**Introduction:** Massive obstetric haemorrhage (MOH) remains one of the leading causes of maternal mortality and morbidity worldwide. A study by the World Health Organization revealed that 25-30% of maternal deaths globally are due to peripartum hemorrhage. During a woman’s life cycle, pregnancy is a period in which she is at risk for hemorrhagic events and obstetrical syndromes that may develop into disseminated intravascular coagulation (DIC). This life-threatening condition is a complication of several obstetrical and non-obstetrical causes. Acute obstetrical hemorrhage is one of the leading causes for DIC in pregnancy and is one of the most avoidable etiologies of maternal death. The pathology, although difficult to categorize clearly, can be subdivided into dilutional coagulopathy (e.g., atonic bleeding, genital tract trauma) and consumption coagulopathy (e.g., placental abruption); both of these pathologies can result in DIC. Hence, prevention of DIC in MOH is largely dependent on prevention and effective management of MOH. As there is no single diagnostic test for DIC and there is a spectrum of clinical severity, the true incidence of obstetrical DIC is not known. In one of the large surveys, antecedent causes for peripartum DIC included placental abruption (37%), postpartum hemorrhage or hypovolaemia (29%), preeclampsia/HELLP (14%), acute fatty liver (8%), sepsis (6%), and amniotic fluid embolism (6%).

Apart from anaesthesia for surgical interventions, anesthesiologists are increasingly called upon to help manage the resuscitation of patients with MOH, which include overseeing transfusion decision-making and the treatment of hemorrhage-related coagulopathy.

**Definitions:** Definitions of MOH vary. MOH is defined as blood loss from uterus or genital tract >1500 ml or a decrease in haemoglobin of >4 gm/dl or acute loss requiring transfusion of >4 units of blood.

Blood loss may be:
1. **Antepartum Haemorrhage (APH)** - after 24th week gestation & before delivery; for example: placenta previa, placental abruption, bleeding from vaginal or cervical lesions.
2. **Postpartum Haemorrhage (PPH)** - after delivery. APH often progresses to PPH.
   - **Primary PPH:** Within 24 hours of delivery (also defined as >500 ml following vaginal delivery and >1000 ml following a caesarean section).
   - **Secondary PPH:** 24 hours to 6 weeks post-delivery; e.g., uterine atony, retained products of conception, genital tract trauma, uterine inversion, abnormal placentation, puerperal sepsis, uterine pathology such as fibroids.

**Assessment of MOH:** Considerable problems are recognised in the accurate measurement of blood loss. Hence definitions based on volume alone have some shortcomings. Both visual and measured loss can be highly inaccurate and difficult to calculate. Loss from placental abruption, uterine rupture or post-
caesarean delivery may be partially or completely concealed. Presence of amniotic fluid makes accurate estimation challenging.

Clinically, women experiencing obstetric hemorrhage are generally in good health, young and initially compensate well for losses until the circulating blood volume is very low. The physiological changes of pregnancy mask the magnitude of the blood loss. Blood loss is generally underestimated both in volume and rapidity, may delay active steps being taken to prepare for or prevent further bleeding. Modified early obstetric warning score (MEOWS) is a useful bedside tool for predicting morbidity and to aid early recognition and treatment of MOH. MEOWS include looking for signs such as tachycardia, hypotension, decreased urine output, pallor, lower abdominal pain, and cold peripheries. The “rule of 30” is useful - if the patient’s systolic BP drops by 30 %, the heart rate rises by 30%, the respiratory rate increases to more than 30/min, the haemoglobin or haematocrit drops by 30% and the urine output decreases to <30 ml/h, the patient is likely to have lost 30% of her blood volume. Active periodic estimation improves the accuracy of estimation.

**Causes of MOH:** may be conveniently remembered using 4 T’s as a mnemonic: Tone (Uterine atony), Tissue (retained products), Trauma (cervical & genital tract trauma during delivery) and Thrombosis (coagulation disorder). Other Risk factors include: Abnormal placentation /abruption, prolonged labour, multiple pregnancy, polyhydramnios, large baby, obesity, previous uterine atony & coagulopathy.

**Prevention of MOH:** Placenta previa and abruption are major causes of significant hemorrhage in the third trimester. Cesarean section is the recommended mode of delivery. The most significant intervention shown to reduce the incidence of PPH and need for blood transfusion is active management of the third stage of labour. This represents a group of interventions including early clamping of the umbilical cord (at 1 to 2 minutes if haemorrhage is not expected), controlled cord traction for placental delivery & prophylactic administration of uterotonic at delivery (e.g. oxytocin). Other measures to prevent or reduce the impact of MOH include •Avoidance of prolonged labour •Minimal trauma during assisted vaginal delivery •Detection & treatment of anaemia during pregnancy •Identification of placenta previa by antenatal ultrasound examination •Antenatal Magnetic resonance imaging (MRI) in suspected placenta accreta/percreta to consider delivery by multidisciplinary planning.

