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POSTPARTUM HEMORRHAGE

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ABSTRACT

Postpartum haemorrhage (PPH) is the primary cause of maternal mortality and morbidity worldwide: in fact, about a quarter of deaths that occur during pregnancy, childbirth or the puerperium are caused by postpartum hemorrhage. There are many causes of postpartum haemorrhage, the most important are: uterine atony, lacerations of the cervix and/or perineum, retention of placental material, coagulation problems, uterine inversion, uterine rupture. This causes of PPH are represented by the '4Ts' formula: tone, tissue, trauma, thrombin.

An important role is played by prevention: identification of risk factors, prophylaxis with oxytocin at the time of delivery, early treatment. The first important thing is the quantification of blood loss because the clinical signs are often blurred and due to frank anaemia resulting in tachycardia, small and frequent pulse, hypotension, sweating, paleness. As previously mentioned, it is important to act early in the case of PPH through maintenance of volaemia and targeted therapies that differ according to the cause of PPH (the 4T algorithm is useful). Early intervention reduces the need for blood transfusions and reduces the incidence of serious complications such as DIC. However, the management of postpartum haemorrhage is not limited to the postpartum phase, but the patient must be monitored in the puerperium, a phase in which the thromboembolic risk is increased. The couple must also be informed of the risk of PPH in future pregnancies.

PPH represents a serious risk for the patient and requires multidisciplinary input and proper preparation of the team working in the delivery room.

Keywords: postpartum hemorrhage; oxitocine; quantitative blood loss; target therapy; delivery room.

EPIDEMIOLOGY OF POST-PARTUM HAEMORRHAGE

Postpartum hemorrhage (PPH) is the leading cause of maternal mortality and morbidity worldwide. About a quarter of deaths that occur during pregnancy, childbirth or the puerperium are caused by post-

partum hemorrhage. The incidence is higher in developing countries (1). Maternal mortality is a dramatic event and an important indicator of the general conditions of health and development of a Country.

The five most common causes of maternal death in Western countries are postpartum hemorrhage, thromboembolic disease, hypertension–preeclampsia, sepsis, and death due to anesthesia.

According to the global report on maternal mortality, produced by the World Health Organization in collaboration with UNICEF, UNFPA, the World Bank and the United Nations Population Division, it is evident that maternal mortality has decreased by almost 44% in the last 25 years worldwide: from 532.000 deaths in 1990 to 303.000 in 2015, with an estimated global ratio of 216 maternal deaths per 100.000 deliveries, a significant decline compared to the 1990 when the global ratio of maternal deaths was 385. The decline of maternal death is due to improved care during the prenatal period, childbirth, and immediate postpartum period. However, even today, 99% of global maternal deaths occur in developing countries, with 66% of cases in sub-Saharan Africa alone. In these countries, the risk of maternal mortality caused by PPH is 1 per 1.000 deliveries, about 100 times higher than the rate observed in the wealthier countries (an average of 1 death for PPH per 100,000 deliveries) (2). In Italy, like other industrialized countries, the maternal mortality ratio has progressively decreased, from 133 per 100.000 in 1955 to 4 per 100.000 deliveries in 2015, one of the best in the world at the levels of France, England, Germany, and United States (3).

Prevention, early diagnosis, and timely and adequate therapeutic intervention is the most effective method to minimize the clinical impact of this complication on the patient. Intrapartum care staff should systematically and routinely implement all interventions to prevent the PPH. Therefore, it is important to create an assistance protocol based on the most recent evidence of efficacy available.

DEFINITION

According to the World Health Organization (WHO), postpartum hemorrhage (PPH) has been defined as greater than 500 mL (severe if it exceeds 1.000 mL) estimated blood loss in a vaginal delivery or greater than 1000 mL estimated blood loss at the time of cesarean section (WHO, 2012).

Primary postpartum hemorrhage is bleeding that occurs in the first 24 hours after delivery, while **secondary postpartum hemorrhage** is defined as bleeding that occurs 24 hours to 12 weeks after delivery (4).

The Royal College of Obstetricians & Gynaecologists (RCOG), on the other hand, defines **minor PPH** when estimated blood loss is between 500 and 1.000 mL and **major PPH** when estimated blood loss exceeds 1.000 mL. Major PPH can also be divided into **major controlled**, in case of controlled blood loss and **major persistent**, in case of compromised health of the mother, such as to cause imminent danger to life.

RISK FACTORS

Risk factors are previous delivery complicated by PPH, multiparity, uterine overdistention from polydramnios or multiple pregnancy, pre-eclampsia, pre-pregnancy coagulopathies, uterine fibromyomatosis, placenta previa, uteroplacental abrup-

tion, prolonged duration of stage 3 of labour, uterine inertia, vaginal operative deliveries and, in the case of caesarean section, a scarred uterus.

However, it should be remembered that, in many cases, post-partum haemorrhage occurs in women without risk factors.

EZIOLOGY

There are many causes of postpartum haemorrhage, the most important are: uterine atony (90%), lacerations of the cervix and/or perineum (5%), retention of placental material (4%), coagulation problems, uterine inversion, uterine rupture.

Uterine atony

Uterine atony refers to the inadequate contraction of the uterus after expulsion of the fetus. It is the result of defective formation of the so-called 'safety globe'.

Physiologically, after delivery of the placenta, the uterine body contracts to ensure hemostasis, facilitated by multiple factors including the high production of endogenous oxytocin. The contraction of the myometrium mechanically compresses the blood vessels supplying the placental bed. This process seems to be favored by the activation of the mammillary-hypothalamic-pituitary reflex, stimulated by the newborn's early attachment to the maternal breast (5).

A lack of balance between postpartum haemostatic factors, hormonal factors and the effectiveness of contraction leads to atony and consequently PPH.

Risk factors for atony include uterine overdistension (multi-fetal pregnancy, fetal macrosomia, polyhydramnios), prolonged or precipitous labour (increased risk of uterine contractile force depletion), poor management of the third stage of labour.

The bimanual examination after a vaginal delivery reveals a boggy, soft and an unusually enlarged uterus (due to the accumulation of blood and clots in the cavity).

The treatment of uterine atony consists primarily of the administration of uterotonic drugs such as oxytocin and bimanual uterine-compression massage (6).

Genital tract lacerations

Genital tract lacerations can involve the uterus, cervix, vagina, and perineum; they represent, after uterine atony, the second leading cause of PPH.

It is estimated that perineal trauma of varying degrees occurs in approximately 85% of vaginal deliveries and 60-70% of these lacerations require suturing (5).

Vagino-perineal lacerations are classified into four categories (5):

1. First degree: involvement of the vulvovaginal mucosa and perineal skin.
2. Second degree: involvement of the perineal muscles and fasciae (superficial transverse muscle, bulbocavernosus, deep transverse muscle, sometimes also the medial bundles of the pubococcygeus); episiotomy is also included in this type of lacerations.
3. Third degree: involvement of the anal sphincter.

4. Complicated third degree or fourth degree: involvement of the anal sphincter and anorectal mucosa.

For appropriate evaluation, to exclude accidental inclusion of the rectal mucosa, a rectal exploration is recommended after surgical repair in episiotomies and in all lacerations of second degree, especially if extensive or technically difficult.

