DOI: 10.7860/JCDR/2017/22659.9463

Review Article

Obstetrics and Gynaecology Section

Recent Advances in the Management of Major Postpartum Haemorrhage - A Review

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ABSTRACT

Postpartum haemorrhage (PPH) is a leading cause of maternal mortality and morbidity worldwide and 75-90% of these haemorrhage results from uterine atony. Delayed and substandard obstetrics care can kill a woman within hours of Major Obstetric Haemorrhage (MOH). Prenatal identification of at risk women, prompt assessment of blood loss, effective management and involvement of multidisciplinary teams is of utmost importance to save the lives of these women. However, even with the best prenatal care, PPH occurs, it can occur without any risk factors. The first step in management is achieving haemodynamic stability, second being arrest of bleeding, both are done simultaneously. Cases of refractory PPH is managed by postpartum hysterectomy which results in complete inability in hosting a future pregnancy, a psychological impact and risk of intra operative surgical morbidities. This review discusses the current evidence based management of PPH, existing controversies in transfusion of blood and blood products and newer advances in this field. It was conducted by searching the English language medical literature using Medline (1994-2015). The current scenario in developing countries mandates research on newer and practicable strategies to tackle PPH which can be implemented effectively and have an upper edge over the existing practices in the management of PPH.

Keywords: Artery embolisation, Compression sutures, Fibrinogen, Tranexamic acid, Transfusion protocols, Vascular ligation

INTRODUCTION

PPH remains a major cause of both maternal mortality and morbidity worldwide more so in developing countries with an estimated mortality rate of 140,000 per year or one maternal death every four minutes [1]. PPH occur in 5% of all deliveries, majorities of death occur within four hours of delivery indicating that it is a consequence of third stage of labour [2].

WHO estimates that of the 5,29,000 maternal death occurring every year, 1,36,000 or 25.7% of death takes place in India and two third of these maternal death occur after delivery, PPH being the most commonly reported complication [3]. The unacceptably high maternal death of 540 per 100,000 live births in India in last few decades remains a major challenge [3]. Hysterectomy is the traditional treatment for cases of refractory PPH, when all other methods to arrest bleeding fails. Advances in interventional radiology and surgical techniques have provided safe and effective alternatives to hysterectomy in many cases. This review discusses the current evidence based management of PPH, existing controversies in transfusion of blood and blood products and newer advances in this field.

Definition

The traditional definition of primary PPH, which is the most common of major obstetric haemorrhage is blood loses over 500 ml or more from the genital tract within 24 hours of the vaginal birth of a baby or 1000 ml or more after a cesarean delivery [4]. PPH can be minor (500 -1000 ml) or major (more than 1000 ml), major can be divided into moderate (1000 -2000 ml) and severe (more than 2000 ml) [4]. The four important causes of PPH are atony, trauma, retained placenta or adherent placenta and coagulation abnormalities. Most common cause is uterine atony, which is episodic and unpredictable. Women known to have risk factors for PPH, appropriate steps for prevention should be incited during antenatal and intra partum periods to reduce this risk. PPH can also occur with no risk factors [5].

Active management of third stage of labour is a feasible, low cost measure to prevent 60-70% of atonic PPH [4]. Monitoring of pulse, blood pressure, bleeding during fourth stage of labour and using bedside tool, Modified Early Obstetric Warning System (MEOWS) in all obstetric inpatient will track maternal physiological parameters which help in early recognition and treatment of the acutely ill patient, is important and crucial to prevent morbidity and mortality.

MATERIALS AND METHODS

This review was conducted by searching Medline (1994-2015) and other online articles from Pubmed, Google scholar by using terms like management of PPH/ haemorrhage, transfusion protocols in obstetric haemorrhage/ haemorrhage, recent advances in PPH/ haemorrhage and it included 36 articles. No attempt was made to analyze any specific aspect of PPH but an overview of effective clinical management strategies and recent advances in treating major PPH was done. We have also highlighted community based emergency care in low resource settings thereby promoting and facilitating a more educated, systematic and effective physician response.

