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EC GYNAECOLOGY
Review Article

Postpartum Hemorrhage and How to be Managed

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Received: August 13, 2017; **Published:** September 23, 2017

Abstract

Postpartum Haemorrhage (PPH) is a major cause of maternal morbidity and mortality. Treatment of acquired coagulopathy observed in severe PPH is an important part of PPH management, but is mainly based on literature in trauma patients, and data thus should be interpreted. This review describes recent advances in transfusion strategy and in the use of tranexamic acid and fibrinogen concentrates in women with PPH.

Keywords: *Coagulopathy; Postpartum Haemorrhage; Transfusion Strategy; Tranexamic Acid; Fibrinogen*

Introduction

Postpartum hemorrhage (PPH) is one of the most frequent life-threatening complications of going into labor and occurs mostly without any warning. The main causes of PPH are uterine atony, retained placenta, and genital tract trauma. Abnormal placentation, placental abruption, and uterine rupture are less frequent but often responsible for severe PPH with acquired coagulopathy. PPH accounts for nearly one-quarter of all maternal deaths worldwide and an estimated 125,000 deaths occur each year [1]. Most of the time, these deaths due to obstetric hemorrhage are considered to be potentially preventable [2]. Maternal mortality is the end result of a worsening process, and PPH is also responsible for half of maternal morbidity [3]. The incidence of PPH has recently increased in most developed countries such as Canada, Australia, and the US and has been notably related to an increased use of oxytocin for labor [4]. Currently, the therapeutic strategies for PPH management are largely standardized; in particular, obstetric, surgical, and radiological interventions play a life-saving role in PPH management. However, medical treatment, namely transfusion and a pro-hemostatic strategy, is also essential and has shown important changes in recent years. This review focuses on advances in transfusion strategy and on the use of pro-hemostatic agents such as tranexamic acid (TA) and fibrinogen concentrates in PPH.

Transfusion strategy in postpartum haemorrhage

Only few data are available to guide transfusion management in the acute phase of PPH. The current guidelines are based mainly on the literature coming from trauma patients. In trauma patients, several cohort studies have demonstrated a decrease in mortality associated with the administration of red blood cells (RBCs) and fresh frozen plasma (FFP) in a 1:1 ratio [5-9]. These results are controversial. First, most of these studies were retrospective. Second, a survival bias cannot be ruled out [10]. The transfusion benefit of a high FFP-to-RBC ratio is not so clear in recent prospective cohort studies. In the prospective, observational, multicenter, major trauma transfusion (PROMMTT) study documenting the timing of transfusion during active resuscitation in 905 trauma patients, Holcomb., *et al*. demonstrated that early and higher FFP-to-RBC ratios were associated with a decreased mortality in patients transfused with at least three units of RBCs during the first 24 hours after admission. No significant difference in mortality at 24 hours or at 30 days was observed. However, in the 1:1:1 group, more patients achieved hemostasis and fewer experienced death due to exsanguination by 24 hours [12]. Finally, the use of

FFP is associated with an increased incidence of complications such as post-injury multiple organ failure, acute respiratory distress, and infections, and the rate of complications increased with the quantities of FFP transfused [13]. For all of these reasons, the quality of the proofs in favor of a benefit in mortality with a transfusion in FFP and RBCs in a 1:1 ratio is considered low. It is also recommended that FFP transfusion be avoided in trauma patients without substantial bleeding [14]. In the obstetrical setting, there is no study on the impact of the FFP-to-RBC ratio on maternal morbidity and mortality [15]. One study in obstetric hemorrhage evaluating this strategy of transfusion with a high FFP-to-RBC ratio was conducted by Alexander., et al. who compared maternal outcomes between women who received whole blood only, women who received RBCs only, and women who received a combination of blood products [16]. In this study, complications attributable to hypovolemia were significantly increased in the combination group as compared with the whole blood and RBC groups [17,18].

