



Postpartum Hemorrhage

Click the next button to continue...





Copyright © 2020 Shelly Betancourt and Michelle Becher

All rights reserved. No part of this publication may be reproduced, distributed, or transmitted in any form or by any means, including photocopying, recording, or other electronic or mechanical methods, without the prior written permission of the publisher, except in the case of brief quotations embodied in critical reviews and certain other noncommercial uses permitted by copyright law. For permission requests, write to the publisher at the address below.

Maternal 911 Education Systems, LLC
475 West Center St.
Ithaca, MI 48847
www.maternal911.com



Maternal 911 and Maternal 911 in Action contains information designed as an educational resource to aid practitioners in providing obstetric care and the use of this information is voluntary. This information should not be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. It is not intended to substitute for the independent professional judgement. Maternal 911 reviews the publication regularly, but may not reflect the most recent evidence.

Maternal 911 makes every effort to present accurate and reliable information. The Maternal 911 and Maternal 911 in Action are publications provided 'as is' without any warranty of accuracy, reliability or otherwise, either express or implied. Maternal 911 does not guarantee, warrant, or endorse the products or services of any firm, organization, or person. Neither co-founder nor any officers, directors, members, employees, participants or agents will be liable for any loss, damage or claim with respect to liabilities, including direct, special, indirect, or consequential damages, incurred in connection with this publication or reliance on the information presented.

Data from completing the modules may be used in research and publications with privacy maintained.



Course Description:

When will the next postpartum hemorrhage occur for a patient under your care? Postpartum hemorrhage is a phenomenon that will continue to plague labor and delivery units. This module will help you to strengthen your knowledge then build upon your base to be better prepared for future hemorrhage encounters.

Approximate Time to Complete: 75 minutes



Click here to download a print version of this course.





The purpose of this module is to improve participant's understanding of postpartum hemorrhage:

- Help participants develop sound critical judgment in the delivery of health care in a labor and delivery unit when postpartum hemorrhage occurs.
- Expand the participant's knowledge base on learning theories and their instructional implications regarding health care delivery in a labor and delivery unit when postpartum hemorrhage occurs.
- Enable participants to develop, implement, and evaluate health care delivery in a practice setting prior to an actual event. This will allow for early recognition of an actual event.
- Enhance the participant's ability to put knowledge into active health care delivery. This will allow for rapid implementation of the necessary steps needed when postpartum hemorrhage occurs.
- Prepare participants to address issues and implement changes in the health care unit as necessary to ensure a safe environment. Equipment and supplies needed when postpartum hemorrhage occurs will be in every labor and delivery room.
- Enable participants to convert proven learning into actual health care delivery.



-  Definition of Post-Partum Hemorrhage
-  PPH
-  Symptoms Related to Blood Loss with PPH
-  Occurrence Rates
-  Risk Factors
 -  Risk Factors for PPH
-  Etiologies
 -  Etiology of PPH
-  Planning & Prevention
 -  Planning & Prevention of PPH
-  Management & Treatment
 -  Management & Treatment
-  Initial Intervention
 -  Management of PPH
-  Medications
 -  Medications
 -  Medications - Oxytocin
 -  Medications - Hemabate
 -  Medication - Methergine
 -  Medication - Misoprostol
 -  Medication - Others
-  Management
 -  Managing PPH - POC
 -  Managing PPH - Tamponade
 -  Managing PPH - Balloon
 -  Managing PPH - Balloon Cont'd
 -  Managing PPH - Fluids

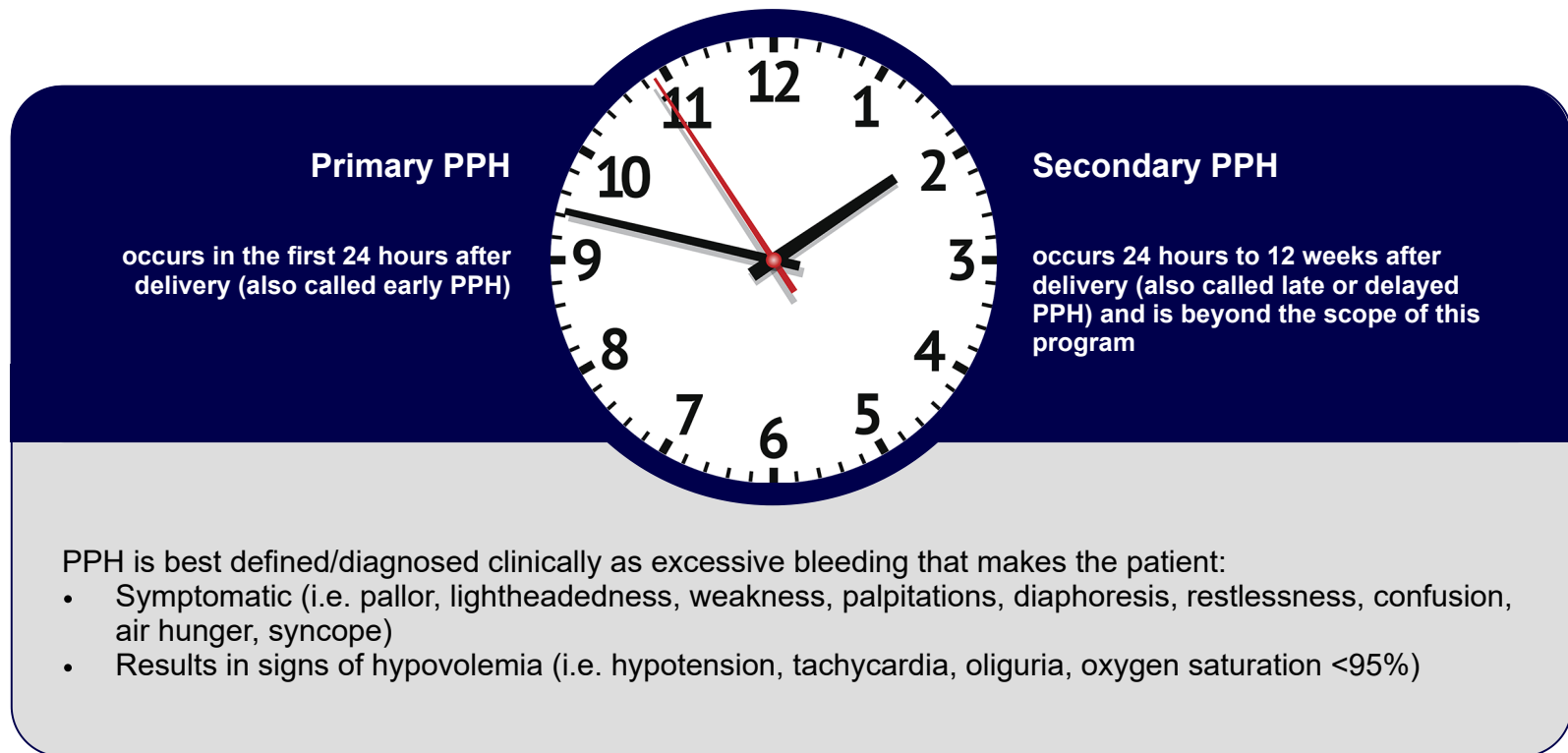
Table of Contents



- Management & Treatment
 - Initial Intervention
 - Management of PPH
 - Medications
 - Medications
 - Medications - Oxytocin
 - Medications - Hemabate
 - Medication - Methergine
 - Medication - Misoprostol
 - Medication - Others
 - Management
 - Managing PPH - POC
 - Managing PPH - Tamponade
 - Managing PPH - Balloon
 - Managing PPH - Balloon Cont'd
 - Managing PPH - Fluids
 - Treatment
 - Management and Treatment of PPH
 - Laboratories
 - Laboratory Testing with PPH
 - PPH - Massive Transfusion Protocol
 - Managing PPH - Transfusion
 - Guidelines from Professional Organizations
 - Complication
 - Complications that May Occur with PPH
 - Summary
 - Summary
 - Course Completed Page



Postpartum Hemorrhage (PPH) is defined as:





Heavy vaginal bleeding is usually noted, but vaginal bleeding may not be abnormal when hemorrhage is internal.

For example, intra-abdominal bleeding related to a cesarean delivery or a broad ligament or vaginal hematoma due to a sulcus laceration.

The focus of this module is on primary postpartum hemorrhage, the first 24 hours.

An international expert panel defined PPH as "active bleeding ≥ 1000 or signs of hypovolemia within the 24 hours following birth that continues despite the use of initial measures including first-line uterotonic agents and uterine massage" [1].



Symptoms related to blood loss with PPH [2]

Blood Loss	Blood Pressure, mmHg	Signs and Symptoms
<500mL vaginal or <1000mL cesarean	Normal/stable	May have no symptoms or elevated heart rate (HR), no change in blood pressure (BP), pulse pressure or respiratory rate (RR)
>500mL vaginal delivery or >1000mL cesarean delivery or change in vital signs	≤85/45mmHg	HR ≥110 beats/minute, O ₂ saturation <95%, RR 20-24, decreased pulse pressure, weakness, and sweating
Continued bleeding with total blood loss remaining <1500mL	BP continues to be ≤85/45mmHg	HR >120 and thread, RR markedly elevated, capillary refill delayed, restlessness, confusion, pallor, and oliguria
>1500mL Massive Transfusion protocol and surgical approach to control bleeding	unstable systolic and further decreasing BP	HR >120, lethargy, air hunger, anuria, and collapse



The incidence of PPH varies widely.

A reasonable estimate is PPH occurs in 1.2% of all deliveries [3].

A United States National Inpatient sample identified 2 and 3% occurrence in 1994 to 2006, followed by a 3% occurrence rate in 2012-2013 [4].

To help lower incidence and help prevent maternal mortality, it is imperative every obstetrical unit has:

1. Readiness to respond to an obstetrical hemorrhage.
2. Recognition and prevention measures in place for all patients.
3. A multidisciplinary approach to excessive maternal bleeding.
4. De-briefing to learn and improve responsiveness.



A study of 154,000 deliveries compared 666 cases of PPH to controls without hemorrhage [5].