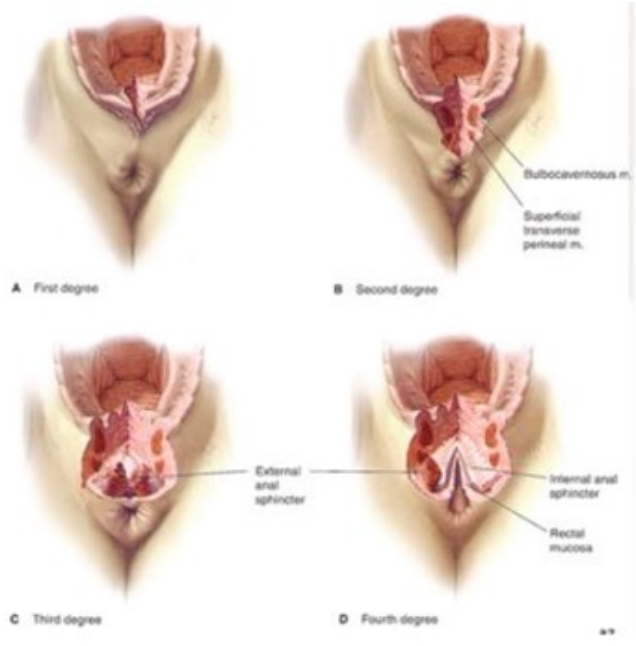


Figure 1 -Cervical-vaginal lacerations

('Emergenze ed urgenze in ostetricia e ginecologia', Felis - CIC Edizioni Internazionali)

Cervical lacerations can be of varying degrees, and they can sometimes cause significant bleeding. Cervical lacerations are observed following expulsion of the fetus, despite complete delivery of placenta having occurred and the uterus being contracted. They are facilitated by the rapid progression of the fetus along the birth canal, by external maneuvers, by the application of forceps or vacuum before complete dilation, or by traumatising obstetrical examinations aimed at accelerating complete dilation (Fig 1).

Vulvar or anus elevator haematomas are other frequent types of lacerations that can occur during delivery. If < 5 cm they often resolve spontaneously and require a conservative approach (ice packs, analgesics, antibiotics). If > 5 cm they generally require surgical intervention: incision, drainage, and possible ligation of the bleeding vessels.

Retained placenta or membranes.

Retention of placental fragments or membranes in the uterine cavity can impede normal contraction of the myometrium, promote atony and be a cause of postpartum haemorrhage. It is therefore essential to evaluate the integrity of the placenta and the completeness of the membranes visually. If the placenta-membrane fragments cannot be removed manually, curettage of the uterine cavity must be performed with large curettes, paying great attention to the risk of perforation.

There can be 3 causes of a **failure to delivery of placenta**:

1. Trapped or incarcerated placenta: the placenta is separated, has detached completely from the uterus but is not expelled spontaneously.
2. Placenta adherens: the placenta remains attached to the uterine wall, can be separated manually with ease.
3. Abnormal placental invasion: a placenta with villi that adhere to the superficial myometrium (placenta accreta); a placenta with villi that adhere to the body of the myometrium, but not through its full thickness (placenta increta); a placenta with villi that penetrate the full thickness of the myometrium and may invade neighboring organs such as the bladder or the rectum (placenta percreta) (5).

A history of uterine scarring (like previous caesar-

ean section) and placenta previa increase the risk of abnormal placental invasion by a factor of 30 (8). Women with a prior caesarean delivery should be closely monitored by ultrasound screening to try to identify pregnancies in which the site of placental implantation is the previous hysterotomic scar (scar pregnancy). These women have an increased risk of abnormal placental invasion.

Coagulation disorders

Physiologically, a series of changes occur in the haemocoagulative system during pregnancy.

In blood tests, a variation can be observed in:

- Factors VII, VIII, IX, X and I
- Factors XI and XIII
- Protein C and protein S
- Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT)

The sum of all these changes, in association with a decrease of blood flow in peripheral circulation, lead to a state of slight hypercoagulability and an increased thromboembolic risk typical of pregnancy and puerperium.

Congenital or acquired coagulopathies may increase the risk of haemorrhage during pregnancy and consequently of post-partum haemorrhage. **Congenital coagulopathies** include haemophilia A (factor VIII deficiency), B (factor IX deficiency) and Von Willebrand disease. Thrombocytopenia and pre-existing platelet disorders such as thrombotic thrombocytopenic purpura and Werlhof's disease may increase the risk of bleeding at the time of delivery. However, it should be noted that most thrombocytopenia observed in pregnancy are acquired: this type of thrombocytopenia is a paraphysiological condition of increased peripheral destruction of plates. This condition requires no treatment and is often mediated by anti-platelet IgG.

Acquired coagulopathies include DIC (Disseminated Intravascular Coagulation), a severe systemic process in which thrombi and haemorrhages are present simultaneously. DIC is always a secondary condition and in obstetrics can occur because of placental abruption, post-partum haemorrhage, retention of a dead fetus or internal abortion, amniotic fluid embolism, septicemia, septic shock, or transfusion disease. In all these cases there is a primary intravascular activation of coagulation with formation of thrombi in the microcirculation and consequent consumption of coagulation factors. Vascular occlusion is opposed by fibrinolysis, which in DIC is a defensive phenomenon to limit damage. This condition must be distinguished from consumption coagulopathy, in which the coagulation deficit is due to the loss of coagulation factors caused by haemorrhage, without any activation of coagulation in the circulation.

Laboratory tests show: reduction of platelets (from consumption in thrombus formation), reduction of fibrinogen, prolongation of PT and aPTT (from consumption of coagulation factors), increase of fibrinogen degradation products (D-Dimer, fibronectin, plasminogen, kallikrein).

Uterine inversion

Uterine inversion is characterized by 'glove-finger' introflexion of the uterine body.

Rarely a spontaneous condition, more often due to abnormal traction on the funiculus to accelerate placental abruption or too vigorous uterine squeezing (Credé manoeuvre).

Other risk factors are uterine overdistension, abnormal placental invasion, tocolysis, use of oxytocin, primiparity, the Kristeller manoeuvre, manual extraction of the placenta or a short umbilical cord.

Clinically, uterine inversion is characterized by the onset of violent pain with a prolapsed sensation, hypotension, and states of shock. The shock condition is due both to the severe blood loss that usually accompanies it (due to inability of the myometrium to contract adequately) and to traction on the infundibulum-pelvic ligaments (neurogenic stimulation) (5).

There are different degrees of severity of uterine inversion (Fig 2) (9).

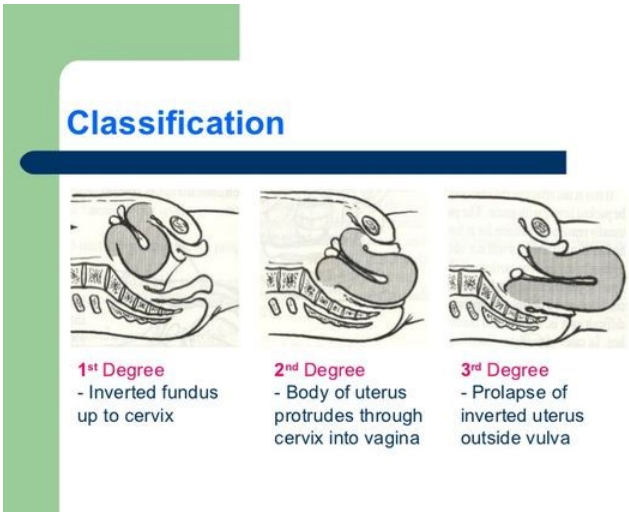


Figure 2- Classification of uterine inversion ('Emergenze ed urgenze in ostetricia e ginecologia', Felis - CIC Edizioni Internazionali)

The early recognition and subsequent treatment of uterine inversion is crucial: the earlier the intervention, the greater the chance of successful uterine reduction. After 30 minutes, a cervical cervix begins to form, which may make manual reduction impossible (6).

Uterine rupture

A **uterine rupture** is defined as a tear in the uterine musculature, which can be of different degrees. There are two types of uterine rupture (Fig 3):

1. Complete: full thickness tears of uterine wall.
2. Incomplete: the myometrium is disrupted but the serosa is intact.

If the rupture also involves adjacent organs (for example bladder), it is defined as **complicated**.

Complete rupture leads to repercussions on contractile dynamics, but often only becomes manifest after vaginal delivery, with haemorrhage and/or shock, persistent vaginal bleeding, and haematuria (in case of bladder injury). At other times it occurs during labour with maternal symptoms such as tachycardia, shock, continuous abdominal pain, modification of the uterine contour, arrest, or lack of co-ordination of contractions, frank haematuria; cardiotocographic abnormalities or rising of the presented part may be observed in the fetus (6).

