Obstetric hemorrhage: improving care by collaborating across borders

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Chapter 8

General Discussion

Main results

In this thesis, I presented the results of the benchmarking process of obstetric hemorrhage-related maternity care in France and the Netherlands. This process was used as a tool to investigate the hypothesis whether different strategies to manage obstetric hemorrhage may explain differences in the incidence of hemorrhage-related severe maternal outcome (SMO). Furthermore, I presented the latest trends in hemorrhage-related maternal mortality in France as well as opportunities to reduce preventable SMO in this context by focusing on subgroups of women with severe obstetric hemorrhage.

Several high-resource countries have reported an increasing incidence of obstetric hemorrhage and hemorrhage-related SMO, yet significant variations in the incidence of SMO persist between such countries. My findings suggest that these observations may be explained by different strategies to manage obstetric hemorrhage. Indeed, my comparative study of national guidelines for obstetric hemorrhage (Chapter 2) brought to light important variations among high-income countries with regards to the prevention, diagnosis and clinical management of obstetric hemorrhage, highlighting areas requiring a stronger evidence-base, such as a common definition and diagnosis of (severe) PPH and the timing and sequence of multiple second-line uterotonics and uterine-sparing interventions.

In terms of SMO, the results of my systematic review and meta-analysis (Chapter 3) showed that reducing the length of the third stage of labor, in particular among women with risk factors for obstetric hemorrhage, might reduce the incidence of hemorrhage-related SMO. Furthermore, the increased incidence of severe obstetric hemorrhage and SMO in the Netherlands as compared to France reported in Chapter 4, suggests possible explanatory mechanisms such as less frequent and later use of second-line uterotonics and uterine-sparing interventions in the Netherlands as compared to France. This finding was supported by our binational review of hemorrhage-related maternal deaths (Chapter 5), reporting that treatment failure among women who died from obstetric hemorrhage in the Netherlands was mostly related to delay in clinical management whereas in France, treatment failure was more often related to deficiencies in the organization of the health care system.

In this thesis, I also gave an update on the latest trends of hemorrhage-related maternal mortality in France, based on data from the French confidential enquiry into maternal deaths (Chapter 6). Maternal mortality from obstetric hemorrhage

dropped by two thirds in France between 2001 and 2015, but the majority of the remainder of these hemorrhage-related maternal deaths could still have been prevented by timely and appropriate interventions and access to healthcare of good quality. I reported a shift in the main cause of fatal hemorrhage from uterine atony to hemorrhage from surgical injury during cesarean section. This shift required further exploration. Therefore, chapter 7 includes the results of a nationwide analysis of women who died from hemorrhage due to surgical injury during cesarean section. My finding reveal a dominant profile among the women who died combining risk factors such as obesity, advanced maternal age, multi-scarred uterus and second-stage cesarean section, all of which are on the rise in many high-resource countries, illustrating the importance of our findings not only for France but also for other countries facing similar trends. In total, 95% of maternal deaths were considered preventable. Identified improvable care factors related mainly to delays in diagnosis and clinical management of surgical injury during cesarean section.

Below, I place the main results of this thesis into a broader context, using the structure of the PDSA-cycle from the general introduction of this thesis. This cycle of international benchmarking will be completed at the end of this chapter by providing the main conclusions and recommendations for clinical practice and future research agendas.

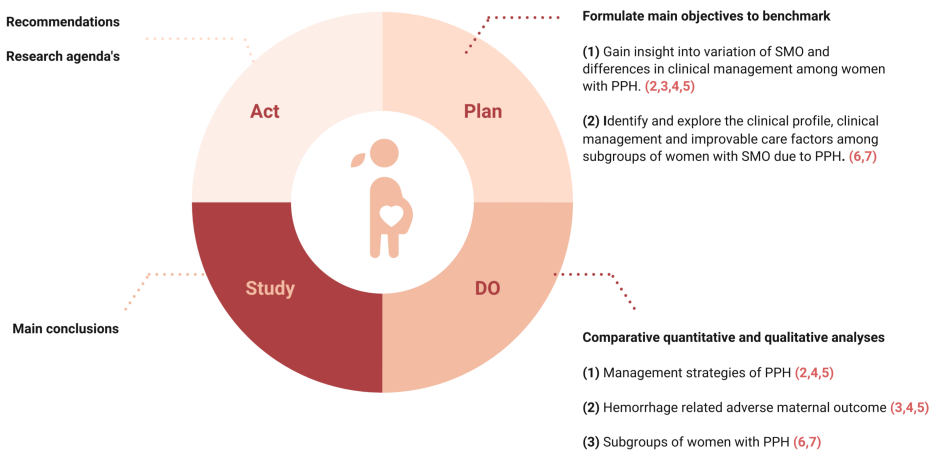

Figure 1. Continuous cycle of international benchmarking of hemorrhage-related maternity care
Abbreviations: SMO = severe maternal outcome; PPH = postpartum hemorrhage

Part I. Obstetric hemorrhage: improving maternal outcomes by exploring management strategies through a global context

1. Overcoming differences in definitions and guidelines on obstetric hemorrhage

A) Observational cross-country studies as an alternative for randomized controlled trials

In the first part of this thesis, I explored the role of variations in clinical management of obstetric hemorrhage and their association with SMO. As highlighted in my comparative study of guidelines on the management of postpartum hemorrhage (PPH) (Chapter 2), there is currently a lack of robust data on how to manage more severe forms of obstetric hemorrhage. At least five factors might explain the paucity of evidence in this context. First, the rarity of eligible women makes it difficult to obtain sufficient study power. Second, conducting randomized controlled trials of uterine-sparing interventions is difficult, given the complex character of these interventions, some of which are difficult to standardize and impossible to double-blind. Third, the nature of hemorrhage poses recruitment challenges due its acute character and the demanding work environment, which interfere the ethics around obtaining consent. In an ideal setting, women could be recruited before labor. Research nurses should inform women on the potential risks and benefits of entering the trial given the context of the immediate postpartum period as women may have fears with regard to separation of their newborn in case of trial participation. Fourth, the acute setting of hemorrhage often provokes stress among the team, making it less likely they will adhere to study protocols. Fifth, given the lack of an established definition of (severe) PPH, appropriate outcome measures for use in clinical trials remain controversial.

In this context, observational cross-country studies may be an alternative option to generate relatively robust evidence on different management strategies of PPH as these can be considered as 'quasi-experimental' studies, aiming to evaluate interventions without using randomization.(1) Therefore, in Chapter 4, I compared management strategies between women with equally severe PPH in France and the Netherlands. Arriving at a relatively homogenous population of women with severe PPH was challenging due to different definitions of severe PPH applied in the French and Dutch databases. The TEMPOH-1 study (Netherlands) included women who received ≥4 units of RBC or a multicomponent blood transfusion within 24 hours following birth because of PPH exceeding 1000 mL whereas the EPIMOMS study (France) included women with blood loss ≥1500 ml; and/or hemorrhage with

transfusion ≥4 red packets cells or radiological arterial embolization or surgical vascular ligation or compressive uterine suture or emergency peripartum hysterectomy or any organ dysfunction (according to the EPIMOMS definition). These differences in inclusion criteria of the source population of our study in Chapter 4 may have resulted in selection bias. In an attempt to select women with equally severe PPH, we extracted from both source populations only those women who fulfilled our definition of severe PPH: (total blood loss ≥ 1500 ml) and (blood transfusion of ≥ 4 units of packed red blood cells AND/OR multicomponent blood transfusion). Although this should theoretically have resulted in a population with equally severe hemorrhage, our definition included a therapeutic measure, namely 'transfusion'. As I will state later on in this discussion, therapeutic measures may depend on medical culture and available resources and could, when included in the definition, introduce selection bias, undermining estimation of the true severity of PPH. If in France women would, for example, be transfused earlier in the course of PPH as compared to the Netherlands, this could hypothetically have resulted in the inclusion of women with clinically 'less severe' forms of PPH. However, by also including a minimum total volume of blood loss of 1500mL into our definition, I believe we likely have reduced this risk of selection bias. Given the absence of other data in this field, the results of this cross-country study (Chapter 4) provide valuable information on the management of severe forms of obstetric hemorrhage and SMO.