In decreasing frequency rates, the following factors are associated with PPH:

- Augmentation of labor with oxytocin
- Induction of labor (IOL)
- Hypertensive disorders
- Large for gestation age (LGA) newborn, those >4000 grams
- Instrumental delivery; vacuum or forceps
- Lacerations
- Placenta accreta
- Failure to progress during the second stage of labor
- Retained placenta

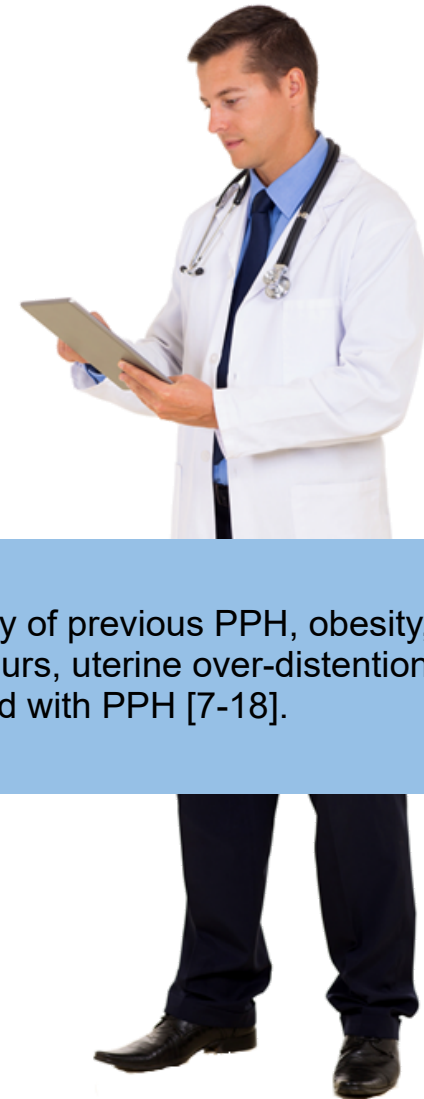




In a large series, the most common risk factors associated with need for massive transfusion during hospitalization for delivery were:

- Abnormal placentation
- Abruptio
- Severe preeclampsia
- Fetal demise [6]

In addition to the risk factors listed above, placenta previa, personal history of previous PPH, obesity, high parity, Asian or Hispanic race, precipitous labor, first stage of labor >24 hours, uterine over-distention, uterine infection, and some drugs, such as antidepressants, have been associated with PPH [7-18].





Women with von Willebrand disease are prone to postabortal bleeding, but are unlikely to experience PPH at term [19].



Women with severe factor XI deficiency or who are hemophilia carriers are at increased risk of both early and late PPH (16 to 22% for early and 11 to 24% for late).



PPH may be due to an acquired hemophilia A (pregnancy-related FVIII autoantibodies) [21].

- The condition should be suspected with the combination of a normal platelet count and normal prothrombin time with prolonged activated partial thromboplastin time (aPTT) not corrected by admixture with normal plasma.



Amniotic fluid embolism (AFE), placental abruption, preeclampsia with severe features, or Hemolysis with a microangiopathic blood smear, Elevated Liver enzymes, and a Low Platelet count (HELLP) syndrome can be the cause of acute coagulopathies.





Undiagnosed bleeding disorders are rarely the cause of PPH; therefore, PPH by itself is not an indicator to screen for inherited bleeding disorders [22].

- One of 50 women in a study, who had PPH, had postpartum screening that identified a bleeding disorder.

A bleeding disorder should be considered if a woman experiences PPH that does not respond to general treatment measures when she has a history of menorrhagia, excessive bleeding after minor injury, or a known family history of a bleeding disorder [23].





Generally, hemostasis begins when the placenta separates from the uterus, which causes the myometrium to contract and vessels to constrict that supplied the placental bed and activates the coagulation pathways. This forms a clot at the previous placental attachment site.

PPH results from a disturbance in one or more of these events.

These disturbances can be associated with incomplete placental separation as seen in placenta accreta, uterine atony, acquired or inherited factor deficiencies, thrombocytopenia, drugs that affect coagulation, and possibly trauma.





Although uterine atony is the most common cause of PPH, it is often responsive to therapy and thus not the most common reason for massive transfusion after delivery [24].

In a large worldwide series, 54 percent of women with PPH received a blood transfusion [85].



Late pregnancy uterine arterial blood flow is 500-700mL/min and accounts for approximately 15% of cardiac outflow. This increase in blood flow is responsible for PPH.

Most women do not hemorrhage because uterine bleeding is controlled by:

- Contraction of the myometrium which constricts the blood vessels supplying the placental bed
- Localized decidual hemostasis





Atony

Trauma

Coagulation Defects

The most common cause of PPH is uterine atony which complicates 1 in 40 births in the United States and is responsible for at least 75% of the cases of PPH [24].

Atony is more common in the following settings; however, atony can occur in the absence of any of these factors:

- Uterine overdistension (multiple gestation, polyhydramnios, macrosomia)
- Uterine infection
- Uterine relaxants
- "Uterine fatigue" after a prolonged or induced labor
- Uterine inversion
- Retained placenta (including succenturiate lobe), or placental fragments (either a normally attached placenta or placenta accreta)



Click here to see more about the etiology of PPH.



PPH generally is caused by diffuse uterine atony which responds to uterotonic drugs and is not a common reason for massive transfusion following delivery [7].

If the uterus appears to be firmly contracted after delivery, other etiologies of hemorrhage should be considered.

However, one should keep in mind that the uterus may not be maximally contracted or a focal area of the uterus may be atonic.

A well-contracted fundus does not exclude the possibility of atony of the lower segment, which is difficult to appreciate on physical examination.

Women with persistent bleeding despite a firm fundus should always undergo a vaginal examination to identify ballooning of the lower uterus, as well as cervical and vaginal lacerations.

click to close



Click here to see more about the etiology of PPH.





Atony

Trauma

Coagulation Defects

Trauma-related bleeding can be due to:

- Lacerations (i.e. perineal, vaginal, cervical, uterine)
- Incisions (i.e. hysterotomy, episiotomy)
- Uterine rupture

Lacerations are more common after instrumental delivery.



*Click the tabs to
see more information.*





Atony

Trauma

Coagulation Defects

Acquired causes included disorders related to the pregnancy; severe preeclampsia, HELLP syndrome, placenta abruption, fetal demise, AFE, sepsis, and surgical site bleeding.

The mechanism is related to hemodilution, failure of liver synthetic function, or disseminated intravascular coagulation (DIC).

Coagulation defects can also be drug related.



*Click the tabs to
see more information.*





To improve outcomes in women who develop PPH, protocol for management should be developed and applied to identify heavy bleeding and hemorrhage before it becomes life threatening [25-27]. Quantifying blood loss (QBL) rather than estimating the blood loss (EBL) is important to help determine the significance of blood loss and maternal health more readily.

The initiation of a PPH protocol was evaluated in an observational study. The findings of the study identified earlier resolution of maternal bleeding before becoming a life threatening event, decreased use of blood products, and a 64 % reduction in development of DIC [28].

Clinical training programs or simulations encourage a team approach to the early recognition of PPH which may improve outcomes by summoning the appropriate healthcare providers before hypovolemia and uncompensated shock occur.

Women who are identified as at risk for PPH should be educated and counseled appropriately for their level of risk and the gestational age.

Planning for a PPH event involves review of resources to ensure delivery is in the appropriate level of care facility, and that there is adequate staffing, intravenous (IV) access, medication, equipment, blood and blood products available.





Also recommended for patient safety is that the labor and delivery department develops a kit that includes the necessary medication and supplies which may be needed during a PPH. This will allow for quick interventions by the health care team.

Conducting team simulation drills on a PPH event will assist in identifying areas needing improvement, such as what supplies and equipment to have in the labor and delivery room or post anesthesia care department to improve performance. These departments are generally where a delivered woman will recover. This practice is recommended by The Joint Commission [29]. Maternal 911 in Action includes simulation drills on PPH.

Identifying deficiencies in clinical knowledge and performance can be demonstrated in simulation-based teaching of management of PPH [30,31].

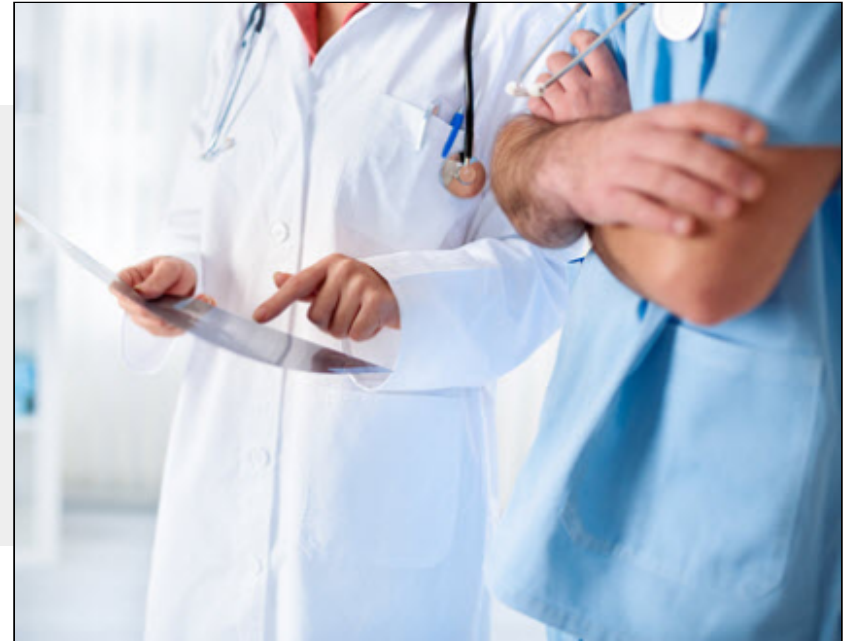
For active management of the third stage of labor, preventive measures such as uterotonic drugs given at delivery of the fetal head may be considered.

In women with iron deficiency anemia, use of iron supplements during pregnancy will increase hemoglobin concentration and improve the woman's baseline status in the event of PPH.



Teamwork and communication failures are responsible for up to 70% of obstetric sentinel events [32].

The Joint Commission, the American College of Obstetricians and Gynecologists (ACOG), and the Institute of Medicine, all recognize teamwork and communication as an important element of patient safety [32,33,34].





The management of PPH is multifaceted and requires care by several teams within the hospital: obstetricians, midwives, anesthesiologists, nurses, blood bank and laboratory personnel, surgical specialists including vascular and urologists, and interventional radiology [22]. Coordination of these teams is essential in outcomes.

When these teams are summoned to come together in an emergency event, they must work without delay to provide life-saving measures. Delay in healthcare delivery could lead to patient death.



