes place in the operating room involving all of the multidisciplinary team. Surgical repair of lacerations, removal of placental tissue and intrauterine balloon tamponade can be performed from a vaginal approach. Additional surgical interventions require laparotomy, with uterine haemostatic suturing (e.g. B-lynch suture) or artery ligation being attempted before hysterectomy [18,88,89]. Even though hysterectomy is often considered last option in uncontrollable PPH, it does not necessarily lead to haemostasis perhaps due to untreated coagulopathy [51,90,91].

Coagulopathy should be considered early on in the events of progressing PPH, with simultaneous focus on both transfusions and surgical control as neither can stand alone [1,92]. As the rate of transfusion in obstetrics is relatively low at 0.5-2.0%, research into the optimal ratio of RBCs, FFP and PLTs is scarce [41,93-95]. A few retrospective studies have shown that a high FFP:RBC ratio was associated with a reduced risk of interventions and a higher success rate of hysterectomy, but none of the studies were in relation to PPH requiring massive transfusion [91,96]. The methods used to monitor coagulopathy in severe PPH are the same as in other patients with severe haemorrhage. The Danish guideline for PPH recommends traditional laboratory tests including platelet count, international normalized ratio (INR), activated partial thromboplastin time (APTT) and fibrinogen early on in the course of events, or if available point-of-care viscoelastic assays [79]. Laboratory tests do not give rapid results, and the haemostasis of the patient can have changed substantially before it is possible to react to the results [87]. It is therefore of great importance to be continuously aware of formation of clots in the operating field.

### **OBJECTIVES**

Through the studies included in this PhD thesis we aim to investigate the causes of severe postpartum haemorrhage and minimize the proportion of women developing severe postpartum haemorrhage by identifying methods for early prevention.

The objectives and hypotheses of this thesis were:

- To assess if pre-emptive treatment with fibrinogen concentrate could reduce the need for red blood cell transfusion in relation to postpartum haemorrhage (*Study I*).

The hypothesis was that pre-emptive treatment with fibrinogen could reduce the need for red blood cell transfusion in women with postpartum haemorrhage.

- To describe the severe cases of PPH requiring massive transfusion including the surgical procedures leading to bleeding control, the causes, and the complications associated with the need of massive postpartum transfusion. And to describe the subgroup of women treated with hysterectomy and compare the use of RBC, FFP, and PLT transfusions with women not treated with hysterectomy during massive postpartum transfusion (*Study II*). The hypothesis was that women treated with a hysterectomy due to massive postpartum transfusion had received less or late fresh frozen plasma and platelets compared to women with massive postpartum transfusions not treated with a hysterectomy.
- To investigate whether the distribution of causes of postpartum blood loss depended on the cut-off used to define PPH. And to investigate the association between quantity of postpartum blood loss, the duration of the third stage of labour, a retained placenta, and other risk factors (*Study III*). The hypothesis was that the distribution of causes of postpartum blood loss depended on the cut-off used to define PPH and that a retained placenta had a higher impact on the quantity of blood loss than the duration of the third stage of labour.

## MATERIAL AND METHODS

Choosing the correct study design depends not only on the research question, but also on practical issues including the setting, how common the condition is, the time frame available, data available, and funding [97]. A randomised control trial (RCT) can lead to high quality evidence of treatment effect, and was the method of choice for [study I](#) [98]. Observational studies have a higher risk of confounding but can be used to identify potential associations between exposures and outcome [99]. We chose to address the research questions in [study II and III](#) through observational studies, identifying two separate cohorts from different registries. Thereby, taking advantage of some of the exclusive data already available in Danish registries, where data on more or less all residents is registered, due to all being assigned a unique Civil Registration Number [100,101].

### National registries

#### The Danish National Patient Registry

The Danish National Patient Registry was established in 1977 and consists of data from all hospitalised patients [102]. It is compulsory for all hospitals in Denmark to report to the registry, and the registry is the general core database for health issues in Denmark and is a source for some of the other more specialised registries and databases such as The Danish National Birth Registry and The Danish Transfusion Database [102].

#### The Danish National Birth Registry

The Danish National Birth Registry contains information regarding all births in Denmark dating back to 1973. The registry has since 1995 received all information regarding maternal demographics, parity, pregnancy, labour and delivery by combining the unique Civil Registration Numbers of both mother and child with data from The Danish National Patient Registry [103].

#### The Danish Transfusion Database

The Danish Transfusion Database receives information directly from regional blood banks and The National Patient Registry, and has done so since 1997. However, full coverage of Denmark was not complete until 2005. The database includes information regarding allogenic transfusions including data on the recipient, serial numbers of the blood products and time of delivery of blood products [104].

#### The Copenhagen Obstetric Database

The Copenhagen Obstetric Database was established in 1996 and receives detailed information on maternal demographics, pregnancy, labour, delivery and details on the new-born directly from midwives and specialist doctors during and after discharge. It has a very high internal validity, and includes additional information that is not registered in The Danish National Patient Registry such as the quantity of blood loss [105].

### Study populations

All of our studies were comprised of women with an assorted range of severity of PPH. [Study I](#) was a randomised controlled double-blinded study where the primary outcome was the need to transfuse RBCs up to six weeks postpartum in women randomised to either placebo or 2 grams of fibrinogen concentrate. A dose of 2 g was chosen based on an average weight of 65.9 kg, with a target fibrinogen level of 4 g/L from a mean fibrinogen level of 3.4 g/L after 500-1,000 ml of postpartum blood loss [84]. Fibrinogen concentrate was given at time of inclusion, and without taking body weight or fibrinogen levels (pre-emptive) into account, to ensure quick administration and in accordance with our objectives. Secondary outcomes included total blood loss, total number of RBCs transfused, haemoglobin <58 g/L, and severe PPH (defined as decrease in haemoglobin >40 g/L, transfusion of  $\geq 4$  RBCs, embolization, arterial ligation, hysterectomy or death). Furthermore, an important part of the trial was monitoring of haemostasis and adverse events related to fibrinogen concentrate.

Inclusion criteria were women with PPH  $\geq 500$  ml requiring manual removal of placenta after vaginal delivery or PPH  $\geq 1,000$  ml after caesarean section or requiring exploration of the uterus after vaginal delivery within 24 hours of delivery. Exclusion criteria were: known inherited coagulation deficiencies, antenatal anti-thrombotic treatment, pre-pregnancy weight <45 kg, or refusal to receive blood transfusions. A multicentre approach at four university affiliated hospitals in the Capital Region of Denmark was decided on, due to the relatively low incidence of PPH and the plan to include 245 women over a two year period [84,98]. The trial was designed as a superiority trial and the sample size was based on the fact that approximately 1% of women giving birth receive blood transfusions and 1.75% have blood loss > 1,000 ml, thereby the incidence of transfusion in PPH > 1,000 ml is 57% [106,107]. With an estimated risk reduction of 33%,  $\alpha=0.005$  and 80% power, we would need to include 107 women in each group. This would lead to a requirement of 245 women, if calculating with a 15 % dropout/missing data. A follow-up period of 6 weeks was chosen to monitor re-bleeding/secondary PPH that is defined up to 6 weeks postpartum; and to monitor thromboembolic complications, where there is a known increase in risk up to 6 weeks postpartum [60].

[Study II](#) was an observational study where we investigated the influence of transfusions on hysterectomy in women with massive postpartum transfusion. To be able to gain a sufficient cohort size, we included women from all over Denmark for a 9-year period from 2001 to 2009. Women were identified by com-

binning data from The Danish National Birth Registry and The Danish Transfusion Database, and included if they received  $\geq 10$  units of RBCs within a 24 hour period up to 6 weeks postpartum. In order to gain sufficient information regarding transfusions, causes, and procedures it was necessary to review all patient charts and extract relevant data. Deliveries from hospitals not included in The Danish Transfusion Database before 2005 were excluded together with women without accessible patient charts, and women receiving blood transfusions due to non-obstetric causes [108].

For our final study, [study III](#), the primary outcome was quantity of postpartum blood loss, where we investigated the distribution of causes and the effect of a retained placenta and the third stage of labour. We used data from The Copenhagen Obstetric Database and included all vaginal deliveries from 22 to 43 weeks of gestation from 2009 to 2013, in order to obtain a large cohort with a high degree of variation in quantity of blood loss. We excluded all cases with blood loss below 50 ml due to interpretation of faulty registration, and all hospitals reporting to the registry for less than one year [109]. We calculated the duration of the third stage of labour from the time of delivery of the neonate until the time of either spontaneous delivery of the placenta or manual removal of the placenta. A retained placenta was defined as diagnosis of AIP, retained placenta or manual removal of either placenta or tissue. The diagnosis “retained placenta” is not used if the placenta is delivered spontaneously.

When comparing causes with different definitions of PPH ([Study III](#)), and between the three studies, each patient was only assigned a single cause. “Retained placenta/tissue” was given as the primary cause for women with retained placenta, retained tissue or AIP. “Lacerations” was given as the primary cause for women without “retained placenta/tissue” and with lacerations of the cervix, vagina or perineum including an episiotomy and paravaginal haematomas. “Other, including atony” was given as the primary cause for women without “retained placenta/tissue” or “lacerations”.

