OBSTETRIC HAEMORRHAGE

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Hemorrhage is a leading cause of maternal mortality. It is the underlying cause in at least 25% of maternal deaths in the developing world.[1]

In pregnancy there are physiologic adaptations in preparation for blood loss:

- Blood volume increase (1000-2000mls) and increased red blood cell mass.
- Hypercoagulable state (increased clotting factors, including fibrinogen).
- Involution of uterus following delivery has a 'tourniquet effect" on the spiral arteries of the gravid uterus.

Blood loss can occur rapidly because gravid uterine blood flow at term is 600-900ml/minute, and when there uterine atony occurs, more than one unit of blood is lost every minute.

Resuscitation may be inadequate during post partum hemorrhage because:

- Precise measurement of blood loss during cesarean section is almost impossible because of difficulties quantifying amniotic fluid. Blood loss in women with primary post partum hemorrhage tends to be grossly underestimated. In a study of Prasertcharoensuk et al [2] the mean visually estimated blood loss in the third stage of labor was approximately 100ml less than measured blood loss. The magnitude of underestimation increased as the blood loss increased.
- There may be no change in the maternal systolic blood pressure until more than 25% of the blood volume is lost in pregnancy.
- Pregnancy causes increased susceptibility to disseminated intravascular coagulation (DIC).

Causes of Obstetric Hemorrhage:[3]

- Antepartum hemorrhage is seen in 4% of pregnancies and is caused by placenta praevia, abruptio placenta or uterine rupture.
- Early postpartum hemorrhage is seen in 10% of deliveries and is caused by uterine atony (1:20 incidence), genital lacerations, retained placenta, uterine inversions (1:6400 incidence).

Uterine atony is the most common cause of significant bleeding in pregnant women after delivery. High risk situations are:

- Over-stretched uterus: As seen in multiple gestation, macrosomia, polyhydramnios.

A Case Report

A 22–yr-old Gravida 1 Para 0, was brought to the operating room after failed induction of labor with oxytocin for 20 hours. Following the delivery of baby she continued to bleed with estimated blood loss (EBL) approaching 2000ml. The obstetrician stated the uterus was atonic.

How should you manage this emergency?

- Tired uterus: As seen in high parity, prolonged labor, prolonged oxytocin use.
- Sick uterus as seen in chorioamnionitis.

Drugs in Postpartum Haemorrhage

Uterotonic therapy, most commonly with oxytocin and/or ergot alkaloids, is one component in the treatment of postpartum hemorrhage. The first line therapy in patients with postpartum hemorrhage (PPH) is oxytocin, which stimulates the force and frequency of uterine contraction. It has an immediate effect and a half-life of 5 to 12 minutes. Intramuscular oxytocin is circulating in the blood within 2-3 minutes.[4]

The main preservative that is used in Syntocinon ampoules (oxytocin) is chlorobutanol and it has a negative inotropic effect on the cardiac muscles.[5,6] Since Syntocinon has a direct effect on the heart, it is recommended to be used intravenously as an infusion in a concentration of 20-40units/l. Oxytocin given as a bolus IV or fast IV infusion produces a decrease in systolic and diastolic blood pressures. It also produces flushing, reflex tachycardia, and an increase in peripheral blood flow. The use of oxytocin has been associated with pulmonary edema, subarachnoid hemorrhage, cardiac arrhythmias, and anaphylactic reaction.

Ergometrine, an ergot alkaloid derivative, increases both the force and the frequency of uterine contraction probably via alpha-adrenergic receptors, tryptaminergic receptors, or both. This drug produces constriction of arteries and veins, raising the blood pressure when administered in therapeutic dosage of 0.2mg intramuscular. The intensity of the pressor response is enhanced when the blood pressure is already elevated, therefore its use is contraindicated in women with hypertension and necessitates routine assessment of blood pressure before its administration. The ergot alkaloids can produce coronary vasoconstriction, and are often associated with anginal pain and ischaemic electrocardiographic changes in patients with history of ischaemic heart

disease.[7] There is also a relatively high incidence of nausea and vomiting.

Ergometrine is used alone or in combination with oxytocin (Syntometrine) in the prevention and treatment of PPH.[8] Syntometrine has the advantage of rapid onset of action of oxytocin combined with the sustained myometrial response of ergometrine. However, the higher incidence of the side-effects when compared with oxytocin makes it less favorable for routine use in the third stage of labor. Syntometrine (ergometrine 500 mcg combined with oxytocin 5 units) should also be avoided when there is hypertension, pre-eclampsia or cardiac disease.