B) Formulation of a uniform definition of both PPH and severe PPH

The current lack of consensus on the definition of both PPH and severe PPH was highlighted by our comparative review of PPH-guidelines (Chapter 2). Variations between definitions of PPH include the following three aspects.

First, the volume of blood loss. The average volume of postpartum blood loss being around 300-350 mL, the World Health Organization (WHO) defines PPH as blood loss of more than 500 mL. Some guidelines apply a 1000 mL cut-off assuming healthy pregnant women may tolerate blood loss of up to 1000 mL without any significant hemodynamic complications, whereas a 500 mL cut-off may increase the use of unnecessary interventions.(2–4) At the same time, using a definition based only on volume of blood loss has been criticized by several authors as such definitions appear to be poor predictors of SMO.(5–7) Furthermore, this definition depends strongly on the method of blood loss measurement. Visual estimation is known to underestimate higher volumes of blood loss, to the disadvantage of a 1000mL cut-off while overestimating lower volumes of blood loss, to the disadvantage of a 500mL cut-off.(8–10) Given that blood loss quantification has also

shown to be feasible and effective in reducing hemorrhage related morbidity in low-and middle income settings, blood loss quantification by either a gravimetric or a volumetric tool, or a combination of both, could be part of a universal definition. Limited data are available on which type of blood loss quantification (calibrated collection drape, a measuring jug or weighed blood soaked swabs and linen) is best.(10–12) One randomized controlled trial of 900 women conducted in India reported that using a volumetric method (calibrated drapes) improved the detection of blood loss greater than 500 mL when compared with the gravimetric technique (RR 1.86, 95% CI 1.11 to 3.11). However, the study setting and patient population cannot simply be copied to high-resource settings. Therefore, in the absence of high quality data, none of the methods of blood loss quantification can be recommended over another.(10,13)

Second, mode of birth. Historically, the WHO defined PPH as blood loss of more than 500 mL after

vaginal birth and more than 1000 mL after cesarean birth based on findings that the average amount of blood loss was higher during cesarean section.(14) This definition has nevertheless been abandoned today by the WHO and most other clinical practice guidelines. Several studies have reported an increased blood loss for (emergency) cesarean section as compared to vaginal birth. However, having two different thresholds for each route of birth masks the difference and thus the fact that cesarean section is an important risk factor for obstetric hemorrhage. (2,9,15–18)

Third, the cardiovascular response of the woman. To account for this response, several professional societies have proposed to include clinical signs of hypovolemia such as tachycardia, tachypnea and hypotension into the definition of PPH.(16,19,20) However, maternity care workers should be aware that inclusion of these parameters can be misleading as these appear late in the course of hemorrhage. Due to an increase in intravascular volume by approximately 50% (i.e. 4–6 L) in pregnant women, blood loss can be considerable before vital signs of hemorrhagic shock, such as tachycardia and hypotension become apparent.

In line with aforementioned elements, I suggest that a universal definition of PPH should include the following elements. First, it should include a specific volume of quantified blood loss either by a volumetric or gravimetric method. For global use, a 500 ml cut-off may be more appropriate to overcome delays before management is initiated in settings facing logistic challenges. To avoid unnecessary interventions in healthy women giving birth in a context with easy access to qualitative care, a

500 mL cut-off could still be of use by providing a trigger for *alert.* These settings could then apply a second cut-off for *action* (for example 1000 mL) at which initial management is started immediately. Second, the definition should be irrespective of mode of birth to avoid masking any differences in terms of hemorrhage risk factors related to mode of birth. Third, it should include the physiological response of the woman to the bleeding by including early clinical signs of hypovolemia such as heart rate, respiratory rate, shock index and clinical signs/symptoms of internal bleeding.

In addition to the absence of a common definition for PPH, Chapter 2 also brought to light important variations with regards to the definition of severe PPH among clinical practice guidelines. Several authors have tried to propose a universal definition for severe PPH. An international multidisciplinary panel agreed to define severe PPH by the term 'persistent hemorrhage' by adding a 'response to treatment' to their definition: *Active bleeding >1000 mL within the 24 hours following birth that continues despite the use of initial measures including first-line uterotonic agents and uterine massage."*(7) Henriquez et al. found that a large proportion of women fulfilling this definition were captured at an *early* stage of hemorrhage as compared to definitions based only on blood loss volume or transfusion. The definition also appeared to be a good predictor of women suffering adverse maternal outcome (in the study of Henriquez et al. 430/471 women with adverse maternal outcome were captured by this definition).(21) According to the same study, a definition based on volume of blood loss alone (>1000 mL) would capture all women with adverse maternal outcome, but at a *later* stage of hemorrhage, exposing more women to the downsides of unnecessary invasive interventions. The International Network of Obstetric Surveillance Systems (INOSS) proposes to define severe PPH as '*postpartum blood loss exceeding 2000 mL AND/OR the need of transfusion of at least four units of red blood cells, within 24 hours after end of pregnancy, in a pregnancy of at least 20 weeks of gestational age*'.(22) The use of therapeutic measures in this definition may limit universal use, given these largely depend on medical culture and available resources. This has also been reported by Brenner et al., who explored the utility of several PPH outcome measures by using data from the WOMAN-2 trial. They report a lower specificity for intervention-based outcomes such as blood transfusion, intravenous fluid administration and use of uterotonics as compared to the shock index, probably because some of these interventions were being performed routinely in the study population.(23) Other authors have suggested to define severe PPH by using a calculated amount of blood loss based on laboratory parameters to overcome limitations of blood loss quantification. They hypothesize that calculated blood loss may be more reliable as blood loss quantification may *underestimate* blood loss in case of uncollected

blood loss or *overestimate* blood loss because of the mixing of blood with amniotic fluid, Although different formulas exist to calculate blood loss, Madar et al. did not find a difference in calculated blood loss depending on which formula was used.(24) Quantified blood loss tends to be lower than calculated blood loss particularly with increasing volumes of blood loss (> 1000mL), making it an interesting outcome in the context of more severe forms of PPH.(2,24) Although calculated blood loss is not of value in clinical practice since not immediately available, it may provide a more objective outcome of the severity of bleeding, and may be used for research purposes.(24,25) Ideally, such scientific definitions should capture all women with SMO. According to Henriquez et al., defining severe PPH by *estimated blood loss of >1000mL* would capture all women with SMO whereas an increased amount of blood loss as a threshold would not.(21) Following the findings of Madar et al., a quantified volume of blood loss of 1000mL would correspond to approximately 2000-3000 mL of calculated blood loss.(24) However, caution is needed as calculations may be biased by maternal pathologies such as hypertensive disorders.(26) Further studies are necessary to evaluate the most appropriate threshold of calculated blood loss as a predictor for SMO.

In chapter two, we report that only 4 of 8 guidelines provide a definition for severe PPH. However, the presence of a definition for severe PPH in guidelines may have several advantages. First, it can improve the conduct of clinical trials by focusing either on women with PPH or severe PPH, given these women do not have the same risk profiles. Second, it can improve guidance in terms of management of both PPH and severe PPH by avoiding second-line management of obstetric hemorrhage such as the use of sulprostone among women with mild PPH and by earlier escalation for women in whom initial management fails. While working as a resident in both France and the Netherlands, I felt that the presence of a definition for severe PPH in the French guideline increased awareness among maternity care workers in France regarding severity of the bleeding. To me, this seemed to result in earlier detection of severe PPH and more rapid escalation to second-line and third-line management of PPH as compared to the Netherlands, where the absence of such a definition in my observation resulted in reduced awareness among clinicains and a more ‘sequential’ way of applying interventions to treat hemorrhage, with longer time gaps between interventions. My observation was confirmed by the findings of Chapter 4, reporting longer time gaps between the failure of initial PPH-management and the administration of second-line uterotonics in the Netherlands as compared to France. As for increased awareness towards the failure of ‘initial management’: a landmark study from the WHO and the University of Birmingham has reported its impact on maternal outcome. This study showed that the implementation of simple methods to quantify blood loss

combined with a bundle of first-line and second-line treatment options of PPH, reduced the risk of severe bleeding by 60% and women were less likely to die. They also report a significant decrease in the use of blood transfusion. The early detection of bleeding complemented by an immediate management bundle to treat hemorrhage reduced delays to escalate to more advanced care. (12)