**Goals of management:** several guidelines / recommendations exist for managing MOH. Therapeutic goals may be summarized as •Haemoglobin > 8g/dl •Platelet count > 75 x 10^9/l •Prothrombin < 1.5 x mean control •activated prothrombin times < 1.5 x mean control •Fibrinogen > 2.0 g/l.

**Management:** On some occasions, cases at high risk of MOH can be predicted; e.g. caesarean section in a lady with a low lying placenta and previous uterine scar (may be at a risk of placenta accreta and massive blood loss). In unanticipated MOH, early arrangements have to be made on emergency basis. Different steps for the management of major PPH are depicted in a flow chart (figure1). •*Prompt communication* between anesthesiologist, obstetrician and haematologist, blood bank, nursing and laboratory staff is essential for effective evaluation and management of excessive blood loss.
Abbreviations: ECG electrocardiogram; FBC full blood count; FFP fresh frozen plasma; Hb haemoglobin; IV intravenous; IM intramuscular; LFTs liver function tests; PLT platelets; RhD rhesus D; U&Es urea and electrolytes.

Figure 1. Flow chart of the different steps for the management of major PPH
Resuscitation, monitoring, investigation and treatment should occur simultaneously
• **Restoration of blood volume:** One of the most important strategies in the control of obstetric hemorrhage is haemostatic resuscitation. The speed with which obstetric hemorrhage occurs makes it life threatening. It may be successfully managed with blood transfusion protocol based management. Resuscitation of massive hemorrhage has shifted towards the earlier administration of higher doses of fresh frozen plasma (FFP) and reducing serious complications and mortality by limiting the conventional use of crystalloids and colloids.

• **Correction of defective coagulation:** Use of fibrinogen concentrates, cryoprecipitate, Tranexamic acid, apart from fresh frozen plasma as a promising alternative for obstetric resuscitation and for minimizing the risks and complications of obstetric hemorrhage

• **Evaluation of response to treatment**

• **Treating the underlying cause of bleeding**

Early use of blood and blood products to correct hypovolaemia instead of excessive crystalloid and / or colloid infusion, prevention of hypothermia, maintenance of acid base balance and prevention of hypocalcaemia are important steps in preventing / reducing MOH and coagulation defects / DIC

**DIC in MOH**

In MOH, in addition to optimizing obstetric management, correction of any coagulopathy is likely to improve outcomes. There is no single laboratory test that can establish or rule out the diagnosis of DIC. As such, a diagnosis of DIC should be made based on an appropriate clinical suspicion (e.g., abruptio placentae, bleeding tendency at surgical wounds, venipuncture sites, gums, nose, urogenital tract, or rectum) supported by relevant laboratory tests (e.g., platelet count, INR, aPTT, FDPs, thromboelastogram). Also, DIC is an extremely dynamic situation and the tests are a snapshot of this dynamic state. In addition, the underlying clinical condition can have an influence on the laboratory tests. However, a combination of tests when repeated (trend) in a patient with a clinical condition known to be associated with DIC can be used to diagnose the disorder with reasonable certainty in most cases.

The key to good outcomes is comprehensive local protocols for early recognition and treatment of MOH by senior clinicians. There are limited data on how best to assess and correct abnormalities of coagulopathy associated with MOH. The recent guidance from the SSC of the International Society on Thrombosis and Haemostasis (ISTH-2016) gives a pragmatic approach.

**Pathophysiology of DIC in MOH:** At term increased levels of procoagulant factors and decreases in anticoagulants induce a prothrombotic state. Coagulopathies associated with MOH differ from those associated with trauma-induced massive hemorrhage. The etiology of the coagulopathy of MOH relates to varying proportions of dilutional coagulopathy, localized consumption, disseminated consumption and/or increased fibrinolysis. Dilutional coagulopathy refers to replacement of blood loss with crystalloid and colloid, leading to dilution of coagulation factors and platelets. Consumption localized to the placental bed and uterus may be marked in placental abruption and may also be a feature of uterine atony and retained or adherent placenta. Disseminated intravascular coagulation (DIC) in a true sense is
more commonly associated with amniotic fluid embolus (AFE), infection and severe cases of abruption and pre-eclampsia. It is unusual to develop an early coagulopathy when bleeding is caused by atony or trauma. Early coagulopathy is associated with placental abruptions and AFE. Bleeds of any etiology that are diagnosed late or when the volume of bleeding has been underestimated may be associated with coagulopathy, highlighting the need for early recognition of MOH.

Monitoring haemostatic impairment: Hemostasis may be assessed by: (i) clinical observation, (ii) laboratory-based PT/aPPT, Clauss fibrinogen and platelet count, and (iii) point of care testing (POCT). No high-level data suggest that any strategy is better and all three may be used simultaneously. Coagulopathies may evolve rapidly and repeated testing and observation of trends is more useful than single measurements.

