MAJOR OBSTETRIC HEMORRHAGE

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Major obstetric hemorrhage (MOH) is one of the leading cause of maternal morbidity and mortality in the obstetric practice. Life-threatening hemorrhage occurs in around one in every 1000 deliveries with significant differences between developed countries and third world countries. It is reported that massive obstetric hemorrhage in Africa and Asia is responsible for 30% of maternal deaths while in the UK and the US it is accountable for 3.4% and 11.4% respectably [1, 2,3]. In 2015, MOH is reported in 8.7 million cases which led to 83 000 deaths [4].

There is no universal statement on the unique definition of massive obstetric hemorrhage. However, according to most institutions it is defined as a blood loss of more than 1 500 ml or a fall in hemoglobin levels under than 4g/dl . Also, blood loss greater than 3000 ml in less than 3 hours (50% of blood volume) or blood loss of 150 ml/minute in 20 minutes (>50% of blood volume) or the need for transfusing more than 4 units of blood during pregnancy, child birth or in the postpartum period may represent MOH.

Major obstetric hemorrhage owns typical features and differs from surgical hemorrhage in non-pregnant population. Several factors are responsible for such a phenomenon: 1. early diagnosis of hypovolemia is impaired; the physiological changes associated with pregnancy (cardiac changes by term is increased in stroke volume by 30%, heart rate by 10-15 b/min and cardiac output by 50%, peripheral vascular resistance decreased) may mask the early signs of shock like tachycardia and increased systemic vascular resistance; hemodynamic collapse occurs only when almost 40-45% of circulating volume is lost. All these factors may lead to delay in recognition of blood loss and initiation of life-saving treatment (16, 17); 2. difficulty in exact blood loss estimation. The ability to estimate blood loss in parturient is compromised due to the mixing of blood with amniotic fluid or concealment of blood in the uterus, peritoneal cavity or retroperitoneal space; 3. high placental blood flow. The uteroplacental unit in the third trimester has a potential source of rapid and life threating bleeding, because it receives 12% of the cardiac output at term pregnancy (i.e. 700 ml/min); 4. inability to recognize the risk factors: special care and attention is needed to identify the risk factors responsible for hemorrhage in the obstetric

period (11). Ultrasonography helps in diagnosing the cause of hemorrhage and may help also to confirm the presence of concealed hemorrhage in asymptomatic patient.

The causes for obstetric hemorrhage: depending on the time of the pregnancy and onset time, MOH can be classified into three types: ante-partal, intra-partal and post-partal. The most common factors for ante and intra partal causes of hemorrhage are: placenta praevia, both placenta accrete and pancreta, placental abruption, uterine rupture and trauma. Placenta accrete (pancreta) are abnormal implantations of the placenta with partial or complete infiltration in the myometrium of the uterus; placenta previa is also an abnormal implantation of the placenta low in the uterus and over the uterine cervix. Placental abruption is abnormal separation of the placental lining from the uterus. Maternal hypertension, preeclampsia, trauma, advanced age, history of previous abruption, multiparity, elderly primigravida and previous uterine surgery are all risk factors for developing a placental abruption or placenta previa. Uterine rupture is regarded as being a life threatening emergency with a very high morbidity and mortality rate although it is regarded as a very rare cause of APH (7).

Post-partal hemorrhage (PPH) is most commonly ascribed as forms of **4 T's** – tone (utery atony), trauma, tissue (retention), thrombin (coagulopathy), table 1.

Table 1. Risk factors for PPH.

Classification	**Risk factor**
Tone *(utery atony)*	*Multiple pregnancy* *Previous PPH* *Obesity (BMI>35)* *Large baby (>4kg)* *Prolonged Labour (>12hrs) / prolonged 2nd stage* *Advanced maternal age (>40 years, primiparous)* *Retained placenta* *Asian ethnicity* *Placenta Praevia*
Tissue	*Retained placenta* *Placenta accreta, increta and percreta (high mortality: associated with previous caesarean section)*
Trauma	*Delivery by caesarean section (emergency>elective)* *Operative vaginal delivery* *Mediolateral episiotomy* *Large baby (>4kg)*
Thrombin	*APH (placental abruption)* *Pre-eclampsia* *Sepsis*
Other	*Pre-existing coagulation problems,*