The only strong recommendation on blood transfusion in PPH is that women receive RBCs as soon as possible in case of massive PPH. Because cross-matched blood is not always available, maternity units should have immediate access (within 5 minutes) to O-negative blood. If the need is less pressing, group-specific blood can be made available more quickly than fully cross-matched blood. Consequently, all maternity units should have their own reserve of blood products if there is no blood bank on-site [19]. Finally, it appears that, more than the predetermined ratio, the early treatment of coagulopathy with FFP and platelets determines maternal morbidity and mortality. Unfortunately, blood transfusion has its own adverse consequences. To decrease transfusion exposure and to control the bleeding, pro-hemostatic agents are used more and more often in women with PPH.

Postpartum hemorrhage and tranexamic acid

TA is an antifibrinolytic agent that inhibits the activation of plasminogen into plasmin. Its use is now clearly established for the control and prophylaxis of menorrhagia [20]. Its efficacy has also been proven in elective surgery such as orthopedic, vascular, hepatic, or urologic surgery and more recently in bleeding trauma patients [21]. A meta-analysis published in the British Medical Journal in 2012 pooled all of the randomized controlled trials comparing TA with no TA or placebo in surgical patients [22]. The results showed that TA reduced the probability of receiving a blood transfusion by one-third in elective surgery, but its effects on thromboembolic events and mortality remained uncertain. In particular, mortality due to hemorrhagic shock was decreased by 15% [21]. In the obstetrical setting, the literature focuses mostly on the prophylactic use of TA to prevent PPH, particularly in the context of elective cesarean delivery. The most recent meta-analysis exploring the preventive effect on PPH and safety of TA versus placebo or no treatment was published in 2015 by the Cochrane database [23]. It included nine trials involving 2453 women who were at low risk of PPH and who were undergoing cesarean delivery and three trials with 832 women who delivered vaginally. These trials were of mixed quality. The results of the meta-analysis showed that overall the incidence of blood loss of greater than 500 mL was lower in women who received TA versus placebo or no intervention. Also, TA was effective in decreasing the incidence of blood loss of greater than 1000 mL in women who had undergone cesarean delivery but not vaginal birth. Blood transfusion was less frequent in women receiving TA versus placebo or no intervention. Finally, the authors found that the use of TA was associated with only mild side effects, such as nausea, vomiting, and dizziness. Concerning the use of TA as a curative treatment of PPH, only one randomized trial has been published until now. In the treatment group, total blood loss at 6 hours after PPH diagnosis was significantly lower, but the difference was questionable (170 versus 221 mL; To summarize, data on the effectiveness of TA in PPH are quite encouraging, but there is still only little reliable evidence coming from randomized controlled trials. However, owing to its low cost and low rate of side effects, the use of TA is currently recommended by several academic societies. Consequently, there is an urgent need for clinical randomized trials of good quality before TA can be strongly recommended as a curative treatment of ppH. Inclusions are over now and the results of this study are due to be published later this year [24-27].

Fibrinogen concentrates in postpartum hemorrhage

Fibrinogen plays a critical role in achieving and maintaining hemostasis and is fundamental to effective clot formation. Fibrinogen plasma level has been demonstrated to be a good predictor of PPH severity, a fibrinogen plasma level of 2 g/L or less had a 100% positive