Laboratory tests are widely available and have well regulated quality control, but are often too slow to be useful in acute and rapidly evolving bleeds and inevitably reflect past haemostatic status. Serial tests are useful, however, for following trends in an evolving clinical scenario. Clauss fibrinogen should always be measured as part of the routine coagulation screen because it falls early and may be reduced to a clinically significant level despite adequate levels of other procoagulant factors. Derived fibrinogen assays (indirectly measured) may be misleading and should not be used. DIC may be uncommon in MOH when diagnosed based on ISTH criteria, and this scoring system is not validated in the context of MOH.

Table 1. Onset and likelihood of coagulopathy depending on cause of postpartum haemorrhage.

<table>
<thead>
<tr>
<th>Cause</th>
<th>% women with fibrinogen &lt;2 g/L at 1000-2000 mL</th>
<th>% women with PT or aPTT abnormal at 1000-2000 mL</th>
<th>% women with platelets &lt;75 at 1000-2000 mL</th>
<th>% women requiring transfusion FFP</th>
<th>% women requiring platelet transfusion</th>
<th>Time of onset of coagulopathy</th>
<th>% of bleeds &gt;2000 mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterine atony n=146</td>
<td>2.2</td>
<td>1.4</td>
<td>0</td>
<td>14</td>
<td>2.4</td>
<td>Late</td>
<td>27</td>
</tr>
<tr>
<td>Genital tract and surgical trauma n=125</td>
<td>1.6</td>
<td>0</td>
<td>0.8</td>
<td>4</td>
<td>0.8</td>
<td>Late</td>
<td>13</td>
</tr>
<tr>
<td>Uterine rupture n=3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>66</td>
<td>0</td>
<td>Late</td>
<td>100</td>
</tr>
<tr>
<td>Retained or adherent placenta n=36</td>
<td>6</td>
<td>6</td>
<td>3</td>
<td>8</td>
<td>3</td>
<td>Late</td>
<td>24</td>
</tr>
<tr>
<td>Placenta previa n=8</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>37.5</td>
<td>0</td>
<td>Late</td>
<td>50</td>
</tr>
<tr>
<td>Placental abruption n=14</td>
<td>38</td>
<td>0</td>
<td>0</td>
<td>42</td>
<td>21</td>
<td>Early (often before PPH recognised)</td>
<td>57</td>
</tr>
</tbody>
</table>

*[Data derived from Collins et al Blood 2014; 124: 585–95].*
DIC is characterized by falling platelets and fibrinogen and rising fibrin degradation products (FDPs). FDPs are raised at term and there are no data available from which to define a cut-off that is diagnostic of DIC during MOH. In an acute bleed it may not be possible to distinguish DIC from other causes of coagulopathy. Recognition of DIC, if possible, is important because of the potential for end-organ micro vascular thrombosis.

POCTs using thromboelastometry (TEM), combined with a treatment algorithm, are associated with reduced bleed volume and blood-product use both outside and within the obstetric setting. The main advantage is that results are known sooner. It is helpful to know that hemostasis is normal so that clinicians can focus on treating other causes of bleeding. If used, a quality control protocol should be agreed with the hematology department. Normal ranges for TEM during pregnancy differ from those in the non-pregnant population. The mean clot firmness and alpha angle (Rotem) and maximum amplitude and alpha angle (TEG) are larger and clot time (Rotem) and reaction time (TEG) are shorter; this should be taken into account when interpreting results. Systemic hyperfibrinolysis can be detected by TEM but TEM lacks sensitivity in less severe cases. Evidence to recommend routine use of TEM for MOH is insufficient. The Fibtem assay can be used as a surrogate measure of fibrinogen during MOH. This assay does not measure the same haemostatic parameter as Clauss fibrinogen but provides a similar indication of haemostatic competence and outcome. Online algorithms using Rotem and TEG during MOH are readily available and may be useful.

The ISTH recommendations for MOH include •to monitor hemostasis with either PT/ aPTT and Clauss fibrinogen or POCTs using thromboelastometry during MOH. If bleeding persists serial measures should be performed •If thromboelastometry is used, blood component replacement should be based on a local algorithm and a quality control protocol agreed with hematology •Lab. monitoring of platelet count •derived fibrinogen assays (indirectly measured) should not be used.

Treatment of haemostatic impairment

Blood product replacement: There are limited data available to inform the treatment of haemostatic impairment during MOH. It is not known whether it is best to correct to normality for the time of delivery or to normality for the non-pregnant population. Fibrinogen falls earlier than other coagulation factors during MOH and may be low despite normal PT/aPTT.