	thrombocytopaenia, women taking anticoagulants

Uterine atony is the most common cause of PPH with prevalence of over 70% of cases. Genital tissue trauma can be associated with operative cesarean delivery, episiotomy and delivery of a neonate of >4kg. The causes of coagulation problems may be pre-existing as congenital disorders or they can be acquired. Most usual ante-natal bleeding disorders seen in pregnancy involve von Willebrand disease and other coagulation factor deficiencies; inherited disorders in platelet number and or their function. Acquired coagulopathy in the post-partal period can be due to DIC that evolves in patients after massive abruptions, amniotic fluid embolism and can also be associated with prolonged carriage of a dead fetus (table 2).

Table 2. The most frequently causes of DIC related to obstetrics:

Causes of DIC related to obstetrics:
Intrauterine death (>2 weeks previously)
Amniotic fluid embolus
Sepsis
Pre-eclampsia
Placental abruption
Retained products of conception
Induced abortion
Excessive bleeding
Acute fatty liver

Dilutional coagulopathy after bleeding can occur due to hemodilution from the replaced blood (80%) with large volume of fluids replacement that do not contain adequate coagulation factors, making patients prone to develop DIC. Hypothermia and acidosis can worsen the situation. The use of anticoagulants (LMWH) during pregnancy can also be associated with PPH. APH and PPH can present as vaginal or can be concealed, so a high clinical suspicion should always be aroused in patients with existing potential risk factors for these conditions.

Management of major obstetric hemorrhage: Basically, one of the main problems in obstetric hemorrhage is to try to differentiate between bleeding caused by tissue and vascular injury and bleeding due to a concurrent impairment of coagulation. Regardless of the primary cause of hemorrhage, inevitably all will result in coagulopathy if early treatment is not successful (8). Management of MOH is focused toward 1. maternal resuscitation and 2. treatment of the cause of the hemorrhage.

In a massive hemorrhage or patient in clinical shock, parturient need active resuscitation. Maternal resuscitation should be done with the aim of volume replacement and improving the oxygen carrying capability (9,10). Irrespective of the degree of hypovolemic shock,

fluid therapy is best guided by continual assessment of maternal vital signs, hemoglobin, acid base balance and urine output. Signs suggestive of hypovolemia in APH patients should be monitored carefully but practitioners should be aware that the extent of bleeding is almost always underestimated in obstetric patients (Table 3).

Table 3. Typical signs in hypovolemic in non-pregnat populations.

Assessment of intravascular depletion: signs suggestive of hypovolemia
a. Hypotension *b. Heart rate > 120 beats/minute* *c. Urine output < 0.5 ml/kg/minute* *d. Capillary refill time < 5 seconds*

* early signs of hypovolemic may be impaired in obstetric patients.

Following factors need to be addressed as first step of maternal resuscitation in MOH (Table 4):

Table 4. First step measures for MOH.

Protocol for resuscitation in massive hemorrhage
Assess airway *Assess breathing* *Evaluate circulation* *Oxygen by mask: 10-15 litres/minute* *Intravenous access - 14 G cannula x 2, central venous cannulation in. CVK in collapsed pts* *Left tilt position* *Keep the mother warm using appropriate available measures* *Until blood is available, infuse up to 3.5 litres of crystalloid (RL 2 litres, avoid hypertonic solutions) and/or colloid (1-1.5 litres) as rapidly as possible* *The fluid should be adequately WARMED.* *Special blood filters should NOT be used as they slow the rate of infusion.*

Special care should be given not to infuse cold fluids in order to prevent hypothermia and coagulopathy. Hypothermia and acidosis significantly impair coagulation. For those reasons, all i.v. fluids should be warmed and the patient's temperature must be maintained if necessary by active warming.

Once 3.5 l of warmed crystalloid (2500ml) and/or colloid (1000ml) have been infused, further resuscitation should continue with blood. Blood transfusion should always be initiated as early as possible in MOH. When crossmatched blood is not available, uncrossed group specific blood or 'O' - negative blood should be given. It is very important to remember that hemorrhage results in the loss of not only red blood cells but also blood components and platelets. There is recent data from military institutions that aggressive replacement of coagulation products may improve outcome . Once four units of packed red blood cells (RBCs) have been transfused, consideration should be given to the replacement of other blood components (1:1 ratio of RBC to FFP) (18). Transfusion of RBCs alone

increases the oxygen carrying capacity of blood but will not correct an underlying coagulopathy.