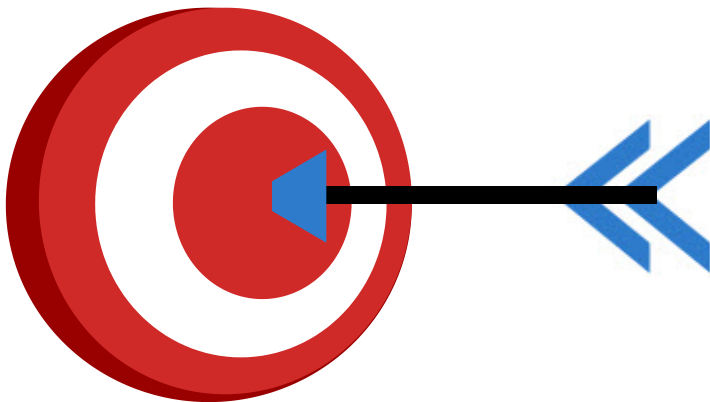
Knowledge, protocols, and simulation training will allow the healthcare team to coordinate their efforts and function well together.



The approach and aggressiveness of interventions will be dependent on the rate and amount of bleeding, vital signs, and laboratory results of complete blood count (CBC), coagulation studies, and level of electrolytes, potassium and ionized calcium.

It is important to provide life-saving treatment/measures before the patient terminally declines.

If one treatment option does not adequately control bleeding, the obstetrical provider should promptly select the next treatment option. Non-operative and operative interventions for PPH can be used alone or in combination [36].



The goal is to:

- Maintain or restore circulation to vital organs
- Maintain or restore tissue oxygenation
- Prevent or reverse coagulopathy
- Identify and eliminate the cause of PPH



If an intervention does not succeed in decreasing hemorrhage, the next treatment should be quickly implemented.

Delayed recognition of condition or uncertainty in treatment may result in further bleeding which may cause dilutional coagulopathy, life-threatening hypovolemia, tissue hypoxia, hypothermia, and acidosis [36].

Delay in controlling hemorrhage may increase the need for a hysterectomy, or may result in hemorrhagic shock, or death.





Although there is no data from clinical trials to help guide management of transfusion specifically in PPH, management of blood component therapy is similar to that in other massive hemorrhage events [22].

Development of a standardized institutional approach to management of PPH improves outcomes.

One component of a standardized institutional approach to management of severe PPH is to implement a standardized massive transfusion protocol for the labor and delivery unit.

Consideration for a massive transfusion protocol would be reasonable.

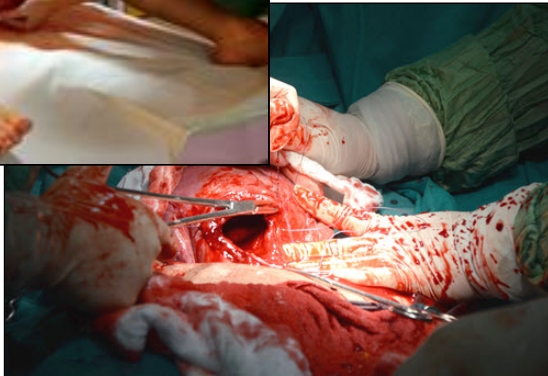


The approach to treatment of PPH differs somewhat depending on the cause and whether hemorrhage occurs after a vaginal birth or after a cesarean delivery.

- Hemorrhaging lacerations caused by trauma will need to be controlled surgically using either the transvaginal or transabdominal approach.
- Coagulation defects will be treated medically with transfusion of blood, blood products or a combination of both.
- If hemorrhage is caused by uterine atony, the treatment will be dependent upon the route of delivery.



If the woman delivers vaginally, less invasive treatment should be initiated to control the hemorrhage. This may start with uterotonic drugs and intrauterine balloon tamponade. Using these measures, laparotomy is usually avoided.



The provider will repair vaginal or cervical lacerations. Caution will be used to prevent ureteral ligation when a laceration extends high in the vagina or anteriorly.

- Vaginal hematomas should not be drained unless expanding to reduce likelihood of further blood loss.



[Click here to see more information.](#)





By comparison, after a cesarean delivery where the abdomen is already open and adequate anesthesia has already been administered, there is much less concern about open operative interventions.

The frequency of the different causes of hemorrhage also differs by route of birth; retained products of conception are more likely after a vaginal birth than after a cesarean delivery since the uterine cavity is readily accessed and visualized during surgery.

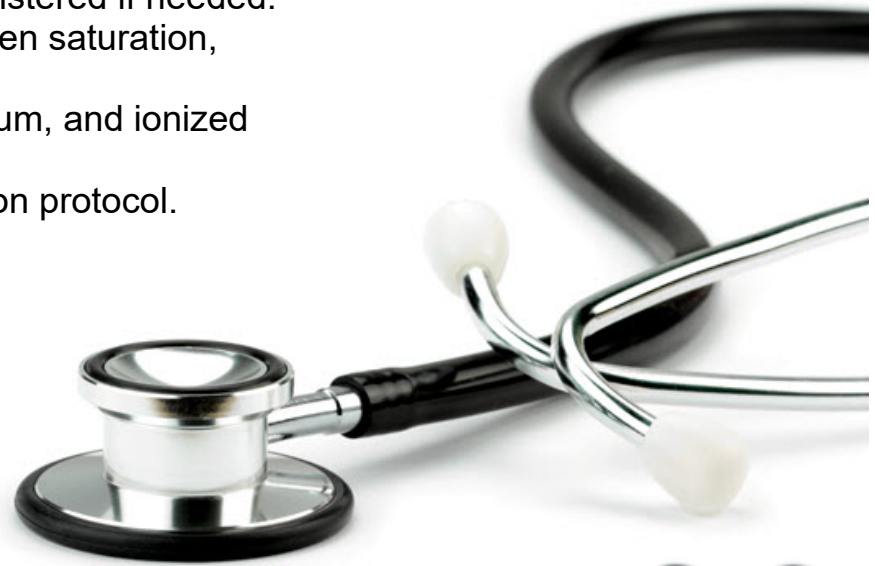




Key components of evaluation and treatment

Rapid evaluation and management of persistent vaginal bleeding after delivery requires:

- A provider to remain at the bedside for evaluation.
- Active management of the third stage of labor with oxytocin and secondary uterotonic drugs such as carboprost, methylergonovine, or misoprostol.
- Early IV access so massive transfusion can be administered if needed.
- Frequent assessment of BP, HR, RR, peripheral oxygen saturation, and urine output.
- Early evaluation of CBC, coagulation studies, potassium, and ionized calcium levels.
- Blood cross-match or initiation of a massive transfusion protocol.



Initial Interventions

- Women with persistent postpartum vaginal bleeding should be closely monitored, provided good IV access, and supported with fluids and blood products, as needed.
- The source of bleeding should be determined and treated; clinical assistance should be requested, as appropriate.
- Baseline laboratory studies include hematocrit/hemoglobin, coagulation studies, electrolyte concentrations, and type and crossmatch of blood products.



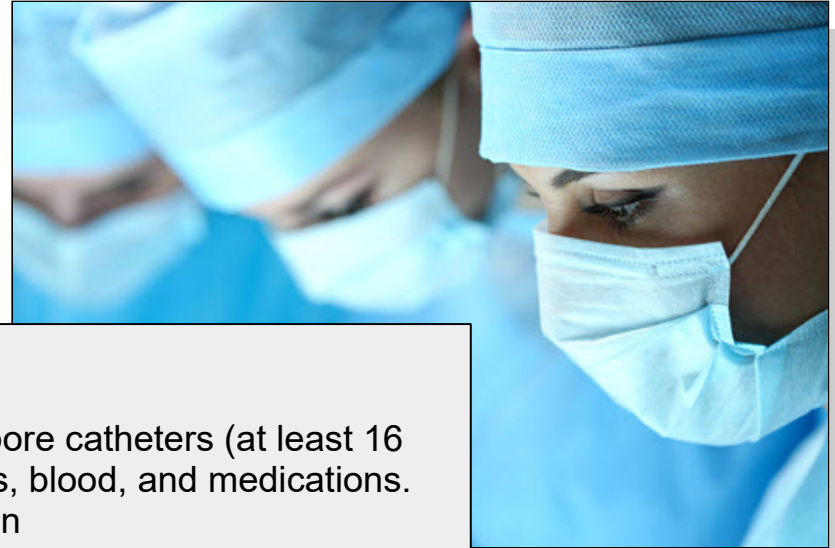
Although the initial interventions described below are often successful, in the setting of cardiovascular instability it is important to avoid prolonged, futile attempts at conservative therapy before proceeding to laparotomy and, if necessary, hysterectomy.

Uterine massage and compression is necessary if uterine atony is present.

Bimanual uterine massage is initiated. The provider places one hand into a fist and inserts vaginally to the anterior fornix and the other hand massages the fundus to compress the uterus between the hands.

Massage should continue until bleeding decreases. If the uterine fundus is firm and bleeding continues, further massage is unlikely to be effective, and other measures should be implemented.





Intravenous Access

IV access should be provided, preferably with two large bore catheters (at least 16 or 18 gauge, ideally 14 gauge), for administration of fluids, blood, and medications.

- Consideration for Intraosseous access is an option

When a patient has severe bleeding, peripheral blood flow will be diminished, making access of peripheral IV access difficult. This patient should have a central venous line placed into the subclavian or internal jugular.

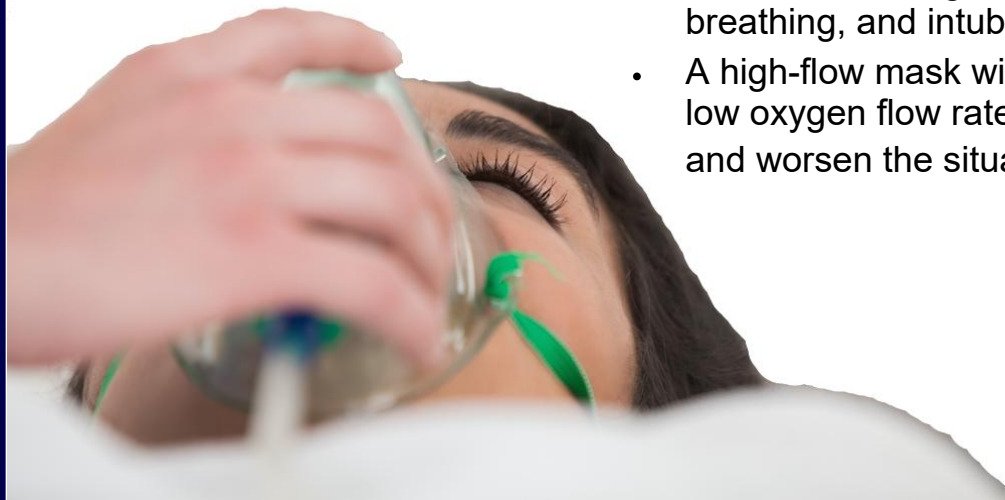
Early recognition of the event will require that the appropriate team is summoned to assist, such as the anesthesia team, or vascular access team, to place the lines.