Based on the limited data available the following guidance is suggested by ISTH but it is acknowledged that clinicians may choose to use different transfusion policies

•recommend that, if POC or laboratory tests of hemostasis are normal, then no FFP is required •suggest that if PPH is ongoing, 15 ml/kg FFP should be infused if the PT/aPTT is prolonged to prevent progression to a ratio 1.5 x normal •suggest that if PT/aPTT is >1.5 x normal, larger volumes of FFP may be required to correct hemostasis •suggest that blood-product replacement based on POCTs supported by a local algorithm is likely to be at least as efficacious as replacement based on laboratory testing •suggest that if no coagulation results are available and bleeding is ongoing, then, after 4 units of RBC, 4 units of FFP should be infused and 1 : 1 RBC : FFP transfusion maintained until haemostatic test results are known •suggest that FFP should not be used before haemostatic tests are available in MOH caused by trauma.
or uterine atony until 4 units RBC have been infused because haemostatic impairment is unlikely. FFP before haemostatic tests are available may be justified for placental abruption, AFE or if recognition of MOH has been delayed •suggest that a fibrinogen of at least 2 g/L should be maintained during ongoing obstetric bleeding, even if PT and aPTT are normal. Either cryoprecipitate or fibrinogen concentrate may be used •recommend against the use of fibrinogen concentrate in an unmonitored or pre-emptive manner •recommend that platelets should be transfused when the platelet count is <75x10^9/L based on laboratory monitoring and against 1 : 1 : 1 RBC : FFP : platelet transfusion ratios •In cases of massive ongoing bleeding where women have been given 8 units of RBCs and 8 units of FFP and no coagulation results or platelet count are available then two pools of cryoprecipitate and one pool of platelets may be given.

**Other haemostatic agents:** The role of tranexamic acid (TA) in obstetric bleeding is not fully established. An open label study of 144 women randomized to TA or placebo after 800 mL blood loss reported a reduction in total blood loss, shorter period of bleeding and fewer women progressing to severe PPH or blood transfusion. A double-blind randomized control trial of TA vs. placebo at elective Caesarean section reported reduced blood loss. The double-blind WOMAN study is investigating the role of TA in PPH after 500 mL blood loss with a primary endpoint of death or hysterectomy.

Recombinant factor VIIa (rFVIIa) has been used in life-threatening PPH or in an attempt to prevent hysterectomy, although this is an unlicensed indication and is associated with an increased risk of thrombosis. An open-label study of 60 μg/kg of rFVIIa vs. placebo in PPH unresponsive to uterotonic demonstrated a reduction in invasive procedures of 93% to 52%, (relative risk 0.56 (0.42–0.76)). There was no difference in bleed volume, blood-product usage or hysterectomy. There were two thrombotic events in the rFVIIa arm. The open-label design may have affected the decision to undertake an invasive procedure and influenced the primary endpoint. It has been recommended that other coagulation factors should be normal before considering infusing rFVIIa. The optimal dose of rFVIIa to use during PPH is unknown but restoration of normal thrombin generation is likely to be achieved with doses lower than 90 μg/kg and doses such as 60 μg/kg may be less thrombotic. If two doses of rFVIIa have not arrested bleeding, further doses are unlikely to work.

Prothrombin complex concentrate (PCC) is occasionally used during PPH. A study is currently investigating its role in combination with fibrinogen concentrate during PPH 2000–3000 mL (NCT01 910675). PCCs are associated with thrombotic events in the non-obstetric population. A deficiency of factor (F) II, VII, IX or X assayed directly or assumed because of an abnormal PT/aPTT is uncommon during PPH.

With regard to these other haemostatic agents the ISTH suggests •women experiencing ongoing PPH should be considered for treatment with 1 gm intravenous tranexamic acid •60μg/kg of rFVIIa can be considered for ongoing PPH unresponsive to standard treatment or to prevent hysterectomy; fibrinogen should be > 2 g/L and platelets > 50x10^9/L. If two doses of rFVIIa have not arrested bleeding, further doses are unlikely to work. •the use of PCC outside of clinical trials is not recommended.

**Anticoagulation:** Hospitals should have locally agreed protocols for venous thromboprophylaxis. In women with massive MOH and coagulopathy, thromboprophylaxis should be started as soon as feasible
after bleeding has been controlled and coagulopathy has been corrected. This should be continued for at least 10 days or until other risk factors are no longer present.

Conclusions: DIC is a serious complication of MOH and a major contributor to mortality. Preventive measures begin with early identification and prevention of MOH itself. The standard diagnostic criteria and the management protocols used in DIC may not be applicable in obstetric patients due to the physiological changes and altered response. Due to limited evidence, expert opinions vary. Reports of several ongoing trials are awaited. Presently the guidance document by ISTH may provide a practical and pragmatic approach to the management of coagulopathy associated with obstetric haemorrhage.

References