Risk factors are previous hysterotomy by caesarean section or gynaecological surgery, mechanical or dynamic dystocia, abnormal presentations, incorrect use of oxytocin, incongruous obstetrical manoeuvres.

The diagnosis is confirmed during surgery: an emergency laparotomy must be performed to identify the site of the rupture and repair it. In the event of haemodynamic instability or a large lesion, consider hysterectomy.

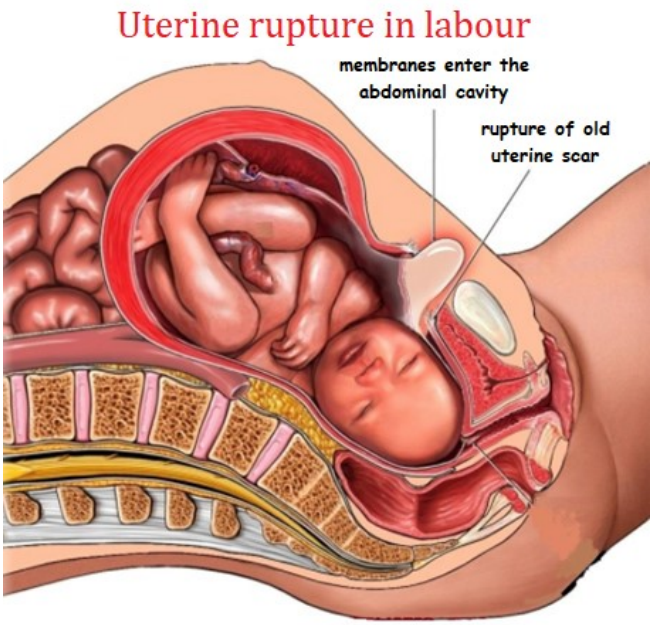


Figure 3 - Uterine rupture in labour

('Emergenze ed urgenze in ostetricia e ginecologia', Felis - CIC Edizioni Internazionali)

CLINICAL FEATURES OF POSTPARTUM HEMORRHAGE

In clinical practice, the causes of PPH are represented by the '4Ts' formula (Table 1):

- **Tone**: for abnormalities of uterine contraction.
- **Tissue**: for retention of amniochorial tissue or retained placenta.
- **Trauma**: for uterine rupture, cervical tears, uterine inversion, or birth canal tears.
- **Thrombin**: for coagulation disorders caused by thrombin dysfunction.

The clinical presentation of PPH can be blurred and blood loss is often underestimated, due to problems with correct quantification. Very often the first clinical signs are late and due to frank anaemia, such as tachycardia, small and frequent pulse, hypotension, sweating, paleness.

In addition, a series of physiological changes occur during pregnancy, so that vital signs may show no

Tone - Abnormalities of uterine contraction

- Uterine over-distention
- Exhaustion of the myometrium (augmented or prolonged labor)
- Infection (chorioamnionitis)
- Anatomical/functional alteration of the uterus

Tissue - Retained products of conception

- Placental tissue
- Succenturiate lobe
- Amniotic membranes
- Abnormal placentation (accreta, increta, percreta)

Trauma - Vascular and soft tissue injury

- Genital tract lacerations (perineum, vagina, cervix)
- Extension/laceration of cesarean section hysterotomy
- Uterine rupture
- Uterine inversion

Thrombin - coagulation disorders

- Pre-existing pregnancy
  - Haemophilia A
  - Von Willebrand disease
- Acquired in pregnancy
  - Immune thrombocytopenia (ITP)
  - Thrombocytopenia
  - Disseminated intravascular coagulation (DIC)
  - Anticoagulant therapy

Table 1 - 4Ts

change until blood loss reaches 2-3 litres. These changes include an increase of up to 50% in plasma volume and about 20% in red blood cells, especially in young and healthy women with good cardiac reserve. Conversely, co-existing factors such as maternal anaemia before delivery or a low body mass index (BMI), can lead to haemodynamic instability even with low blood loss.

In addition to visual assessment, graduated bags and weighing of blood-soaked drapes, laparotomy cloths and gauze should also be used to correctly estimate blood loss.

The poster released by the Royal College of Obstetrics and Gynecologists in 2006 is an important aid to quantifying blood loss (Fig 4).

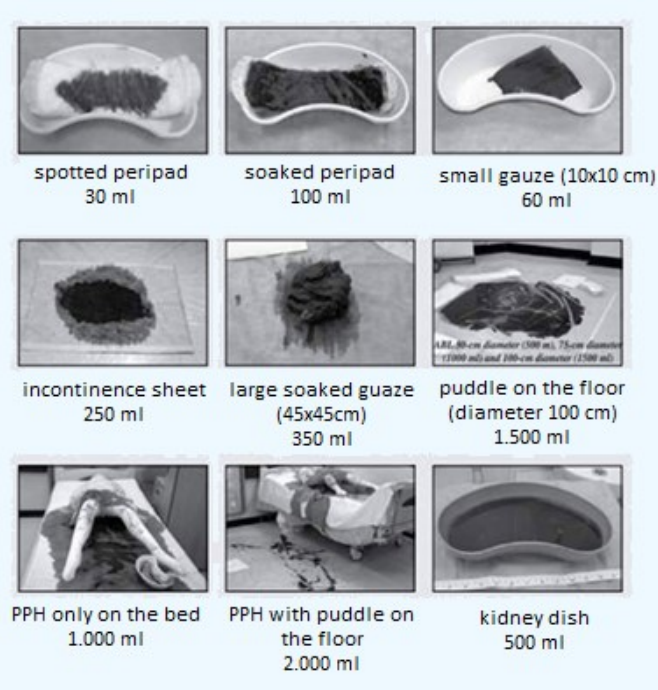


Figure 4 - Quantifying blood loss

('Emergenze ed urgenze in ostetricia e ginecologia', Felis - CIC Edizioni Internazionali)

It is essential to identify early the onset of clinical signs of haemodynamic instability and arterial hypotension in order to assess the degree of shock (10) (Tab 2).

Blood loss	Systolic pressure	Signs and symptoms	Shock degree
500-1000 ml (10/15%)	Normal	Palpitations, tremor, tachycardia	Compensated
1000-1500 ml (15/25%)	Slight decrease (80-100 mmHg)	Weakness, sweating, tachycardia	Mild
1500-2000 ml (25/35%)	Sharp decrease (70-80 mmHg)	Agitation, pallor, oliguria	Moderate
2000-2500 ml (35/45%)	Deep decrease (50-70 mmHg)	Collapse, air hunger, anuria	Severe

Table 2 - Shock degree

In clinical practice, an important parameter to evaluate is the Shock Index (SI), which was created to assess the severity of hypovolaemic shock. The Shock Index is equivalent to the ratio of heart rate (measured in beats/minute) to systolic blood pressure (in mmHg). Normal values are between 0,5 and 0,7. This indicator in the obstetric population has a normal range between 0,7 and 0,9.

In 2014, Le Bas and co-workers introduced the Obstetric Shock Index (ISO), a more specific indicator of haemodynamic instability in pregnant patients for use in cases of major postpartum haemorrhage (11).

Recently, the adoption of graphic vital signs monitoring and early warning systems, 'The Early Obstetrics Warning Systems' (EOWS), has been promoted: the aim of these systems is to facilitate the early identification of rapidly evolving clinical situations and to reduce the incidence of serious maternal morbidity. In the United Kingdom, the Confidential Enquiry into Maternal Death recommended in its 2007 triennial report (11) the adoption of a monitoring system called "The Modified Early Obstetrics Warning System" (MEOWS). The subsequent 2011 report (12) described MEOWS as having the potential to improve outcomes for obstetric emergency conditions such as sepsis and hemorrhage through early recognition. While these systems represent a promising strategy, they are currently still being refined and validated, but available data seem to support their usefulness in identifying patients at risk of criticality at an early stage. ISO values >1 is indicative of a certain degree of severity and predictive of the need to administer transfusion therapy.