Oxytocin and ergometrine should not be exposed to high temperatures and light. Studies have found that 90% of the active ingredients are lost after 1 year of storage at 21-25^{0}C.[9] These storage requirements are an important barrier to the effective use of oxytocics in the developing world.

It has been suggested that prostaglandins may be the ideal agents for routine prophylactic use in the third stage of labor. Unlike ergometrine-related agents, prostaglandins do not cause hypertension[10], and have strong uterotonic effects. Misoprostol, the prostaglandin E1 analogue, is the most recent drug to be identified as a useful agent in the prevention and treatment of PPH.

The vaginal route of misoprostol is more potent and side-effects are lower compared to the oral route, but the vaginal route could be inappropriate because of bleeding. It has been reported that misoprostol 800-1000 mcg given rectally[11,12] is an effective intervention in women with severe PPH. Almost all the studies report shivering and pyrexia as side effects of misoprostol and those are shown to be dose-related with a duration of up to 12 hours after administration.

Although misoprostol should not be first choice in the routine management of third stage of labor, in developing countries where resources may be limited and refrigeration of drugs is a problem, misoprostol offers the advantages of being cheap, easy to administer, not requiring special storage and has a long shelf life of several years.

The short duration of action of natural prostaglandins, coupled with a high incidence of side effects, prompted the development of methylated prostaglandin derivates. Hemabate (15-methyl-PGF2 alpha) 250mcg, is as effective as Syntometrine in the treatment of refractory atony[12]. When administered as an intramyometrial injection it has an onset of action of 5 minutes, while its intramuscular use has an onset of action of 45 minutes before maximal effect is seen.[13] Hemabate is expensive and has a high incidence of adverse gastrointestinal side effects such as diarrhea. Asthmatic patients are particularly sensitive to Hemabate since it has the potential to cause bronchoconstriction and intrapulmonary shunting.[14]

Non-pharmacological Management of Postpartum Hemorrhage

The treatment for uterine atony starts with simple interventions but may progress to a hysterectomy if continuous bleeding persists. The treatment options include:

- *Uterine massage*. The first and most accessible option available to the obstetrician in the operating room following a cesarean section is massaging the uterus. Hemostasis following placental separation is initially a mechanical process where the myometrium constricts the spiral blood vessels to stop bleeding. If this does not occur, hemorrhage ensues. Continuous communication between the obstetrician and the anesthesiologist during this time is extremely important. Uterotonics should be given and fluid replacement initiated without delay.

- *Uterine packing*. Packing the uterus with thrombin packs or gauze is a simple and non-invasive technique to attempt to tamponade the bleeding. This technique can be used following vaginal or cesarean delivery. There are concerns regarding infection and prophylactic antibiotics should be administered.

- *Compression sutures*. Alternatives to packing the uterus were sought secondary to concerns regarding infection and pressure necrosis. Lynch et al. used vertical sutures to envelope and compress the uterus. By opposing the anterior and posterior walls of the uterus, blood flow is reduced.[15] This is a simple procedure but evidence is limited to case reports. A modification of this technique makes it possible to apply compression sutures without opening the uterus.[16]

- *Internal iliac (hypogastric) artery ligation*. Bilateral internal iliac artery ligation has been advocated as an effective means of controlling hemorrhage in the postpartum period. Although pelvic blood flow is only reduced by 49%, the pulse pressure is reduced by 85% creating a much reduced pressure and promoting hemostasis.[17] Bilateral hypogastric artery ligation is found to be a relatively easy, safe and successful procedure that can be attempted as an initial surgical approach for severe PPH, especially when uterine conservation is desired.[18] Aortic angiographic studies have identified anastomotic branches of the lumbar, sacral and rectal arteries as the origin of the main collateral vascularisation preventing ischemia and tissue necrosis in bilateral hypogastric artery ligation.[19] A systematic policy of attempting a conservative approach whenever possible is likely to decrease hysterectomy rate, especially when performed early when basic haemostatic procedures have failed. After failure of primary conservative procedure, hysterectomy should be performed promptly.[19]