### Coordinating a randomized controlled trial

The randomised multicentre double blinded clinical trial ([Study I](#)) was initiated by Dr. Anne Juul Wikkelsø [84]. I was appointed project coordinator after the first patients had been enrolled in the trial, and became responsible for all major aspects of the project for the remainder of the study period. This involved all practicalities, accountability for all patient consents, coordinating blood tests 24/7, securing additional funding, and responsibility for upholding regulations from The Department of Good Clinical Practice, The Ethics Committee, and The Danish Health and Medicines Authority. The anaesthetist was responsible for patient consent, trial drug administration and primary data collection. Other personnel groups also played a large role in the study including anaesthetic nurses taking care of randomisation, drug dispensation, and blood sampling; and obstetricians and midwives supplying information regarding the trial to as many women as possible before delivery. The project coordinators’ main focus regarding training of these four different personnel groups was therefore on adherence to protocol especially regarding informed consent, randomisation, and blinding.

### Informed consent

Informed consent is required by law according to the Helsinki declaration regarding participation in research studies [110]. For our study, informed consent was obtained either before delivery during preparation for a caesarean section or an epidural, or after

delivery in the emergency situation when PPH requiring intervention had been determined. Obtaining informed consent during an emergency situation is known to be difficult, perhaps even more so after delivery in a situation of anxiety and pain [111–113]. The study group had sought approval from the local Ethics Committee regarding possibility of surrogate consent, but this had been rejected [114]. It was, therefore, crucial that I had focus on all formalities regarding the informed consent. Furthermore, all included women were asked about their experiences regarding the inclusion process in the trial during follow-up.

### Randomisation

Randomisation together with allocation concealment are the most essential factors in controlling for confounders and eliminating selection bias [115]. In our study the randomisation process was computer generated by a third party company before initiation of the study, and was stratified by centre and in blocks of four to optimise the control for confounders. Furthermore treatment allocation was concealed by using a centralised service with concealed envelopes. Once randomised, personnel not involved in the treatment of the patient dispensed placebo or fibrinogen concentrate in opaque syringes, thereby concealing allocation to all personnel in charge of further treatment [84].

### Blinding

Blinding is used to control for information bias, where interpretation of results otherwise can be influenced by knowledge of allocation [116]. Triple-blinding was a fundamental part of the study’s protocol and involved blinding of patients, personnel involved in treatment, trial investigators, and statisticians [84]. Blinding of fibrinogen measurements was also necessary to prevent clinicians from identifying patients with increasing levels of fibrinogen after infusion of the study drug. Therefore, all fibrinogen analyses at inclusion were analysed by a separate laboratory. To assess the success of blinding we asked all primary anaesthetist involved in the inclusion process and all included women whether they had suspicion of treatment allocation and why.

### Fibrinogen measurements

All blood samples for fibrinogen were collected, frozen and stored during the study period. After completion of the study all samples were analysed using the Clauss method [117] at one single laboratory, thereby eliminating methodological issues related to different testing. The normal lower limit of fibrinogen was set at 3.7 g/L, [118] but the threshold for hypofibrinogenaemia was set at 2.0 g/L in accordance with the findings from Charbit et al. [81]

### Variables

The three studies had different data available, but the majority of variables used are the same. The variables included in each study are listed in Table 1.

**Table 1.** List of all variables included in study I, II and III.

Variable	Study I	Study II	Study III
Maternal age		X <sup>a</sup>	X
Parity	X	X <sup>a</sup>	X
Gestational age at delivery	X	X <sup>a</sup>	X
Previous Caesarean section	X	X <sup>a</sup>	X
Multiple gestation	X	X <sup>a</sup>	X
Hypertensive disorders	X	X <sup>a</sup>	X
Antepartum haemorrhage	X	X	X
Previous postpartum	X	X <sup>a</sup>	

haemorrhage			
Fertility treatment		X	
Amniotic fluid abnormalities		X	X
BMI before pregnancy	X	X <sup>a</sup>	
Maternal weight at term	X		
Birthweight	X	X <sup>a</sup>	
Time and date of birth		X	X
Duration of labour			X
Induction of labour		X <sup>b</sup>	X
Augmentation of labour		X <sup>b</sup>	X
Time of birth of the placenta			X
Site of birth	X	X	X
Placenta praevia	X	X <sup>a</sup>	X
Abnormal invasive placenta	X	X <sup>a</sup>	X
Foetus presentation			X
Preterm premature or premature rupture of membranes			X
Neonatal outcome		X	
Episiotomy	X	X <sup>b</sup>	X
Retained tissue	X	X <sup>c</sup>	X
Placental abruption	X	X <sup>b</sup>	X
Uterine rupture	X	X <sup>b</sup>	X
Genital tract lacerations	X	X <sup>c</sup>	X
Mode of delivery	X	X <sup>b</sup>	X
Reason for non-vaginal delivery		X	
Epidural analgesia	X		X
Fever during labour			X
Shoulder dystocia			X
Uterine inversion	X	X	X
Quantity of blood loss	X *	X	X
Blood transfusions	X **	X	
Other causes of postpartum haemorrhage		X	
Time of start of bleeding	X	X	
Time of haemostasis		X	
Cumulated use of colloids or crystalloids	X *	X	
Cumulated use of uterotonics	X *	X	
Cumulated use of fibrinogen, tranexamic acid, or recombinant factor VIIa	X *	X	
Surgical procedures performed	X	X	
Timing of consent	X		
Blood pressure and heart rate	X *		
Measurements of fibrinogen, haemoglobin and platelets	X *		
Postoperative complications	X	X	
Adverse events after study drug	X		
Thromboembolic complications	X	X	
Death	X	X	
Assessment of blinding	X		

\* Measured at inclusion and 15 minutes, 4 hours and 24 hours after study drug.

\*\* Measured at inclusion and 15 minutes, 4 hours, 24 hours, 7 days, 6 weeks postpartum.

<sup>a</sup> Antenatal risk factors (age >35, BMI >35, Parity >3, birthweight >4,000g, Gestational age >42 weeks).

<sup>b</sup> Labour and delivery risk factors (mode of delivery = caesarean section or operative vaginal delivery)

<sup>c</sup> Postpartum risk factors

## Statistical analyses

The results of [study I](#) were analysed as an intention-to-treat (ITT) population and as a per-protocol population. The ITT analysis was performed prior to disclosure of allocation and included all participants with informed consent that had been randomised, irrespective of whether they fulfilled exclusion criteria or whether they received the complete allocated treatment. The per-protocol analysis was performed after disclosure of allocation and excluded any participants that fulfilled exclusion criteria or received incomplete allocated treatment. Chi<sup>2</sup> test was used for binary outcome measures and Student's t-test or Wilcoxon rank-sum test for continuous measures of unadjusted analyses. These results are presented as relative risks with a 95% confidence interval (CI). Logistic regression analysis was used for adjusted analyses of association between baseline variables, allocated treatment, stratification variable (centre) and primary outcome. Logistic regression analysis was also used for post hoc analysis of association between significant baseline variables including stratification variable (centre) and primary outcome. These results are presented as odds ratios (OR) with a 95% CI. Changes in fibrinogen and haemoglobin levels during the first 24 hours after study drug infusion were compared between groups using longitudinal analysis (mixed-effect model).

For [study II](#) we used univariate logistic regression analyses to evaluate differences between women treated with and without hysterectomy. Analyses used to determine differences included Chi<sup>2</sup> test for categorical variables, t-test for normally distributed continuous variables, and Kruskal-Wallis for non-normally distributed continuous variables.

The outcome measure of quantity of blood loss in [study III](#) was logarithmic transformed (log<sub>10</sub>) due to substantial skewed non-normal distribution. Univariate and multivariate linear regression analysis were used to evaluate variables and their influence on quantity of postpartum blood loss. These results are presented as  $\beta$ -coefficients and 95% CI. Interpretation is quite simple: you obtain the percent change in the predicted quantity of postpartum blood loss for each variable by raising 10 to the power of the  $\beta$ -coefficient and subtracting 1.00.

For all studies a two-sided p-value of <0.05 was considered statistically significant. All data analyses were carried out using either R statistical software (R Foundation for Statistical Computing, Vienna, Austria) or SPSS 22.0 (SPSS, Chicago, IL, USA).