predictive value for severe PPH [28]. This study also demonstrated that the risk for severe PPH was 2.6 fold higher for each 1 g/L decrease in fibrinogen plasma level. Therefore, the assumption that fibrinogen supplementation could be beneficial to treat PPH has been made, although this is likely an over-interpretation of the study results. It should indeed be noted that the study by Charbit., *et al.* was not randomized and did not demonstrate that decreased fibrinogen concentration was a causal factor of PPH severity. This study demonstrated only that decreased fibrinogen concentration was associated with PPH severity. Therefore, basing our hemostatic strategy on this argument requires further study. For example, in the UK, the only licensed source of fibrinogen is FFP or cryoprecipitate, which also contains von Willebrand factor, factor VIII, factor XIII, and fibronectin. Fibrinogen concentrates offer rapid restoration of the fibrinogen concentration with a small-volume infusion, for a comparable cost, and with a minimal preparation time. Fibrinogen concentrates are considered by many to be preferable to cryoprecipitate, although there are no studies comparing the efficacy of these two products [29,30]. The efficacy and safety of fibrinogen concentrates have been proven in congenital fibrinogen deficiencies [31]. Additionally, some *in vitro* and animal studies with thromboelastography monitoring have shown that the addition of fibrinogen concentrates corrects the coagulation disorders induced by experimental hemodilution [32,33]. Clinical data on the efficacy of fibrinogen concentrates in the management of hemorrhage are still scarce. These trials included 384 patients overall and were all performed in the setting of perioperative bleeding in scheduled cardiovascular surgery, except one trial including patients undergoing radical cystectomy [34,35]. Overall, These trials have several methodological flaws: small sample size, no prolonged follow-up, no intention-to-treat analysis, and no or poor blindness design. The protocol of fibrinogen concentrate administration differed between studies in terms of dose and of therapeutic target (prophylactic or curative treatment) as well as the control group [36-41]. Consequently, it is difficult to extend these results to the obstetrical setting. In trauma patients, only observational studies have been published [42]. In retrospective studies, the administration of fibrinogen concentrates was associated with a decrease in transfusion needs and with the correction of biologic hemostatic disorders [43-46]. In one of these studies, the observed mortality was lower than predicted mortality for patients who received fibrinogen concentrates [47]. In particular, the severity of hemorrhage and confounding factors concerning blood loss volume were not taken into account, inducing an indication bias. No randomized controlled trial on the impact of fibrinogen concentrates in trauma patients has yet been published. To summarize, data on fibrinogen concentrate efficacy and safety in bleeding trauma patients are too limited for a conclusion to be drawn. The use of fibrinogen concentrate in PPH has been explored in seven observational studies, in which a total of 222 women participated [43,48-51]. The only controlled study is a before-and-after study of 77 women with PPH [52]. The authors did not find any difference in blood loss, transfusion requirement, or need for a surgical hemostatic procedure. Consequently, this study could draw conclusions only on the inefficacy of the use of fibrinogen concentrates as a pre-emptive treatment for severe PPH in patients with normal fibrinogenemia [53]. Therefore, we still need valid data before administration of fibrinogen concentrate as a curative treatment of PPH can be firmly recommended.

Additional strategies

Recombinant human FVIIa generated great hope several years ago when early case reports suggested immediate efficacy in refractory PPH [54-68].

Conclusions

Until now, no study has proven that a specific transfusion strategy or the use of any pro-hemostatic agent would improve maternal outcomes in the context of PPH. Levels of evidence of TA and fibrinogen concentrate efficacy and safety in PPH are low. Randomized controlled trials in the context of severe PPH are difficult to perform.

Bibliography

1. Hogan MC., *et al*. "Maternal mortality for 181 countries, 1980-2008: a systematic analysis of progress towards Millennium Development Goal 5". *Lancet* 375.9726 (2010): 1609-1623.

2. Knight M., *et al*. "Saving Lives, Improving Mothers' Care - Lessons learned to inform future maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009-12". Oxford: University of Oxford. Reference Source (2014).

3. Enquète Nationale Confidentielle sur les Morts Maternelles, France 2007-2009. Rapport du Comité National d'experts sur la Mortalité Maternelle (CNEMM) (2013).

4. Zhang W., *et al*. "Incidence of severe pre-eclampsia, postpartum haemorrhage and sepsis as a surrogate marker for severe maternal morbidity in a European population-based study: the MOMS-B survey". *British Journal of Obstetrics and Gynaecology* 112.1 (2005): 89-96.

5. Belghiti J., *et al*. "Oxytocin during labour and risk of severe postpartum haemorrhage: a population-based, cohort-nested case-control study". *BMJ Open* 1.2 (2011): e000514.

6. Borgman MA., *et al*. "The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital". *Journal of Trauma* 63.4 (2007): 805-813.

7. Holcomb JB., *et al*. "Damage control resuscitation: directly addressing the early coagulopathy of trauma". *Journal of Trauma* 62.2 (2007): 307-310.