The ISO, however, has the limitation of being unreliable in pre-eclamptic patients, because the pathology-related increase in blood pressure values may result in an erroneously reassuring value.

PREVENTION

There are measures that can be implemented to reduce the risk of PPH in women with known risk factors. In women with prenatal anaemia, it is indicated to perform anaemia screening for diagnostic classification, haemoglobinopathy counselling-screening and eventual martial therapy (15). Prevention in women with Congenital Haemorrhagic Diseases is based on a multidisciplinary approach and the measures used consist of the evaluation of blood concentrations of coagulation factors and possible prophylactic therapy (16).

it is important to gather information about the woman's intention to accept transfusions and intraoperative blood salvage techniques at the first prenatal visit. If the patient refuses blood transfusions, she should be fully informed of the risks involved in this refusal, and of the evidence of increased maternal mortality and morbidity by referring her to appropriate healthcare facilities. In this type of woman, it is also advisable to optimize, before delivery, the haemoglobin concentration, to include a list of all acceptable blood products for the patient in the medical record, and to consider the early use of drugs and mechanical and surgical procedures to avoid the need for blood component transfusions.

Measures to reduce blood loss in vaginal delivery are (16):

- In all women, administer 10 IU IM of oxytocin after anterior shoulder expulsion or immediately after fetal expulsion before clamping and cutting the cord.
- In women with increased risk of PPH, administer 10 IU IM of oxytocin after anterior shoulder expulsion or immediately after fetal expulsion before clamping and cutting the fetus, followed by a slow infusion of 8-10 IU/hour in isotonic solution for 2-4 hours.
- In the absence of signs of fetal distress, do not clamp the umbilical cord until 1 to 3 minutes after fetal expulsion, waiting, if the woman wishes, until the end of pulsation of the umbilical cord.
- In the absence of signs of fetal compromise, do not clamp the umbilical cord until 1 to 3 minutes after fetal expulsion; wait, if the woman wishes, until the end of pulsation of the umbilical cord.
- Exercise controlled traction of the umbilical cord only after administration of oxytocin, clamping of the umbilical cord and recognition of signs of placental abruption.

Oxytocin is also the drug of first choice for the prevention of PPH in caesarean sections: in women with a low risk of PPH t is recommended to administer 3-5 IU of oxytocin as a slow intravenous bolus (not less than 1-2 minutes; not less than 5 minutes in women with cardiovascular risk), followed by a slow infusion of 8-10 IU/hour in isotonic solution for 2-4 hours (16).

FRAMEWORK AND INITIAL THERAPY

The management of postpartum haemorrhage requires a multidisciplinary team that includes experienced gynaecologists, obstetricians, anaesthetists, nurses and in some cases interventional radiologists.

In PPH, the aim is twofold: to maintain haemodynamic stability and to identify the cause of bleed-

ing. Maintaining adequate haemodynamic support and avoiding hypothermia and acidosis, in fact, help to prevent the onset of disseminated intravascular coagulation (DIC) (4).

In the case of **minor PPH** (blood loss 500-1000ml), the following measures should be implemented:

- Monitoring the patient's vital parameters every 15 minutes: blood pressure, heart rate, oxygen saturation (SpO2), respiratory rate, temperature.
- Monitoring of diuresis by placement of a permanent bladder catheter.
- Placement of two large-caliber venous accesses, one of which is to be reserved for uterotonics therapy and one for infusion of solutions to maintain blood volume.
- Determination of blood group and antibody screening (Type and screen).
- Performance of haematochemical and coagulation tests, including fibrinogenemia.
- Infusion of crystalloids.
- Consider requesting blood components and/or blood products.
- Consider repeat haematochemical examinations in the event of worsening haemorrhage.
- Determine the origin of the bleeding, remembering the rule of "4Ts".
- Provide targeted treatment of PHE.

In cases of **major PPH** (blood loss ≥1000 ml), the following measures should be implemented:

- Circulation, Air, Breath (CAB) approach: assess airway and respiratory rate and, in case of abnormal breathing, initiate assisted ventilation; assess blood pressure, heart rate, oxygen saturation (spO2), ECG, continuous temperature and diuresis using the bladder catheter.
- Keeping the woman warm to avoid hypothermia.
- Consider a central venous vessel for rapid infusion.
- Performance of haematochemical and coagulation tests, including fibrinogenemia, creatinine, electrolytes, and liver function tests.
- Perform venous gas analysis (VBG) to assess lactate levels (keep lactate levels <2 mmol/L) and consider possible arterial gas analysis (ABG).
- Request 4 units of compatible packed red blood cells and fresh frozen plasma from the blood transfusion center as required.
- Replenish circulating volume with crystalloids or colloids, while waiting for packed red blood cells, if not readily available.
- Start of transfusion therapy, preferably with packed red blood cells, as quickly as possible (consider possible underestimation of blood loss for volemic restoration)
- Consider administering tranexamic acid.
- Consider repeat haematochemical examinations in the event of worsening haemorrhage.

The management of post-partum haemorrhage should be focused on the following objectives:

1. Hb > 8 g/dl
2. Platelet count > 50x109/l
3. PT ratio less than 1.5 of normal
4. APTT less than 1.5 of normal
5. Fibrinogenemia > 2g/l

Maintenance of volaemia

In case of post-partum haemorrhage, the mainstay of resuscitation is the maintenance-restoration of volaemia and oxygen-carrying capacity.

Volaemia can be maintained by the administration of:

- **Crystalloids**: Ringer's lactate or isotonic solution in a ratio of 3:1 to the volume of blood lost.
- **Colloids**: gelatines or hydroxyethyl starch (HES) in a ratio of 1:1 to the volume of blood lost.
- **Red blood cells**: a packed red blood cells contains 280 ml and raises the haematocrit by 2-3%. There is currently no unambiguous consensus on the haemoglobin cut-off point at which haemoglobin transfusion should be initiated. Historically, transfusion was used for haemoglobin (Hb) values ≤ 10 mg/dl in case of acute anaemia; today the choice is based on the risk/benefit ratio. Italian Guidelines recommend transfusing for Hb concentrations < 7 g/l. In urgent cases, it is essential to quickly infuse O Rh D negative and K negative blood cells, even while waiting for the pre-transfusion tests. If the patient's blood group is known and the pre-transfusion antibody tests are negative, transfusion of compatible blood cells is performed.
- **Fresh-frozen plasma**: if bleeding persists, in the absence of coagulation tests, transfusion of fresh frozen plasma should be started. For every 4 bags of concentrated blood plasma transfused, infuse fresh frozen plasma at a dose of 15-20 ml/kg, with a ratio of 1:4. In case of active haemorrhage and altered coagulation parameters, infusion of fresh frozen plasma at a dose of 15-20 ml/kg should be considered, with the aim of maintaining PT and APTT at less than 1.5 of normal. If a Rh D negative woman receives Rh D positive fresh frozen plasma, anti-D immunoprophylaxis is not recommended. Following infusion of fresh-frozen plasma, the main complications that can be observed are transfusion-associated circulatory overload (TACO) and Transfusion-related Acute Lung Injury (TRALI).
- **Cryoprecipitates**: during pregnancy there is a physiological increase in fibrinogenemia; values < 2 g/L are therefore already indicative of significant damage. Infusion of cryoprecipitates results in a greater increase in fibrinogen levels than fresh frozen plasma. If a Rh D negative woman receives Rh D positive cryoprecipitates, anti-D immunoprophylaxis is not recommended.
- **Platelets**: transfusion of platelet concentrates should be initiated in the case of platelet counts < 75x109/L. If an Rh D negative woman receives Rh D positive platelets, anti-D immunoprophylaxis is recommended.

TARGET THERAPY

Early action should always be attempted by identifying and correcting the suspected cause of postpartum haemorrhage.

Uterine atony

In cases of uterine atony, the mainstay of treatment is the maintenance of uterine contractility by physical measures or uterotonic drugs.