To define severe PPH, I suggest distinguishing a clinical definition to guide clinicians facing severe hemorrhage and a scientific definition for a quantitative and more objective estimate of the volume of blood loss and as a proxy of SMO. For the universal clinical definition for severe PPH, I would recommend a definition without the use of intervention-based outcomes, as stressed by the experts in our binational review (Chapter 5). The definition of persistent hemorrhage as presented above could be used in all clinical settings and guide clinical management, allowing for differentiation between women at increased risk of SMO (justifying escalation of management) and those who are not. As a scientific definition, I would rather suggest using a definition based on calculated blood loss. According to the studies of Madar and Henriquez, a cut-off of 2000 mL of calculated blood loss would include the majority of women with SMO.(21,24)

C) An international guideline to improve the implementation of evidence

Although the different recommendations in terms of clinical management among the included guidelines in our study may reflect the paucity of high-quality data, this may also be partly explained by suboptimal guideline development. I assessed the quality of the guidelines through The Appraisal of Guidelines, Research and Evaluation revision (AGREE-II), and brought to light a moderate quality of some guidelines (Chapter 2), mainly due to suboptimal rigor of development, absence of editorial independence and lack of clarity in the formulation and visualization of recommendations.(27) Even though I reported that half of the guidelines were of high quality, some recent studies suggest that high AGREE-II scores do not ensure that recommendations are optimal.(28) For example, a guideline may be scored as a high quality guideline on the AGREE-II tool despite a lack of guidance on how to adhere to these high quality recommendations which could result in suboptimal guideline implementation.(29) In this light, the most recent FIGO guideline on PPH recommends that every maternity care hospital needs to '*adopt a hemorrhage bundle and train to all elements of these bundles, from arrival on obstetrics service to transfer to higher level of care'.*(30–33) These bundles represent a selection of recommendations from existing guidelines and the 'bundle' form would improve guideline implementation in daily practice. Such elements are not necessarily evaluated by the AGREE-II tool.

To improve guideline quality and adherence, we stress the need for a collaborative effort to develop an international guideline on the management and prevention of PPH (Chapter 2). An attempt to arrive at an international consensus for guidance on the management of PPH in high-resource countries has been made by the Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis (NATA), the International Federation of Gynaecology and Obstetrics (FIGO), the European Board and College of Obstetrics and Gynaecology (EBCOG), and the European Society of Anaesthesiology (ESA).(34) However, in practice, the use of consensus statements remains limited, and certainly more limited than clinical practice guidelines, given the lower level of evidence-based support and the absence of algorithms and stakeholder participation, reducing the probability of uptake.(35–37) An international high-quality guideline that could be of interest is the guideline from the WHO which is regularly updated and subject to a rigorous assessment of evidence.(38) Nevertheless, uptake of WHO guidelines has shown to be challenging both in low- and middle-income as well as in high-income settings. Saluja et al. suggested this may be explained by the fact that WHO guidelines are too long and too technical, lacking adequate implementation plans.(39) Furthermore, in high-resource settings, recommendations from the WHO-guideline may be of limited use as available resources and access to all care options available in these settings are only taken into account to a limited extent.(40) Recognizing these challenges, the FIGO published in 2022 an extensive document with recommendations on the prevention and management of PPH, providing more precise tools for guidance implementation in the form of PPH bundles. However, the authors yet again address their recommendations specifically to low- and middle-income countries. (30)

On their website, the WHO states that their guidelines are designed to *'help end-users make informed decisions on whether, when and how to undertake specific actions such as clinical interventions, diagnostic tests or public health measures, with the aim of achieving the best possible individual or collective health outcomes'*. That being said, there may be an interest for an adaptable guideline in which the WHO guideline serves as a standard with PPH recommendations and bundles tailored to different contexts. Collaborative multi-national platforms such as the INOSS could engage in translating WHO recommendations to high-resource settings by starting a participatory process with women and local professionals to improve guideline-implementation.

2. Uterine-sparing interventions: adequate indicators to benchmark hemorrhage-related maternity care?

To benchmark hemorrhage-related maternity care and maternal outcome, measurement indicators are necessary, as displayed in the PLAN-step of my benchmarking cycle. Several professional organizations and stakeholders such as the WHO and EURO-PERISTAT propose sets of core indicators, generally divided in critical care intervention-related indicators and maternal outcome-related indicators. (41,42) Critical care interventions are those required in the management of life threatening and potentially life-threatening events. Maternal outcome indicators generally refer to mortality and severe maternal morbidity but can also refer to less severe adverse maternal outcome. (43–45)

In table 2 of chapter 1, one can see that recommendations on uterine-sparing interventions vary between France and the Netherlands, making these relevant critical care intervention indicators to benchmark the quality of hemorrhage-related maternity care between both countries. Kayem et al. suggested that a high rate of uterine-sparing therapies to treat obstetric hemorrhage could reflect an increased incidence of severe PPH, leading to both an increased need for uterine-sparing interventions and more adverse maternal outcome.(46) However, my data (Chapter 4) challenge this hypothesis, as I demonstrate a higher incidence of severe PPH (defined as: (total blood loss ≥ 1500 ml and blood transfusion of ≥ 4 units of packed red blood cells AND/OR multicomponent blood transfusion)) and increased adverse maternal outcome (defined as a composite of bleeding ≥ 2.5L, hysterectomy and mortality) in the Netherlands, despite later and fewer instances of uterine-sparing interventions. Perhaps this may be explained by the fact that I assessed the use of these indicators among a selected population that already had severe PPH. For instance, the use of uterine-sparing interventions among all women with obstetric hemorrhage in the Netherlands could hypothetically be higher than I reported in Chapter 4 if among these women bleeding had been stopped by uterine-sparing interventions before they met the inclusion criteria of our study. However, this is unlikely as the source population including women with milder forms of PPH (total blood loss ≥ 1000 ml) and (blood transfusion of ≥ 4 units of packed red blood cells AND/OR multicomponent blood transfusion) showed similar trends in the marginal use of uterine sparing interventions. Therefore, my findings could also suggest that a low use of uterine-sparing interventions among women with severe PPH such as reported in the Netherlands indicate that management could be improved by resorting to these interventions earlier in the course of hemorrhage.

If my hypothesis is correct, this would indicate that the higher hemorrhage-related MMR as reported by enhanced obstetric surveillance data in France as compared to the Netherlands is more likely to be explained by a failure in the management of

obstetric hemorrhage at the near miss stage, thus, after uterine-sparing interventions to arrest bleeding have been applied. According to our binational review in Chapter 5, this could be the result of organizational aspects such as a lack of communication, poorly organized transfer of the critically ill patient, and much larger distances in France. Another explanation could be that other components of management, such as critical care management, are of lower quality in France. In chapter 5 I report a delay in transfusion management in 5/7 women who died from obstetric hemorrhage in France versus 4/7 in the Netherlands yet the low number of maternal deaths included in our study does not allow to draw any conclusions on a potentially lower quality of critical care management in France. Nevertheless, chapter 6 reveals that although critical care in France improved over time among women who died from obstetric hemorrhage after implementation of the national PPH guideline, there are still opportunities for improvement related to critical care.

In chapter 4, I also compared maternal outcome indicators between countries. Interestingly, the incidence of a composite of adverse maternal outcome (bleeding ≥ 2.5L, hysterectomy and mortality) among women with severe PPH was higher in the Netherlands as compared to France, mainly due to a significantly higher incidence of major bleeding (≥2.5 L). These findings have to be balanced against the fact that peripartum hysterectomy was less frequently performed in the Netherlands compared to France regardless of mode of birth. This raises the question: is it worse to have a larger volume of blood loss without hysterectomy or a smaller amount of blood loss but a hysterectomy?