## RESULTS

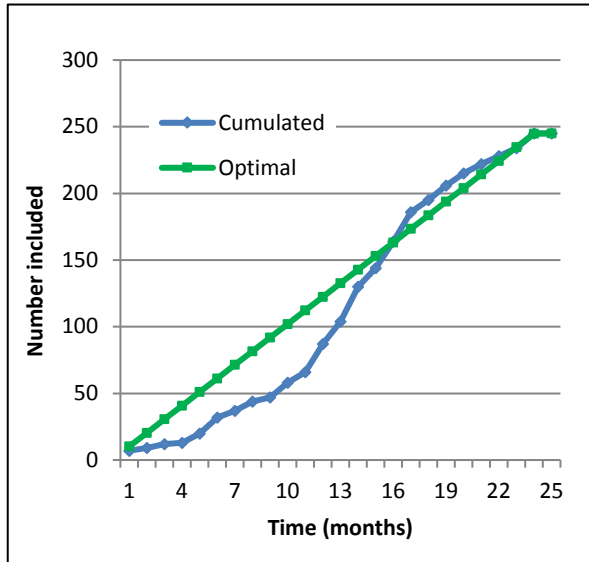
### Study I: Pre-emptive treatment with fibrinogen concentrate for postpartum haemorrhage: randomized controlled trial

This was the first published RCT with fibrinogen concentrate in obstetrics. A total of 249 women were randomised during the planned study period of two years (Figure 1). No-one was lost to follow-up but five women were excluded due to insufficient informed consent, three of whom did not receive intervention. This left 244 women for the ITT analysis; 123 in the fibrinogen group and 121 in the placebo group (Figure 2). The mean estimated blood loss at inclusion was 1,459 ml (SD  $\pm$ 476) with the majority (84%) included after vaginal delivery and due to retained placental tissue (64%). The mean fibrinogen concentration at inclusion was 4.5 g/L, with 2.2% below 2 g/L. The fibrinogen concentrate dose of 2 g/L corresponded with a dose of 26mg/kg and significantly increased the fibrinogen concentration 0.40 g/L (CI: 0.15-0.65) compared to the placebo group 15 minutes after administration.

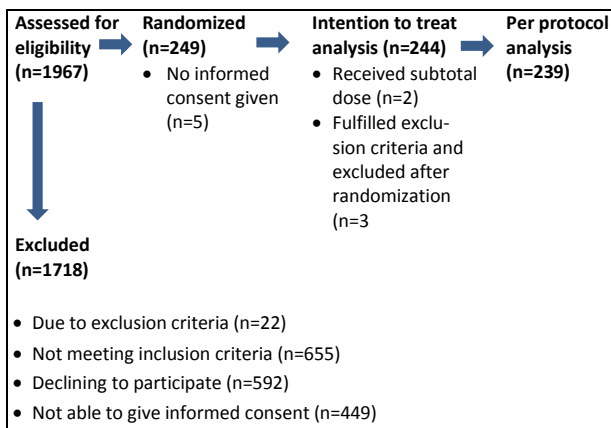
A total of 25 (20.3%) of the fibrinogen group and 26 (21.5%) of the placebo group received a RBC transfusion during the 6 week follow-up, with no significant difference in RBC transfusion at any time point registered (Table 2). The majority of

women received their blood transfusions within the first 24 hours, and all first transfusions were initiated within the first week. We found no significant difference between the two groups in regard to any of the remaining secondary outcomes (Table 2).

**Figure 1.** Optimal and cumulated inclusion rates of patients.



**Figure 2.** Flow diagram of enrolment. (Adapted from "Pre-emptive treatment with fibrinogen concentrate for postpartum haemorrhage: randomized control trial" [98]).



We did, however, find a significant association between fibrinogen concentration after intervention and the risk of transfusion, but this effect was no longer significant after adjustment in the multivariable analysis (Table 3).

There was no difference in adverse events in the two groups at 24 hours post-intervention, including dizziness, shivering, headache, abdominal pain, nausea or vomiting. Furthermore, there were no thromboembolic complications in either group by the 6-week follow-up and very few readmissions, with no difference between the groups.

Out of the 235 anaesthetists that evaluated blinding, a total of 220 (94%) had no idea about treatment allocation. However, nine (4%) guessed that their patient had been allocated to fibrinogen due to the presence of foam in the tubes, and one knew their patient had been allocated to placebo due to deliberate un-blinding as a result of universal urticaria.

**Table 2.** Unadjusted analysis of primary and secondary outcome measures. Intention to treat analysis. (Adapted from "Pre-emptive treatment with fibrinogen concentrate for postpartum haemorrhage: randomized control trial" [98]).

Outcome	Fibrinogen	Placebo	Relative risk (95% CI)	p-value
Any RBC transfusion at 6 weeks	25 (20.3%)	26 (21.5%)	0.95 (0.58-1.54)	0.88*
Any RBC transfusion at 4 hours	4 (3.3%)	10 (8.3%)	0.39 (0.13-1.22)	0.11*
Any RBC transfusion at 24 hrs	14 (11.4%)	19 (15.7%)	0.72 (0.38-1.38)	0.35*
Any RBC transfusion at 7 days	25 (20.3%)	26 (21.5%)	0.95 (0.58-1.54)	0.88*
Total number of RBCs Post-intervention	1,700 [1,500-2,000]	1,700 [1,400-200]	66 [-78;210]	0.37***
Severe PPH	20 (40.0%)	24 (52.2%)	0.77 (0.49-1.19)	0.31*

\* Chi<sup>2</sup> test, \*\* Wilcoxon test, \*\*\* t-test

CI = Confidence interval, RBC = Red Blood Cell.

**Table 3.** Post hoc univariate and multivariate analysis for odds ratios of RBC transfusion. Intention to treat analysis. (Adapted from "Pre-emptive treatment with fibrinogen concentrate for postpartum haemorrhage: randomized control trial" [98]).

Variable	Univariate analysis		
	Odds ratio	95% CI	p-value
Fibrinogen level at 15 minutes	0.65	0.47-0.87	0.005
Centre No.2	0.38	0.12-1.07	0.08
Centre No.3	0.51	0.19-1.30	0.16
Centre No.4	0.68	0.32-1.52	0.34
Trauma	2.82	1.50-5.46	0.002
Tissue	2.11	1.07-4.45	0.04
Baseline estimated blood loss (ml)	3.56	1.88-6.96	<0.001

Baseline haemoglobin (g/L)	0.95	0.93-0.97	<0.001
Baseline crystalloids (L)	1.49	1.02-2.19	0.04
Crystalloids post-intervention (L)	1.62	1.14-2.31	0.007
Systolic blood pressure <100mmHg	2.60	1.03-6.28	0.04
Multivariate analysis			
Variable	Odds ratio	95% CI	p-value
Fibrinogen level at 15 minutes	0.9	0.6-1.34	0.605
Centre No.2	0.66	0.16-2.67	0.561
Centre No.3	0.38	0.08-1.68	0.211
Centre No.4	0.6	0.19-1.96	0.391
Trauma Tissue	3.96	1.54-11.04	0.006
Tissue	2.17	0.82-6.3	0.133
Baseline estimated blood loss (ml)	3.36	1.32-9.03	0.013
Baseline haemoglobin (g/L)	0.38	0.24-0.58	<0.005
Baseline crystalloids (L)	1.32	0.75-2.37	0.342
Crystalloids post-intervention (L)	1.97	1.21-3.38	0.009
Systolic blood pressure <100mmHg	0.62	0.14-2.91	0.535

CI = Confidence interval

Out of the 1,967 women assessed for eligibility in the trial 22 (1.3%) fulfilled exclusion criteria, 592 (30%) declined to participate, and 449 (23%) were unable to give informed consent due to: 1) the acute situation (10%), 2) their psychological state (7%), 3) the language barrier (29%), 4) were uninformed of the study (48%), or 5) had other reasons (6%) (Figure 2). A total of 186 of the included women (76%) had had a positive experience of the trial, but 39 (16%) would have liked more information, 12 (5%) found timing of consent difficult, and 2 (1%) regretted participating in the trial.

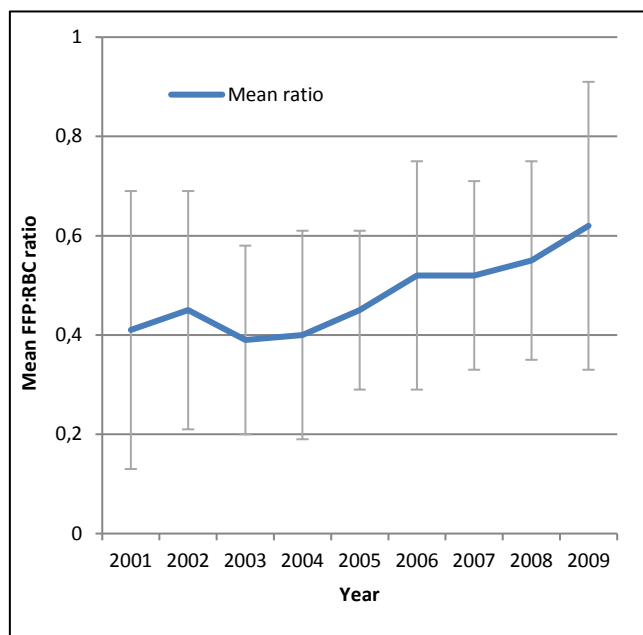
#### Study II: Massive postpartum transfusion: a multidisciplinary observational study

A total of 245 women received massive transfusion of  $\geq 10$  units of RBC due to PPH, with 128 (52.2%) requiring hysterectomy in an

effort to gain haemostasis. A total of 163 (66.5%) gave birth by caesarean section, 19 (7.8%) by instrumental delivery and 63 (25.7) by vaginal delivery. The median total blood loss was 8,000 ml ranging up to 53,000 ml, and with 57 women (24.2%) receiving more than 20 units of RBCs. The women spent a median of 9 days (IQR: 6-14) in hospital, with 170 (69.4%) spending a minimum of 24 hours in an Intensive Care Unit. Two women (0.8%) died, and an additional six (2.4%) had a cardiac arrest.