Uterine massage and bimanual compression are essential to promote contractility of the myometrium. **Uterine massage** should be performed by placing one hand on the abdomen at the level of the fundus stimulating the uterus by repetitive massaging or squeezing movements. This massage should be continued until the myometrium contracts or bleeding stops (Fig 5). If uterine massage fails, **bimanual compression** can be attempted:

with the addition of one hand in the vagina compressing the two uterine arteries (Fig 6).

It is advisable to facilitate the expulsion of uterine clots, alerting the woman to the discomfort, and to insert a permanent catheter to keep the bladder empty and to monitor diuresis.

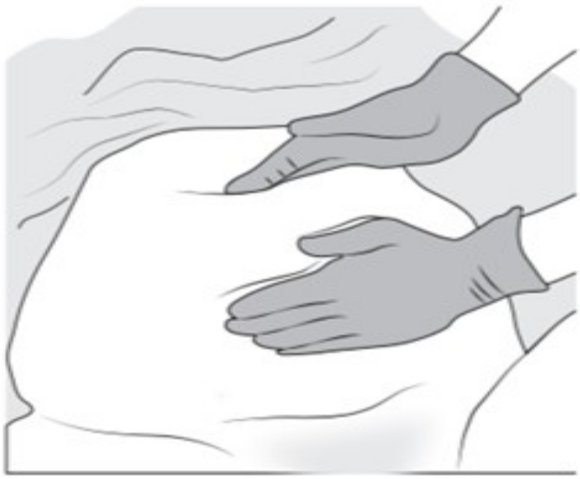


Figure 5 - Uterine massage

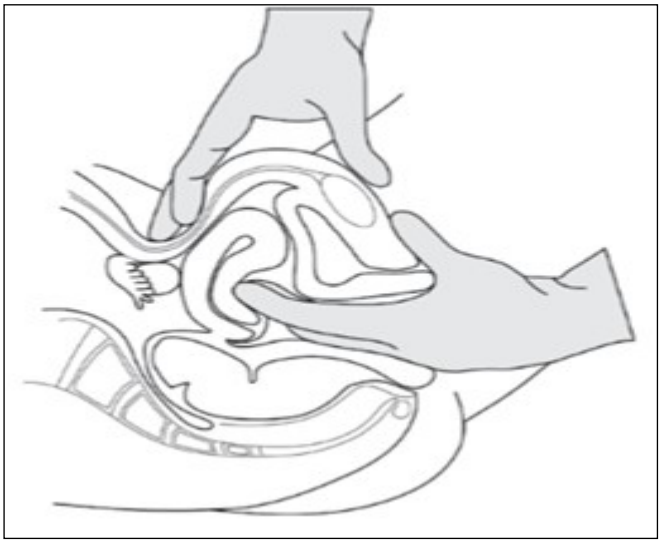


Figure 6 - Bimanual compression ('Emergenze ed urgenze in ostetricia e ginecologia', Felis - CIC Edizioni Internazionali)

At the same time, the administration of uterotonic drugs should be started. The uterotonic drugs used in clinical practice are mainly oxytocin, ergometrine and sulprostone.

Oxytocin is a neuropeptide synthesized in neurons of the supraoptic and paraventricular nucleus of the hypothalamus. It is produced physiologically during pregnancy, with maximum concentration at the time of delivery and gradual reduction after the delivery of placenta. It acts directly on uterine smooth muscle receptors at the time of delivery, as well as on the mammary gland by increasing or inducing milk ejection.

The chemical constitution and pharmacological properties of synthetic oxytocin are identical to those of natural pituitary hormone. Oxytocin is an orally inactive drug because it is destroyed by the intestine. It is generally administered intravenously as a slow infusion (5-20 IU in 500 ml saline), as a bolus (5-10 IU in 1-2 minutes) or as an intramuscular injection (5-10 IU). The main undesirable effect of rapid bolus administration is acute hypotension of short duration, accompanied by flushing and reflex tachycardia. It is metabolized by the liver and kidney and the plasma half-life is a few minutes. Given its rapidity of action, it is the uterotonic drug of first choice and plays a key role in the active management of the third stage of labour.

Ergometrine is an ergot alkaloid that has a powerful contractile action on the uterine musculature. At high doses it also induces a vasoconstricting action. Its action is probably due to a mixed agonist-antagonist activity on alpha-adrenergic, dopaminergic, and serotonergic receptors. Uterine stimulation begins 10 minutes after oral administration, 7 - 8 minutes after intramuscular administration and immediately (40 seconds) after intravenous administration. Elimination of ergometrine appears to be principally by metabolism in the liver. Compared to oxytocin, ergometrine has a less rapid, but more prolonged action.

The main adverse effects are hypertension, nausea, vomiting, diarrhea, pallor, cold extremities, tachycardia. Ergometrine is used in the first-line treatment of PPH at a dosage of 2 vials of 0.2 mg intramuscular alone or in combination with oxytocin 5 IU intravenous (6).

Sulprostone is a synthetic prostaglandin E2 derivative. The main pharmacological action of sulprostone is on smooth muscle with a stimulating effect on the uterine muscle. The structural modifications that differentiate sulprostone from natural prostaglandins make the effect of this drug particularly selective in the uterus and minimize its action in other smooth muscles. This results in a clear dissociation between the desired, therapeutically important effects and the undesired ones. As with natural prostaglandin E2, one of the actions of sulprostone is a reduction in sympathetic activity, with possible undesirable effects such as bradycardia, headache, and arterial hypotension. In clinical practice, it represents a second-line drug for the treatment of PPH. One vial of Sulprostone (0.5 mg) should be diluted in 250 ml or 500 ml of saline for slow intravenous infusion, up to a maximum dose of 1.5 g in 24 hours.

According to the guidelines on postpartum haemorrhage, published in October 2016 by the Italian Ministry of Health, pharmacological treatment includes (Table 3):

1° Line	Oxytocin (5 IU as a slow intravenous bolus) *or* Ergometrine (2 vials with 0.2 mg by intramuscular injection) *or* ✦ Oxytocin (5 UI as a slow intravenous bolus) + Ergometrine (2 vials with 0.2 mg) to be combined with maintenance oxytocin infusion therapy (10 IU in isotonic solution for 2 hours)
2° Line	Ergometrine (2 vials with 0.2 mg by intramuscular injection) *and/or* ✦ Sulprostone (1 vial with 0.5 mg intravenously in 250 ml; 0.1 to 0.4 mg/h up to a maximum of 1.5 mg over 24 hours)

Table 3 - Pharmacological treatment of uterine atony

Two other uterotonic drugs used in clinical practice are carbetocin and tranexamic acid.

Carbetocin is a long-acting oxytocin analogue. Like oxytocin, carbetocin selectively binds to receptors in the smooth muscle of the uterus: it stimulates contraction, increases the frequency of contractions, and increases muscle tone. Carbetocin is administered at a dosage of 100 mcg intravenously. Carbetocin has a tolerability profile like oxytocin; intravenous administration of the drug is frequently associated with nausea, itching, flushing, headache and tremor (12). The use of carbetocin compared to oxytocin in women with a previous caesarean section is associated with a significantly reduced need for additional uterotonic agents but was not more effective than oxytocin in prevention of PPH of varying severity (>500 ml and >1.000 ml), mean estimated blood loss and adverse events; it also showed similar undesirable effects in type and frequency compared to oxytocin (13,14).

Tranexamic acid (TXA) is a substance with a marked antifibrinolytic action. The antihaemorrhagic action is essentially due to inhibition of plasminogen activation. The peak plasma concentration is immediately after administration, while the half-life is approximately 3 hours. The use of tranexamic acid (1 g intravenously administered 5 to 20 minutes before the skin incision in caesarean section) in combination with standard oxytocic

prophylaxis significantly reduces blood loss (>500 ml) and the use of additional uterotonics (15). The same data have not been confirmed for vaginal delivery (16). The use of tranexamic acid should be considered in cases of PPH unresponsive to first- and second-line drugs, as suggested by the latest Royal College of Obstetricians & Gynaecologists (RCOG) guidelines for the prevention and management of postpartum haemorrhage.