Oxygenation

- Oxygenation is maximized by administering oxygen (10 to 15 liters/minute) by face mask and transfusion to improve oxygen-carrying capacity and delivery.
- An anesthesiologist should assess the patient's airway and breathing, and intubate if indicated.
- A high-flow mask with the correct flow rate is important since a low oxygen flow rate may result in carbon dioxide (CO₂) retention and worsen the situation.





Medications that help to abate PPH will now be reviewed.

- Oxytocin (Pitocin)
- Carboprost tromethamine (Hemabate)
- Methylergonovine (Methergine)
- Misoprostol (Cytotec)
- Dinoprostone (Prostin E2)
- Carbetocin (Oxytocic agent)
- Tranexamic acid (Lysteda)





Oxytocin 40 units in 1 liter (L) of normal saline intravenously at a rate sufficient to control uterine atony or 10 units intramuscular (IM) including the myometrium.

Lower doses of oxytocin IV, for a short period of time, have proven to be as effective as higher doses, such as 80 units in 500mL, infused over 30 minutes [37].

- Rapid infusion of high-dose oxytocin can lead to hypotension and cardiovascular collapse.
- It is recommended if a high-dose of oxytocin is used it should be a smaller volume, such as 15 units in 250mL, to reduce the dose administered over the short period of time.





Carboprost Tromethamine (Hemabate)



Contraindicated if woman has asthma. For PPH Carboprost (15 methyl-PGF₂alpha, Hemabate) 250 micrograms (mcg) IM every 15 to 90 minutes can be administered as needed to control bleeding. A total cumulative dose of 2 milligrams (mg) or eight doses can be used.



After one or two doses of Carboprost, if the bleeding has not diminished, it is recommended to move on to another uterotonic agent because approximately 75% of women will respond after a single dose.



Using a six-inch spinal needle, Carboprost can be injected directly into the myometrium transabdominally or vaginally with or without ultrasound guidance.



Carboprost 250mcg can be diluted in 20mL of normal saline for injection into the myometrium.



As with any IM injection, aspirate to ensure the needle is not in a vein. If so, relocate and repeat aspiration prior to the injection.





Methylergonovine (Methergine)

Methylergonovine 0.2mg intramuscularly or directly into the myometrium (never intravenously), if:

- No hypertension
- No Raynaud's phenomenon
- No scleroderma

If needed, may be repeated every 2 to 4 hours.

Quickly move on to a different uterotonic agent if there is not a good response following the first dose.





Misoprostol (Cytotec)

Where injectable uterotonics are unavailable or contraindicated Misoprostol (PGE1) is useful for treatment for PPH.

There is no evidence that misoprostol is more effective than other uterotonics either for primary therapy of PPH or as an adjunctive treatment to oxytocin infusion [39].

Slide 1 of 4





Misoprostol (Cytotec)

The optimum dose and route of misoprostol administration is unclear [40-46].

Recommendation is to use 400mcg sublingually.

- Sublingual misoprostol is absorbed rapidly.
- Peak concentration in 30 minutes.
- Peak concentration is higher and sustained for approximately 3 hours compared with oral administration due to avoidance of the first-pass hepatic metabolism.
- Larger doses over 400mcg are associated with an increasing potential for hyperthermia.

◀ Slide 2 of 4 ▶





Misoprostol (Cytotec)

Limited data is available to support dosing; however, a systematic review concluded that a dose of 400mcg sublingually appeared to be as effective as 600mcg sublingually and had fewer side effects [47].

A randomized trial identified other possible approaches for misoprostol administration; 200 mcg orally with 400mcg sublingually or 400, 600, or 800mcg sublingually [43,47,48 49,50].

The World Health Organization (WHO) suggests a single dose of 800mcg sublingually [51,52].

Oral misoprostol is rapidly absorbed and reaches peak concentration within 30 minutes. Due to hepatic metabolism, the oral route is absorbed at a lower level than sublingual administration and declines over two hours.

◀ Slide 3 of 4 ▶





Misoprostol (Cytotec)

Rectal administration:

- Takes up to one hour to peak compared to 30 minutes for oral or sublingual [53,54].
- 800 to 1000mcg is the most commonly used dose [47,49,55 56].
- Duration of action is 4 hours, which is longer than the 2-3 hours with oral or sublingual routes.

Due to heavy bleeding, it is not recommended to use the vaginal route of administration.

Misoprostol can be administered to women with hypertension or asthma.

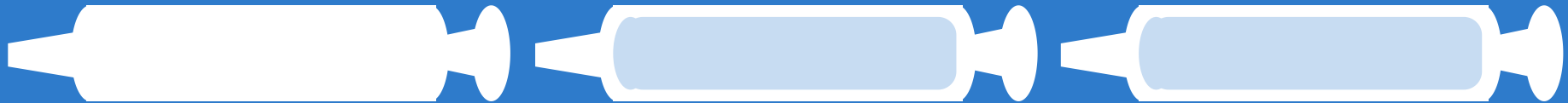
Monitoring of the maternal temperature is important because pyrexia >40 degrees Celsius can occur when increasing misoprostol dose. Elevated temperature should be treated with acetaminophen.

Slide 4 of 4





Dinoprostone (PGE₂) mg vaginal or rectal suppository can be administered every two hours as an alternate prostaglandin to misoprostol (PGE₁).



Medication - Others



*Click each syringe to
see more information.*





Carbetocin, a long-acting analog of oxytocin, is in use in many countries (but not the U.S.) for prevention of uterine atony and hemorrhage [57].



Medication - Others



*Click each syringe to
see more information.*





Trandexamic Acid (TXA)

- Intravenous tranexamic acid (TXA) is recommended by the World Health Organization (WHO) to be used early, even within 3 hours, following vaginal birth or cesarean delivery in addition to standard care for women diagnosed with postpartum hemorrhage (PPH).
- TXA is a competitive inhibitor of plasminogen activation and can reduce bleeding by inhibiting the breakdown of fibrinogen and fibrin clots.
- By giving within 3 hours of birth, maternal death from hemorrhage may be prevented, regardless of the cause. There were no noted adverse maternal effects from the medication.

[Click for more information on tranexamic acid](#)





- TXA for PPH should not be utilized more than 3 hours after birth.
 - The benefits of TXA appear to decrease by 10% for every 15-minute delay, with no benefit seen after 3 hours from birth.
- TXA should be initiated as soon as possible after the onset of bleeding and within 3 hours of birth and should be considered part of the standard PPH treatment package (i.e. uterotonics, non-surgical and surgical interventions).
- Regardless of whether the postpartum hemorrhage is from the genital tract trauma or other causes, TXA should be used in all cases.
- TXA administration involves a fixed dose of 1 gram in 10mL (100mg/mL) IV at 1mL per minute (administered over 10 minutes).
 - A second dose of 1g IV if bleeding continues after 30 minutes or if bleeding restarts within 24 hours of completing the first dose.
 - A bolus of TXA should be avoided due to a potential risk of transient lowering of blood pressure.
 - A decreased dose should be given when she has renal insufficiency.
 - TXA should not be given with solutions containing blood products, penicillin or mannitol.
- The half-life of TXA is 2 hours and antifibrinolytic effect lasts for 7-8 hours.





Contraindications to TXA

- Avoid in women with clear contraindications:
 - Known thromboembolic event in pregnancy
 - History of coagulopathy
 - Active intravascular clotting
 - Known hypersensitivity to TXA
 - In patients with subarachnoid hemorrhage or DIC



Removal of retained products of conception (POC) [57,58]

- Examine the uterus for any retained POC, placenta fragments or fetal membrane. The POC can be removed manually or with ring forceps.
- Bedside ultrasound can be used to guide removal of POC.
- Curettage with a banjo curette or 16mm suction catheter can be used if manual removal is unsuccessful.





Uterine tamponade

- Uterine tamponade is effective in many patients with atony or lower segment bleeding
- Either a balloon or a pack can be used for tamponade, but a balloon device designed for uterine tamponade is preferable because it can be placed quickly, allows some assessment of ongoing hemorrhage, and is probably more effective [59].

On-going monitoring of hemoglobin, potassium, ionized calcium, urine output, and blood loss is performed regardless of the method used for uterine tamponade [60].

- This is especially important when gauze, such as Kerlix, is used because a moderate amount of blood can be concealed behind the pack.

If gauze packing is not successful in controlling the bleed it is not advisable to repack [60].

If successful, the balloon or pack is removed after 24 hours.





Administer a broad spectrum antibiotic IV while gauze packing is in place, such as:

- Gentamicin, 1.5mg/kg every eight hours, and either:
 - Metronidazole, 500mg every eight hours
 - Clindamycin, 300mg every six hours
- These medications are generally administered for 24 hours and discontinued when the pack is removed.