Assessments of Blood Loss

The important steps in the management of PPH are predicting PPH and assessment of blood loss during third stage of labour. Visual estimation of blood loss after delivery is inaccurate, this was shown in a study after simulated vaginal delivery there was a 16% underestimation at 300 ml loss, whereas, this increases to 41% underestimation at 2000 ml blood loss [6]. Massive obstetrics haemorrhage is variably 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 packed cell transfusion, or any haemorrhage associated with haemodynamic instability [7]. Accurate methods such as blood collection drapes for vaginal

deliveries, weighing of soaked swabs, active periodic estimation, a written and pictorial guide to aid visual estimation in labour wards may improve the accuracy of the estimation of blood loss [8].

Protocol for the Management of Major PPH

Management involves four components all of which must be taken simultaneously, communication, resuscitation, monitoring investigation and arresting the bleeding. Main therapeutic goals of management of massive haemorrhage is to maintain haemoglobin >8 gm/dl, platelet count >75 x 10^9/l, prothrombin <1.5 x mean control, activated prothrombin time <1.5 x mean control, fibrinogen >1.0 gm/l [8]. The cornerstones of resuscitation during PPH are restoration of both blood volume and oxygen carrying capacity, which includes establishing two 14 gauge intravenous lines, 20 ml blood sample for diagnostic tests includes full blood count, coagulation screen including fibrinogen, urea and electrolytes and cross matching minimum of 4 units blood.

A high concentration of oxygen (15l/minute) should be administrated. Pulse rate, blood pressure, oxygen saturation using oximeter, electrocardiogram and automated blood pressure recording, considering central and arterial lines, Foley's catheter to measure urinary output and commencing record chart for fluid balance, blood, blood product and procedures. Using appropriate measures, patient should be kept warm in a flat position. Blood should be transfuse as soon as available, till then, 3.5 liters of warmed crystalloid Hartmann's solution (2 liters) and/or colloid (1-2 liters) infused. Recombinant factor VII, a therapy should be based on the results of coagulation. Compatible blood is the best fluid to replace and should be transfused as soon as available, if fully crossmatched blood is not available then uncrossmatched group specific blood or 'O' Rh-D negative blood may be safest to give in an acute emergency [5].

Arrest of Bleeding

There may be one or more causes for PPH related to four Ts', Tone, Tissue, Trauma, Thrombin. The most common cause of primary PPH is uterine atony, clinical examination should be done to exclude other or additional causes. Regardless of the cause of MOH, uterine massage, bimanual uterine compression to stimulate contraction, administration of uterotonic drugs should be instituted, until the bleeding stops.

If the pharmacological method fails to control bleeding in case of atonic PPH, exclude other or additional causes by undertaking clinical examination in theatre and the next intervention mechanical method of control by balloon catheter tamponade is instituted before considering surgical procedures [5] [Table/Fig-1].

Mechanical Methods

Balloon tamponade: The various types of balloons used are Foley's catheter, Rusch balloon, Bakri balloon, Sengstaken-Blackmore oesophageal catheter or sterile glove and condom. Akhter et al., described the use of condom catheter to tamponade uterine bleeding in women with PPH in Bangladesh [9].

This was a prospective study involving 152 cases of PPH, 23 of which were managed using condom catheter. It was successful in all cases with no further intervention. It was kept for 24-48 hours (mean 36 hour) before removal [9]. Balloon tamponade was effective in 91.5% of cases and recommended that, this is a relatively simple technology and should be a part of existing protocol in the management of PPH [10]. This intervention as tamponade test serves as first line surgical management. A positive test controls PPH following inflation and a negative test where bleeding does not stop with inflation, it is likely to be coming from a genital organ laceration. Cases with negative balloon tamponade test and failure to arrest bleeding by intra uterine balloon tamponade in uterine atony requires immediate surgical interventions.

