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Recombinant factor VIIa and other pro-haemostatic therapies in primary postpartum haemorrhage

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Blood products are an essential component of the management of postpartum haemorrhage, although there is lack of evidence to guide optimal use. Prospective intervention studies, including randomized trials, are needed to clarify optimal timing and dosage. The new generation of virally inactivated blood products, such as fibrinogen concentrate, might further enhance our knowledge of the value of individual blood components. It seems likely that antifibrinolytic agents will receive less attention in future. However, rFVIIa promises to be a powerful tool in managing massive obstetric haemorrhage, although many questions concerning its efficacy and safety in differing clinical scenarios remain unanswered.

Key words: obstetric haemorrhage; postpartum haemorrhage; recombinant factor VIIa.

INTRODUCTION

Although obstetric, surgical and radiological interventions play a life-saving role in the management of postpartum haemorrhage (PPH), this chapter focuses on the utility of haemostatic therapies, an area that has shown huge advances in recent years. Included are the transfusions of fresh frozen plasma (FFP), packed red cells, cryoprecipitate and

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platelets, and the haematological management of massive transfusion and disseminated intravascular coagulation (DIC). Drug therapies such as antifibrinolytics and the relatively newer agent, recombinant activated factor VIIa are also considered.

PHYSIOLOGICAL CHANGES TO THE HAEMOSTATIC SYSTEM IN PREGNANCY

Numerous haematological changes occur during pregnancy. In part, these prepare the mother for birth by protecting against haemorrhage. Their unwanted consequence, however, is to make thrombosis a more common event. These changes include an increase in clotting factors, such as factor VIII, von Willebrand factor (vWF) and fibrinogen and a decrease in the activity of the natural anticoagulant, protein S, due to elevation of C4b binding protein. Fibrinolytic activity is reduced due to an increase in fibrinolytic inhibitors, including alpha-2-antiplasmin, alpha-2-macroglobulin, thrombin activatable fibrinolysis inhibitor (TAFI) and the plasminogen activator inhibitors PAI-1 and placentally derived PAI-2. In addition, plasminogen and tissue plasminogen activator might be decreased.

In the postpartum period, the fibrinolytic system rapidly returns to its pre-pregnancy state, a process that is fully achieved within hours, in part reflecting the loss of the placental plasminogen activator inhibitor PAI-II. The coagulation system takes a greater time to correct, but by 6 weeks postpartum it can be expected that normal levels of most coagulation factors should be observed, although some, such as protein S, might take longer to recover.

The need for these pro-haemostatic changes is apparent when one considers that uterine blood flow increases during pregnancy from $<$5% to 12% of cardiac output, reaching a rate of 700–900 mL per minute at term.[1] At the point of birth, the potential for catastrophic haemorrhage is obvious. The physiological mechanism essential to achieving haemostasis is contraction of the uterus, influenced by endogenous prostaglandins and oxytocin. As the placenta separates, myometrial contraction causes closure of the terminal ends of the spiral arteries. Preceding fibrin accumulation within the walls of the spiral arteries aids this process, and following the birth of the placenta further fibrin deposition rapidly occurs over the site of attachment.

EFFECT OF BLEEDING ON HAEMOSTASIS

Obstetric haemorrhage is frequently complicated by an acquired coagulopathy, caused by dilutional or consumptive effects on clotting factors, platelets and fibrinogen. One blood volume, rapidly replaced with red cells and crystalloid/colloid might be associated with individual clotting factor levels of $<$30% of normal. As volume loss occurs, vasoconstriction and a fall in blood pressure cause fluid shift into the vascular space, further exacerbating the dilutional effects of fluid resuscitation. In addition, anaemia contributes to impaired platelet responses. Red cells normally travel through blood vessels in the fast stream in the centre of the lumen, causing platelets to diffuse radially and thereby increasing the chance of adhesion to sites of injury. Decreases in haematocrit allow fast passage of platelets in the central luminal flow, reducing platelet–endothelial-cell interaction. In addition, lower production of adenosine diphosphate (ADP) and thromboxane from red cells, and reduced availability of haemoglobin to scavenge nitrous oxide, inhibit platelet activation and cause vasodilation. Massive haemorrhage with hypovolaemic shock causes tissue hypoxia, acidosis, hypothermia and systemic inflammatory responses, which can trigger disseminated intravascular coagulation (DIC).