Recombinant activated factor VII (rFVIIa) has recently been introduced off-label in the management of postpartum haemorrhage. It is generally administered in selected cases unresponsive to other treatments or in emergencies, as adjuvant therapy, before performing a hysterectomy.

In the case of **uterine atony not responsive to uterotonics**, it is necessary to perform an examination under narcosis to ensure that there is no placental or membrane residue and to detect and repair any trauma in the birth canal.

Intrauterine tamponade with a **Bakri balloon** is nowadays the treatment of first choice in the event of drug therapy failure (Fig 7). In term of mechanism of action, the intrauterine balloon exerts inward to outward pressure against the uterine wall, resulting in compression of uterine blood vessels. This device is an inflatable balloon on a double lumen shaft, is 54 cm long and has a filling capacity of 100 to 500 mL. For correct positioning, a gynaecological examination must be performed to assess the volume of the uterus. Clamping the cervix with two ring forceps, and with the help of another ring forceps, the Bakri balloon is inserted, making sure to place it entirely beyond the cervical canal and the internal ostium. At this point the balloon is inflated with sterile saline; the inflation volume depends on the objective examination of the uterus and the gestational age, up to a maximum of 500 ml. A tamponade bag is then inserted into the vagina and the diuresis bag is connected to the device's drainage connector to monitor the extent of blood loss.

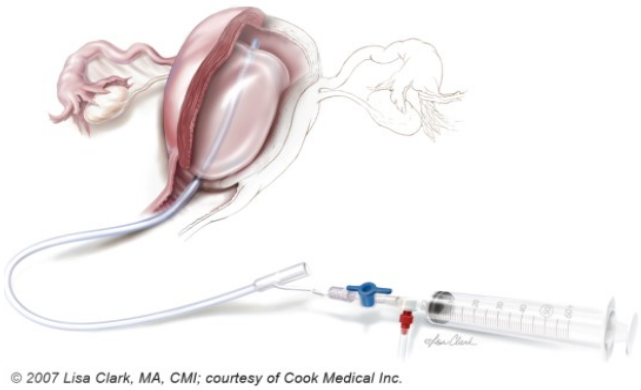


Figure 7 -Bakri Balloon

The device can be maintained in the uterine cavity for up to 24 hours. During this period, the patient needs to be closely monitored for worsening bleeding and/or the occurrence of DIC (17). Bakri Balloon can also be used in cases of postpartum haemorrhage following caesarean section. In this case, the uterine volume must be determined by intraoperative examination and the Bakri balloon is inserted directly into the uterine cavity through surgical incision. The balloon is inserted into the uterine segment breach and exits through the cervix, inserting the inflation connector first. Finally, the uterine breach is closed, taking care to avoid puncturing the balloon during suturing. The Bakri Balloon is currently the most widely used device in clinical practice and has replaced devices used in the past for similar ends, such as the Foley catheter, Rush's Balloon, and the Sengstaken-Blakemore tube.

The effectiveness of uterine tamponade in stopping postpartum haemorrhage is assessed by a 'tamponade test': it is defined as 'positive' if life-

threatening hemorrhage is arrested, 'negative' if it does not. If the test is negative, there is an indication to undergo a laparotomy (18).

Perineal trauma

Vulvovaginal or cervical injuries can lead to major bleeding. Therefore, in case of copious bleeding after delivery, a systematic check of the integrity of these structures and the eventual repair of lacerations and emptying of haematomas are necessary. Perineal lacerations should be repaired with continuous non-locking tension-free suture for all layers, with resorbable material. This surgical technique is associated with less perineal pain (19).

In the presence of cervical lacerations, it would be advisable to always transfer the patient to the operating room to assess and repair the lesion under anaesthesia: this allows for optimized vision of the lacerations through correct posture, light, the use of valves and help from assistants.

Retained placenta or membranes.

If clots, residual membranes, or placental cotyledons are detected within the uterine cavity, they must be removed by examination of the uterine cavity under narcosis. Exploration of the uterine cavity can be done using swabs mounted on ring forceps (with abrasive action on the walls) or by using large curettes. These manoeuvres must be performed with great care because the pregnant uterus is highly exposed to the risk of perforation. Generally, the average time between delivery and expulsion of the placenta is 8-9 minutes. If delivery of the placenta does not occur spontaneously within 30 minutes, placenta retention occurs. Longer time intervals lead to an increased risk of haemorrhage, which doubles after 10 minutes. In the case of placental retention haemorrhage, manual removal must be performed. As soon as the uterine cavity has been emptied, uterine massage, bimanual compression, and infusion of uterotonic drugs must be performed to prevent the onset of atony (Fig 8).

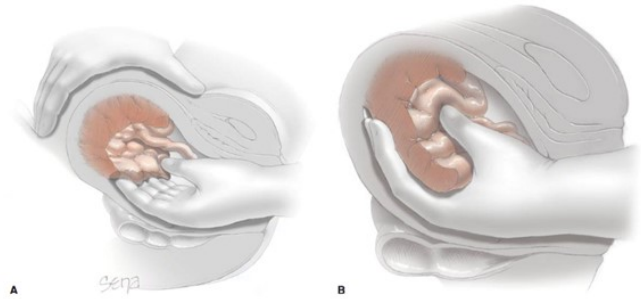


Figure 8 - Manual removal of placenta.

('Emergenze ed urgenze in ostetricia e ginecologia', Felis - CIC Edizioni Internazionali)

One hand grasps the fundus, the other hand is inserted into the uterine cavity and the fingers are swept from side to side as they are advanced. When the placenta has become detached, it is grasped and removed.

Uterine inversion

Uterine inversion is accompanied by conspicuous haemorrhage, sudden and intense pain and is rapidly complicated by shock (Fig 9).

If delivery of the placenta has already occurred and uterine inversion is of recent onset (within 30 minutes), the first step is to attempt to manually reduce the uterus to its anatomical location. **Manual removal** is performed by pushing up on the fundus with the palm and fingers in the direction of the long axis of the vagina.

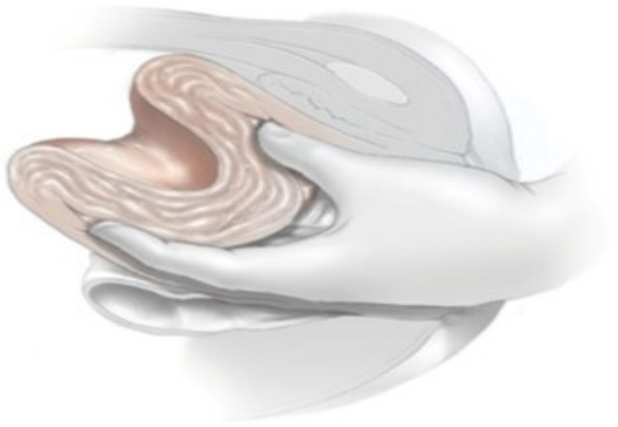


Figure 9 - Manual removal of placenta

('Emergenze ed urgenze in ostetricia e ginecologia', Felis - CIC Edizioni Internazionali)

If the placenta is still attached, it is usually not removed until tocolytic drugs are given: $MgSO_4$ 2g intravenously over 5-10 minutes or β-mimetic (if there is no severe hypotension, shock, or active haemorrhage). Then proceed with removal of the placenta and manual reduction. Once reduction is successful, uterotonic drugs should be administered instead.

If the previous procedures fail, the surgical option should be considered (9). There are two possibilities:

- **Huntington procedure**: laparotomic traction of the round ligaments and uterine fundus to restore the uterus to its proper position; repositioning may be more easily achieved by incising the ring posteriorly with a vertical incision along with manual pushing of the fundus.
- **Haultain procedure**: incising posterior of the vaginal-cervical ring and carrying up the posterior wall of the uterus until it is reinverted to its normal anatomy.