A major problem pertaining to peripartum hysterectomies and uterine-sparing interventions are the length of the time gaps present in the sequential manner in which these are performed. When do you determine that an intervention failed, justifying escalation of management? Indeed, the problem is: if you would have waited, accepting some additional blood loss, you might not have needed these interventions. It is indeed interesting to see that despite the larger volumes of blood loss among the women in the Netherlands, rates of peripartum hysterectomy were lower than those in France. Among the women with extreme blood loss (>8L) (n=41) in the Netherlands, only half had a peripartum hysterectomy (Chapter 4). Future research may assess the association between the volume of blood loss and other indicators of adverse maternal outcome such as ICU admission, acute kidney injury and posttraumatic stress. It should also assess these outcomes among women who had a hysterectomy for postpartum hemorrhage.

In summary, although uterine-sparing interventions reveal important differences in the management of obstetric hemorrhage between countries, these interventions

may not be the optimal indicators of the quality of hemorrhage-related maternity care given the conflicting results as to whether or not a high incidence of these interventions actually reflects lower quality of care. In the meantime, an extensive list of auditable indicators has been proposed by European Board and College of Obstetrics and Gynaecology.(47) Among these indicators, the following organ dysfunction-based indicators could be used to benchmark the quality of hemorrhage related maternity care, in order to avoid measurement issues due to differences in practice: disseminated intravascular coagulation, post-partum hysterectomy, renal failure (due to hypovolemia), cardiac arrest, and hemorrhagic shock.

3. Reducing the length of the third stage of labor: an opportunity to reduce hemorrhage-related adverse maternal outcome?

While working as a clinician in both France and the Netherlands, I noticed a more interventionist approach during the third stage of labor in France compared to the Netherlands. I observed that uterine massage, cord clamping and uterine exploration as well as manual removal of the placenta were performed in earlier stages of PPH in France as compared to the Netherlands. Particularly uterine exploration and manual removal of the placenta were, it appeared to me, performed at a relatively low threshold. My observation can perhaps partly be explained by the fact that uterine exploration and manual placenta removal in France can be performed by midwives under epidural analgesia at the labor ward while in the Netherlands these interventions are generally performed by the obstetrician under general anesthesia in a surgical theatre. This fact, as well as the earlier stated higher prevalence of the use of epidurals in France as compared to the Netherlands, might induce a lower threshold to perform manual removal of the placenta in France.(48,49) However, given the inconveniences for the woman, I wondered whether there was a benefit in terms of maternal outcome in case of earlier manual placenta removal. These reflections gave rise to the systematic review in Chapter 3 on the length of the third stage of labor and its association with adverse maternal outcome. The necessity of such a review was also emphasized by the lack of consensus on the optimal length of the third stage of labor.(50–52)

The main limitations of Chapter 3 relate to the reported heterogeneity and the proportion of included studies that have a high risk of bias. I reported a low P-value for the χ^2 test of heterogeneity, suggesting significant statistical heterogeneity. This means that although the included trials seemed to measure the same outcome, the results were not always consistent with regard to the size of the reported benefit

for a reduction of the third stage of labor. To address heterogeneity, I performed several subgroup analyses.(53) Although these explained some of the reported heterogeneity, the latter remained present in some of the analyses probably due to methodological issues among the included studies such as differences in study design and patient population. The high risk of bias was mainly due to the fact that women in the included studies were included independently from the cause of bleeding and based on visual estimation of blood loss in some studies which has been shown to underestimate blood loss of ≥500 ml by 30–50%.(8,9,54) In addition, pooling of studies was difficult due to various definitions of adverse maternal outcome. Recently, several authors have suggested that meta-analyses should also include a prediction interval; an 'interval within which the effect size of a new study would fall if this study was selected at random from the same population of the studies already included in the meta-analysis'.(55,56) Indeed, for clinicians, this prediction interval may provide more relevant information as it tells us how a certain effect varies among the population thereby reflecting the uncertainty of the effect of the inclusion of a new study on the overall summary results of the meta-analysis. Although I report an odds ratio of 5.5 for PPH among women presenting risk factors for PPH (previous PPH, primiparity, obesity, prolonged or augmented labor, multiple pregnancy, previous cesarean section, polyhydramnios and macrosomia), the prediction interval showed a wide range of variability (0.02 to 32), suggesting that the risk of PPH in future studies might be very different. The wide range could also reflect an imprecise estimation of the summary effect size due to the reported heterogeneity. Although some may argue that the results from the prediction interval could have been an argument to only perform a narrative synthesis of the results of our systematic review, I think that the findings of Chapter 3 still provide relevant conclusions, taken into account that these need to be drawn cautiously.

The findings of my systematic review suggest it may be time to adjust the duration of the third stage of labor from the finding that the risk of both mild and severe PPH increases five-fold once the third stage of labor exceeds 15 minutes, particularly among women with risk factors for PPH. The pathophysiology of a 'prolonged' third stage of labor, induced by retained placenta, is unknown. Three major mechanisms have been suggested: (1) inadequate myometrial contractility (2) placental hypoperfusion (3) invasive placentation.(57,58)

The first hypothesis derives from studies suggesting that some women may be predisposed to retained placenta due to localized retroplacental contractility failure. A study among 250 women in Denmark reported a recurrence risk as high as 25%. Advanced maternal age or the presence of fibroids might be explanatory

factors.(58–61) Some studies have suggested that contractility failure may follow prolonged use of oxytocin during labor either as a result of oxytocin-induced oxidative stress, making the placenta more 'vulnerable' to retention or by directly altering myometrial contractility.(57) However, these findings may be compounded by the presence of chorioamnionitis complicating prolonged labor. Active management of the third stage of labor, including the use of prophylactic oxytocin, is recommended to facilitate spontaneous placental separation.(62) Although active management reduces the duration of the third stage of labor, a randomized controlled trial did not confirm a reduction of the incidence of retained placenta.(63) Oxytocin, in various forms of administration, has also been suggested as a pharmacological treatment for the impaired contractility of the myometrium to expulse the placenta. However, to date, there are no data supporting the efficacy of uterotonics in this context.(58,64,65)

The second hypothesis is strengthened by findings from a case–control study in Sweden reporting an increased association between retained placenta and placental hypoperfusion due to pathologies such as preeclampsia and fetal growth restriction.(66)

The third mechanism results from previous uterine trauma such as prior cesarean section and assisted reproductive technology which increase the risk of invasive placentation and thus the risk of adherent placenta. (67,68)

These three hypotheses refer to classical risk factors for PPH (history of retained placenta, pre-eclampsia and history of uterine trauma) which strengthens the conclusion of my systematic review that earlier intervention may be particularly relevant among women with risk factors for PPH as they may have an increased risk for retained placenta.

Despite the potential benefits of a reduction of the third stage of labor in terms of SMO, I did not find any robust evidence that earlier manual placenta removal reduces this risk of SMO. Also, manual placenta removal is an inconvenient intervention for the woman and may be associated with complications. Evidence of endometritis following manual or surgical removal of retained placenta has been inconsistently demonstrated and so has the role for prophylactic antibiotics during manual placenta removal to reduce this risk.(47,48) Some authors have stated that manual removal of the placenta itself increases the risk of PPH by inducing uterine atony but I did not find data supporting such a statement in women giving birth vaginally.(69,70) However, such a mechanism has been reported in case of cesarean section where routine manual removal of the placenta seems to be associated with

a higher risk of blood loss, PPH and blood transfusion as compared to spontaneous placental birth.(71,72) Others have stated that manual placenta removal may result in lesions to the genital tract or intra-abdominal lacerations, yet these data are derived from case reports and such lesions seem to be rare if the procedure is performed by a skilled birth attendant.(73,74) Systematic inspection of the genital tract after performing a manual removal of the placenta, may detect lacerations early. I did not find any data on women's experiences of manual placenta removal in absence of severe PPH, which itself can be a traumatic event for women and their partners.(75) Many women experience labor related morbidity in the postpartum period, and levels of postpartum anxiety and depression have been reported as high as 9—24% and 11-17% respectively.(76) The impact of earlier placenta removal on the 'Golden Hour' after birth needs to be further evaluated.