MEDICAL TREATMENT (Uterotonics)			
Medications	**Dose**	**Contraindications Or cautions**	**Side effects/ Comments**
Oxytocin	5 IU slow IV X 2 (may have repeat dose) Or 40 IU /500 ml Hartmann's solution at 125 ml/hour	Overdose or prolonged use can cause water intoxication. IV push dosing may cause hypotension	Rare
Ergometrine	0.5 mg slow IV/IM	Hypertension/ toxemia, patients with HIV taking protease inhibitors, patient with vascular disease, hepatic or renal or sepis	Nausea, vomiting and increased B/P
Carboprost	250 µg IM every 15 minutes up to 8 times Direct Intra myometrial 0.5 µg	Active or history of pulmonary disease (asthma), renal hepatic or cardiac disease	Nausea, vomiting, and diarrhea
Mispoprostol	1000 µg rectally	Cardiovascular disease	Nausea, vomiting, diarrhea, pyrexia, shivering
MECHANICAL METHODS		Intra uterine balloon tamponade Consider Interventional Radiology (Selective arterial Embolisation / Balloon Occlusion)	
SURGICAL TREATMENT		Brace Suture Bilateral uterine artery ligation Bilateral Internal iliac ligation Hysterectomy (Second consultant)	

[Table/Fig-1]: Summary of management of major PPH.

Radiological management: Uterine artery embolisation is useful in situations in which preservation of fertility is desired when surgical options have been exhausted in controlling PPH both atonic and traumatic.

Major drawback is 24 hour availability of interventional radiologist with appropriate facilities and team, patient should be haemodynamically stable enough to be transferred to a radiology suite.

Complications include local hematoma formation at the site of injection site, infection, ischemic phenomenon including uterine necrosis though rarely. It can be done as elective or emergency intervention [11]. Emergency indications are persistent atonic PPH and surgical complications, uterine tears at the time of cesarean section, bleeding following hysterectomy. Access to the anterior division of internal iliac artery is via a femoral artery approach and is done by injecting gelatin particles. Use of polyvinyl alcohol particles is however, permanent. It usually offer very high success rate of 75 -100%.

Elective can be done in known or suspected cases of placenta accrete such as placenta previa or previous cesarean section scar diagnosed by Ultrasonography (USG) or Magnetic Resonance Imaging (MRI). The strategy used for elective cases in minimizing blood loss, number of blood transfusion and ICU admission usually incorporates placement of balloon catheters within internal iliac artery or uterine artery, which works with balloon inflation and if it doesn't then it can be a route for embolisation as well [12]. Intravascular Aortic Balloon Occlusion (IABO) has emerged as prophylactic, simple, safe and minimally invasive method in management of life threatening PPH and in the conservative management of abnormal placentation. It has similar results in terms of blood loss and absence of need of blood products as internal lilac artery occlusion but requires further research by using control group before regarding this method, as an ancillary procedure of choice during scheduled cesarean hysterectomy in known or suspected cases of abnormal placentation [12].

Hysterectomy was avoided in 10 out of 14 cases of major PPH by arterial embolisation, this was reported by Penney et al., in Scottish confidential audit [13].

Surgical treatment: For surgical management multiple surgical options are available, to include a variety of uterine compression sutures, vascular ligations and Peripartum Hysterectomy.

Uterine compression sutures: In severe PPH not responding to pharmacological and mechanical methods, the treatment used was peripartum hysterectomy to prevent maternal deaths even in primi and in young women. With the increasing rates of cesarean section, complications like placenta previa, placenta accreta, rupture uterus contributes to severe PPH apart from atony. Introduction of compression sutures made a revolution in decreasing the incidence of hysterectomy for severe PPH. Credit goes to Christopher B-Lynch who in 1997 introduced compression sutures to control bleeding avoiding peripartum hysterectomy. These compression sutures exert a mechanical compression of the uterine vascular sinuses without occluding either uterine arteries or uterine cavity [14]. Several modifications of this technique developed mainly aiming at greater simplicity and applicability with equivalent efficacy like Chi-Square sutures, Hayman sutures, Pereira suture, Cervico Isthumic Compression sutures etc [15].