• In recent years *uterine tamponade* has been used to gain hemostasis and determine whether further surgical measures will be needed to control the bleeding. Inserting a Sengstaken-Blakemore esophageal catheter into the uterus and inflating it with normal saline will create a tamponade. A Foley catheter has also been described for this technique however the balloon is often too small (30cc) to create a tamponade in a uterus immediately postpartum. This technique has been used successfully in cases of uterine atony[20,21] as well as placenta accreta.[22]

• *Uterine artery balloon occlusion*. Catheter arterial embolization has been a recognized method of controlling hemorrhage since the 1960's and more recently, has been used successfully to control postpartum hemorrhage. Uterine artery embolization has several advantages including identification of the specific bleeding site, preservation of the uterus and fertility, and less bleeding from collateral circulation because of more distal occlusion of the bleeding vessels.[23] The technique has good success and low complication rates.[24] One recent review found that embolization was successful in 95% of the 138 published cases of postpartum hemorrhage with a complication rate of 8.7%.[25] The most common complication was a low-grade fever. Some practical issues that need to be considered are the need for a trained interventional radiologist and a fully equipped x-ray department 24 hours a day. Embolization obviates the need for a laparatomy and if need be, arterial ligation can be attempted afterward if bleeding persists. A team approach between the anesthesiologist and the obstetrician can prove useful in identifying patients at high risk for hemorrhage who may benefit from having a prophylactic catheter placed to expedite the embolization technique if needed. Currently it is unclear as to the optimal timing for embolization. However where facilities exist, it is suggested that it should be incorporated into the algorithm at an earlier stage after more conservative measures have failed.[26]

• ***Hysterectomy***. In life-threatening hemorrhage, hysterectomy is the most definitive treatment. This procedure is technically difficult and should not be delayed until the patient is unstable and deteriorating quickly. Early action should be taken to obtain large bore intravenous access, start infusions of crystalloid and colloid, and call for blood products. Maintenance of body temperature with a warm air blower and fluid warmer is essential. An arterial line may be useful and vasopressors should be available. Obtain laboratory studies (full blood count, clotting values, electrolytes) and monitor urine output closely. Patients who are under regional anesthesia may require conversion to general anesthesia if they are hemodynamically unstable or requiring large volume transfusions. Intravenous anesthetics may be necessary (ketamine is ideal) as all volatile agents worsen uterine atony. A subtotal hysterectomy is an acceptable alternative as long as bleeding is not from the cervical branch of the uterine artery or from tears in the lower uterine segment.[27]

Other Treatments

Factor VIIa

Human recombinant factor VIIa is a vitamin K-dependent protein that has been approved by the United States FDA for the treatment of bleeding in Hemophilia A or B patients, acquired inhibitors, and congenital factor VII deficiency. Recombinant factor VIIa promotes clotting through the extrinsic pathway by forming a complex with tissue factor located on the subendothelial surface of damaged blood vessels.[28] This complex then activates factors IX and X which go on to generate thrombin.[29] Currently there are several case studies published where factor VIIa has been used in cases of intractable postpartum hemorrhage.[30, 31] This being said, there is little scientific evidence and it is considered an "off-label" use of the product. It is not currently approved by any health authority for use in obstetrics. In all of the case studies the factor VII was given as a bolus in doses ranging from 60 to 120mcg/kg, effects were seen in as little as ten minutes. The major drawbacks of Factor VIIa are the short half-life (two hours) and the high cost ($ US 1400 per milligram). [32] Repeat dosing may be necessary in cases of ongoing hemorrhage adding the already high cost. Reported adverse effects of recombinant factor VIIa include disseminated intravascular coagulopathy, thrombosis, and myocardial infarction.[33] Clinical conditions that are mediated by tissue factor exposure may carry an increased risk of thrombotic events. In DIC, there is systemic tissue factor exposure to the circulation and administration of factor VIIa could theoretically lead to a more severe coagulopathy and microvascular thrombosis.[34] This is significant in hemorrhaging patients because DIC may develop quickly. While it appears that recombinant factor VIIa may prove useful in life-threatening postpartum hemorrhage when conventional surgical, interventional and blood product support measures have failed,[35] its safety and efficacy is yet to be determined.

Cell Saver

Intra-operative cell salvage has been considered relatively contraindicated in obstetrics because of the fear of amniotic fluid contamination and embolism. In fact, the manufacturer of the equipment states that the use of cell saver is contraindicated in obstetric cases. Because the exact mechanism of the syndrome is not known, the adequacy of the washing process cannot be thoroughly evaluated. A tissue factor derived from amniotic fluid may be responsible for the disseminated intravascular coagulopathy that develops.[36] Other investigators believe that other fetal components may be involved such as fetal squames, lanugo, and/or phospholipids.[37] Without knowing what exactly causes amniotic fluid embolism, we cannot be certain we are removing it with the washing process.