Haemorrhage started either just before or just after delivery (median 0 minutes, IQR: -7; +8 minutes), but first surgery after vaginal delivery was not performed before a median of 70 minutes (IQR: 41-157) after haemorrhage started. For all deliveries the median time from haemorrhage to the first RBC transfusion was 120 minutes (IQR: 49-229). The mean ratio of FFP:RBC given at the end of surgery leading to haemostasis was 0.45 ( $\pm 0.23$ ), with a significant increase from the 2001 to 2009,  $p=0.005$  (Figure 3). The majority of RBC transfusions in women requiring hysterectomy were given before or during hysterectomy (median 13, IQR: 10-19).

**Figure 3.** Mean FFP:RBC ratio of all women from 2001 to 2009. Whiskers indicating Interquartile range.



FFP = Fresh Frozen Plasma, RBC = Red Blood Cell.

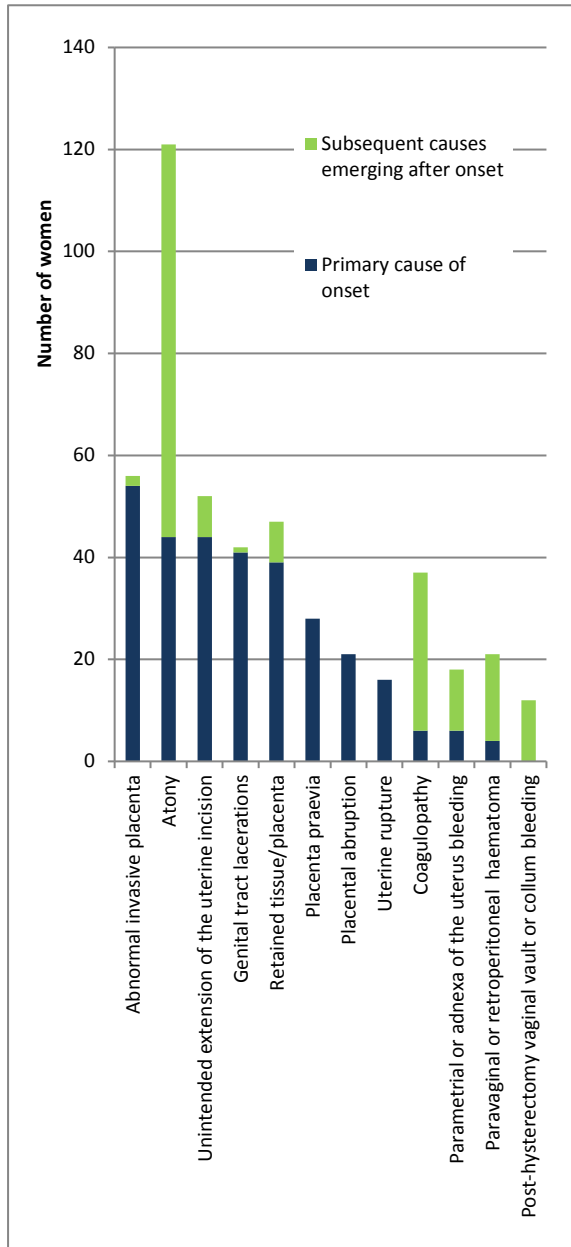
From the data we had available, we identified 23 known risk factors seen either antenatally, during labour and delivery, or postpartum (Table 1). A total of 244 (99.6%) had at least one of these risk factors, 191 (78%) had an antenatal risk factor, 217 (89%) had a labour or delivery risk factor, and 80 (33%) had a postpartum risk factor.

Causes of PPH were divided into causes of onset and subsequent causes not involved in the onset of PPH. There was a wide variation in causes overall and also a variation in the two subgroups of causes with the main causes of onset dominated by atony ( $n=93$ ; 38%), abnormal invasive placenta ( $n=62$ ; 25%), unintended extension of the uterine incision ( $n=59$ ; 24%), genital tract lacerations ( $n=60$ ; 24%), and retained tissue ( $n=42$ ; 17%) and subsequent causes dominated by atony ( $n=77$ ; 53%), coagulopathy ( $n=31$ ; 21%) or haematomas ( $n=17$ ; 12%) (Figure 4).



In the 64 cases of AIP, only 6 were identified prior to delivery, all of which needed a hysterectomy. A total of 36 (56%) of women with an AIP had placenta praevia, 36 (56%) had a previous caesarean section of which 26 (41%) had both. Leaving a total of 18 women (28%) that had neither. However, the 36 women with placenta praevia and AIP constituted 86% of women with placenta praevia.

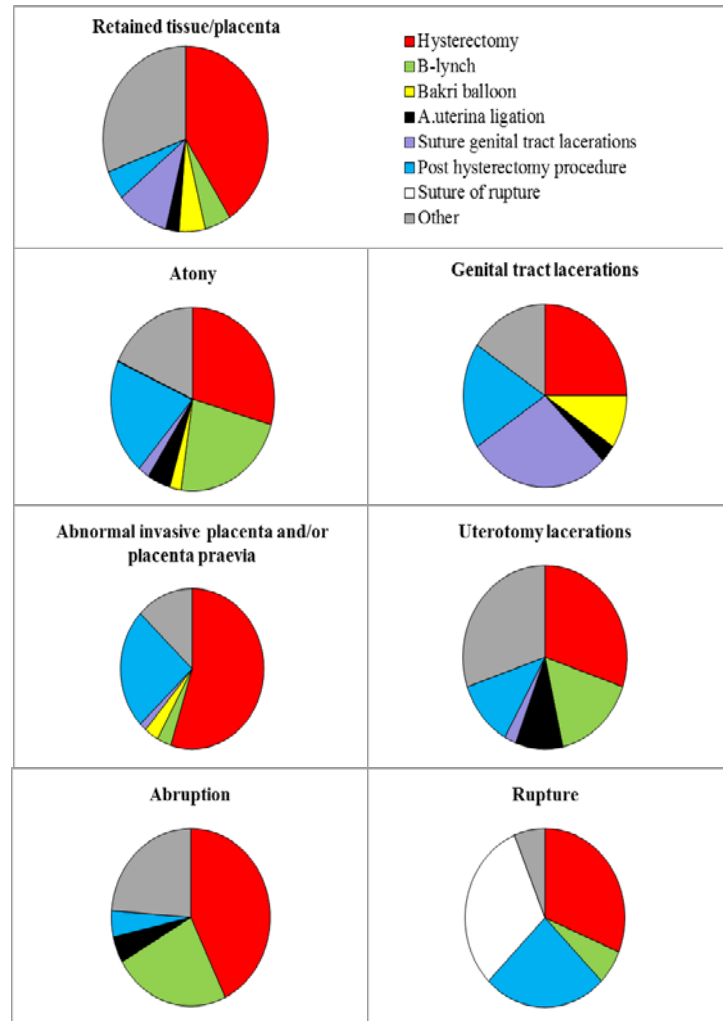
**Figure 4.** Total number of women with each cause divided into primary causes and subsequent causes emerging after onset of haemorrhage. Multiple causes were possible. (Adapted from the manuscript "Massive postpartum transfusion: a multidisciplinary observational study" [108])



A wide variation of procedures was performed in an attempt to gain haemostasis. Hysterectomy was performed most widespread (n=128, 52%), closely followed by suturing of genital tract lacerations (n=95, 39%), intrauterine palpation (n=85, 35%), extra suturing of the uterotomy (n=76, 31%), and B-lynch (n=71,

29%). There was a large variation in the procedures' ability to gain haemostasis, with 100% of splenectomies (n=4), 70% of hysterectomies (n=90), and 67% of embolizations (n=2) gaining haemostasis. The procedure that gained haemostasis varied between the different causes. Hysterectomy had the most substantial role in gaining haemostasis in cases of AIP and/or placenta praevia, placental abruption and retained tissue (Figure 5).

**Figure 5.** Procedures that gained haemostasis for each primary cause of onset.



We found that the 128 women requiring hysterectomy had a higher rate of previous caesarean section (p=0.002), placenta praevia (p<0.001), and AIP (p<0.001). Furthermore, they had greater blood loss (p<0.001) and received more units of RBCs (p<0.001), FFP (p<0.001) and PLTs (p<0.001) than women not requiring a hysterectomy. The FFP:RBC ratio was also higher in the hysterectomy group at time of haemostasis (p=0.010), but they received significantly more RBCs before their first PLT transfusion (p=0.006) (Table 4).

A total of 38 (29.7%) of the hysterectomies performed did not lead to haemostasis. Women requiring further surgical management had a significantly higher rate of previous caesarean section and received higher volumes of RBCs, FFP, PLTs and colloids, and also had a higher ratio of FFP:RBC before initiating the surgery that led to haemostasis (Table 5).