The analgesia provided for manual removal of the placenta and uterine exploration also requires reflection.(69,77,78) Effective anesthesia during manual removal of the placenta may reduce delays by improving uterine relaxation and pain control. These findings are supported by Chapter 4 and 5. A recent Cochrane review addressing which anesthetic technique should be applied for manual removal of placenta identified only one randomized controlled trial evaluating two different methods of pain management of women undergoing manual removal of a retained placenta. The authors therefore concluded there is currently insufficient evidence as to which anesthetic technique should be applied when performing these procedures, emphasizing the need for 'well-designed, multi-center, randomized, controlled trials to evaluate the effectiveness and safety of different types of anesthesia and analgesia during manual removal of a retained placenta'.(79)

I did not find any studies comparing delay between vaginal childbirth and manual placenta removal according to mode of anesthesia and how this relates to maternal outcome. Nevertheless, to reduce any delays before manual placenta removal, the experts in my binational review (Chapter 5) recommended that manual placenta removal could be safely performed at the labor ward with an epidural already in place, since this is the faster option and without the risks associated with general anesthesia, such as airway compromise and aspiration.(69,77,78) However, before implementing such a recommendation, potential downsides need to be explored such as the need of increased availability of anesthesiologists at the labor ward and training of midwives or nurses to assist during the intervention. Also, more data are needed on patient satisfaction and intraoperative discomfort regarding the different types and routes of analgesia during this procedure. Current practice and data may be highly biased by cultural beliefs. For example, when I came back from France to the Netherlands, many anesthesiologists found my proposition to

perform manual placenta removal or uterine exploration under spinal or epidural analgesia rather 'veterinary', whereas during my stay in France such practice had been considered standard care. Women may have similar or different ideas, and these should be considered.

Ultimately, given the potential inconvenience related to earlier intervention to reduce the third stage of labor, systematic manual removal of the placenta cannot be recommended (Chapter 3). However, I propose increased vigilance for signs of bleeding, particularly among women presenting with risk factors for PPH in case the third stage exceeds 15 minutes. Obstetricians should be aware that among these women, earlier manual placenta removal might outweigh the downsides of the intervention once bleeding goes beyond physiology. In contrast, in low-risk women, expective management is justified in settings with easy access to operating rooms and blood products. For countries such as the Netherlands, this is relevant as the impact of earlier intervention may highly affect the management of low-risk women with physiological birth, who give birth at home or in a birth center with a primary care midwife, as these women would need earlier and more frequent transfer to second-line care.

In the future, randomized controlled trials should be designed particularly among women with risk factors for PPH. It would be interesting to investigate whether SMO decreases when manual removal of placenta is performed at 15 minutes instead of 30 minutes. Women with risk factors for PPH could be pre-included before birth. Randomization into one of the treatment arms (TSL >15 minutes or TSL > 30 minutes) could happen once the inclusion criterion of a third stage of labor of 15 minutes is reached. Primary outcome could be adverse maternal outcome (defined as PPH (blood loss >500 mL) and/or severe PPH (calculated blood loss >2000mL) and/or blood transfusion and/or peripartum hysterectomy and/or mortality. Secondary outcomes could address patient satisfaction, complications due to anesthesia for the intervention and treatment costs. Taking into account a 10% anticipated protocol deviation and 1% losses-to-follow-up, 850 women would be required per group if we would want to detect a 33% difference in adverse maternal outcome (based on the pooled incidence in our systematic review) between the two treatment arms (two-tailed [alpha] = 0.05, [beta] = 0.2). Based on the natural log distribution of spontaneous placenta birth following an active third stage of labor among the general population of pregnant women, 16% of women giving birth vaginally will have a third stage of labor of >15 minutes and 7% of women >30 minutes.(80,81) In a population with risk factors for PPH, probably even fewer women will arrive at a third stage of 30 minutes as signs of bleeding may necessitate intervention before this cut-off. To arrive at sufficient power, this RCT

would therefore ideally be performed in a multi-center setting. However, while discussing with different maternity care workers in France, the Netherlands and Switzerland about such a trial, the willingness to participate varied. For midwives in the Netherlands, the primary argument not to participate was the discontinuity of care, whereas this downside would not exist for midwives in France, who are allowed to perform themselves manual removal of placenta. In Switzerland, willingness to participate was particularly low among anesthesiologists as they feared that the trial may have logistic consequences during night shifts when human resources may be reduced. Therefore, before setting out to perform such a challenging trial, we suggest performing a cross-sectional feasibility study by sending out surveys among obstetricians, midwives and anesthesiologist in several countries that would be eligible for participation to assess willingness to participate.

4. Improved time-management of interventions in the course of hemorrhage – a tool to reduce hemorrhage-related adverse maternal outcome?

To assess whether certain management strategies for obstetric hemorrhage resulted in more frequent failure to stop severe bleeding, which could explain differences in hemorrhage-related SMO, I benchmarked the identified measurement indicators concerning both maternal outcome and critical care intervention indicators through quantitative and qualitative analyses in the DO-step of our benchmarking cycle.

Enhanced data from national surveillance systems have shown a MMR due to obstetric hemorrhage between 2013-2018 of 0.9 per 100,000 livebirths in France versus 0.4 per 100,000 livebirths in the Netherlands. In contrast with these data, my comparative study of women with equally severe PPH in the Netherlands and France (Chapter 4), revealed an increased incidence of SMO among women with severe PPH in the Netherlands as compared to France. Furthermore, I reported more maternal deaths in the Netherlands after vaginal birth. Although this difference was not statistically significant, my study was probably not powered to arrive at such a result. The reported differences in terms of maternal mortality in my observational study as compared to data from the Netherlands Audit Committee may be explained by the absence of linkage of enhanced data from the surveillance system with vital statistics for the period 2011-2023 in the Netherlands, resulting in underreporting of maternal deaths. Underreporting was also confirmed by a Dutch study identifying three maternal deaths due to obstetric hemorrhage between 2006 and 2019, which were not reported to the confidential enquiry.(82) These findings have perhaps contributed to the recent introduction of a

crosslinking system in the Netherlands. This is an important achievement as the limitations of enhanced systems without data linkage for maternal death case finding were also brought to light by a recent study from INOSS comparing enhanced data on maternal mortality data from eight countries.(83) Another explanation could be that while the EPIMOMS study only included women from the French territory without the overseas departments, the ENCMM, in contrast to Netherlands Audit Committee, also includes maternal deaths from overseas departments (Réunion, Guadeloupe, Martinique and French Guyane). Given that the MMR in these overseas departments is higher than in metropolitan France (2.6 versus 0.8 per 100,000 livebirths) this could also partly explain why the hemorrhage-related MMR in France is higher as compared to the Netherlands and why I was not able to confirm this fact in Chapter 4.

The increased use of uterine-sparing interventions reported in Chapter 4 in France did not result in a reduced hysterectomy rate in this country, which was nearly double as high as compared to the Netherlands. A study conducted through INOSS, reported an incidence of peripartum hysterectomy in France as compared to the Netherlands of 5.4 versus 2.7 per 10,000 births respectively and our findings are in line with these data.(84) The authors reported a strong correlation between national cesarean section rates and prevalence of peripartum hysterectomy. Nevertheless, national cesarean section rates in France (21%) and the Netherlands (17%) are comparable and not likely to explain the considerably different hysterectomy rates reported in my study. This was confirmed by the analyses according to mode of birth, which showed that the reported differences in terms of hysterectomy between both countries are not likely explained by the fact that more women with severe PPH in France gave birth by cesarean section. The increased use of peripartum hysterectomy and uterine-sparing interventions in France as compared to the Netherlands may also be another reflection of the more 'interventionist' approach of obstetricians in France which I observed at several stages of PPH management. For example, 17 women in France -who were not included in my study due to blood loss <1500mL- had a peripartum hysterectomy. Causes of blood loss among these women were various and this finding could therefore not be explained by these hysterectomies being 'elective' during cesarean section because of accreta spectrum disorders. This suggests that obstetricians in France perhaps anticipate too soon, not waiting for the effect of second-line uterotonics that would have arrested bleeding without further intervention if only given the time to act, thereby exposing women to the downsides of these interventions such as bladder injury and loss of fertility. On the other hand, obstetricians in the Netherlands may have too high a threshold to perform this type of procedure, and prefer to resort to non-surgical options such as radiological

artery embolization and intra-uterine tamponade to treat severe PPH. This may be compounded by the broad implementation of minimally invasive procedures and centralization of advanced surgical gynecological procedures, resulting in a decrease in surgical skills among young residents.(85,86) In addition, resident graduates in the Netherlands are currently encouraged to 'sub' specialize during two years after four years of basic gynecology training. Although this allows for highly developed skills in their domain of interest (i.e. oncology, urogynecology, obstetrics etc.), drawbacks are decreased surgical exposure outside the chosen sub specialization.