8. Maegele M., *et al*. "Changes in transfusion practice in multiple injury between 1993 and 2006: a retrospective analysis on 5389 patients from the German Trauma Registry". *Transfusion Medicine* 19.3 (2009): 117-124.

9. Borgman MA., *et al*. "The effect of FFP: RBC ratio on morbidity and mortality in trauma patients based on transfusion prediction score". *Vox Sanguinis* 101.1 (2011): 44-54.

10. Ho AM., *et al*. "Prevalence of survivor bias in observational studies on fresh frozen plasma: erythrocyte ratios in trauma requiring massive transfusion". *Anesthesiology* 116.3 (2012): 716-728.

11. Holcomb JB., *et al*. "The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks". *JAMA Surgery* 148.2 (2013): 127-136.

12. Holcomb JB., *et al*. "Transfusion of plasma, platelets, and red blood cells in a 1: 1: 1 vs a 1: 1: 2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial". *Journal of the American Medical Association* 313.5 (2015): 471-482.

13. Watson GA., *et al*. "Fresh frozen plasma is independently associated with a higher risk of multiple organ failure and acute respiratory distress syndrome". *Journal of Trauma* 67.2 (2009): 221-230.

14. Spahn DR., *et al*. "Management of bleeding and coagulopathy following major trauma: an updated European guideline". *Critical Care* 17.2 (2013): R76.

15. Saule I and Hawkins N. "Transfusion practice in major obstetric haemorrhage: lessons from trauma". *International Journal of Obstetric Anesthesia* 21.1 (2012): 79-83.

16. Alexander JM., *et al*. "Whole blood in the management of hypovolemia due to obstetric hemorrhage". *Obstetrics and Gynecology* 113.6 (2009): 1320-1326.

17. Burtelow M., *et al*. "How we treat: management of life-threatening primary postpartum hemorrhage with a standardized massive transfusion protocol". *Transfusion* 47.9 (2007): 1564-1572.

18. Skupski DW., *et al*. "Improving hospital systems for the care of women with major obstetric hemorrhage". *Obstetrics and Gynecology* 107.5 (2006): 977-983.

19. Butwick AJ and Goodnough LT. "Transfusion and coagulation management in major obstetric hemorrhage". *Current Opinion in Anaesthesiology* 28.3 (2015): 275-284.

20. Matteson KA., *et al*. "Nonsurgical management of heavy menstrual bleeding: a systematic review". *Obstetrics and Gynecology* 121.3 (2013): 632-643.

21. Shakur H., *et al*. "Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial". *Lancet* 376.9734 (2010): 23-32.

22. Ker K., *et al*. "Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis". *British Medical Journal* 344 (2012): e3054.

23. Novikova N., *et al*. "Tranexamic acid for preventing postpartum haemorrhage". *Cochrane Database of Systematic Reviews* 6 (2015): CD007872.

24. Ducloy-Bouthors AS., *et al*. "High-dose tranexamic acid reduces blood loss in postpartum haemorrhage". *Critical Care* 15.2 (2011): R117.

25. WHO Guidelines Approved by the Guidelines Review Committee: WHO recommendations for the prevention and treatment of postpartum haemorrhage. Geneva, Switzerland (2012).

26. Shakur H., *et al*. "The WOMAN Trial (World Maternal Antifibrinolytic Trial): tranexamic acid for the treatment of postpartum haemorrhage: an international randomised, double blind placebo controlled trial". *Trials* 11 (2010): 40.

27. de Lloyd L., *et al*. "Standard haemostatic tests following major obstetric haemorrhage". *International Journal of Obstetric Anesthesia* 20.2 (2011): 135-141.

28. Charbit B., *et al*. "The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage". *Journal of Thrombosis and Haemostasis* 5.2 (2007): 266-273.

29. Cortet M., *et al*. "Association between fibrinogen level and severity of postpartum haemorrhage: secondary analysis of a prospective trial". *British Journal of Anaesthesia* 108.6 (2012): 984-989.