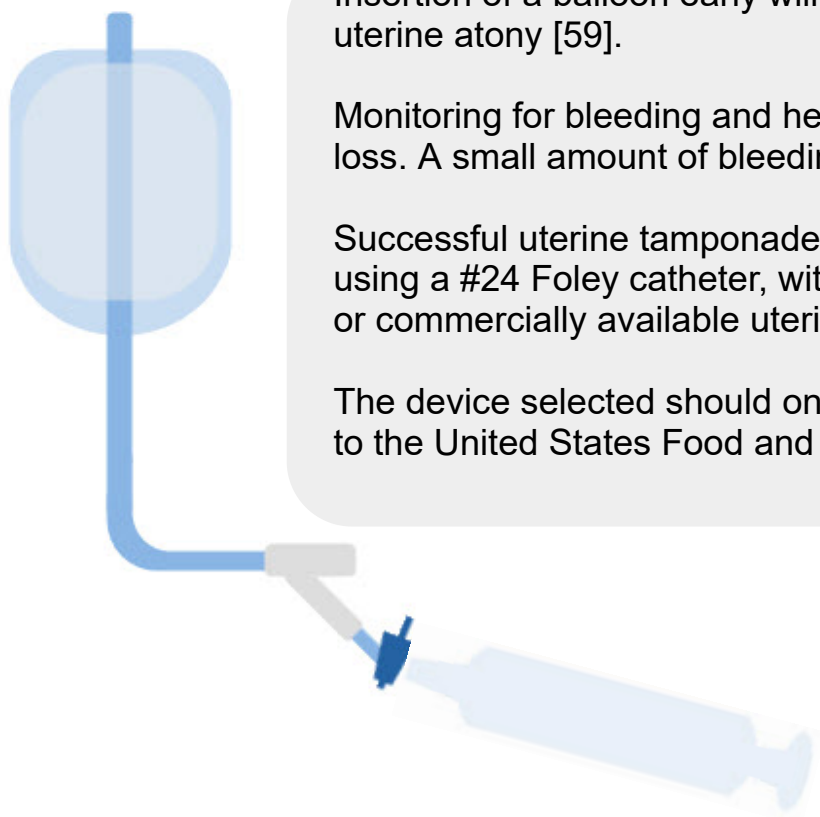
Intrauterine Balloon Catheter

Insertion of a balloon early will reduce blood loss while attempting to treat uterine atony [59].

Monitoring for bleeding and hemoglobin levels will evaluate for continued blood loss. A small amount of bleeding over time can add up.

Successful uterine tamponade can be achieved with an improvised tamponade using a #24 Foley catheter, with a 30mL balloon, Sengstaken-Blakemore tube, or commercially available uterine balloon tamponade devices.

The device selected should only be filled until bleeding is controlled and only to the United States Food and Drug Administration approved fill volume [61].





Balloon Tamponade Continued

It is believed the mechanism of action is related to a decrease in uterine artery perfusion pressure either by direct compression of the uterine artery or uterine wall conformational changes [61].

A description of these devices and their placement is addressed in the training portion of Maternal 911 in Action Postpartum Hemorrhage.

During treatment with a uterine balloon tamponade, ongoing evaluation of blood loss, blood levels, and outcome of blood replacement is crucial in the event she will require surgery to stabilize her condition.

If bleeding continues with the tamponade in place, the provider should promptly recognize that surgery or embolization may be necessary.



Fluid Resuscitation and Transfusion

- Urine output should be closely monitored using a bladder catheter with a urometer.
- To avoid hypothermia, all fluid and blood components should be normothermic.

Warm blankets should be used to assist in keeping her warm.

Crystalloid

- Replacement of blood components are based upon expert opinion as no universally accepted guidelines are available [62,63].
- While waiting for blood and blood products to arrive to the bedside, crystalloid volume expanders can be used to maintain hemodynamic stability.
- Transfusion of red cells will be used to improve and maintain tissue oxygenation.
- Treatment goal is to maintain systolic BP at 90mmHg and urine output at >30mL/hour.
- Monitor effectiveness of treatment, blood loss should be evaluated every 15 to 30 minutes and laboratory evaluation every 30 to 60 minutes to guide further blood product replacement.

A woman with preeclampsia is treated similar to a trauma patient because she will have contracted intravascular volume and be hemoconcentrated. This increases her risk of tissue hypoperfusion.



Compensated shock may present in the woman with an increasing HR and tachypnea with a stable BP. When these symptoms present, the PPH protocol should be instituted even if light vaginal bleeding is observed.

In the postpartum period, hemoglobin and hematocrit may be poor indicators of acute blood loss since they may not decline immediately after acute bleeding.

Aggressive volume resuscitation with packed red blood cells (PRBC) and other blood products is used for treatment of hypovolemic shock.



Management and Treatment of PPH



To allow time, considering early use of balloon tamponade may be useful to decrease blood loss.

If she has an extremely low fibrinogen level, cryoprecipitate and fibrinogen concentrate are indicated. Fibrinogen level cannot be increased with fresh frozen plasma alone without requiring excessive volume infusion.



A woman with placenta accrete, increta, percreta, or a large uterine rupture may need an early hysterectomy to control the hemorrhage.

A hysterectomy should be promptly performed in a woman who is diagnosed or suspected to have DIC to prevent further hemorrhage or death.

However, in a woman with uterine atony, a hysterectomy is generally the last resort. These women can usually be managed with medical therapy and less invasive surgical interventions.



Management and Treatment of PPH Cont'd





If persistent bleeding continues in a hemodynamically stable woman in which capacity of blood replacement has been provided, arterial embolization is an appropriate treatment option.

- This procedure is not to be performed on an unstable patient who has to be transferred to a radiology suite. This patient is managed for uncontrolled PPH with unknown cause.

Generally, an unstable and/or coagulopathic patient should receive bimanual uterine compression, balloon tamponade, aortic compression, transfusion of blood and blood products such as fibrinogen concentrate, prothrombin, and complex concentrations to stabilize for general anesthesia and surgery.

When considering an emergency hysterectomy, the patient should have stable coagulation with adequate IV access for massive transfusion and electrolyte imbalance treatment. Surgery should be in a setting in which treatment can be provided, such as management of uncontrolled retroperitoneal hemorrhage and/or myocardial depression.





Baseline laboratory evaluation should include:

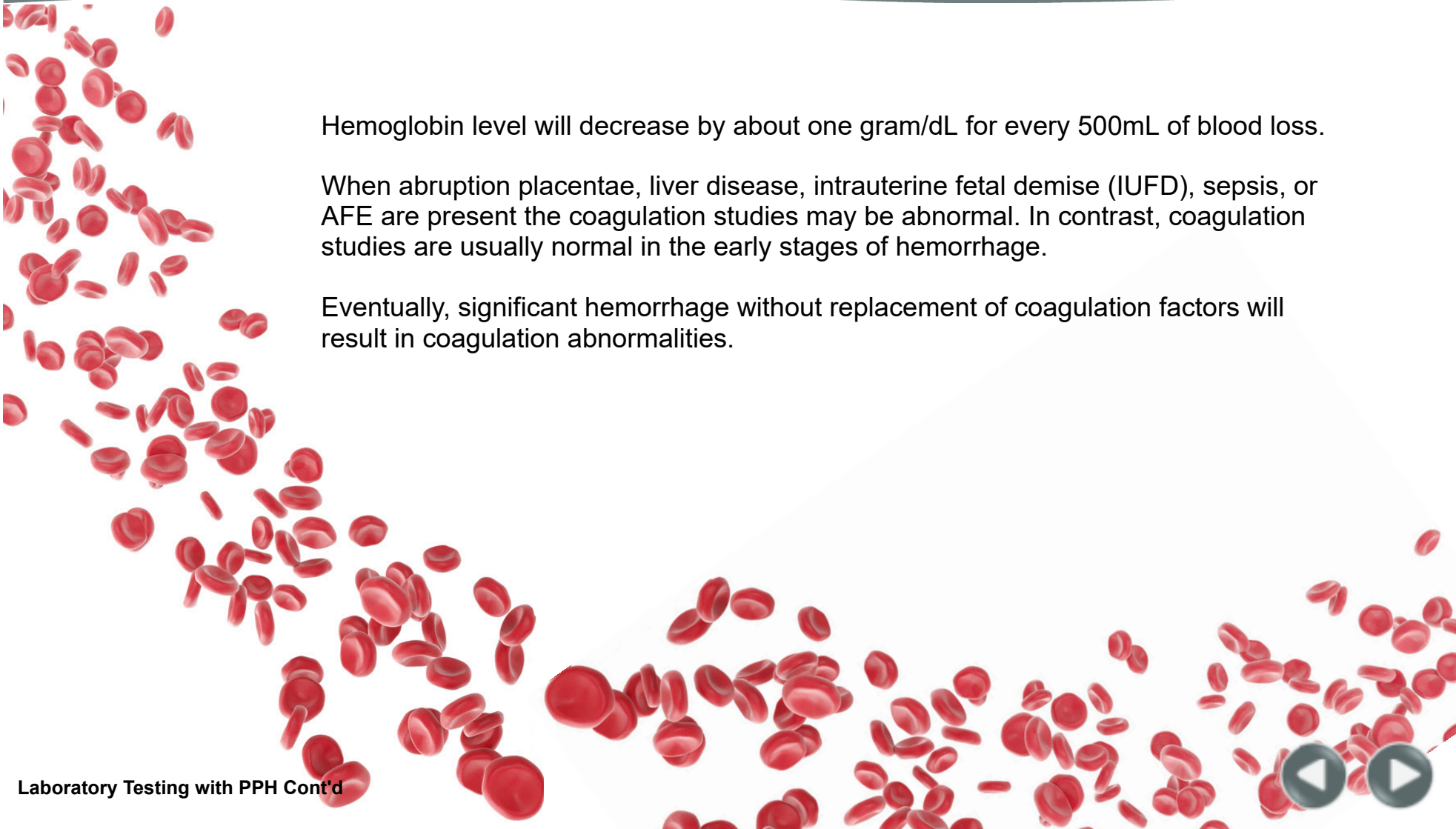
- CBC with platelet count
- Type and cross matched for multiple units of PRBC
- Coagulation studies:
 - Fibrinogen concentration
 - Prothrombin time (PT)
 - Activated partial thromboplastin time (aPTT)

In addition, the patient should be typed and crossed for multiple units of packed red blood cells.

Remember, the initial hemoglobin and hematocrit does not reflect the amount of blood loss, but upon further evaluation will identify the loss over time.



*Click each here to
see more information.*



Hemoglobin level will decrease by about one gram/dL for every 500mL of blood loss.

When abruption placentae, liver disease, intrauterine fetal demise (IUFD), sepsis, or AFE are present the coagulation studies may be abnormal. In contrast, coagulation studies are usually normal in the early stages of hemorrhage.

Eventually, significant hemorrhage without replacement of coagulation factors will result in coagulation abnormalities.



Prior to the return of the first set of laboratory studies, a red top tube of 5mL blood can be observed for clotting.

The patient is likely to have adequate fibrinogen stores if the blood tube clots within 8 to 10 minutes and remains intact.

The patient is likely to have markedly deficient blood clotting factors if the blood in the tube does not clot or the clot dissolves [4].



The fibrinogen level at the time of diagnosis of PPH is predictive of severity and can be used to guide the aggressiveness of management [64-67].