Uterine compression sutures related complications like pyometra, uterine inflammation leading to chronic endometritis, systemic sepsis, ischemic uterine necrosis, uterine suture erosion, uterine synechiae have been reported by several studies [16,17]. We have a similar experience of a case treated with B-Lynch suture, followed by bilateral uterine and hypogastric artery ligation for severe PPH; however, we faced a difficult situation, when the patient developed synechia, and extensive pelvic adhesions jeopardizing any further scope of pregnancy [18].

Fertility after application of uterine compression sutures: Vast majority of cases do not show any serious complications in future pregnancies and no higher rates of infertility. Ovahba et al., reported eight pregnancies out of 20 women who underwent uterine compression sutures; six had term delivery with four cases of cesarean section and two cases of uncomplicated vaginal delivery [19].

The risk of potential complication appears to be higher when non absorbable sutures are used. Uterine compression sutures irrespective of its type should not prevent the blood drainage from the uterine cavity and it should not affect the uterine vascularity. Monofilament sutures with an absorption time of 90–120 days can decrease this complications and subsequent hysteroscopic assessment should be done especially after putting stepwise devascularization and compression sutures [20].

Vascular ligations [21]: The objective is to decrease blood flow to the uterus, in order to arrest life threatening PPH before hysterectomy when medical therapy is unsuccessful.

1. Bilateral uterine artery ligation: 90% of the uterus blood supply in pregnancy comes from these vessels. If this measure fails to control bleeding, the next step is ovarian artery ligation.
2. Bilateral ovarian artery ligation: it arises from abdominal aorta and forms utero-ovarian vascular anastomosis. A suture is placed on the ovarian artery through a vascular area in mesoovarium. If this also fails to control then the next step is internal iliac artery ligation.
3. Internal iliac artery ligation: it causes almost 85% reduction in pulse pressure in those arteries distal to ligation thereby, causing arterial pressure system into one with pressure approaching those in venous circulation and provides haemostasis via clot formation. It needs expertise in doing this and avoids complication of injury to vessels and ureter.

Hysterectomy: Peripartum hysterectomy can be a total or subtotal, it is done as a last resort when all other methods to control PPH fail. The common indications are abnormal placentation with placenta increta, acreta and percreta, rupture uterus where repair not possible, persistant atonic PPH. Incidence of hysterectomy varies from 1 in 331 to 1 in 6978 deliveries [22]. It should not be delayed too long till the women is moribund. Subtotal hysterectomy is the choice unless there is a trauma to cervix or lower uterine segment. The maneuver of aortic compression is at times useful for control of bleeding in the surgical field for severe cases.

Transfusion Protocols

Massive transfusion protocol is essential in institutional management of major obstetric haemorrhage. It should be recommended when there is uncontrolled haemorrhage or when use of more than 10 unit packed cells is anticipated [23]. Early use of blood products is generally required in MOH to avoid dilutional coagulopathy.

There is no consensus on the use of components of the transfusion in women suffering from PPH or in obstetrics. Research in transfusion medicine has pointed towards use of packed blood cell and FFP in a ratio of 1:1 and 1:2 and targeted use of platelets in an effort to avoid dilutional coagulopathy with regular measurement of haemoglobin and clotting by conventional tests [24]. Transfusion protocols have advantages in decreasing mortality, multiorgan failure and increase ventilator free days. It also have some disadvantages of transfusion related lung injury, circulatory overload, immunomodulation and iron overload which can be avoided by regular measurements of haemoglobin and clotting to guide transfusion.

In most cases, transfusion therapy is not based on the actual coagulation state because conventional laboratory test usually takes 45-60 minutes and conventional test on plasma ends with the formation of fibrin strands. Viscoelastic test like, Thromboelastography (TEG) and Thromboelastometry (ROTEM) can test whole blood coagulation, clot strength, stability and lysis with a particular reference range, which can be used for management of obstetric cases seen amongst the recent trends in PPH management [25]. At present transfusion monitoring still require a combination of conventional test of Hb and coagulation, perhaps there will be wide practice of point of care testing alone in future based on further studies.