SURGICAL THERAPY

In the event of failure of first- and second-line drug treatment, surgical treatment should be considered. The type of surgery should be chosen according to the mode of delivery, the level of experience of the health personnel and the resources available. The surgical approach may be conservative or demolitive, with possible recourse to hysterectomy. The conservative surgical techniques described in the literature can be divided into compression and vascular techniques. The first ones include the B-Lynch technique and its variants; vascular techniques include uterine artery ligation, progressive devascularization of the uterus and hypogastric artery ligation.

Uterine compression sutures

Compression uterine sutures are a conservative surgical treatment to be performed in cases of severe postpartum haemorrhage to avoid hysterectomy. The first technique was devised in 1997 by British gynaecologists Christopher B-Lynch, the name of the best known of these sutures. It is a relatively recent technique that aims to create equally distributed compression over the body and uterine fundus for haemostatic purposes. **B-Lynch technique** requires a hysterotomy and is therefore especially indicated in cases of haemorrhage following caesarean section (20).

Description of technique (Fig 10):

1. The abdomen is opened by Pfannenstiel incision or, if the patient has had caesarean section, the same incision is re-opened.
2. The uterus is exteriorized, a lower segment incision is made, or sutures of a recent caesarean section are removed, and the cavity entered. The uterine cavity is examined and eventually evacuated. In cases where bleeding is diffuse

(as in uterine atony, coagulopathy, placenta accreta or placenta increta), a bimanual compression is then first tried to assess the potential chance of success of the B-Lynch suturing technique. Bimanual compression is applied to the uterus, placing one hand on the anterior wall and one on the posterior wall, and if bleeding stops, suturing can be performed.

3. The right-handed surgeon should stand on the patient's left side. A round bodied needle is used to puncture the uterus 3 cm from the right lower edge of the uterine incision and 3 cm from the right lateral border. The catgut is threaded through the uterine cavity to emerge at the upper incisional margin 3 cm above and approximately 4 cm from the lateral border. The catgut now visible is passed over to compress the uterine fundus approximately 3-4 cm from the right cornual border. The catgut is introduced posteriorly and vertically to enter the posterior wall of the uterine cavity at the same level as the upper anterior entry point. The catgut is pulled with moderate tension while the assistant applies manual compression. The catgut is passed back posteriorly through the same surface marking as the right side of the suture lying horizontally. The catgut is introduced through posteriorly and vertically over the fundus to be anteriorly and vertically compressing the fundus on the left side as occurred on the right.
4. The hysterotomy breach is sutured and finally the two ends of the suture are tied and pulled together. During all surgical times, the assistant surgeon must always keep the uterus compressed, to maintain good wall compression.

Complications are compression-related uterine necrosis, formation of haematometra or pyometra, and inflammatory or ischaemic processes.

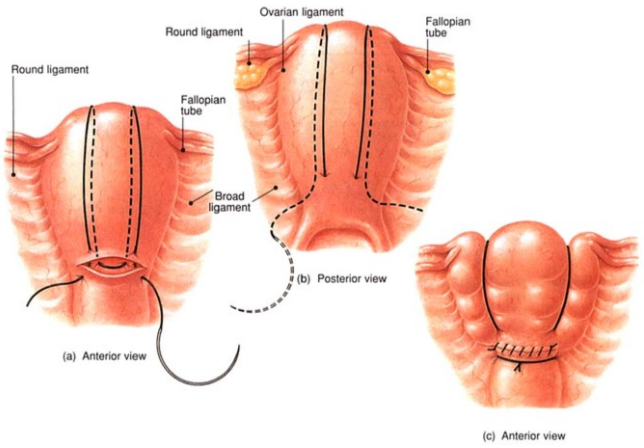


Figure 10- B-Lynch suture
('Emergenze ed urgenze in ostetricia e ginecologia', Felis - CIC Edizioni Internazionali)

Recently, modifications have been introduced to the B-Lynch technique so that easier uterine haemostatic sutures can be performed. The **Hayman technique**, introduced in 2002, is a modification of the B-Lynch suture that is performed without a hysterotomy; it can be used in women after vaginal delivery (21). This technique is very successful in cases of PPH resulting from uterine atony or placenta previa (22).

Description of technique (Fig 11):

1. The abdomen is opened by Pfannenstiel incision or, if the patient has had caesarean section, the same incision is re-opened.
2. The uterus is exteriorized and, using a straight needle, two longitudinal compressive sutures are performed, approximately at the level of those described by B-Lynch. The sutures pierce the uterus from the anterior wall to the full-thickness posterior wall just above the bladder reflection passing in a loop over the uterine fundus.

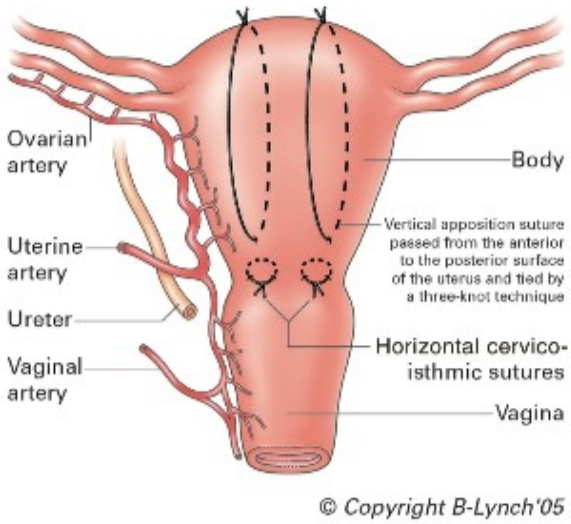


Figure 11- The Hayman technique

('Emergenze ed urgenze in ostetricia e ginecologia', Felis - CIC Edizioni Internazionali)

Another variant is the **Cho Technique** (Fig 12) introduced in 2000, in which a needle transfixes the uterus with four multiple square sutures to approximate anterior and posterior uterine walls. Suturing involves the application of full-thickness suture at the level of the cervical-isthmus portion to include the lateral uterine wall and the cervical-vaginal segment. The indication is the presence of specific areas of bleeding as in the case of placental abnormalities (23).

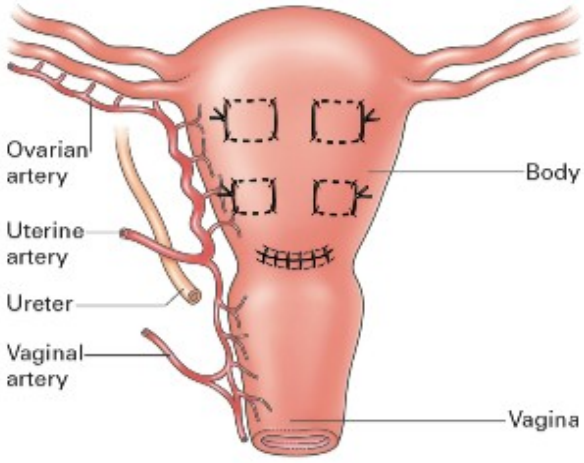


Figure 12 - The Cho technique

('Emergenze ed urgenze in ostetricia e ginecologia', Felis - CIC Edizioni Internazionali)

B-Lynch sutures and its variants are relatively new techniques, so few gynaecologists are yet sufficiently experienced in their practice, and there are yet no comparative studies demonstrating the greater effectiveness of one technique over another.

Uterine artery ligation

Bilateral uterine vessel ligation aims to reduce the blood supply to the uterus. The technique involves ligation of the uterine vascular bundle along its course at the side of the uterine border, in the upper part of the lower uterine segment (27).

Description of technique:

1. Lateralization of the ureter through a loop.
2. Identification of the internal iliac artery and its ligation at the level of the upper third of its anterior branch, below the emergence of the superior gluteal artery.
3. Repeat the same steps on the opposite side.