In studies, a fibrinogen level less than 200mg/dL was predictive of severe PPH. These women needed transfusion of multiple units of blood, blood products, arterial embolization, surgical management of bleeding, or maternal death occurred [64-66,68].

When PPH occurs, the fibrinogen level is a better predictor of ongoing major blood loss than PT, aPTT, or platelet count [37,69].

Caution ↓200

The coagulation panel should be repeated every 30 to 60 minutes until PPH is controlled.

Electrolytes

- In any massive transfusion situation where multiple units of blood are rapidly transfused, electrolytes should be monitored, with prompt treatment of abnormalities.
- The most common electrolyte abnormalities are hyperkalemia and low ionized calcium levels.
- Both electrolyte disturbances can lead to cardiac arrest or significantly depressed cardiac function that precludes optimal resuscitation.





Ionized calcium should be measured at baseline and then every 15 minutes during a massive transfusion.

An ionized calcium level $<1\text{mmol/L}$ (normal 1.1 to 1.3mmol/L) impairs coagulation and places the patient at risk of cardiac arrest.

Emergency replacement may be accomplished with 10% calcium chloride (1g/10mL vial calcium chloride) 1g/100mL saline over 2 to 5 minutes via a central line.

Alternatively, 10% calcium gluconate (1g/10mL) 1 to 2g over 2 to 3 minutes can be given intravenously for every four units of PRBCs transfused [10].

Hypocalcemia is more important in predicting hospital mortality than the fibrinogen concentration, lowest platelet count, or presence of acidosis [71].





Following the transfusion of multiple units of PRBCs, the patient can develop hyperkalemia.

Hyperkalemia occurs at higher levels when the PRBCs are older units. The potassium (K) concentration increases from 2 to approximately 45mEq/L when a unit of blood ages from 2 to 42 days; therefore, the patient's K level can become dangerously high with massive transfusion.

K⁺





If time allows, hyperkalemia may be prevented by using an in-line K⁺ filter or using washed units of PRBCs. During a PPH emergency with massive blood transfusion this practice is unlikely.

Continued electrolyte evaluation is necessary for early detection of hyperkalemia.

When hyperkalemia is detected, treatment with 10 to 20 units of regular insulin in 500mL of 10% dextrose IV over 60 minutes can be considered [72].

Repeat bolus doses of regular insulin 10 U may be required [28].

- Another treatment consideration could be 10 U of regular insulin as a bolus dose.
- The action of insulin administration is that it lowers the serum potassium concentration by driving potassium into the cells.
- To monitor for hypoglycemia, the serum glucose should be measured every hour for 5 to 6 hours after the administration of insulin.





Massive Transfusion Protocol

Many protocols exist so an institution should implement the one most appropriate for their organization.

- Texas Children's Hospital Pavilion for Women.
- Stanford University Medical Center: an initial package consisting of 6 units RBCs, 4 units fresh frozen plasma (FFP), and 1 apheresis platelet unit [73].
- Brigham and Women's Hospital: immediate availability of 2 units RBCs and 2 units of FFP followed by 4 units each of RBCs and FFP and thawing of one pool (6 bags) cryoprecipitate.
- California Maternal Quality Care Collaborative OB Hemorrhage Protocol: For patients with unstable vital signs, suspicion of DIC, or blood loss >1500 mLs, transfuse pRBC, FFP, and platelets in a ratio of 6:4:1 or 4:4:1. If coagulopathy persists after 8 to 10 units pRBCs and coagulation factor replacement, recombinant activated factor VIIa is a reasonable option.





Estimated blood loss (EBL) should be converted to quantitative blood loss (QBL). The loss should be quantified every 15 to 30 minutes. Quantifying the blood loss will likely lead to a more accurate loss. Laboratory evaluation of blood loss should occur every 30 to 60 minutes. These findings will further guide replacement needs.

To evaluate for dilutional coagulopathy effects of RBC transfusion, monitoring of the PT, aPTT, platelet count or a viscoelastic test should be performed after every 5 to 7 units of RBC.

Blood and blood product replacement should be based on the above stated results.

Transfusing RBCs, platelets, cryoprecipitate, and fresh frozen plasma (FFP) to achieve the following targets are reasonable actions:

- Hemoglobin greater than 7.5g/dL
- Platelet count greater than 50,000/mm³
- Fibrinogen greater than 300mg/dL
- PT less than 1.5 times the control value
- aPTT less than 1.5 times the control value



Stop aggressive massive transfusion of plasma, platelets, and cryoprecipitate once hemostasis and hemodynamic stability are achieved.

There are risks associated with further transfusion, such as fluid overload and transfusion complication, once the bleeding is controlled and the patient is stable.

The optimal ratio of blood product replacement, RBC:FFP: platelet, is controversial [62,73,74].

A sensible and realistic approach may be one unit of FFP for every 2 to 3 units of RBCs or 4 units of FFP for every 6 units of RBCs [75-77].

Domestic and foreign trauma centers, a military hospital, and clinical experience in Iraq and Afghanistan, suggest that until the patient is stable and there is absence of coagulopathy, she receive one unit of FFP for every 1-2 units of RBCs [78-81].



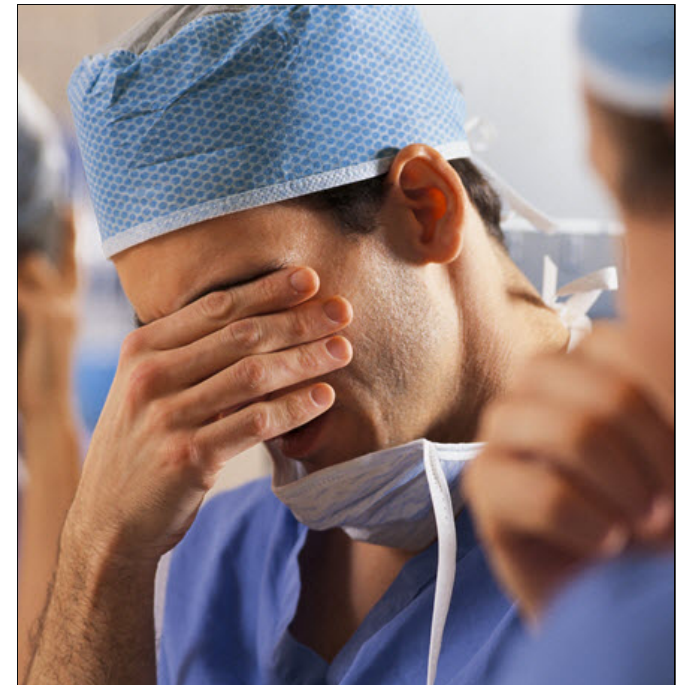
Guidelines for diagnosis, management, and prevention of postpartum hemorrhage have been developed by several organizations and are generally similar and consistent with the approach described in the Up-to-Date topics.

- California Maternal Quality Care Collaborative (CMQCC) best practices for management of obstetrical hemorrhage www.cmqcc.org/ob_hemorrhage/ob_hemorrhage_compendium_of_best_practices)
- Royal College of Obstetricians and Gynaecologists (RCOG) guideline for prevention and management of postpartum hemorrhage www.rcog.org.uk
- World Health Organization (WHO) guideline for prevention and treatment of postpartum haemorrhage http://apps.who.int/iris/bitstream/10665/75411/1/9789241548502_eng.pdf
- Society of Obstetricians and Gynaecologists of Canada (SOGC) guideline for prevention and management of postpartum hemorrhage www.sogc.org
- American College of Obstetricians and Gynecologists (ACOG) practice bulletin for postpartum hemorrhage
- New York health advisory recommendations for reducing the risk of maternal death from hemorrhage www.health.state.ny.us/professionals/protocols_and_guidelines/maternal_hemorrhage/

PPH can cause maternal morbidity and mortality.

This catastrophic event may lead to:

- Death
- Hypovolemic shock and organ failure: renal failure, stroke, myocardial infarction, postpartum hypopituitarism (Sheehan syndrome)
- Fluid overload (pulmonary edema, dilutional coagulopathy)
- Abdominal compartment syndrome
- Anemia
- Transfusion-related complications, including severe electrolyte abnormalities (predominantly hyperkalemia and hypocalcemia).
- Acute respiratory distress syndrome
- Anesthesia-related complications
- Sepsis, wound infection, pneumonia
- Venous thrombosis and embolism
- Unplanned sterilization due to need for hysterectomy
- Asherman syndrome (related to curettage if performed for retained products of conception)





Sheehan Syndrome aka Postpartum Hypopituitarism

- This is a rare condition but can be life-threatening.
- During pregnancy the pituitary gland becomes enlarged and can infarct when hypovolemic shock occurs.
- Mild to severe pituitary damage can occur with an infarction. This can result in secretion of one, several, or all of its hormones.

Sheehan syndrome should be considered if a woman presents following delivery with lactation failure, amenorrhea, or oligomenorrhea. She may also present with hypotension, hyponatremia, or hypothyroidism, which are manifestations of hypopituitarism. This event can occur in the immediate postpartum period to years following delivery.

If following control of hemorrhage and volume replacement she remains hypotensive, she should have evaluation of adrenal function and other hormone deficiencies. This evaluation can be performed 4 to 6 weeks postpartum but should not be overlooked.

Slide 1 of 3





Abdominal Compartment Syndrome

This is a rare life-threatening condition that causes intra-abdominal organ hypertension.

The patient may present with a tensely distended abdomen and progressively worsening oliguria. This may lead to the development of multi-organ failure.

Post operative cesarean delivered women have been reported to have intra-abdominal pressure at levels seen in abdominal compartment syndrome [82].

◀ *Slide 2 of 3* ▶





Thromboembolism

Thromboembolism is a risk factor following transfusion in trauma patients [83].

Therefore, women who have been treated for PPH with transfusions should have compression stockings or a pneumatic compression device applied as soon as possible and receive thromboprophylaxis until discharge [84].

Thromboprophylaxis should be initiated 12 to 24 hours after bleeding is controlled and coagulation tests are normal or near normal values [84].



Slide 3 of 3





Postpartum hemorrhage (PPH) can be defined as excessive bleeding that makes the patient symptomatic (i.e. lightheadedness, palpitations, diaphoresis, confusion) and/or results in signs of hypovolemia (i.e. hypotension, tachycardia, oliguria, decreased oxygen saturation).

The most common causes of PPH are atony, trauma, and acquired or congenital coagulation defects.

