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

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Summary and General discussion

Summary

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

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

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

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

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

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

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

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

General discussion

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

Study population

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

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

Quality of data

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

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

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

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

Dealing with time-dependent confounding

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

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

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

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

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

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

Residual confounding

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

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

Coagulopathy in women with persistent postpartum haemorrhage: lessons learnt

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

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

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

3) which coagulation tests diagnose this coagulopathy the best;

4) which women will benefit from haemostatic interventions;

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

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

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

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

Where do we go from here?

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

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

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

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

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