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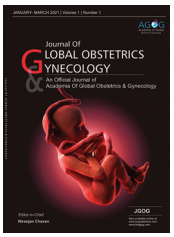

Postpartum Hemorrhage – A Hematologist's Role in an Obstetrician's Nightmare!

Abhay A Bhave, Sundar Shewale

Lilavati Hospital and Research Centre, Bandra West, Mumbai, Maharashtra, India

ABSTRACT

Postpartum hemorrhage (PPH) is one of the leading causes of maternal mortality worldwide that is potentially preventable by identification of high risk factors, timely diagnosis and prompt management. However, most women with severe PPH may not have an identifiable risk factor/s which makes its occurrence and severity difficult to predict leading to obstetric intervention and/or blood components exposure. Clinical awareness to detect an evolving coagulopathy is the key to diagnose and pre-empt PPH related morbidity and mortality.

Key words: Post partum hemorrhage, Maternal deaths, Blood transfusion, Coagulopathy, Fibrinogen, Tranexamic acid

INTRODUCTION

Maternal mortality is defined as the death during pregnancy or within 42 days of delivery or termination of pregnancy.[1] Postpartum hemorrhage (PPH) is a major risk factor for maternal morbidity and mortality accounting for two-thirds of cases of obstetric hemorrhage which results in approximately one-quarter of all maternal deaths worldwide.[2]

DEFINITION OF PPH

It is commonly defined as a blood loss of 500 ml or more within 24 h post partum. Severe PPH is bleeding more than 1000 ml. Persistent (ongoing) PPH is active bleeding >1000 ml within 24 h following delivery that continues despite the use of initial measures such as 1st line uterotonics and uterine massage. Secondary PPH is defined as abnormal or excessive bleeding from the birth canal between 24 h and 12 weeks postnatal.[3-5]

Practically, the following definitions may be more useful: bleeding that causes tachycardia >110 beats/min and/or systolic hypotension <90 mmHg, or significant bleeding needing emergency transfusion of O RhD negative (O NEG) red cells.[6]

Corresponding Author:
Dr. Abhay A Bhave, MD, FRCPA (Australia), Haematologist, Lilavati Hospital and Research centre, Bandra reclamation, Bandra west, Mumbai 400050, Maharashtra, India.
E-mail: bhaveabhay@hotmail.com

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Most women with PPH respond to initial measures of uterine massage and therapeutic uterotonics. However, if bleeding continues despite these interventions, the situation can rapidly escalate with severe blood loss, maternal morbidity, and even mortality.[7]

IMPACT OF PPH

The survivors of this life-threatening hemorrhage can suffer from long-term health complications which includes loss of fertility and psychological trauma[8] irrespective of the social strata, making it extremely important to be prevented by early recognition and intervention with a multidisciplinary team. In addition, there is always a risk of transfusion transmissible infections, alloimmunization, allergies, and immune modification if she is exposed to blood component therapy, which can impact future quality of life.

RISK FACTORS FOR PPH

While some women have risk factors for PPH that can be identified during pregnancy, at labor or at the time of delivery, most women with PPH do not have any risk factors, which make its occurrence and severity difficult to predict.[9] Hence, all pregnant women must be considered to be at risk of PPH and assessed for possible risk factors for developing PPH throughout pregnancy.[7]

From an obstetric view, the common risk factors for PPH include uterine issues, placental issues, underlying coagulopathy with bleeding tendency, amniotic fluid embolism, and acute fatty liver of pregnancy to genital tract trauma, often referred to as the "4 T's" (tone, tissue, trauma, and thrombin).[10]

Coagulopathy as a risk factor is seen in almost 25% of major obstetric hemorrhage either due to consumption of clotting factors, dilution of remaining factors by fluid volume replacement, or endothelial activation from hypothermia and acidosis. In addition, ongoing hemorrhage from surgical trauma or laceration or uterine atony and placental abruption causes early hypofibrinogenemia and amniotic fluid embolism rapidly lead to disseminated intravascular coagulation if unrecognized.[11]

A detailed history of patient and family should be taken before delivery or ideally even before pregnancy to identify women with bleeding tendency such as von Willebrand's disease, carriers of hemophilia and with rare inherited disorders such as congenital hypofibrinogenemia, deficiencies of factor VII, factor X, factor XI, and factor XII, Glanzmann's thrombasthenia, or Bernard-Soulier syndrome as they have a higher risk of bleeding than the normal population.[12] These coagulation defects can be confirmed by specialized laboratory tests.

WARNING SIGN OF PPH

Ongoing significant postpartum bleeding in a woman with a well-contracted uterus with no evidence of genital tract trauma or retained placenta should alert the clinicians to the possible presence of coagulopathy and suspect it more so if the blood that is lost is thin, watery, and not clotting.[7]

HEMATOLOGICAL TESTS TO IDENTIFY A TENDENCY TOWARD PPH

A decrease in plasma fibrinogen level and platelet count both are early warnings of PPH. A retrospective study demonstrated that a platelet count $<100 \times 10^9$/L or a fibrinogen concentration <2.9 g/L during labor was associated with an almost 20-fold increase in the incidence of PPH. A falling platelet count in early PPH or a falling Clauss fibrinogen predicts progression to transfusion and invasive procedure. The role of replacement of fibrinogen has been extensively studied in trials.[13-17] This trend could possibly warn the obstetrician and the patient toward possibility of bleeding and counsel them for need of blood component therapy.

However, hypofibrinogen with hyperfibrinolysis and thrombocytopenia can be subtle and easily missed unless the obstetrician is aware of it. This lack of awareness of the pathophysiology may worsen the risk of existing obstetric factors, tilting the balance toward PPH. The emerging coagulopathy can be identified by some global coagulation profile tests (CBC, PT. APTT or PTT, and fibrinogen)[14] or thromboelastogram (TEG),[18] where a classical graph can be identified with hypofibrinogenemia.