Although there are many known risk factors for PPH, knowledge of these risk factors is not always clinically useful in prevention of hemorrhage.



Click each box to review the course.





The approach to management of PPH varies depending on the cause and whether the patient has had a vaginal birth or cesarean delivery.

Traumatic, hemorrhaging lesions are managed surgically and coagulopathy is managed medically, with replacement of blood products.

The treatment of atony depends on the route of delivery, as there is less concern about the morbidity of open operative interventions when the patient's abdomen is already open.



Click each box to review the course.





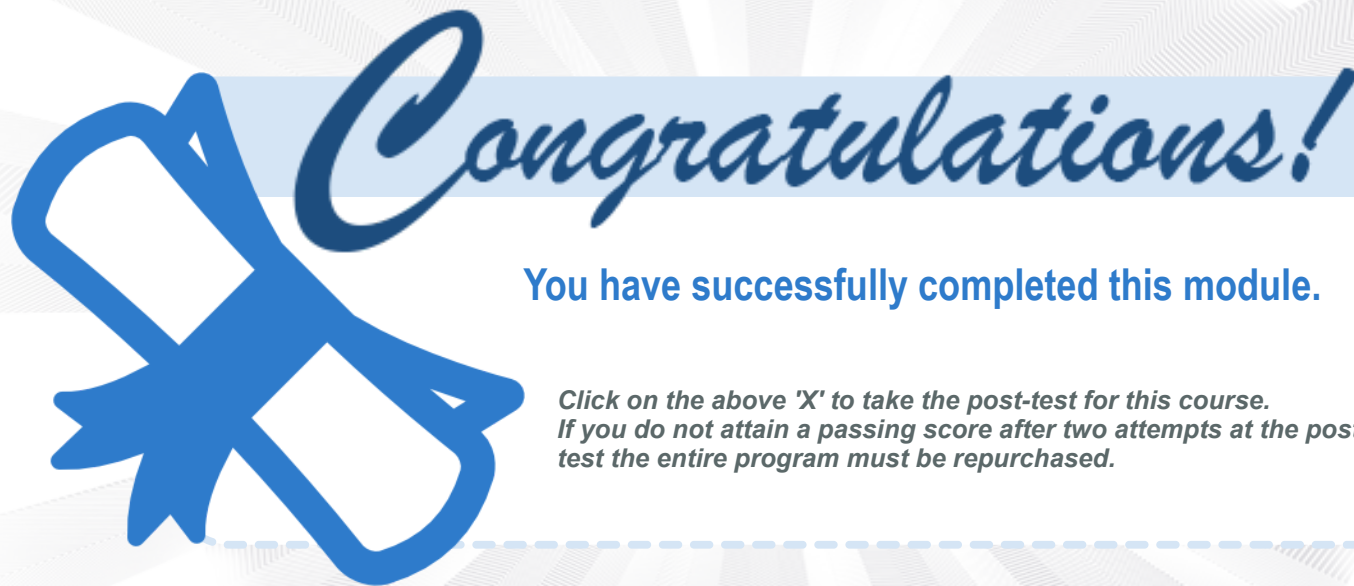
Massive transfusion requires close monitoring of volume status, hemodynamic effects, coagulation parameters, and electrolyte levels.

Resuscitative efforts can be compromised by cardiac dysfunction from potassium and calcium imbalances that result from rapid transfusion of stored blood.

Because of ease of treatment and a lesser incidence of severe side effects, we recommend that patients with anemia be treated with an oral, rather than a parenteral, iron preparation.

Women with a prior PPH have as much as a 15% risk of recurrence in a subsequent pregnancy. This recurrence rate is dependent on underlying conditions such as the risk of placental abruption.





You have successfully completed this module.

*Click on the above 'X' to take the post-test for this course.
If you do not attain a passing score after two attempts at the post-test the entire program must be repurchased.*

1. Practice Bulletin No. 183: Postpartum Hemorrhage. Committee on Practice Bulletins-Obstetrics Obstet Gynecol. 2017;130(4):e168.
2. <https://www.cmqcc.org/resource/ob-hem-emergency-management-plan-table-chart>
3. Sheldon WR, Blum J, Vogel JP, Souza JP, Gülmezoglu AM, Winikoff B. WHO Multicountry Survey on Maternal and Newborn Health Research Network. Postpartum haemorrhage management, risks, and maternal outcomes: findings from the World Health Organization Multicountry Survey on Maternal and Newborn Health. BJOG. 2014;121 Suppl 1:5
4. Callaghan WM, Kuklina EV, Berg CJ. Trends in postpartum hemorrhage: United States, 1994-2006. Am J Obstet Gynecol. 2010;202(4):353.e1.
5. Sheiner E, Sarid L, Levy A, Seidman DS, Hallak M. Obstetric risk factors and outcome of pregnancies complicated with early postpartum hemorrhage: a population-based study. J Matern Fetal Neonatal Med. 2005;18(3):149.
6. Mhyre JM, Shilkret A, Kuklina EV, Callaghan WM, Creanga AA, Kaminsky S, Bateman BT. Massive blood transfusion during hospitalization for delivery in New York State, 1998-2007. Obstet Gynecol. 2013;122(6):1288.
7. Bateman BT, Berman MF, Riley LE, Leffert LR. The epidemiology of postpartum hemorrhage in a large, nationwide sample of deliveries. Anesth Analg 2010; 110:1368.
8. Rouse DJ, Leindecker S, Landon M, et al. The MFMU Cesarean Registry: uterine atony after primary cesarean delivery. Am J Obstet Gynecol 2005; 193:1056.
9. Cheng YW, Delaney SS, Hopkins LM, Caughey AB. The association between the length of first stage of labor, mode of delivery, and perinatal outcomes in women undergoing induction of labor. Am J Obstet Gynecol 2009; 201:477.e1.
10. Blomberg M. Maternal obesity and risk of postpartum hemorrhage. Obstet Gynecol 2011; 118:561.
11. Wetta LA, Szychowski JM, Seals S, et al. Risk factors for uterine atony/postpartum hemorrhage requiring treatment after vaginal delivery. Am J Obstet Gynecol 2013; 209:51.e1.
12. Kramer MS, Berg C, Abenhaim H, et al. Incidence, risk factors, and temporal trends in severe postpartum hemorrhage. Am J Obstet Gynecol 2013; 209:449.e1.
13. Sharp GC, Saunders PT, Greene SA, et al. Intergenerational transmission of postpartum hemorrhage risk: analysis of 2 Scottish birth cohorts. Am J Obstet Gynecol 2014; 211:51.e1.
14. Bruning AH, Heller HM, Kieviet N, et al. Antidepressants during pregnancy and postpartum hemorrhage: a systematic review. Eur J Obstet Gynecol Reprod Biol 2015; 189:38.
15. Oberg AS, Hernández-Díaz S, Frisell T, et al. Genetic contribution to postpartum haemorrhage in Swedish population: cohort study of 466,686 births. BMJ 2014; 349:g4984.
16. Giannella L, Mfuta K, Pedroni D, et al. Delays in the delivery room of a primary maternity unit: a retrospective analysis of obstetric outcomes. J Matern Fetal Neonatal Med 2013; 26:593.
17. Grzeskowiak LE, McBain R, Dekker GA, Clifton VL. Antidepressant use in late gestation and risk of postpartum haemorrhage: a retrospective cohort study. BJOG 2016; 123:1929.
18. Nyfløt LT, Sandven I, Oldereid NB, et al. Assisted reproductive technology and severe postpartum haemorrhage: a case-control study. BJOG 2017; 124:1198.

19. Lukes AS, Kadir RA, Peyvandi F, Kouides PA. Disorders of hemostasis and excessive menstrual bleeding: prevalence and clinical impact. *Fertil Steril*. 2005;84(5):1338.
20. Kadir RA, Lee CA, Sabin CA, Pollard D. Pregnancy in women with von Willebrand's disease or factor XI deficiency. *Economides DL Br J Obstet Gynaecol*. 1998;105(3):314.
21. Zehnder JL, Leung LL. Development of antibodies to thrombin and factor V with recurrent bleeding in a patient exposed to topical bovine thrombin. *Blood*. 1990;76(10):2011.
22. Kadir RA, Kingman CE, Chi C, et al. Is primary postpartum haemorrhage a good predictor of inherited bleeding disorders? *Haemophilia* 2007; 13:178.
23. Kadir RA, Aledort LM. Obstetrical and gynaecological bleeding: a common presenting symptom. *Clin Lab Haematol* 2000; 22 Suppl 1:12.
24. Marshall AL, Durani U, Bartley A, Hagen CE, Ashrani A, Rose C, Go RS, Pruthi RK. The impact of postpartum hemorrhage on hospital length of stay and inpatient mortality: a National Inpatient Sample-based analysis. *Am J Obstet Gynecol*. 2017;217(3):344.e1.
25. Rizvi F, Mackey R, Barrett T, et al. Successful reduction of massive postpartum haemorrhage by use of guidelines and staff education. *BJOG* 2004; 111:495.
26. Shields LE, Wiesner S, Fulton J, Pelletreau B. Comprehensive maternal hemorrhage protocols reduce the use of blood products and improve patient safety. *Am J Obstet Gynecol* 2015; 212:272.
27. Skupski DW, Brady D, Lowenwirt IP, et al. Improvement in Outcomes of Major Obstetric emorrhage Through Systematic Change. *Obstet Gynecol* 2017; 130:770.
28. Shields LE, Smalarz K, Reffigee L, et al. Comprehensive maternal hemorrhage protocols improve patient safety and reduce utilization of blood products. *Am J Obstet Gynecol* 2011; 205:368.e1.
29. http://www.jointcommission.org/Sentinel_Event_Alert___Issue_30_Preventing_infant_death_and_injury_during_delivery_Additional_Resources/
30. Maslovitz S, Barkai G, Lessing JB, Ziv A, Many A. Recurrent obstetric management mistakes identified by simulation. *Obstet Gynecol*. 2007;109(6):1295
31. Deering SH, Chinn M, Hodor J, Benedetti T, Mandel LS, Goff B. Use of a postpartum hemorrhage simulator for instruction and evaluation of residents. *J Grad Med Educ*. 2009 Dec;1(2):260-3.
32. Joint Commission on Accreditation of Healthcare Organizations. JCAHO sentinel event alert #30. 2004.
33. Kohn, LT, Corrigan, JM, Donaldson, MS, Eds; Committee on Quality of Health Care in America, Institute of Medicine. *To Err Is Human: Building a Safer Health System*. Washington, DC: National Academy Press; 1999.
34. ACOG Committee Opinion No. 447: Patient safety in obstetrics and gynecology. American College of Obstetricians and Gynecologists Committee on Patient Safety and Quality Improvement. *Obstet Gynecol*. 2009;114(6):1424.
35. Dahlke JD, Mendoz-Figueroa H, Maggio L, et al. Prevention and management of postpartum hemorrhage: a comparison of 4 national guidelines. *Am J Obstet Gynecol* 2015; 213.e1