30. Collis RE and Collins PW. "Haemostatic management of obstetric haemorrhage". *Anaesthesia* 70.1 (2015): 78-86,e27-e28.

31. Bornikova L., *et al*. "Fibrinogen replacement therapy for congenital fibrinogen deficiency". *Journal of Thrombosis and Haemostasis* 9.9 (2011): 1687-1704.

32. Fenger-Eriksen C., *et al*. "Thrombelastographic whole blood clot formation after ex vivo addition of plasma substitutes: improvements of the induced coagulopathy with fibrinogen concentrate". *British Journal of Anaesthesia* 94.3 (2005): 324-329.

33. Fries D., *et al*. "Effect of fibrinogen on reversal of dilutional coagulopathy: a porcine model". *British Journal of Anaesthesia* 95.2 (2005): 172-177.

34. Cui Y., *et al*. "Perioperative monitoring of thromboelastograph on blood protection and recovery for severely cyanotic patients undergoing complex cardiac surgery". *Artificial Organs* 34.11 (2010): 955-960.

35. Fenger-Eriksen C., *et al*. "Fibrinogen substitution improves whole blood clot firmness after dilution with hydroxyethyl starch in bleeding patients undergoing radical cystectomy: a randomized, placebo-controlled clinical trial". *Journal of Thrombosis and Haemostasis* 7.5 (2009): 795-802.

36. Galas FR., *et al*. "Hemostatic effects of fibrinogen concentrate compared with cryoprecipitate in children after cardiac surgery: a randomized pilot trial". *Journal of Thoracic and Cardiovascular Surgery* 148.4 (2014): 1647-1655.

37. Karlsson M., *et al*. "Prophylactic fibrinogen infusion reduces bleeding after coronary artery bypass surgery. A prospective randomised pilot study". *Thrombosis and Haemostasis* 102.1 (2009): 137-144.

38. Lancé MD., *et al*. "Perioperative dilutional coagulopathy treated with fresh frozen plasma and fibrinogen concentrate: a prospective randomized intervention trial". *Vox Sanguinis* 103.1 (2012): 25-34.

39. Rahe-Meyer N., *et al*. "Effects of fibrinogen concentrate as first-line therapy during major aortic replacement surgery: a randomized, placebo-controlled trial". *Anesthesiology* 118.1 (2013): 40-50.

40. Tanaka KA., *et al*. "Transfusion and hematologic variables after fibrinogen or platelet transfusion in valve replacement surgery: preliminary data of purified lyophilized human fibrinogen concentrate versus conventional transfusion". *Transfusion* 54.1 (2014): 109-118.

41. Ranucci M., *et al*. "Randomized, double-blinded, placebo-controlled trial of fibrinogen concentrate supplementation after complex cardiac surgery". *Journal of the American Heart Association* 4.6 (2015): e002066.

42. Aubron C., *et al*. "Efficacy and safety of fibrinogen concentrate in trauma patients--a systematic review". *Journal of Critical Care* 29.3 (2014): 471.e11-e17.

43. Fenger-Eriksen C., *et al*. "Fibrinogen concentrate substitution therapy in patients with massive haemorrhage and low plasma fibrinogen concentrations". *British Journal of Anaesthesia* 101.6 (2008): 769-773.

44. Innerhofer P., *et al*. "The exclusive use of coagulation factor concentrates enables reversal of coagulopathy and decreases transfusion rates in patients with major blunt trauma". *Injury* 44.2 (2013): 209-216.

45. Nienaber U., *et al*. "The impact of fresh frozen plasma vs coagulation factor concentrates on morbidity and mortality in trauma-associated haemorrhage and massive transfusion". *Injury* 42.7 (2011): 697-701.

46. Schöchl H., *et al*. "Transfusion in trauma: thromboelastometry-guided coagulation factor concentrate-based therapy versus standard fresh frozen plasma-based therapy". *Critical Care* 15.2 (2011): R83.

47. Schöchl H., *et al*. "Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM)-guided administration of fibrinogen concentrate and prothrombin complex concentrate". *Critical Care* 14.2 (2010): R55.