The experts in our binational review stressed that among the majority of fatal cases due to PPH in the Netherlands, surgical management including peripartum hysterectomy was only marginally explored (Chapter 5) and could have been considered earlier. They stressed the need to involve an experienced obstetrician with advanced surgical sills in case hemostatic surgery might be needed. As peripartum hysterectomies remain rare events, attending planned complex surgery and simulation training might be relevant to maintain and improve these skills (Chapter 6).(85,87,88) This was also highlighted by the findings of Chapter 6, in which I reported that also among obstetricians in France, there is a need to improve surgical skills.

The more rapid escalation in the course of PPH management in France was confirmed by the timing of uterine-sparing interventions in France in my study. I report a longer time frame between the moment that first line-management of PPH fails and administration of second-line uterotonics in the Netherlands as compared to France. This could perhaps partly explain why women in the Netherlands have higher volumes of blood loss at the time of the first uterine-sparing intervention in the course of bleeding. The importance of timely treatment has also been demonstrated in a Canadian cohort of 3300 vaginal births, reporting that each 5-minute additional delay in the administration of a second-line uterotonic was associated with higher odds of hypotension and transfusion.(89) Along the same line of thought, uterine-sparing interventions are applied later in the course of refractory PPH in the Netherlands. Although I did not calculate a correlation coefficient between the timing of the uterine-sparing interventions and the total quantity of blood loss, my findings suggest that an increased time frame between the moment first-line management fails and sequential management with second line uterotonics and uterine sparing interventions may result in a higher volume of blood loss.

Additional blood loss beyond a critical threshold may subsequently result in coagulopathy and more SMO. Nevertheless, some may disagree to use blood volume as an indicator for SMO, given that the volume of blood loss 'tolerated' depends on a woman's clinical features. For example, total blood volume is determined by height and weight but altered by the presence of fat tissue which is relatively non-vascular. In shorter patients with a high BMI, the blood volume during pregnancy does not increase proportionally due to the presence of adipose tissue which can result in an underestimation of the clinical effects of blood loss, leading to inadequate resuscitation and false reassurance.(90,91) Thus, one might argue that higher volumes of blood loss may to some extend be accepted in the absence or presence of certain patient characteristics, if inconvenience for the woman is limited. As such, one may choose to accept additional volumes of blood loss in a healthy woman by balancing possible complications of more transfusion therapy and a longer hospital stay against loss of fertility. As stated above, further observational studies are necessary to describe clinical outcomes of women with significant blood loss.

The major weakness of the quasi-experimental study design applied in Chapter 4 is the lack of randomization. Although my study suggests certain associations between the different interventions preceding the measurement of maternal outcome, the inability to sufficiently control for important confounders implies that we cannot demonstrate causality between the timing and use of uterine-sparing interventions and adverse maternal outcome stressing the need for additional evidence on timing and sequence of interventions. Given the possible benefits such as increased awareness on severity of bleeding and improved data collection, we would advocate for the use of timelines when reporting the chain of events in the course of PPH. Such timelines are currently used in France and were highlighted by the experts of our binational confidential enquiry (Chapter 5) as a major strength of the French PPH management.

Part II. Obstetric hemorrhage: reducing preventability by exploring subgroups of women with fatal obstetric hemorrhage

5. Hemorrhage-related maternal mortality: can lessons be learned from national and international reviews of hemorrhage related maternal deaths?

In France, the hemorrhage-related maternal mortality ratio has been decreasing over the last decade. Explanatory factors have not yet been clearly identified but are likely to relate to increased awareness about obstetric hemorrhage and implementation of clinical practice guidelines. However, as visualized in figure 1 of

the introduction, the MMR in France is still higher as compared to the Nordic countries and the proportion of women in whom death could possibly have been avoided, still suggests areas for care improvement.

I hypothesized that a binational qualitative review of hemorrhage-related maternal deaths could be an additional method to improve hemorrhage-related maternity care by reviewing cases through a different "contextualist" framework by experts from two different care contexts. Given that France and the Netherlands have implemented a permanent enhanced obstetric surveillance system in 1995 and 1981 respectively, I organized a binational confidential review of fatal obstetric hemorrhages (Chapter 5). This review gave rise to the detection of improvable care factors not yet identified by national reviews by experts having a different context of care.(92)

Although Chapter 5 clearly shows the benefits of data sharing on rare events such as maternal mortality, the collaboration between enhanced surveillance systems is hampered by several administrative barriers.(92,93) I experienced such barriers in my binational review as data exchange was challenging due to concerns about privacy and confidentiality. Action is needed from governments and other stakeholders to support and facilitate collaboration between countries and enhanced obstetric surveillance systems to ensure high-quality data collection and facilitate exchange. Also, I emphasize the need of having a clinician who is familiar with both health care systems when organizing binational confidential reviews for three reasons. First, to provide relevant background information on health care systems in participating countries to improve understanding around certain management strategies. Second, to overcome language barriers and capture relevant subtilities in medical records to be read 'between the lines'. Third, to direct the discussion towards specific targets and provide clarifications where necessary. The need of having a clinician familiar with both healthcare systems was omnipresent among the experts in our binational review. I was happy to fulfil this role and noticed the importance of my experiences and observations from both countries to facilitate the discussion between the experts.

Other areas for obstetric hemorrhage care improvement may be identified by exploring the uptake of recommendations on the management of obstetric hemorrhage. The monitoring of the response of implemented interventions is an essential element in the continuous cycle of care improvement according to the WHO's maternal death surveillance and response system.(94) In Chapter 6, I evaluated to what extent the implementation of the French national guidelines on PPH from 2004 led to a modification of clinical care by evaluating a more recent

cohort of women who died from obstetric hemorrhage.(95) In Chapter 6, I studied only extreme events (i.e. maternal deaths), which has its downsides. Indeed, Souza et al. suggest that the study of maternal deaths may no longer be sufficient, emphasizing to expand the focus not only to severe morbidity but also towards a more global approach of maternal wellbeing.(96) Despite these drawbacks, I still feel that confidential enquiries remain a valuable way to evaluate guideline implementation. Indeed, our study reports an improvement in many aspects of critical care in these extreme cases such as improvements in hemodynamic continuous monitoring and transfusion management. The findings of Chapter 6 are also relevant outside France and provide evidence for the efficacy of general awareness of PPH among clinicians and other stakeholders.

My data show that implementing a recurring audit cycle can provide crucial information on the implementation of previously formulated recommendations (Chapter 6). Also, the results add to the understanding of improvements that can still be made. By assessing trends by trienniums, as is currently done in France, more robust comparisons can be made as compared to the assessment of trends by decades. However, this may be challenging for some countries such as Switzerland and the Netherlands, given the small number of maternal deaths in these countries. Such countries may reflect on possibilities to perform a surveillance of indicators of severe morbidity. ^

Other challenges exist about the monitoring of uptake of recommendations. Indeed, the lack of human and financial resources to perform such evaluations complications this task.(97,98) Financial support from national health authorities and active stakeholder participation, which may include established professional associations such as national associations of gynecology and obstetrics, national health related advisory committees and women's associations, may increase uptake of recommendations and facilitate their monitoring. As such, the Italians performed an observational study to assess adherence to a PPH bundle, including the promotion of multidisciplinary facility-based clinical audit of severe hemorrhage, distance-learning activities on prevention and treatment of PPH, and a national evidence-based guideline on PPH, which was implemented after enhanced data revealed a four times increased hemorrhage-related MMR in Italy as compared to the UK.(99–101) The methodology proposed by the Italians could be adopted by other countries to acquire better insight in guideline adherence among women with (severe) PPH to provide potential targets for care improvement and opportunities to improve the quality of national guidelines.(102) As for Italy, a statistically significant decrease in hemorrhage-related MMR was observed from 2.49 per 100,000 live births [95% CI 1.75 to 3.43] in the years 2007-2013 prior to bundle

implementation to 0.77 per 100,000 live births [95% CI 0.31 to 1.58] in the years (2014-2018) after implementation of the bundle. Their study reports improved adherence to guidelines.