**Table 4.** Characteristics of women with massive postpartum transfusions with and without hysterectomy. Comparison by univariate logistic regression. Data presented as n (%), mean ± SD or median [IQR]. (Adapted from the manuscript “Massive postpartum transfusion: a multidisciplinary observational study” [108])

	Hysterectomy	No hysterectomy	p-value
<b>Maternal characteristics</b>			
Maternal age	34.0 ± 4.6	31.3 ± 5.1	< 0.001
Gestational age (missing n=12)	266 ± 23.9	274 ± 24.1	0.012
Parity	2.4 ± 1.2	1.6 ± 0.8	< 0.001
Previous caesarean section	50 (39.1)	24 (20.5)	0.002
Placenta praevia	36 (28.1)	6 (5.1)	<0.001
Emergency caesarean section	59 (46.1)	66 (56.4)	0.11
Birthweight >4,000g	15 (11.7)	29 (24.8)	0.009
<b>Characteristics of PPH and treatment</b>			
Number of RBCs before first PLT (missing n=62)	10 [6-13]	8 [5-10]	0.006
Number of FFP before first PLT (missing n=62)	4 [2-5]	2 [1-4]	0.025

RBC = Red Blood Cell, FFP = Fresh Frozen Plasma, PLT = Platelets.  
**Bold indicates significant p < 0.05**

**Table 5.** Comparison of characteristics of women requiring hysterectomy not leading to haemostasis with hysterectomy leading to haemostasis. Data presented n(%), mean ±SD or median [IQR].

	Hysterectomy, non-haemostasis, n= 38	Hysterectomy, haemostasis, n=90	p-value
<b>Maternal characteristics</b>			
Previous Caesarean section	21 (55.3)	29 (32.2)	0.020*
<b>Characteristics of PPH</b>			
Time from start of life threatening haemorrhaging to haemostasis (hours:minutes)	11:52 [5:48-20:52]	3:00 [2:00-4:52]	0.000**
<b>Characteristics of transfusions</b>			
Total no. of RBC at haemostasis	20 [15-27.5]	14 [11-19]	0.000**
Total no. of FFP at haemostasis	10 [6-17.5]	7.5 [4-10]	0.007**
Total no. of TRC at haemostasis	3.0 [1-3]	2.0 [0.75-3]	0.035**
FFP:RBC ratio before start of haemostasis	0.45±0.28	0.28±0.31	0.007***

<b>surgery</b>			
Total crystalloids (ml)	8,000 [7,000-11,200]	6,000 [5,000-8,000]	0.000**
Recombinant Factor VIIa, any	13 (36.1)	15 (17.4)	0.034*
<b>Complications</b>			
Hospitalization (days)	11 [8-19]	9 [6-16]	0.048**
Total blood loss (ml)	11,100 [9,000-14,000]	8,800 [7,500-11,000]	0.003**
Time in intensive care (n=242) (days)	1 [0.75-2.5]	1 [0.5-1]	0.006**

PPH = Postpartum haemorrhage, RBC = Red Blood Cell, FFP = Fresh Frozen Plasma, PLT = Platelets

\*Chi<sup>2</sup> test, \*\* Kruskal-Wallis analysis, \*\*\* t-test. Bold indicates p < 0.05

### Study III: Causes and predictors of postpartum blood loss: a cohort study

We identified 43,357 vaginal deliveries with a median of blood loss of 300 ml (IQR 200-400). There was a significant change in the distribution of causes the higher the cut-off used for defining PPH in the cohort. In cases of blood loss ≥500 ml (n=7,514) retained placenta accounted for 12%, lacerations 57%, and other causes including atony the remaining 31%. When increasing the cut-off to blood loss ≥1,000 ml (n=2,198) retained placenta accounted for 34%, lacerations 44%, and other causes including atony 22%. Further increase in the cut-off to blood loss ≥1,500 ml (n=1,113) led to retained placenta accounting for 47%, lacerations 37%, and other causes including atony 16%. Finally, in the cohort with a cut-off of blood loss at ≥2,000 ml (n=546) 53% were caused by retained placenta, 34% by lacerations, and 14% by other causes including atony.

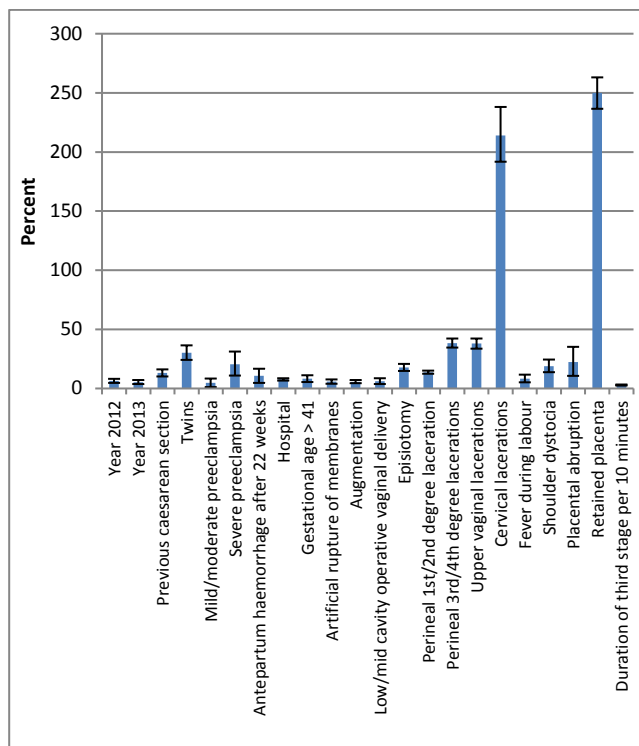
A multivariate linear regression model was used to identify all available risk factors with a significant effect on the prediction of quantity of blood loss. This model accounted for 23.2% of the variability in quantity of postpartum blood loss (R<sup>2</sup>=0.232).

Figure 6 represents the variables with the highest significant effect on prediction of quantity of postpartum blood loss in the final multivariate analysis model, illustrated in percent change. Uterine rupture, uterine inversion and eclampsia all had very high significant effects, but had very wide CIs as they consisted of less than five cases each, and have therefore not been included in the illustration. The effect of the duration of the third stage of labour was decreased substantially in the multivariate analysis compared to the univariate analysis, a reduction that was mainly facilitated by including “retained placenta” in the model (see full model analysis in the manuscript: “Causes and predictors of postpartum blood loss: a cohort study” [109]). Figure 6 illustrates the minimal effect the third stage of labour has on the predicted quantity of postpartum blood loss if a retained placenta is identified. We also identified factors with a negative effect on prediction of quantity of postpartum blood loss, i.e. a protective effect on blood loss. These included second or third parity (-3.17%, CI: -4.3 to -1.8), oligohydramnios (-6.0%, CI: -10.7 to -1.1), chorioamnionitis (-29.7%, CI: -46.3 to -7.7), gestational age 22-32 weeks (-19.8%, CI: -24.1 to -15.1) and gestational age 33-36 weeks (-6.9%, CI: -10.3 to -3.6).

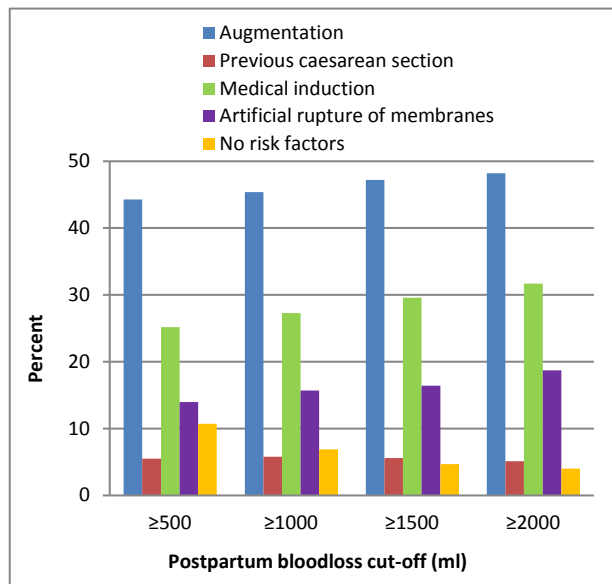
Some of the identified risk factors are caused by procedures performed by obstetricians and midwives at a previous delivery or at the delivery in question (e.g. augmentation, previous caesarean section, medical induction or artificial rupture of

membranes). These iatrogenic risk factors play an increasing role, the larger the cut-off used for defining PPH. Furthermore, fewer women had none of the risk factors included in the model, the larger the cut-off (Figure 7).

**Figure 6.** Percent change each risk factors affected the mean predicted quantity of blood loss. Whiskers represent Confidence Intervals.