Case Report
A 36 year old female, gravida 6, para 5, Jehovah's witness with five previous abdominal deliveries presents with complete placenta praevia. At 37 weeks gestation, she is scheduled for a caesarean section and preoperatively her Hb is 10g/dl.

The following are risk factors for placenta accreta[39]:

- Placenta previa
- Previous cesarean section
- Advanced maternal age (after age 35)
- Multiparity
- Previous uterine curettage

This patient has almost all of the risk factors for developing placenta accreta. The American College of Obstetrics and Gynecology warns that the rate of placenta accreta following 2 or more caesarean sections and an anterior or central placenta praevia is 40%40. After five cesarean sections, the incidence of placenta accreta is 50%. As anesthesiologists, our main concern must be the patient's risk of hemorrhage.

The antepartum period should be used to optimize and prepare the patient for the operating room. Imaging investigations would be useful to confirm abnormal placentation. This can be done with an MRI or less expensively with vaginal color Doppler sonography. Color Doppler is 96% specific, giving a positive predictive value in high-risk patients of 87% and a negative predictive value of 95%.[41] At least two large bore intravenous catheters should be placed. If the facilities are available, this patient would be a good candidate for a prophylactic femoral catheter placement in preparation for uterine artery embolization should hemorrhage ensue.

Cell saver should be arranged for intraoperative use as most Jehovah's witnesses will accept cell saver blood if it is kept in a closed circuit.

Although hysterectomy is the standard management when intractable bleeding from placenta accreta occurs[47], this has devastating consequences for future fertility. In 1986, Arulkumaran and colleagues[48] first described a conservative method of management of placenta accreta, in which they used systemic methotrexate 50mg as an intravenous infusion, administered on alternate days with a total dose of 250mg. The placenta was expelled on day 11 postpartum. Several similar cases have been reported using methotrexate, however the route of administration, treatment schedules and total doses vary considerably[49]. Although the conservative treatment of placenta accreta with methotrexate seems to be an acceptable alternative for radical surgery, an agreed protocol must be developed. 49 Prophylactic antibiotics should be administered for the entire duration of the procedure.

In 2000, Waters et al looked at cell saver blood from a cesarean section after filtration through a leukocyte depletion filter.[37] The blood was then compared to a maternal blood sample drawn from a catheter placed slightly above the uterine veins in the vena cava. A significant reduction in particulate contaminants (lamellar bodies, fetal squamous cells) was found using the filter although the filtered blood did have increased fetal red blood cells. Because fetal blood cells routinely enter maternal circulation during delivery, it is believed that only in the case of Rhesus incompatibility will this be significant. To prevent isoimmunization, anti-D immune globulin should be administered to the mother. The leukocyte depletion filter appears successful in further reducing contamination of particulate matter in cell saver blood but in cases of obstetric hemorrhage it also reduces the flow rate of the intravenous system to 30ml/min or 80ml/min using a 300mmHg pressure bag. This is an obvious disadvantage during massive hemorrhage. Though unproven, another safety measure to decrease contamination is the use of a double suction set up where the cell saver suction device was used only after delivery of the placenta and the fetal membranes.

It is important to remember that because the incidence of amniotic fluid embolism is rare, 1:8000 to 1:80,000 deliveries,[37] the studies and case reports that are currently available in the literature are insufficient to assess the risk of using cell saver blood in obstetric hemorrhage. It is unlikely that the safety of cell salvage in obstetrics will ever be firmly established. Cell saver use should be limited to times when it is the only way to increase oxygen-carrying capacity and sustain life as in the following case report.