The best marker for developing coagulopathy and blood loss is well correlated by fibrinogen levels, whereas, prothrombin time and partial thromboplastin time somehow are not very useful, this has been revealed by a survey. It is also an early predictor of severity of PPH, a level of < 2 gm/l has a 100% Positive Predictive Value (PPV) for severe PPH [26].

Cryoprecipitate contain approximately 10 times the concentration of fibrinogen as FFP, in order to raise the fibrinogen level by 1 gm/l, 30 ml/kg of FFP needs to be given compared with 3 ml/kg of cryoprecipitate. So, FFP is not the product of choice to restore fibrinogen levels. Upto 1 litre of FFP and 10 units of cryoprecipitate may be given empirically in face of relevant bleeding while waiting for coagulation studies [27].

Fibrinogen concentrate, a virally inactivated lyophilized powder that can be stored at room temperature, no thawing or blood typing is required, it restores fibrinogen levels rapidly. The results of fibrinogen concentrate in initial treatment for severe PPH, (FIB-PPH) trail in order to reduce the requirement of blood transfusion stated that pre-emptive treatment with fibrinogen concentrate for severe PPH in patients with normofibrinogenaemia is not justified but the role of fibrinogen substitution in severe PPH with hypofibrinogenaemia is yet to be studied [28].

Intra Operative Cell Salvage in Obstetrics

It is an option in women who refuse traditional blood transfusion as well as in MOH situations. It may not be substituted for allogenic blood transfusion but is an adjunct to acute resuscitation in PPH and also can reduce the exposure to allogenic blood transfusion and its associated risks and is cost effective. It contains only red cells with

essentially no platelets or clotting factors. The risk of amniotic fluid embolism is very low if leucocytes depletion filter are used. Infection is also uncommon [29].

Recombinant Activated Factor VII

There is lot of controversy regarding its usage and it is very expensive. Current recommendation is that, it should be used after failure of conventional methods. Major concern is, it causes thrombin burst, promoting clotting in open vessels and there is a potiential for thrombotic complication. Women with severe PPH are particularly susceptible to severe hypofibrinogenaemia and these are cases where factor VIIa is considered.

It should be given only when hematocrit is adequate, platelet count is >50x10^9/l, fibrinogen >1 gm/l, pH>7.2 and temperature >34^{0}C. Dose is 90 µg/Kg IV over 3-5 minutes, repeated only if necessary. Franchiniet et al., reported 65 women treated with rFVIIa for PPH and observed reduced bleeding and 30 of the 65 women underwent peripartum hysterectomy [30].

Role of Tranexamic Acid

It is being tried both prophylactically and also for treatment of PPH in cases of continued bleeding due to uterine atony, uterine ruptures and lower genital tract trauma. Gungorduk et al., used prophylactic tranexamic acid administration in a prospective randomized placebo controlled trial in 660 women who underwent elective Lower Segment Caesarean Section (LSCS). They have observed reduced mean estimated blood loss and need of additional uterotonic agents following to LSCS in the treatment group. It can decrease the bleeding and reduce the need for further transfusion without any major side effects [31]. Initial dose is a slow IV bolus of 1gm followed by further 1 gm four hours later. Sentilhes et al., in his review with various RCT's dealing with prevention and treatment of PPH with tranexamic acid use, concludes that, the benefits definitely overscores the side effects for both vaginal and caesarean delivery. The current level of evidence is however, lacking and the use is yet to be established in the given context [32]. Perhaps the outcome of the largest trial sponsored by WHO (WOMAN trial) for determining the effect of the early administration of TXA on death, hysterectomy, and other morbidity (surgical intervention, blood transfusion and risk of non fatal vascular events) will throw some light on this debatable issue [33].

Prevention and Treatment in Low Resource Settings

PPH is the major cause of direct maternal death in low resource settings where there are no birth attendants or they lack skills or equipment to manage PPH and shock.

The vices like poverty, discrimination, limited health accessibility, continue to haunt women living in low socio economic status apart from their vulnerability to concurrent disease. This attributes further to maternal deaths despite having safe motherhood activities.