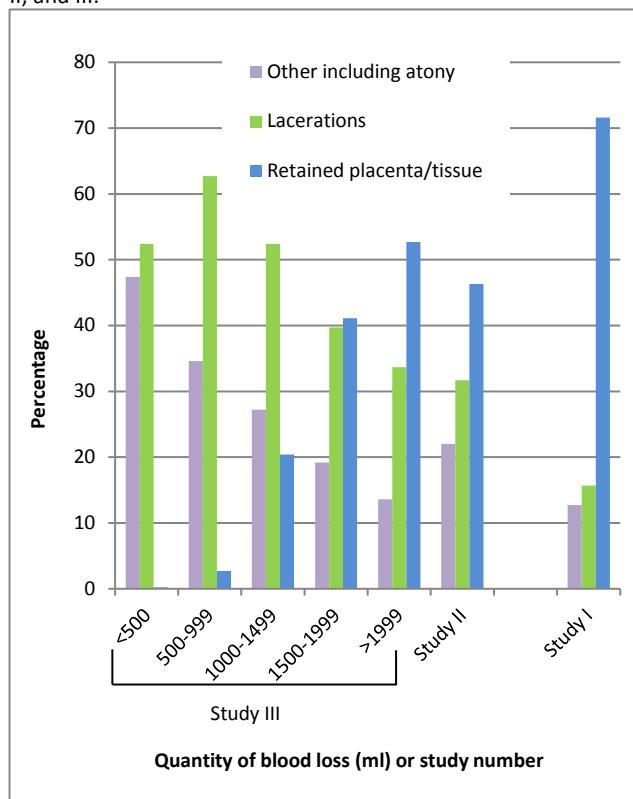
**Figure 7.** Percentage of women with iatrogenic risk factors or no risk factors for different definitions of postpartum blood loss. (Women with “no risks” had none of the following risk factors: previous caesarean section, multiple pregnancy, hypertensive disorders, antepartum haemorrhage, oligohydramnios or chorioamnitis, gestational age <42 weeks, augmentation or induction of labour, low/mid cavity operative delivery, episiotomy, lacerations, fever during labour, uterine inversion, shoulder dystocia, epidural analgesia, uterine rupture, placental abruption and retained placenta)



**Causes of PPH in vaginal deliveries: Study I, II and III**

In all three studies, we identified the causes of PPH. Even though they are not all assessed in the same way, it is still interesting to compare them, as they represent three different severities of PPH. Study III consisted of vaginal deliveries, where each case was assigned a single cause. Therefore, we applied the same method to study I and II, including only vaginal deliveries and giving all women only one cause. “Retained placenta/tissue” was assigned first, then “lacerations” and finally “others, including atony” (see methods and materials). Study II and III are population based studies. As study II was comprised of the most severe cases of PPH it can be seen as a continuation of study III that mainly consisted of cases with PPH <2-3L (figure 8). Study I included a selected cohort of women able and willing to give informed consent, and is therefore not directly comparable to the population based studies, but it is still shown to the right in figure 8. Figure 8 illustrates the increasing role of a retained placenta and the decreasing role of atony the higher the blood loss in cases of PPH.

**Figure 8.** Distribution of causes for all vaginal deliveries in study I, II, and III.



**DISCUSSION**

**Overall findings**

- Severe PPH could not be prevented with a fixed pre-emptive dose of fibrinogen in women with normofibrinogenaemia. The study was not large enough to evaluate rare complications such as thromboembolisms.
- Women with massive postpartum transfusion had a high incidence of severe morbidity and hysterectomy. Only 70% of the hysterectomies resulted in haemostasis. Women treated with hysterectomy had higher blood loss, and received more transfusions of RBCs, FFP

and PLTs, than women not treated with hysterectomy during massive postpartum transfusion.

- The distribution of causes of PPH varied depending on the severity of PPH, with atony playing a smaller role and retained placenta a larger role than first anticipated. Retained placenta was, furthermore, a strong predictor of quantity of blood loss and diminished the effect a prolonged duration of the third stage of labour had on prediction of quantity of blood loss.

## Strengths and limitations

### Study I

Completing an RCT in an acute setting in obstetrics in the time frame planned, and only using independent funding is an accomplishment and strength in itself. What further strengthened the study were the successful block randomisation and allocation concealment reducing confounders and selection bias, and double-blinding of the majority of clinicians and all patients, thereby limiting performance bias. Furthermore, the external validation is strengthened through our ability to include women, through a multicentre set-up with few exclusion criteria. Limitations in this study are, however, also present. Considerably fewer women included in the trial received RBC transfusions than first anticipated (placebo group 21.5%, estimate for sample size calculations 57%). The fact that we did not meet a transfusion rate of 57% results in a lower statistical power. If we wanted to find a risk reduction of 33% (and 15% dropout) we would have needed to include 1,021 women. Therefore the study was not powered to evaluate the planned effect of fibrinogen concentrate. In a recent randomised controlled trial of 56 women with severe PPH >1,000 ml, 31 women (55%) received at least one blood transfusion, however, they also found no risk reduction when increasing the fibrinogen level from approximately 3 g/l to 4 g/L.

One of the reasons for our low rate of transfusions could be the inability to include women with the most severe PPH, either due to the women being incapable of giving an informed consent or due to the clinicians being unable to cope with further challenges in an already critical situation. This is discussed further below. We have as yet not been able to extract data regarding women who were not included in the study with regard to their quantity of PPH. Another reflection of the low inclusion rate of the most severe cases of PPH, can be seen in the low rate of women with fibrinogen concentrate <2 g/L at inclusion, which was the group expected to have the highest effect of an increase in fibrinogen. Even four hours after intervention when the estimated blood loss was close to 3 L, the mean fibrinogen level in the placebo group was above 4 g/L. Our findings of a higher level of fibrinogen in women with severe PPH are discussed below.

Even though 120 women received 2g of fibrinogen concentrate it was not enough to assess the risk of thromboembolic complications. In our population the risk of venous thromboembolic complications is estimated at 0.7-2.0/1,000 pregnancies [60], therefore even if fibrinogen concentrate caused a two-fold increase in risk, we would not necessarily have seen a single case in our cohort during the six week follow-up.

### Study II

With massive transfusion being a rare occurrence in obstetrics, a cohort of this size, with only six case files missing, gives a good description of a group of extremely severe cases. Identification of the cohort through Danish national registries representing the majority of births in Denmark in the chosen period increased the external validity. Detailed validation of the data obtained through

patient files using standardised abstraction forms for all patients, excluding women receiving massive transfusion due to non-obstetric complications, strengthened the internal validity, and by using only one abstractor we minimised interrater variability.

Some aspects of selection bias have been accommodated through well-defined inclusion criteria of  $\geq 10$  RBC transfusions and childbirth, establishing a cohort from national registries of known high validity [103,119]. However, selection bias in general is one of the major limitations of this study, due to non-random assignment of not only treatment, but in our case probably also the outcome of hysterectomy, both of which could be highly influenced by confounders, that we could not take into consideration. These confounders include experience level of the clinicians involved in treating these severe cases and availability of blood products. Both of these correlate to some extent with a large birth place. Size of birth place was included in the analyses, but this can in no means take the whole effect into account. Multivariate analysis increases selection bias further, excluding all cases with missing values in variables included, perhaps causing a selection of more severe cases where recording of information was more thorough. All in all determination of causation is not possible due to confounding-by-indication where the decision to perform hysterectomy could be influenced by failure of treatments attempted before the decision to perform hysterectomy. Furthermore, our findings could be due to random error, as the level of significance at  $p < 0.05$  still leaves a risk of 1/20 that our findings could be obtained by chance.

### Study III

Cohort studies of this size increase the probability of identifying true association, and by using multivariate regression analysis we were able to account for multiple factors that could influence the prediction of quantity of postpartum blood loss. Known high validity of the Obstetric Database strengthens this study [105], and as the population included has known homogeneity with the rest of Denmark, external validity is increased [120]. The limited exclusion criteria reduced selection bias, but could not eliminate this completely due to exclusion of cases with missing data. In addition missing data contributed to further limitations, as we were not able to include possible confounders (previous PPH, BMI and birthweight) in the model. As in study II there is a risk of random error, albeit smaller as the majority of p-values fall below 0.001.

## Clinical trials in emergency obstetrics

Clinical trials are important in all fields of medicine, but are fairly rare in emergency obstetrics probably due to challenges with informed consent and the recruitment process [111,113]. We also met several of these challenges and had an initial slow inclusion rate in study I, partly due to the multi-centre set-up and 24 hour recruitment under emergency situations. Under these circumstances it is not possible for the project coordinator to be on site for each inclusion but relies instead on the staff on duty feeling properly prepared for all aspects of the inclusion process. It is well known that slow recruitment is one of the main problems in clinical trials, with as little as 31% of trials meeting recruitment targets, even fewer in emergency medicine [121,122]. We managed to overcome the slow inclusion rate once all four sites had got used to inclusion, but the trial was still affected by some of the known obstacles of trials in emergency obstetrics, as illustrated by the large number of women declining to participate (30%) or unable to give informed consent (23%). This could be the reason that we did not include women with the most severe PPH,

thereby not meeting our transfusion rates used for the sample size calculation.

Recent qualitative studies have identified areas related to the organisation, the staff recruiting, and the process of informed consent as the major obstacles [121–125]. Organisational barriers include the setup of the trial and the incentives of the organisation to focus on research [122,124]. Although we recruited from university affiliated hospitals, we felt that some of the centres were less used to being involved in clinical trials, and some of the staff expressed that they were not hired to do research. The ability for an organisation to inform staff and patients about research taking place can play a role in both staff' and patients' attitudes to research. On the homepages of the four hospitals in our study only one (Nordsjællands Hospital) has direct information regarding research on their front page. In comparison Yale and Harvard affiliated hospitals have information regarding research trials being conducted there, on the front page of their home pages (<http://www.ynhh.org> and <http://www.massgeneral.org/>). Other obstacles influencing the recruiting staff involve conflicts in regard to time available, feeling the need to prioritise the clinical side of work at the expense of research, or not wanting to approach vulnerable patients [122,125]. An improvement of these factors could enhance the ability to include patients during an emergency setting, e.g women with severe PPH.