Uterine Inversion
Uterine inversion is a rare complication which is associated with profuse hemorrhage and shock. It occurs when fundal pressure and inappropriate traction on the cord is applied during the third stage of labor in the presence of atonic uterus with open cervix, particularly if there has been fundal implantation of the placenta. The usual clinical presentation is major hemorrhage and abdominal pain. The fundus cannot be palpated and the uterus may fill the vault or protrude from the vagina. Uterine inversion is classified by its extent as incomplete or complete, depending on whether the fundus extends beyond the cervix. It is also classified by its duration as acute or subacute, depending on whether cervical contraction has occurred.[42]

Inversion of the uterus produces profuse and continued post partum bleeding. Bleeding from the placental site is exaggerated as a consequence of restricted venous outflow from the uterus. The degree of blood loss is related to the time the uterus remains inverted. The initial cardiovascular response may reflect a vasovagal reflex due to traction on the

peritoneum, resulting in hypotension and bradycardia. The inverted uterus may also exert traction on the sympathetic nerves thereby contributing an element of neurogenic shock.[43, 44]

Uterine inversion therefore presents a unique problem for the anesthesiologist. First, hypovolemia must be treated and an attempt must be made to restore the intravascular volume and hemodynamic stability. Secondly, anaesthesia is often necessary to allow the obstetrician to perform the maneuvers necessary in replacing the uterus. Third, if manual replacement is not possible and the cervix has already begun to contract, pharmacological intervention may be necessary to achieve rapid relaxation of the uterus to facilitate its reinsertion. The anesthesiologist may therefore face the difficult situation of having to provide analgesia and rapid uterine relaxation with a volatile inhaled anesthetic or nitroglycerine (GTN) in a hypovolemic patient.

Because profuse hemorrhage will continue from the exposed inverted uterus until it is replaced, time is a critical factor in the patient's treatment. While the obstetrician provides manual external pressure on the inverted uterus, rapid intravenous fluids and vasopressors may be required to maintain or improve the arterial blood pressure.

Prompt repositioning requires anesthesia as the patient is often in severe pain, and the choice between a general and regional anesthetic technique needs to be made. Regional block causes sympathetic blockade which is dangerous in the presence of inadequate intravascular volume.

General anesthesia with a potent inhalation anesthetic relaxes the uterus, and use of higher than usual concentrations of potent volatile inhalation agents are often necessary for optimum uterine relaxation for these procedures with the attendant risk of cardiovascular system depression.

Nitroglycerine causes rapid and reliable uterine relaxation, and its use may avoid the need for general anesthesia. Several reports have described the safety and efficacy of intravenous nitroglycerin for uterine relaxation.[45,46]

Nitroglycerine has the advantage of a rapid onset of action (30-40 seconds) in combination with a short-lived effect of approximately one minute. Doses of 50-200 mcg have been used successfully to achieve relaxation without causing significant hypotension or other unwanted side effects.[47] The rapid onset of action of intravenous nitroglycerine creates uterine relaxation in a much shorter time than would otherwise be achieved if an anesthesiologist were relying on the uptake of inhaled anesthetics. The short duration of action allows it to dissipate, obviating the need for reversal.

In patients where epidural anaesthesia was used for labor and delivery, administration of small incremental doses of intravenous nitroglycerine in combination with epidural local anesthetics achieve uterine relaxation and comfort while maintaining stable hemodynamics.

Sublingual GTN is easily and rapidly administered and has demonstrated an equally fast onset of action and, in addition, the preparation is more readily available. The onset of action after sublingual administration is seen within 30-45 seconds which peaks at 90-120 seconds and lasts for up to 5 min.[48] It has been reported that the administration of 800mcg of sublingual GTN has resulted in complete relaxation and reduction of a partially re-inverted uterus within approximately 30 seconds.

Terbutaline and magnesium sulphate have been used for uterine relaxation in this setting. The onset of action of these drugs may be unacceptably long for an acute medical condition, particularly for magnesium sulphate which takes at least 10 minutes to take effect. Moreover, the duration of action is also long and the uterine effects of magnesium sulfate and terbutaline may need to be subsequently reversed.

Once the uterus is replaced, all medications that were administered to produce uterine relaxation should be stopped and uterotonic agents should be administered.

Summary

Postpartum hemorrhage is a major cause of maternal morbidity and mortality. In fact, in many developing countries, postpartum hemorrhage is the leading cause of maternal mortality. Several treatment options are available. Whereas in the past, postpartum hemorrhage almost inevitably lead to hysterectomy and therefore loss of fertility, today, more conservative alternatives can be used with preservation of fertility. These conservative approaches have proven to be useful, especially when performed early when basic haemostatic procedures have failed. However, hysterectomy should not be delayed when the conservative approach fails particularly in remote areas where supplies of fluids and blood may be limited. Close monitoring, good teamwork and timely clinical decision making are vital.

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