36. James, AH, McLintock, C., Lockhart, E. Postpartum hemorrhage: when uterotonics and sutures fail. *Am J Hematol* 2012; 87 Suppl 1:S16.
37. Munn, M.B., Owen, J., Vincent, R., et al. Comparison of two oxytocin regimens to prevent uterine atony at cesarean delivery: a randomized controlled trial. *Obstet Gynecol* 2001; 98:386.
38. Mousa, H. A., Blum, J., Abou, E., Senoun, G., et al. Treatment for primary postpartum haemorrhage. *Cochrane Database Syst Rev* 2014; :CD003249.
39. Hofmeyr, G. J., Gülmezoglu, A. M., Novikova, N., Lawrie, T. A. Postpartum misoprostol for preventing maternal mortality and morbidity. *Cochrane Database Syst Rev* 2013; :CD 008982.
40. Hofmeyr GJ, Walraven G, Gülmezoglu AM, et al. Misoprostol to treat postpartum haemorrhage: a systematic review. *BJOG* 2005; 112:547.
41. O'Brien P, El-Refaey H, Gordon A, et al. Rectally administered misoprostol for the treatment of postpartum hemorrhage unresponsive to oxytocin and ergometrine: a descriptive study. *Obstet Gynecol* 1998; 92:212.
42. Lokugamage AU, Sullivan KR, Niculescu I, et al. A randomized study comparing rectally administered misoprostol versus Syntometrine combined with an oxytocin infusion for the cessation of primary post partum hemorrhage. *Acta Obstet Gynecol Scand* 2001; 80:835.
43. Walraven G, Dampha Y, Bittaye B, et al. Misoprostol in the treatment of postpartum haemorrhage in addition to routine management: a placebo randomised controlled trial. *BJOG* 2004; 111:1014.
44. Hofmeyr GJ, Ferreira S, Nikodem VC, et al. Misoprostol for treating postpartum haemorrhage: a randomized controlled trial [ISRCTN72263357]. *BMC Pregnancy Childbirth* 2004; 4:16.
45. Blum J, Winikoff B, Raghavan S, et al. Treatment of post-partum haemorrhage with sublingual misoprostol versus oxytocin in women receiving prophylactic oxytocin: a double-blind, randomised, non-inferiority trial. *Lancet* 2010; 375:217.
46. Winikoff B, Dabash R, Durocher J, et al. Treatment of post-partum haemorrhage with sublingual misoprostol versus oxytocin in women not exposed to oxytocin during labour: a double-blind, randomised, non-inferiority trial. *Lancet* 2010; 375:210.
47. Hofmeyr GJ, Gülmezoglu AM, Novikova N, et al. Misoprostol to prevent and treat postpartum haemorrhage: a systematic review and meta-analysis of maternal deaths and dose-related effects. *Bull World Health Organ* 2009; 87:666.
48. Hofmeyr GJ, Walraven G, Gülmezoglu AM, et al. Misoprostol to treat postpartum haemorrhage: a systematic review. *BJOG* 2005; 112:547.
49. Tang OS, Schweer H, Seyberth HW, et al. Pharmacokinetics of different routes of administration of misoprostol. *Hum Reprod* 2002; 17:332.
50. Tang OS, Gemzell-Danielsson K, Ho PC. Misoprostol: pharmacokinetic profiles, effects on the uterus and side-effects. *Int J Gynaecol Obstet* 2007; 99 Suppl 2:S160.
51. Shojai R, Desbrière R, Dhifallah S, et al. [Rectal misoprostol for postpartum hemorrhage]. *Gynecol Obstet Fertil* 2004; 32:703.
52. Nasr A, Shahin AY, Elsamman AM, et al. Rectal misoprostol versus intravenous oxytocin for prevention of postpartum hemorrhage. *Int J Gynaecol Obstet* 2009; 105:244.

53. Anandakrishnan S, Balki M, Farine D, et al. Carbetocin at elective Cesarean delivery: a randomized controlled trial to determine the effective dose, part 2. *Can J Anaesth* 2013; 60:1054.
54. Chandler WL, Ferrell C, Trimble S, Moody S. Development of a rapid emergency hemorrhage panel. *Transfusion* 2010; 50:2547.
55. de Lloyd L, Bovington R, Kaye A, et al. Standard haemostatic tests following major obstetric haemorrhage. *Int J Obstet Anesth* 2011; 20:135.
56. Hiippala ST, Myllylä GJ, Vahtera EM. Hemostatic factors and replacement of major blood loss with plasma-poor red cell concentrates. *Anesth Analg* 1995; 81:360.
57. Su LL, Chong YS, Samuel M. Oxytocin agonists for preventing postpartum haemorrhage. *Cochrane Database Syst Rev* 2007; :CD005457.
58. Anandakrishnan S, Balki M, Farine D, et al. Carbetocin at elective Cesarean delivery: a randomized controlled trial to determine the effective dose, part 2. *Can J Anaesth* 2013; 60:1054.
59. Howard TF, Grobman WA. The relationship between timing of postpartum hemorrhage interventions and adverse outcomes. *Am J Obstet Gynecol* 2015; 213:239.e1.
60. Hsu S, Rodgers B, Lele A, Yeh J. Use of packing in obstetric hemorrhage of uterine origin. *J Reprod Med* 2003; 48:69.
61. Belfort MA, Dildy GA, Garrido J, White GL. Intraluminal pressure in a uterine tamponade balloon is curvilinearly related to the volume of fluid infused. *Am J Perinatol* 2011; 28:659.
62. Spahn DR, Rossaint R. Coagulopathy and blood component transfusion in trauma. *Br J Anaesth* 2005; 95:130.
63. Fuller AJ, Bucklin B. Blood component therapy in obstetrics. *Obstet Gynecol Clin North Am* 2007; 34:443.
64. Charbit B, Mandelbrot L, Samain E, et al. The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. *J Thromb Haemost* 2007; 5:266.
65. Cortet M, Deneux-Tharaux C, Dupont C, et al. Association between fibrinogen level and severity of postpartum haemorrhage: secondary analysis of a prospective trial. *Br J Anaesth* 2012; 108:984.
66. Collins PW, Lilley G, Bruynseels D, et al. Fibrin-based clot formation as an early and rapid biomarker for progression of postpartum hemorrhage: a prospective study. *Blood* 2014; 124:1727.
67. van der Bom JG. Viscoelastometric testing, fibrinogen and transfusion during post-partum haemorrhage. *Br J Anaesth* 2017; 119:352.
68. Gayat E, Resche-Rigon M, Morel O, et al. Predictive factors of advanced interventional procedures in a multicentre severe postpartum haemorrhage study. *Intensive Care Med* 2011; 37:1816.
69. Lousquy R, Morel O, Soyer P, et al. Routine use of abdominopelvic ultrasonography in severe postpartum hemorrhage: retrospective evaluation in 125 patients. *Am J Obstet Gynecol* 2011; 204:232.e1.
70. Elmer J, Wilcox SR, Raja AS. Massive transfusion in traumatic shock. *J Emerg Med* 2013; 44:829.
71. Ho KM, Leonard AD. Concentration-dependent effect of hypocalcaemia on mortality of patients with critical bleeding requiring massive transfusion: a cohort study. *Anaesth Intensive Care* 2011; 39:46.

72. Mount DB, Zandi-Nejad K. Disorders of potassium balance. In: Brenner and Rector's The Kidney, 8th ed, Brenner BM (Ed), WB Saunders Co, Philadelphia 2008. p.547.
73. Burtelow M, Riley E, Druzin M, et al. How we treat: management of life-threatening primary postpartum hemorrhage with a standardized massive transfusion protocol. *Transfusion* 2007; 47:1564.
74. Gonzalez EA, Moore FA, Holcomb JB, et al. Fresh frozen plasma should be given earlier to patients requiring massive transfusion. *J Trauma* 2007; 62:112.
75. Roback JD, Caldwell S, Carson J, et al. Evidence-based practice guidelines for plasma transfusion. *Transfusion* 2010; 50:1227.
76. Spahn DR, Bouillon B, Cerny V, et al. Management of bleeding and coagulopathy following major trauma: an updated European guideline. *Crit Care* 2013; 17:R76.
77. Allard S, Green L, Hunt BJ. How we manage the haematological aspects of major obstetric haemorrhage. *Br J Haematol* 2014; 164:177.
78. Holcomb JB, Jenkins D, Rhee P, et al. Damage control resuscitation: directly addressing the early coagulopathy of trauma. *J Trauma* 2007; 62:307.
79. Ketchum L, Hess JR, Hiippala S. Indications for early fresh frozen plasma, cryoprecipitate, and platelet transfusion in trauma. *J Trauma* 2006; 60:S51.
80. Davenport R, Curry N, Manson J, et al. Hemostatic effects of fresh frozen plasma may be maximal at red cell ratios of 1:2. *J Trauma* 2011; 70:90.
81. Pasquier P, Gayat E, Rackelboom T, et al. An observational study of the fresh frozen plasma: red blood cell ratio in postpartum hemorrhage. *Anesth Analg* 2013; 116:155.
82. Abdel-Razeq SS, Campbell K, Funai EF, et al. Normative postpartum intraabdominal pressure: potential implications in the diagnosis of abdominal compartment syndrome. *Am J Obstet Gynecol* 2010; 203:149.e1.
83. Geerts WH, Code KI, Jay RM, et al. A prospective study of venous thromboembolism after major trauma. *N Engl J Med* 1994; 331:1601.
84. Pacheco LD, Saade GR, Gei AF, Hankins GD. Cutting-edge advances in the medical management of obstetrical hemorrhage. *Am J Obstet Gynecol* 2011; 205:526.
85. WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *Lancet*. 2017.
86. WOMAN Trial Collaborators. 2017. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *Lancet*. 389(10084):2105-2116. doi: 10.1016/S0140-6736(17)30638-4.