48. Guasch E., *et al*. "Hemorragia obstétrica: estudio observacional sobre 21.726 partos en 28 meses". *Revista Española de Anestesiología y Reanimación* 56.3 (2009): 139-146.

49. Weinkove R and Rangarajan S. "Fibrinogen concentrate for acquired hypofibrinogenaemic states". *Transfusion Medicine* 18.3 (2008): 151-157.

50. Weiss G., *et al*. "Observational study of fibrinogen concentrate in massive hemorrhage: evaluation of a multicenter register". *Blood Coagulation and Fibrinolysis* 22.8 (2011): 727-734.

51. Kikuchi M., *et al*. "Fibrinogen concentrate substitution therapy for obstetric hemorrhage complicated by coagulopathy". *Journal of Obstetrics and Gynaecology Research* 39.4 (2013): 770-776.

52. Ahmed S., *et al*. "The efficacy of fibrinogen concentrate compared with cryoprecipitate in major obstetric haemorrhage--an observational study". *Transfusion Medicine* 22.5 (2012): 344-349.

53. Wikkelsø AJ., *et al*. "Pre-emptive treatment with fibrinogen concentrate for postpartum haemorrhage: randomized controlled trial". *British Journal of Anaesthesia* 114.4 (2015): 623-633.

54. Bouwmeester FW., *et al*. "Successful treatment of life-threatening postpartum hemorrhage with recombinant activated factor VII". *Obstetrics and Gynaecology* 101.6 (2003): 1174-1176.

55. Lavigne-Lissalde G., *et al*. "Recombinant human FVIIa for reducing the need for invasive second-line therapies in severe refractory postpartum hemorrhage: a multicenter, randomized, open controlled trial". *Journal of Thrombosis and Haemostasis* 13.4 (2015): 520-529.

56. Glynn JC and Plaat F. "Prothrombin complex for massive obstetric haemorrhage". *Anaesthesia* 62.2 (2007): 202-203.

57. Huissoud C., *et al*. "Bedside assessment of fibrinogen level in postpartum haemorrhage by thrombelastometry". *British Journal of Obstetrics and Gynaecology* 116.8 (2009): 1097-1102.

58. Mallaiah S., *et al*. "Introduction of an algorithm for ROTEM-guided fibrinogen concentrate administration in major obstetric haemorrhage". *Anaesthesia* 70.2 (2015): 166-175.

59. Guise JM., *et al*. "STORC safety initiative: a multicentre survey on preparedness & confidence in obstetric emergencies". *Quality and Safety in Health Care* 19.6 (2010): e41.

60. Mazzocco K., *et al*. "Surgical team behaviors and patient outcomes". *American Journal of Surgery* 197.5 (2009): 678-685.

61. Flin R and Maran N. "Basic concepts for crew resource management and non-technical skills". *Best Practice and Research Clinical Anaesthesiology* 29.1 (2015): 27-39.

62. (CAIPE) CftAoIE. Reference Source (2016).

63. Lapkin S., *et al*. "A systematic review of the effectiveness of interprofessional education in health professional programs". *Nurse Education Today* 33.2 (2013): 90-102.

64. Weaver SJ., *et al*. "Team-training in healthcare: a narrative synthesis of the literature". *BMJ Quality and Safety* 23.5 (2014): 359-372.

65. Fung L., *et al*. "Impact of crisis resource management simulation-based training for interprofessional and interdisciplinary teams: A systematic review". *Journal of Interprofessional Care* 29.5 (2015): 433-444.

66. Phipps MG., *et al*. "Outcomes from a labor and delivery team training program with simulation component". *American Journal of Obstetrics and Gynecology* 206.1 (2012): 3-9.

67. Shields LE., *et al*. "Comprehensive maternal hemorrhage protocols improve patient safety and reduce utilization of blood products". *American Journal of Obstetrics and Gynecology* 205.4 (2011): 368.e1-e8.

68. Dupont C., *et al*. "Clinical audit: a useful tool for reducing severe postpartum haemorrhages?" *International Journal for Quality in Health Care* 23.5 (2011): 583-589.

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