6. Surgical injury during cesarean section – new opportunities to improve hemorrhage-related maternity care

In Chapter 6, I report a significant drop in the proportion of uterine atony and the atony-specific MMR, which no longer is the main leading cause of fatal hemorrhage in France. While other countries have reported a rise in hemorrhage-related maternal mortality due to placenta accreta, I did not observe such a trend. This could perhaps be explained by a relatively low prevalence of risk factors for placenta accreta in France, in particular previous cesarean section. Indeed, an Italian study reported a prevalence of placenta accreta spectrum of 0.84‰ versus 0.48‰ in France, suggesting an important role for previous cesarean section rate (16.8% in Italy versus 11.4% in France).(103,104) Another explanation might be different management strategies for placenta accreta spectrum disorders. A recent population-based study comparing SMO among women with placenta accreta spectrum disorder in the UK (where cesarean hysterectomy is the gold standard) and France (where conservative management is routine practice) found that life threatening hemorrhage among these women was less common in France.(105)

In contrast to the decreasing contribution of uterine atony to fatal hemorrhage in France, I report in Chapter 6 an increase in the contribution of surgical injury during cesarean section from 0.05 per 100,000 livebirths in 2001-2003 to 0.17 per 100,000 livebirths in 2013-2015. This cause of hemorrhage has not yet been thoroughly investigated from enhanced data. To further reduce preventability of hemorrhage-related maternal deaths, the WHO recommends assessing subpopulations of women sustaining fatal hemorrhage. Hence, I assumed an analysis of hemorrhage-related maternal deaths from this cause could be of relevance for France but also for other high-income countries (Chapter 7). The relevance of such an analysis is even more important considering the rising cesarean section rates in many high-income countries. My findings underline the need the remain critical towards the obstetrical indication to perform a cesarean section. As such, the experts of ENCMM, highlighted that in 4/18 of the women who died from hemorrhage due to surgical injury during cesarean section, the indication of cesarean section was inappropriate.

Currently, few data exist as to the contribution of surgical injury during cesarean section to hemorrhage-related SMO. A study of maternal near misses from severe hemorrhage during cesarean section in South Africa described the risk factors and improvable care factors for bleeding during cesarean sections but included all causes of hemorrhage.(106) The same was true for a French case-control study identifying risk factors for relaparotomy for intra-abdominal hemorrhage after cesarean section.(107)

Comparisons on the incidence and burden of this etiology remain difficult as heterogeneity exists in terms of the definition of the cause of hemorrhage. For example, in France, surgical injury during cesarean section is classified as a separate cause of obstetric hemorrhage and defined as 'any intra-abdominal surgical lesion related to cesarean section' whereas the United Kingdom speaks of 'genital tract trauma' including both surgical trauma after vaginal birth and cesarean section.(108,109) The international classification of diseases (ICD-10) of the WHO refers to obstetric hemorrhage due to 'obstetric trauma' with a subclassification of (1) rupture of uterus before onset of labor (2) rupture of uterus during labor (3) obstetric laceration of cervix (4) obstetric high vaginal laceration alone and (5) obstetric hematoma of pelvis. Although this classification is extensive, it does not distinguish between the underlying mechanisms of the obstetric trauma: i.e. injuries due to the surgical procedure of cesarean section (obstetric hematoma), injuries due to vaginal assisted birth (high vaginal laceration, obstetric laceration of cervix, obstetric trauma of pelvis) or injuries due to labor itself (uterine rupture, or high vaginal laceration). This hampers understanding of the prevention and management of such trauma. International consensus is therefore needed on the definition of surgical injury during cesarean section as well as on the subclassification of such lesions. I propose a subclassification based on the anatomical origin of the bleeding (Table 1). A classification based on the anatomical origin of the lesion has been proposed by other authors, yet I am the first recommending a classification dedicated to obstetric trauma associated with cesarean section.(107,109,110) To validate this classification, I aim to plan an international Delphi validation study, which could be carried out through INOSS network.

Table 1. Classification of surgical injuries during cesarean section

Type of surgical injury	Definition
Uterine incision site	Bleeding from a large extension of the hysterotomy in the parametria or a tear of the lower uterine segment with notable bleeding
Arterial vessel injury	Bleeding from arterial injury of epigastric, uterine, vesical, or cervico-vaginal branches
Broad ligament hematoma	Hematoma in the broad ligament which can either have a venous or arterial source, with the possibility to enter the retroperitoneal space
Injury of the bladder flap	Lesion at the level of the vesico-uterine pouch with or without omission of the bladder flap
Unknown	Origin of bleeding not identified

My analysis of all maternal deaths from surgical injury during cesarean section between 2007-2018 revealed a dominant profile among the women who died from this cause of hemorrhage, combining maternal obesity, advanced maternal age, multi-scarred uterus and second-stage cesareans. These observations are relevant as temporal trends have shown a gradually increasing incidence of obesity, advanced maternal age and cesarean section rates. The association between emergency cesarean sections and second-stage cesarean sections and surgical injury has also been highlighted by other studies. A French study showed a significant increased risk for major intraoperative complications, mainly PPH, in women with a ‘code red’ cesarean section as compared to a ‘code green’ cesarean section (16.9% vs. 9.9%, p=0.05; OR 1.9; 95% CI [1.1–3.1]).(109,111) Several authors have highlighted the increased risk of surgical injury during second-stage cesarean sections, mainly due to the manual extraction of the deeply impacted fetal head. (24-26) In chapter 7, the experts also stressed the need to remain critical towards the indication of the cesarean section, and to favor instrumental birth over cesarean section if the fetal head is sufficiently engaged.

In Chapter 7, I demonstrate that an important proportion of the traumatic cesarean sections was performed during nightshifts stressing the need to further investigate the role of nightshifts in the incidence of substandard care. Several hypotheses may explain the association between nightshifts and SMO in this context. First, reduced fitness to perform among obstetricians during night hours may increase the risk for surgical injuries. Second, postpartum surveillance may be suboptimal due to the medical team resting, being less alert to signs of bleeding. Third, there may be an increased barrier for junior doctors, often the first in line the night duties, to call in the obstetrician or the anesthesiologist in case of abnormal vital parameters.

My findings on the role of nightshifts are in contrast with another French study which did not identify nightshifts as a risk factor for intra-abdominal hemorrhage after cesarean section. However, their findings are difficult to apply to other healthcare institutions as it concerns a single-center study in a high-volume tertiary maternity in France with rapid on site availability of human and medical resources during night hours.(107)

To improve post-cesarean section surveillance, I suggest standardization of clinical parameters by early obstetric warning scores. The use of the shock index [HR/SBP] could be of interest here yet has been poorly investigated as an early marker for hemodynamic compromise and as a predictor for SMO.(112,113) Results of another French study show that among women with PPH after cesarean section the shock index increased already 20 minutes before diagnosis of hemorrhage.(114) Maternity care workers should also be aware that an increased shock index can be caused by other conditions such as sepsis and when bleeding is excluded.

An important element raised both by Chapter 5 and Chapter 7 concerns the communication and coordination between the anesthesiologist and the obstetrician during obstetric hemorrhage. Suboptimal coordination of hemorrhage was particularly prevalent in hospitals with <1000 births probably as a result of the lack of exposure to such obstetric emergencies, reducing the adequacy with which these are managed. A growing body of evidence has shown the association between the organizational context in which health care workers operate and the quality of care they provide. Organizational factors such as staffing of hospitals and the length of shifts and presence of anesthesiologist and obstetrician on site directly impact the incidence of maternal morbidity.(115–118) Furthermore, positive organizational environment in which health care workers feel safe has been known to promote a wide range of patient outcomes such as mortality, hospital-acquired infections and patient well-being.(119,120)

The role of low-volume hospitals in acute obstetric care has been intensely debated and centralization has been suggested to improve maternal outcome.(121–125) A recent systematic review did not find any evidence that such centralization aggravates maternal outcome due to longer travel times.(123,126) As compared to the Netherlands, France still has a relatively large number of low-volume hospitals (cf figure 4 in the introduction). This issue was also discussed by the experts in the binational confidential enquiry (Chapter 5). To reduce substandard care from insufficient or inadequate communication, they suggested the implementation of surgical checklists and ‘sign-outs’ with the entire team to raise awareness on possible complications during the surgery and to adapt postpartum surveillance

directives to the individual patient context. To improve communication between maternity care workers, simulation training is recommended, given its proven efficacy.(127,128) Implementation of such training should be part of PPH-care bundles.