The best way to guide transfusion procedure is based on regular full blood count and coagulation studies, however in a major hemorrhage, waiting for coagulation results from the laboratory must not delay transfusion of coagulation factors. Treatment goals transfusion used by the UK military provide useful guidelines for patients with MOH. The following may serve as a guide to the main hematological goals in the management of massive blood loss (Table 5).

Table 5. Guide to use of blood products in MOH.

UK military
Hb > 8g.dl-1 If less, transfuse RBCs INR < 1.5 If prolonged, transfuse Fresh Frozen Plasma (FFP) Platelets > 50 x 10^9.l-1 if less, transfuse platelets Fibrinogen > 1.5g l-1 if less, transfuse cryoprecipitate 1unit/5kg

Suspicion of disseminated intravascular coagulation should prompt earlier administration of platelets and cryoprecipitate.

Monitoring treatment of MOH: Rapid administration of large quantities of stored blood components in MOH will result in a profound metabolic disturbance. The severity of this metabolic disturbance is unpredictable but must be anticipated and managed to prevent avoidable morbidity and mortality. Close monitoring is essential to guide therapy and minimize the potential complications of massive transfusion. Pathology monitoring may be via the laboratory or through the use of Point of Care Testing (POCT).

The two most important biochemical disturbances complicating massive transfusion are hyperkalaemia and hypocalcaemia. Maintenance of normal calcium concentrations during hemorrhage helps prevent coagulopathy also. Ten milliliters of 10% calcium chloride per 4 units packed red cells or blood are part of the routine management of hemorrhage by the military.

Fresh frozen plasma should be given in a ratio to 1:1 to blood and early transfusion of platlets should be considered (11). With the recommendations in the British Committee for Standards in Hemathology quideline, fresh frozen plasma is usually given empirically without waiting for the coagulation screening in patients in which we consider to have coagulation alteration (placental abruption, amniotic fluid embolism, dead fetus) or in face of extended bleeding (18). Treatment with 1 liter of FFP and 10 units of cryoprecipitate (2 packs) can be given, while awaiting coagulation studies (17). The goal is to maintain thrombin and fibrinogen generation while replacing factors of coagulation as early as

possible (12). Giving unnecessary plasma and platelets should be discouraged in order to reduce the risk of transfusion-related acute lung injury. Point of care coagulation tests may aid decision-making and reduce unnecessary transfusions.

Fibrinogen is essential for coagulation and is a vital component in the coagulation pathway. It is massively consumed during major obstetric hemorrhage and levels rapidly decrease early in the hemorrhage. During pregnancy, fibrinogen levels increase and women should be considered severely hypofibrinogenaemic and transfused fibrinogen if levels falls below 1.5 g/l. It is recommended to give fibrinogen rich products (FFP; cryoprecipitate, fibrinogen concentrate) with the aim to keep fibrinogen levels above 2gr/L. Low fibrinogen levels <2gr/L are predictors for major obstetric hemorrhage. The other advantage of giving cryoprecipitate and fibrinogen concentrate is that they don't cause volume overload or haemodilution (12).

Prothrombin complex concentrate (PCC) is a derivate from the cryoprecipitate supernatant from large plasma pools, from which antithrombin and factor XI are removed. 2 variants exist - 3 factor PCC (factor II, IX, X) and 4 factors PCC (factor II, VII, IX, X). Before the era of recombinant factors it has be used as a treatment for hemophilia. Now its clinical use is mainly as replacement therapy in emergency settings. Several studies have shown that PCC can reduce the need for transfusion in patients with major hemorrhage (20). It can be administered prophylactically in patients with coagulopathy (prolonged PT/INR) or can be administered in patients with postoperative bleeding with a normal coagulation profile (off label indication).