As mentioned before informed consent is requested by law, and requires not only that a patient can receive information and understand it, but also that someone is capable of giving sufficient information [110]. The fact that 23% were unable to give informed consent in our trial could possibly reflect not only difficulties receiving information, but also difficulties providing information in the acute situation. In a recent study enrolling patients postpartum at time of diagnosis of a retained placenta, staff expressed they had limited time to give information and often ended up giving very simplified information [125]. The women recruited to the trial expressed gratitude to receiving sparse information at a point in time when they felt anxious and exhausted. However, in hindsight, the majority felt that they had not given a fully informed consent and would have preferred more information antenatally. The staff on the other hand found that it might scare women if all women were to be informed of the study, where only 2% would become possible candidates, even though this pathway is recommended by the RCOG [126]. Our study had tried to give summary information antenatally, but failure to fulfil this can be seen in the fact that 48% of women declining to participate felt uninformed on the study and 16% of included women would have like more information. If antenatal information had been successful, this too could have improved our ability to include women with the most severe PPH.

### Coagulopathy in PPH

Coagulopathy was found in 35% of cases in [study II](#), some of which had not been recognised at the time of events. This together with the large proportion of hysterectomies not resulting in haemostasis, supports the notion that coagulopathy is not always identified or considered during the attempt to gain haemostasis through surgery alone [1,20,70]. Even though the transfusion rate used in our sample size calculation was not met in [study I](#), we found no significant effect of early pre-emptive fibrinogen as a strategy for preventing development of a more severe PPH due to coagulopathy. Therefore, perhaps we should focus on viscoelastic assays early on to give a more goal directed treatment. Several studies have recognised the potentials of viscoelas-

tic assays in identifying coagulopathy in women with PPH [61,127], but not all delivery units have access to these assays, and can we reject the effect of pre-emptive fibrinogen for all cases of PPH based on one single trial? – probably not. As mentioned before the transfusion rate in [study I](#) was lower than anticipated, and the included women had higher levels of fibrinogen than expected in relation to the study by Charbit et al [81]. This could indicate that the women in our trial had less severe bleeding and perhaps received smaller volumes of crystalloids and colloids than the study population of Charbit et al, where no data on blood loss or crystalloid/colloid infusion is available. We found a decreased risk of transfusion in the group with an increased fibrinogen concentration after intervention in the univariate analysis, which corresponds with the findings from Charbit et al. However, after including blood loss, crystalloids, colloids etc. in our multivariate analysis, the difference was no longer significant (Table 3). This leads us to question whether the findings from Charbit et al would have been significant if they had done the same, or whether the lower fibrinogen concentration simply was a result of more severe PPH and dilution, as identified in a similar study [128].

We know that coagulopathy develops due to both dilution and consumption [63], and a low fibrinogen concentration is a sign of coagulopathy. However, we do not know at which specific level a low fibrinogen critically impairs coagulation leading to further blood loss in women postpartum. A Cochrane study found it possible that fibrinogen concentrate reduces the need for blood transfusions, but included studies investigating both pre-emptive treatment and treatment of known or suspected hypofibrinogenaemia in various fields of medicine [129]. Studies measuring antenatal fibrinogen levels have shown diverging results [128,130], but hopefully future trials will demonstrate whether women with more severe PPH could benefit from pre-emptive fibrinogen substitution [86], or whether substitution should be based on viscoelastic assays where the effect of dilution is taken into account [85]. So far a pilot study investigating the effect of fibrinogen concentrate in women with PPH and low levels of fibrinogen (measured by viscoelastic assay “FIBTEM”), showed no reduction in the need for blood transfusion [131].

There are some circumstances where there is no time to wait for analyses, but where focus instead should be on immediate life-saving measures. This includes profuse uncontrollable PPH, where substitution with RBCs is inevitable, cases similar to the population in [study II](#) requiring  $\geq 10$  units of RBCs. In this cohort we found that women not requiring hysterectomy received their first PLT transfusion after fewer RBC transfusions, but received a lower FFP:RBC ratio at time of haemostasis than women requiring a hysterectomy. Identifying risk factors is a complex matter in a study like this, as we cannot tell the difference between factors that were a consequence of hysterectomy, and factors that influenced the decision to perform hysterectomy. We know that women treated with hysterectomy required more transfusions, longer time in surgery and longer hospitalisation, but we also know that they bled more and perhaps this led to the decision of hysterectomy and additional blood transfusions. Likewise a higher FFP:RBC ratio could be due to a longer time in surgery, giving the anaesthetist time to consider a more balanced transfusion. However, the treatment with PLTs is more complex. Transfusion of first PLT after fewer RBCs in women requiring hysterectomy could be because there was no profuse bleeding and the clinicians were less stressed and had time to consider platelets (which is the opposite of our considerations regarding FFP), or that women receiving more RBCs before their first PLTs –

and thereby more dilution –bled more profusely due to coagulopathy, which in turn led to hysterectomy. The only other study investigating the effect of PLT transfusions in PPH concluded in their retrospective study, that the 12 women receiving PLT transfusions had either antenatal thrombocytopenia, placental abruption or blood loss >5,000 ml, and there was therefore no need for early fixed-ratio transfusion of PLTs [132]. This conclusion was based on the fact that PLT transfusion was only used in these cases and therefore not necessary in other cases. However, without comparison on outcome in these two groups, it is difficult to conclude whether sufficient women received PLT transfusions. A study using an in-vitro model found that a fixed rate of PLT:FFP:RBC of 1:1:1 in postpartum women was associated with decreased coagulopathy measured by viscoelastic assay [133], and studies of massive transfusion in other populations have shown increased survival with a fixed rate of early PLT transfusions, thereby supporting the use of fixed ratios [75,134,135].

We found no benefit of a high FFP:RBC ratio in [study II](#), but other studies on severe PPH have reported a reduction in the need for interventional procedures and an increase in the success rate of hysterectomy compared to lower ratios [91,96]. The majority of studies of massive transfusion due to PPH have, however, not compared ratios between groups, but only stated the overall ratio in their cohorts ranging from 0.3 to 0.8 [136–139]. The overall mean FFP:RBC ratio in [study II](#) of 0.48 is within this range. The FFP:RBC ratios in the more recent years of [study II](#) (2008-2009) had higher ratios, probably due to the increased focus on balanced transfusions and introduction of a transfusion protocol in 2007 in Denmark [140].

### Predicting the few and treating the cause

In [study III](#) risk factors affecting the prediction of postpartum blood loss were identified in a multivariate linear regression model. However, we also saw that only 11% of women with blood loss  $\geq 500$  ml, and 5% of women with blood loss  $\geq 1,000$  ml, had none of the identified risk factors. Likewise in [study II](#) we found only one patient (0.04%) requiring massive transfusion that had no risk factors for PPH. The majority of risk factors identified in the two studies were the same, but [study II](#) also included caesarean section deliveries, cases of placenta praevia, previous PPH, age >35 years, and BMI >35 as risk factors. [Study III](#) included extra data regarding fever during labour, amniotic fluid abnormalities, uterus inversion, shoulder dystocia and epidural analgesia as risk factors, making the studies less comparable. Despite of this, it seems evident that the vast majority of most severe cases of PPH have at least 1 risk factor. This is in line with a recent study of women with PPH requiring  $\geq 8$  RBC transfusions, where 3% (5/181) did not have any risk factors [141]. Other studies have shown a higher proportion of cases without risk factors e.g. 30% of cases with PPH and transfusion [46], and 61% of cases with PPH  $\geq 500$  ml, probably due to a variation in included risk factors. As noted previously many of the identified risk factors have a small effect on predicted blood loss and are also seen in women not developing excessive blood loss. However, risk factors should not be ignored, but instead help the clinician take extra precaution, even in cases with one or two low effect risks.

Up until now, prolonged duration of the third stage of labour has been considered one of the risk factors that has a high effect on postpartum blood loss [23,24,26,44]. In [study III](#) we found that the majority of this effect was due to a retained placenta, including cases requiring manual removal and cases of AIP. This is quite controversial, as the main focus in recent years has been on early manual removal of placenta irrespective of whether

there is ongoing haemorrhage [23,24,28]. In contrast our results suggest that if there is no retained tissue or the need for manual removal, then a prolonged duration of the third stage of labour will not lead to excessive blood loss. This approach requires early identification of a retained placenta, a condition recognised in all three of our studies and similar studies as a major cause of PPH [9,39,40]. To date this has proven difficult, with only up to 50% of the most severe cases being identified prior to delivery [34,142,143].

Retained placenta and other causes of PPH including lacerations and uterine atony, were found to change in distribution the larger the quantity of blood loss in [study III](#). Especially atony seemed to play a much smaller role than the traditionally ascertained 70% [18]. [Study III](#) and Figure 8 comparing the three studies has probably underestimated the role of atony due to cases only being assigned this cause as an exclusion diagnosis in the absence of lacerations or retained placenta. This change in distribution could also be due to an effect on atony of early administration of uterotonics, that is advised in the Danish guideline [79]. This could lead to progression of PPH for cases where uterotonics have no effect.