Postpartum anemia (PPA) occurs 48 h after delivery in approximately 50% in Europe and 50–80% in developing countries and can contribute to the onset of PPH. PPA should be considered severe if Hb is <7 g/dl. Population-based studies have indicated an association between antenatal anemia (Hb <9 g/dl) with greater blood loss at delivery and postpartum haemorrhage.[19] This prompts treatment of antenatal anemia (hemoglobin level <11 g/dl at first contact and 10.5 g/dl at 28 weeks) with iron (oral or IV) or Vitamin B12 deficiency or as per the underlying cause of anemia to prevent or reduce the risk of PPH.[12]

MASSIVE HEMORRHAGE AND BLOOD COMPONENT THERAPY

Recognition of major PPH entails a rapid response with red blood cells transfusion to maximize oxygen delivery to prevent tissue hypoxia, development of acidosis, organ failure, and worsening of shock.[7] Blood samples should be urgently sent for blood group along with the coagulation profile to cross match 2–4 units of packed red cells. Blood bank should be informed of the possible need for additional components. In emergency, if the blood group is unknown, then immediate transfusion with **Grou**p O, rhesus D (RhD) negative is mandated followed by switch to group-specific blood as soon as feasible.[7]

In the event of massive hemorrhage (PPH >1500 mL), we have to initiate the massive transfusion protocol (MTP) using empiric fixed ratios of red blood cells, fresh frozen plasma (FFP), and platelets for better outcomes.[20]

However, empiric transfusion, especially in the absence of coagulation tests which confirms the coagulopathy, may lead to excessive transfusion of blood and plasma products leading to increased risk of complications, such as transfusion-associated circulatory overload and transfusion-associated lung injury. Hence, judicious transfusion is the need of that hour based on clinical evidence than fear!

In a multicenter, double-blind, randomized, placebo-controlled trial, researchers concluded that a fibrinogen level of >2 g/L appeared sufficient for achieving hemostasis in the setting of PPH.[21]

If there is severe hypofibrinogenemia (<2 g/L), the International Society on Thrombosis and Haemostasis (ISTH) recommends using either cryoprecipitate (~15 g/1000 mL) or fibrinogen concentrate (20 g/1000 mL) to maintain fibrinogen >2 g/L to manage PPH. At this point, avoid early or excess FFP transfusion as it has low fibrinogen content (2 g/1000 mL) and could lead to hemodilution due to its volume as opposed to cryoprecipitate or fibrinogen concentrates to improve the fibrinogen levels.[22]

While studies have supported efficacy of FFP in massive obstetric hemorrhage, they are against pre-emptive use in early hemorrhage when fibrinogen level is normal. FFP transfusion guided by results from TEG/ROTEM that can predict the need for FFP, has led to judicious use of blood components with reduced blood utilization, lower risk of circulatory overload preventing unnecessary transfusions.[7]

So when should we use FFP? A recent review suggested that FFP will be needed once other coagulation factor deficiencies sets in at a later stage in PPH, that can only be replaced by the FFP at 15 mL/kg to maintain activated partial thromboplastin time/prothrombin time about 1.5 × normal.[7] Usually, this occurs after 4–6 packed red cells transfusions have been transfused.

As far as thrombocytopenia is concerned, there is a consensus that platelets should be transfused at platelet counts $<75 \times 10^9$/l aiming to maintain a level $>50 \times 10^9$/L during ongoing PPH[22]

either with random platelets (of any group) or single-donor platelets (preferred but expensive and needs a directed donor) on intermittent basis till the bleeding stops.

In life threatening PPH, once 8 units of RBC and FFP have been transfused and if tests of hemostasis remain unavailable , then we should initiate platelet transfusion to prevent onset of dilutional or massive transfusion associated coagulopathy which itself can increase risk of morbidity and mortality.[22] Alternatively as discussed earlier, point-of-care tests could guide appropriate use of other blood components.

ROLE OF INHIBITORS OF FIBRINOLYSIS IN PPH

The CRASH-2 study demonstrated that use of tranexamic acid (an inhibitor of fibrinolysis) resulted in a 21% reduction in mortality due to bleeding. As a result of this study, the World Health Organization now strongly recommends early use of IV tranexamic acid (within 3 h of birth) in addition to standard care for women with clinically diagnosed PPH after vaginal birth or lower segment cesarean sections.[23,24]

The WOMAN study is a placebo-controlled trial conducted in 21 countries that assessed the impact of tranexamic acid in women with PPH >500 mL after vaginal birth or >1000 mL after cesarean section. Administration of 1 g of tranexamic acid (with a second dose given for ongoing bleeding) resulted in an overall reduction in death related to bleeding of 19% (RR, 0.81; 95% CI, 0.65–1.00) when given within 3 h.[25]

SUMMARY

PPH-related mortality is potentially preventable with timely diagnosis and management. Survivors of the life-threatening hemorrhage can have several health related issues that impact future quality of life if PPH is inappropriately treated. The key to a successful outcome is identification of the high risk PPH patient antemortem during pregnancy labor immediate post-operative, by prompt resuscitation, monitoring, investigation, and arrest of bleeding, all which happens simultaneously. Use of tranexamic acid has been encouraged to reduce the amount of blood loss.

It is imperative that every hospital or facility should be able to recognize the onset of PPH, have a MTP protocol in place with trained personnel, take consent for blood transfusion after counseling, and adhere to this protocol strictly at the time of crisis preferably at a site that has a blood bank, quality assured laboratory, and emergency facilities including an intensive care unit.

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