Despite the limited evidence for its use, *activated factor VIIa* can be used as a treatment option for the coagulopathy caused by a MOH, but only if the patient has adequate concentrations of fibrin-more than 1 g/l and platelets-more than 20x109/l. Using activated factor VIIa raises a major concern about the risk of thrombosis (13). According the Green-top Guideline No. 56, recombinant factor VII should only be used if coagulopathy cannot be corrected by massive blood component replacement as it causes poorer outcome in women with AFE (16).

Tranexemic acid (TA) is an antifibrinolytic and is recommended by the WHO to be used in MOH, independently of the cause. The WOMAN trial revealed that TA should be started in the first 3 hours after PPH in a dose of 1gr, repeating the dose in the next 30 minutes if the bleeding doesn't cease. Prolonging its initial use reduces its effect, with no effect if given 3 hours after onset (14,15).

Patients in which we have clinical suspicion for major bleeding should be promptly treated based on preemptive knowledge. Throughout the treatment Hb, hct and coagulation

profile should be repeatedly screened but time should not be wasted to wait for laboratory results. If available TEG and ROTEM can be used to guide the treatment of the coagulopathy.

The main therapeutic goal management of massive blood loss are summarized in Table 6.

Table 6. Treatment targets for massive transfusion.

Physiology	Hematology	Biochemistry
Systolic Blood pressure of 90mmHg *Urine output of at least 0.5ml/kg/hr* *Core Temp > 36 C*	*Haemoglobin >8 g/l* *Haematocrit > 3%* *Platelet count > 75 x 109 /l* *Fibrinogen > 1.5 g/l* *PT and APTT < 1.5 x mean control* *pH >7.3*	*Ionised Ca2+ >1.0 mmol/* *Lactate < 2 mmol/l l* *Base Deficit 3%* *K+ < 5.0 mmol/l* *Core Temp > 36 C*

** From a guideline from the British Committee for Standards in Hematology.*

Pharmacological treatment options include uterotonic drugs. These drugs treat and prevent uterine atony as the main cause of PPH and can control and prevent the development of a MOH. Various uterotonic drugs are used, all of which should be used with caution:

Oxytocin is the first line treatment for uterine atony but it should be used with care in patients with decreased vascular volume because it can precipitate tachycardia and hypotension. It reduces the risk of PPH by 60% (7). It causes vascular muscle relaxation which can cause hypotension with a reflex tachycardia. This may occur particularly if it is given as a bolus dosage so this bolus should not exceed 5 units i.v., which may be repeated and should always be given slowly. This is commonly followed by an infusion at 10 units h^{-1}.

Ergometrin is recommended as a second-line uterotonic. It can be given i.v. but the risk of severe adverse reactions is increased. It can worsen hypertension and is contra-indicated in hypertensive conditions and preeclampsia as it tmay provoke prolonged severe hypertension. The recommendation usage is i.m. (500 μg) or slow i.v. (250–500 μg) only in a life-threatening emergency.

Carboprost - methyl prostaglandin F_{2-a} is used when other uterotonic drugs fail to cease PPH due to uterine atony. It is contraindicated in patients with asthma due its ability to cause bronchospasm. It can also cause nausea and vomiting.

Misoprost - prostaglandin F1 is also when other uterotinic drugs fail to control the bleeding. It can cause transient increase in temperature and shivering.

Surgical management may be needed to manage MOH. This includes removing of the residual placenta, intra-uterine ballon tamponade, uterine and hypogastric artery ligation or uterine suture and abdominal hysterectomy (HTA). The decision to perform a HTA should be considered in patients in which previous medical procedures are not successful and the patient continues to bleed and become hemodynamic unstable. The focus of resuscitation in these patients should be preservation of theirs life rather than preservation of theirs uterus.

CONCLUSION

Obstetric hemorrhage is frequently underestimated, so identification of risk factors and early recognition of MOH is priority for successful outcome. The role of anesthesiologist is crucial but the management of hemorrhage should be multidisciplinary with precise plan of action. All obstetric units should have a protocol for the management of hemorrhage and immediate access to O-Rhesus negative blood. Call for senior help is important. Early transfusion of blood and blood components reduced the incidence and severity of coagulopathy and other complications. If hypofibrinogenemia is identified during PPH, fibrinogen substitution may be an important early intervention. Mandatory testing of coagulation is recommended to allow rational use of products.

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