In total, 94% of the maternal deaths due to obstetric hemorrhage caused by surgical injury during cesarean section was considered preventable. We identified multiple improvable care factors providing potential targets for prevention and care improvement among women with surgical injury during cesarean section. I hope these will be taken up by researchers and policy makers. Indeed, future updates of PPH guidelines could dedicate a chapter to this cause of hemorrhage, as is currently done for uterine atony and placenta accreta spectrum disorder. Such a chapter could contain specific guidelines for identifying women at high risk for this cause of hemorrhage, intra-operative management of such lesions and postoperative surveillance.

Conclusion

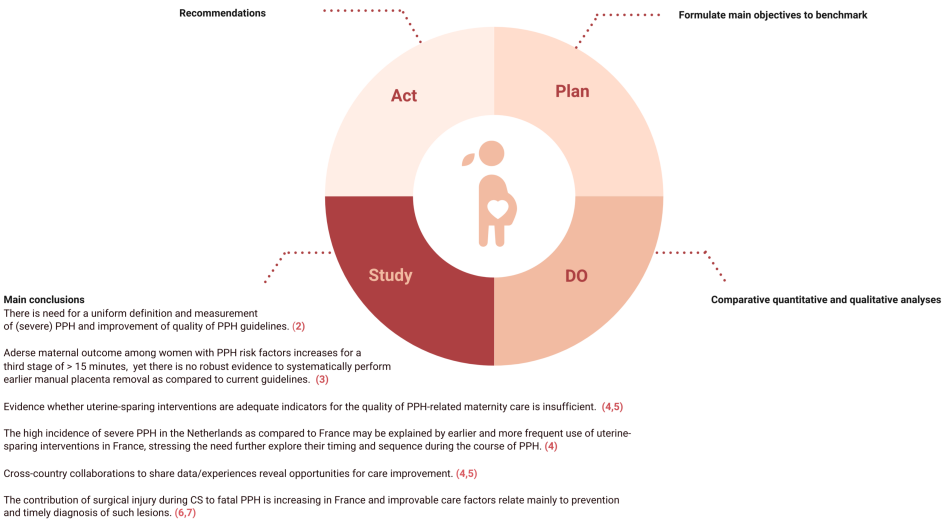

Figure 2. *Continuous cycle of international benchmarking of hemorrhage-related maternity* care – 'Study' step
Abbreviations: PPH = postpartum hemorrhage; CS = cesarean section

In the first part of this thesis, I provided insights into the management strategies of obstetric hemorrhage and how these may relate to disparities in maternal outcome by benchmarking hemorrhage-related maternity care between France and the

Netherlands. The results of this thesis suggest that variations in the duration of the third stage of labor, timing of second-line uterotonics and uterine-sparing interventions could be explanatory mechanisms for observed disparities in hemorrhage related adverse maternal outcome between high-income countries.

Yet, my findings and clinical experience in both countries also emphasize that therapeutic measurement indicators should be interpreted cautiously, since culture rather than severity of bleeding seems to impact on the choice and timing of treatment options to stop bleeding. The findings of part 1 of this thesis underscored the permanent interest of cross-country collaborations by sharing (enhanced) data and reviewing these through a different context of care. If we collaborate more intensively, it might be possible to improve hemorrhage-related maternity care and reduce the high rates of preventability among women suffering obstetric hemorrhage.

In the second part of this thesis, I reported trends in fatal hemorrhage in France and highlighted the increasing contribution of surgical injury during cesarean section. Among the subpopulation of women with surgical injury as the cause of PPH, I assessed characteristics and improvable care factors, bringing to light new opportunities to improve hemorrhage-related maternity care.

In summary, potential targets brought to light by my thesis that may improve (the assessment of) hemorrhage-related maternity care, are: (1) definitions for (severe) PPH and the quality of guidelines on prevention and management of obstetric hemorrhage; (2) the development of indicators to assess quality of hemorrhage related maternity care; (3) the optimal length of the third stage of labor and the timing of manual removal of the placenta among women with risk factors of PPH; (4) timing and sequence of the use of second-line uterotonics and uterine-sparing interventions in the course of hemorrhage; (5) cross-country collaborations to share data and experiences; (6) prevention, diagnosis and management of surgical injury during cesarean section.

Recommendations and future research agendas

Following the clinical targets described above, I now arrive at several key recommendations and a research agenda to promote the quality of hemorrhage-related maternity care as conform the STUDY and ACT-step of the benchmarking cycle. These key recommendations have been presented at the national congress of the ‘Nederlandse Vereniging voor Obstetrie en Gynecologie’ and will be presented at the French national congress of the Societé Française de Médecine Périnatale

(SFMP). I aim to publish an overview of my findings in the French national journal for maternity care workers: 'Gynécologie Obstétrique Fertilité & Sénologie' and in the similar 'Nederlandse Tijdschrift voor Obstetrie en Gynecologie' (NTOG).

Recommendations

1. A universal definition for PPH, based on a quantified amount of blood loss and regardless mode of birth, is necessary to allow for an early identification of women at risk for SMO. A 500 mL cut-off could be suitable for global use by providing a *trigger for action* in low- and middle-income settings and a *trigger for alert* in high resource settings.
2. To define severe PPH, I suggest to formulate a clinical definition to guide management for clinicians facing severe hemorrhage and a scientific definition for a quantitative objective estimate of blood loss as a proxy of SMO to improve the quality of comparative studies.
3. There is an urgent need for a joint statement in which collaborative multi-national platforms such as INOSS could engage to translate WHO recommendations on the prevention and management of PPH to high-resource settings.
4. Data about the adequacy of uterine-sparing interventions as an indicator for the quality of hemorrhage-related maternity care are conflicting and observational studies may rather make use of other indicators to benchmark the quality of maternity care such as the organ dysfunction-based indicators proposed by the European Board and College of Obstetrics and Gynaecology (disseminated intravascular coagulation, post-partum hysterectomy, renal failure (due to hypovolemia), cardiac arrest and hemorrhagic shock).
5. Increased vigilance for signs of PPH is needed among women with risk factors for PPH if the third stage of labor exceeds 15 minutes.
6. The use of timelines when reporting the chain of events in the course of PPH should be recommended in current PPH guidelines, since it can be instructive for maternity care workers to evaluate delays in clinical care and improve data collection for future research.
7. Cross country collaborations should be prioritized by all stakeholders in the form of clinical and research exchanges of young obstetricians, and through the facilitation of data sharing.
8. Obstetricians need to remain critical as to the indication to perform a cesarean section, particularly in the second stage of labor.

9. A harmonized definition and a clear subclassification of surgical injury during cesarean section are necessary to facilitate studies on this increasing contributor to obstetric hemorrhage-related SMO.
10. I recommend dedicating a Chapter in obstetric hemorrhage guidelines to the prevention, diagnosis and management of surgical injury during cesarean section to improve clinical care in this situation.
11. To improve hemorrhage-related maternity care, medical and human resources essential to provide qualitative acute obstetric care must be specified at the national level.

Future research agenda's

1. I recommend a randomized controlled trial to assess the association between earlier manual removal of placenta and adverse maternal outcome.
2. Prospective cross-country studies to improve understanding on the use of timing of uterine-sparing interventions in the course of severe obstetric hemorrhage and their association with SMO are needed as a valuable alternative for randomized controlled trials.
3. Future research directions may focus on the role of organizational aspects of care, such as volume of hospitals and nightshifts, on hemorrhage-related severe maternal outcome.
4. Future research needs to assess the association between blood loss volume and SMO to define which amount of bloodloss could serve as a proxy for SMO.
5. Observational studies are needed to assess the uptake of guidelines and lessons learned into clinical practices in order to further reduce preventable SMO.

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