The original data for [study I and II](#) were assigned causes after review of patient charts, with [study II](#) dividing the causes further into causes of onset and causes arising after onset. Very few other studies have included secondary atony in their analysis, but it is described in case reports, and one study found that 27% of cases treated with internal iliac ligation due to PPH had secondary atony [1,144]. This is very close to our findings, perhaps suggesting that this is an underestimated cause in many cases of PPH. It is difficult to determine the physiology behind secondary atony. We know that haemostasis after placental delivery is obtained through both contraction and coagulation [52,59], then perhaps if one of these factors is insufficient the effect of the other is reduced. For example if coagulopathy develops due to ongoing haemorrhage then the placental site loses its' coagulative ability, causing blood to gradually fill the uterine cavity until the uterus finally cannot keep up due to exhaustion, and atony arises. In comparison atony arising after sufficient coagulation at the placental site might cause minimal haemorrhage.

Identifying the cause of haemorrhage is of great importance, as treatment strategies are different for different causes. Not only is it now obvious that coagulopathy cannot be treated with hysterectomy, but extensive lacerations in the genital tract including cervix also have limited effect of a hysterectomy [1]. But these causes can be overseen if focus is primarily on atony already from the start of PPH, due to an exaggerated role of atony in traditional literature.

### CONCLUSION

For normofibrinogaemic patients with severe PPH, pre-emptive treatment with 2 grams of fibrinogen concentration showed no effect on the need of RBC transfusions postpartum. There were no thromboembolic complications due to fibrinogen concentrate, but the cohort was not of sufficient size to evaluate this.

In more severe cases of PPH, where women were treated with massive transfusion the morbidity and rate of hysterectomy were high. Women treated with hysterectomy had higher blood loss, more transfusions of RBCs, FFP and PLTs, more RBC transfusions before initiating PLT transfusion, and longer hospitalisation than women not treated with hysterectomy. Furthermore, only 70% of the hysterectomies actually resulted in haemostasis.

The distribution of causes varied significantly depending on the cut-off used to define PPH, with atony playing a smaller

role than first anticipated. A retained placenta played an increasing role the higher the cut-off used. The predictive effect of a prolonged duration of the third stage of labour on quantity of blood loss was diminished by the influence of a retained placenta.

## PERSPECTIVES

The results of our studies contribute with findings regarding prevention and treatment of severe PPH, thereby providing new evidence for guidelines and new paths to follow in future research, so that we can avoid some of the severe cases of PPH, that are associated with such high morbidity.

Our experiences with informed consent in the clinical trial have the potential of helping others if steps are taken to improve focus on research from an organisational level. This could involve easy accessible information on websites or in waiting rooms regarding ongoing trials, benefits of research, and results of previous trials that have influenced treatment regimes. Hopefully this could help prepare patients for the possibility of being confronted with research protocols during an emergency situation, and giving women that want to know more, the possibility of access to in depth information. Staff should also be informed of the importance of research trials taking place, and can perhaps become more comfortable with enrolment strategies if all staff involved are prepared and support each other in these often hectic situations.

The absent effect of pre-emptive fibrinogen in our study will hopefully change some of the guidelines already existing that recommend fibrinogen concentrate if PPH exceeds approximately 1500 ml [145–147]. Not only did we not find any benefits of this treatment, but the safety in relation to thromboembolic complications has not been clarified. Therefore, treatment should be given with precaution and only in cases where the benefits have been proven. Today the use of fibrinogen for PPH is the main focus for several ongoing trials with the most recent taking our results into account [85,86]. New trials together with our findings of coagulopathy in the most severe cases of PPH can hopefully draw further attention to the role of coagulopathy and the importance of early recognition and treatment before it becomes uncontrollable. This could in turn lead to fewer hysterectomies becoming necessary, and not being performed in cases of coagulopathy where removal will not lead to haemostasis.

For cases of profuse bleeding, where actions need to be taken immediately, our findings support the benefits of an early platelet transfusion. Training in transfusion algorithms alongside practice drills for PPH could benefit not only patients, but also obstetricians and anaesthetists by improving their collaboration in these emergency situations.

Our findings of the decreased role of atony in the onset of PPH should emphasise the need for early identification of other causes, perhaps including quick transfer to an operating theatre, to facilitate thorough investigation for retained tissue or cervix lacerations. Treatment of atony should, however, not be forgotten as PPH can have multiple causes not necessarily arising simultaneously. Furthermore, if identification of the majority of cases of retained placenta is deemed possible in the future, then sufficient precautions can be made to prevent excessive blood loss, focusing less on the duration of the third stage of labour and more on immediate manual removal of a known retained placenta. In addition, the majority of women suffering from PPH were found to present with at least one risk factor before or during labour, that together with the identified effects of each risk factor can guide the clinician on where to prepare for PPH.

Finally, we found that the distribution of causes varied depending on the cut-off used to define PPH, illustrating that studies regarding PPH are not always comparable. Perhaps the question is not what definition to use, but whether we need a definition of PPH. It is practical in a clinical setting to have a definition of PPH that can be used to trigger treatment strategies. In our large cohort study 83% of all vaginal births lost less than 500 ml of blood. The traditional cut-off of 500 ml seems therefore relevant for initiating investigation of the causes, even though estimates in this range are known to be somewhat inaccurate [21]. A cut-off for quantity of blood loss or blood transfusions for defining severe PPH in order to initiate certain treatment strategies seems less warranted. Treatment of severe PPH should be based on individual observations, taking not only blood loss, cause of PPH, and dilution into account but also measurements of coagulation and vital functions. A definition of severe PPH could, however, be based on the need for transferral to an operating theatre, as this is known to have a major impact on women's experience during childbirth [125]. The definition or diagnosis could then be used to make sure these women were given extra attention postpartum. Definitions are, however, vital for research purposes where comparisons of studies or systematic reviews depend on uniform definitions. Definitions for research purposes could be obtained through Delphi procedures, where consensus is achieved from a group of experts, for example through the INOSS collaboration [148,149].

## FUTURE STUDIES

The role of fibrinogen concentrate for prevention of development of severe PPH in women with hypofibrinogenaemia has yet to be investigated.

With regards to PPH requiring massive transfusion, the ideal study would be an RCT evaluating different transfusion protocols. Due to the scarce incidence of these cases an RCT would have to involve a multinational collaboration and would be affected by challenges in gaining informed consent. Taking this into consideration a larger observational study might be more feasible and would perhaps give us answers to some of our questions.

An RCT investigating the benefits of transfusion guided by viscoelastic assays is on the other hand feasible in an obstetric population with less severe PPH, and could perhaps lead to prevention of haemorrhage due to coagulopathy.

We need studies investigating early identification of retained placenta. These studies should not only focus on ultrasound modalities but should also consider investigating biomarkers involved in the placental development.

## SUMMARY

This thesis is comprised of three studies focusing on severe postpartum haemorrhage (PPH). PPH is a major cause of maternal morbidity and mortality worldwide. Risk factors include retained placenta, prolonged duration of the third stage of labour, previous caesarean section, and operative vaginal delivery. Occurrence and development of PPH are, however, unpredictable and can sometimes give rise to massive haemorrhage or even hysterectomy and maternal death. Severe haemorrhage can lead to coagulopathy causing further haemorrhage and requiring substitution with blood transfusions. The aim of this thesis was to investigate causes of severe PPH and investigate methods of early prevention.

The first study was a randomised controlled double-blinded trial investigating the effect of treatment with pre-

emptive fibrinogen on women with severe PPH. The primary outcome was the need for red blood cell transfusion at 6 weeks postpartum. A total of 249 women were randomised to either 2 grams of fibrinogen or placebo. The mean concentration of fibrinogen increased significantly in the intervention group compared to the placebo group (0.40 g/L, confidence interval: 0.15-0.65), but there was no difference in the need for postpartum blood transfusions (relative risk 0.95, confidence interval: 0.15-1.54). No thromboembolic complications were detected.

The second study was a population-based observational study including 245 women receiving  $\geq 10$  RBCs due to PPH. The cohort was identified by combining data from The Danish Transfusion Database with The Danish Medical Birth Registry, with further data extraction and validation through review of patient charts. The main causes of massive postpartum transfusion were atony (38%) and abnormal invasive placenta (25%). Two of the women in the cohort died, an additional six had a cardiac arrest, and a total of 128 women (52%) required a hysterectomy. Hysterectomy was associated with increased blood loss, increased number of blood transfusions, a higher fresh frozen plasma to red blood cell ratio ( $p=0.010$ ), and an increased number of red blood cells before first platelet transfusion ( $p=0.023$ ). Hysterectomy led to haemostasis in only 70% of cases.

The third study was a register-based cohort study, including 43,357 vaginal deliveries from two large Danish maternity units. Different cut-offs were used to define PPH. There was a difference in distribution of causes depending on the cut-off used, with atony playing a decreasing role and a retained placenta an increasing role the higher the cut-off used. In a multivariate linear regression model retained placenta was identified as a strong predictor of quantity of blood loss. The duration of the third stage of labour was a very weak predictor after adjusting for the influence of a retained placenta.

In conclusion, an improved diagnosis of the causes of PPH especially retained placenta, together with an early recognition and treatment of coagulopathy, seem to be important in reducing severe PPH in an aim to minimize associated maternal morbidity.

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