Even with major advances in prevention of PPH women are still dying. What is needed in these women is community based emergency care/ home base life saving skills. Community workers can be taught with techniques such as uterine massage and emergency preparedness as the key to effectiveness of treatment is early identification of haemorrhage and prompt action [34].

1. Uterine massage: Massage of fundus of uterus through the abdomen after placenta delivery until uterus is contracted. It was repeated at every 15 minutes during first two hours to keep the uterus contracted.
2. Misoprostol: Though, oxytocin is ideal due to its effectiveness in 2-3 minutes with minimal side effects and can be used by all women but it needs refrigeration and administered in injectable route. If oxytocin is not available or administration is not feasible, single dose of 800 µg of misoprostol, sublingually, is a safe effective treatment of PPH resulting due to uterine atony. If bleeding persist after the administration of uterotonics the immediate life saving measures are bimanual compression. Bimanual compression is done by placing one hand in the vagina and clenched into a fist and other hand on the fundus of uterus. Squeezing the uterus between two hands by applying pressure to stop or slow the bleeding, uterus has to keep compressed till next medical support.
3. Aortic Compression: It is a life saving measure when there is heavy PPH whatever the cause. It does not prevent or delay any of the steps in management of PPH. Circulating blood volume is restricted to the upper part of the body and thereby to the vital organs, blood pressure is kept higher, blood is prevented from reaching bleeding area in pelvis and volume is conserved. By cutting off the blood supply to pelvis via compression, patient can be prepared to shift higher center, simultaneously doing other measures.
4. Non Pneumatic Anti Shock Garment (NASG): Use of antishock garment for the treatment of hypovolumic shock for transfer to higher center. NASG reverses the shock by compressing the lower body vessels. So that circulating blood is directed mainly to the core organs heart, lungs, brains, adrenals.

This device with its pneumatic action effectively prevents obstetric haemorrhage, maternal mortality and morbidity by impending the blood flow to the uterus through its vascular compression [35].

Obstetric haemorrhage is the result of uterine atony, but other entities may also cause or contribute to acute bleeding. Sibai et al., in his article has summarized 10 evidence based recommendations on the management of severe postpartum haemorrhage that may help in reducing acute and long term maternal complications [36] [Table/Fig-2].

1. Plan and rehearse a step by step approach	Early recognition of haemorrhage, Identifying cause of bleeding, quick and effective evaluation and management of bleeding
2. Know the symptoms and signs of severe PPH	Symptoms: anxiety, restlessness, tachypnea, hunger to air, confusion. Signs : tachycardia, hypotension, cold clamminess, pale, oliguria or anuria
3. Call for help	Within 10 minutes after making the diagnosis of PPH
4. Identify women at very high risk of hysterectomy and end organ dysfunction	Cases like placenta previa, placenta accreta, uterine rupture, number of previous cesarean section
5. Perform uterine compression sutures	Within one hour of delivery.
6. Diagnosed cases of placenta previa or accrete	Plan delivery by a multidisciplinary team
7. Conservative management of placenta accrete and placenta percreta	Considered only in carefully selected women who desire future fertility Planned cesarean hysterectomy is the treatment of choice for multiparous women.
8. Exclude Von willebrand disease	Requires multidisciplinary approach
9. Have Fibrinogen concentrate on hand	For cases of intrauterine death of fetus, abruption, amniotic fluid embolism etc.
10. Implement a protocol for massive transfusion	By administration of adequate blood and blood products, oxygen delivery and correction of DIC.

[Table/Fig-2]: Ten practical evidence based recommendations for managing severe PPH.

CONCLUSION

Globally PPH is the leading cause of maternal mortality and morbidity. Prevention plays a very important role by identifying

high risk factors and active management of labour. Management is medical, mechanical, surgical and radiological. A multi disciplinary approach is essential in severe haemorrhage. Availability of blood and blood products is essential. It is very important to identify the aetiology, though uterine atony is common. Prediction and assessment of blood loss remains the cornerstone for prompt and effective management of PPH.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Jul 09, 2016**
Date of Peer Review: **Aug 02, 2016**
Date of Acceptance: **Oct 25, 2016**
Date of Publishing: **Feb 01, 2017**