The main risks are not recognizing the hypogastric artery and tying the external iliac instead, with possible ischaemic damage to the lower limb; injuring the parallel vein, which is then difficult to suture, especially in atypical anatomical situations (emergency, large uterus); accidentally injuring the ureter (24).

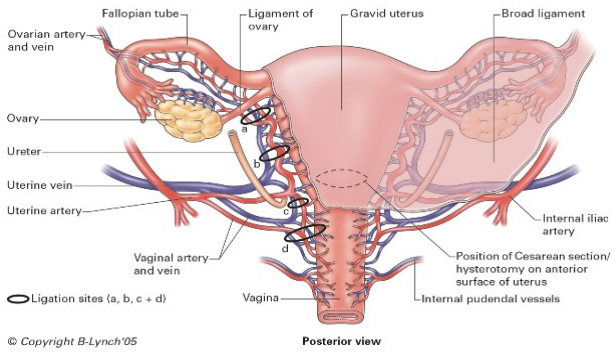


Figure 13 - Hypogastric artery ligation

('Emergenze ed urgenze in ostetricia e ginecologia', Felis - CIC Edizioni Internazionali)

Uterine artery embolization

Uterine artery embolization represents a further therapeutic option for the treatment of postpartum haemorrhage. The technique involves femoral arterial access with placement of an introducer, selective catheterization of the uterine arteries for proper mapping of the vessels, and subsequent administration of embolizing agents chosen by the interventional radiologist based on the angiographic findings. The embolizing agents, appropriately mixed with contrast agent to allow scopic visualization, may be resorbable, such as gelatin sponge, and non -resorbable, such as polyvinyl alcohol particles. After embolization, an angiographic check is performed to verify vascular deafferentation (6). It requires the availability of a specialized angiography room and the presence of an interventional radiologist; it is therefore not practicable in all hospitals. The success rate of the procedure appears to be around 90%, although it appears to be less effective in cases of placenta percreta or coexisting coagulopathy (25).

Peripartum hysterectomy

Hysterectomy following postpartum haemorrhage should be performed in the presence of unstable haemodynamic conditions or persistent bleeding despite conservative medical and surgical treatment.

The decision to perform a hysterectomy should be made by an experienced gynaecologist and carried out promptly.

Hysterectomy should be performed early especially in cases where bleeding is a consequence of placenta accreta or uterine rupture. Subtotal hysterectomy is preferable to total hysterectomy because of the faster execution, unless there is a cervical lesion at the base of the bleeding, or the placenta is tenaciously adhered to the lower segment (4).

The surgical technique is that of routine hysterectomy, subtotal or total, but it must be borne in mind that the gravid uterus is more vascularized than the non-pregnant uterus and the tissues are more edematous and hypertrophic.

DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

Disseminated intravascular coagulation (DIC) is a syndrome characterized by the systemic activation of coagulation, with the formation of intravascular deposits of thrombin and fibrin that lead to thrombosis of small- and medium-caliber vessels resulting in organ dysfunction and bleeding. The condition may manifest as bleeding, organ failure, massive bleeding or asymptomatically. The different clinical picture depends on the type of coagulopathy, for example sepsis, obstetric disease, liver disease or trauma.

DIC is always a 'secondary' pathological condition: it is associated with other clinical conditions capable of activating it, which in the obstetrical field may be amniotic fluid embolism, sepsis and severe cases of placental abruption and pre-eclampsia, while it is not frequent in PPH. However, massive bleeding of any etiology, in the event of underestimation of blood loss and/or late diagnosis, may be associated with DIC, confirming the importance of early recognition of PPH.

A distinction must be made between consumption coagulopathy and DIC: in the first one, the haemocoagulative deficit is a consequence of the loss of coagulation factors due to haemorrhage without any activation of coagulation within the circulation; in the second one there is a primary intravascular activation of coagulation that only secondarily leads to consumption of coagulation factors. Consumption coagulopathy in fact occurs following a major haemorrhage that produces excessive consumption of coagulation factors and does not cause uterine atony. DIC, on the contrary, is always triggered by a primary pathology (pre-eclampsia, sepsis, placental abruption, amniotic fluid embolism, retention of a dead fetus) that activates it and, through circulating fibrinogen/fibrin degradation products (FDP), can cause uterine atony. As a result of this pathogenetic distinction, in the case of DIC the clinician must always expect the onset of uterine atony, which will aggravate the clinical situation, whereas in the case of consumption coagulopathy atony will not complicate the clinical situation except when atony is primarily the cause of haemorrhage. It should also always be remembered that in severe and persistent haemorrhage, dilution coagulopathy may develop because of the rapid administration of crystalloids and/or colloids used in the emergency to restore circulating volume with consequent dilution of coagulation factors and platelets; it is therefore important to replace fluids with transfusion of haemocytes and other blood components/haemoderivatives as soon as possible.

Abnormalities of the haemostatic system in patients with DIC may be due to the sum of two different components: hypercoagulability and fibrinolysis. When hyperfibrinolysis predominates, the main symptom of DIC is bleeding, as is often observed in patients with obstetric disease. When hypercoagulability predominates, the main symptom is organ dysfunction, as is frequently the case in sepsis. When both conditions are active and strong, massive bleeding occurs, which can lead to death in the absence of timely transfusion therapy. If, on the other hand, both conditions are weakly acting, we speak of asymptomatic or compensated DIC.

In contrast to congenital haemocoagulative disorders, which are linked to the deficiency of a single factor, DIC has a multiple etiology. In the case of EPP, coagulopathy recognizes an origin from dilution, disseminated consumption and/or increased fibrinolysis.

Diagnosis

There is no single laboratory test that can confirm or exclude the diagnosis of DIC. For this reason, it is crucial to assess both clinical conditions and laboratory test results. It should also be considered that coagulopathy is characterized by a dynamic picture in continuous clinical and laboratory evolution and laboratory tests represent only a snapshot susceptible to rapid change. The clinical condition underlying DIC may, in turn, interfere with laboratory test results. However, in most cases of suspected coagulopathy, a combination of repeated tests can be used to diagnose the coagulative imbalance with reasonable certainty. More than the absolute value of the individual parameters examined, it is their trend in serious controls over time that helps in diagnosis.

A 2014 review recommends the use of a score for the diagnosis of DIC. A score for the diagnosis of DIC has recently been proposed for pregnant women. The score is based on three parameters: prothrombin time difference (PT), platelet count and fibrinogenemia. Apart from the diagnostic scores,

which are not yet sufficiently validated due to the difficulty of using them during an emergency, it is essential to identify the underlying pathology responsible for the onset of DIC at an early stage. A previous diagnosis of pre-eclampsia, sepsis, placental abruption, amniotic fluid embolism or retention of a dead fetus must necessarily suggest DIC even before the results of haemocoagulation tests are available, especially in cases in which uterine atony is associated. Coagulopathy can evolve rapidly and repeat tests and observation of their progress over time are more useful than a single determination. Haemostatic status can be monitored over time by clinical observation, assessment of PT/aPTT, fibrinogen assay, platelet count, and use of point-of-care test (POCT) based on thromboelastography (TEG), or thromboelastometry (ROTEM).

It should be noted that:

1. In patients with PPH, both PT and aPTT alone seem of limited use in coagulation monitoring.
2. Other markers of haemostasis, such as antithrombin and protein C, are often decreased in DIC and appear to have significant prognostic value. However, these tests are not routinely available in emergencies, and are neither sensitive nor specific for DIC.
3. Centers using point-of-care monitoring by thromboelastography (TEG) or thromboelastometry (ROTEM) to guide the transfusion of blood products in uncontrolled major DIC should ensure that the transfusion protocol algorithm has been validated, and that periodic quality control of the system is performed. As no solid evidence is available on the use of these methods in the case of uncontrolled major PPH nor during DIC, if a clinical center has no experience in the use of TEG/ROTEM, it is preferable to use traditional laboratory tests repeated at regular intervals during PHE to guide the transfusion of blood products.

Treatment

Four guidelines on the diagnosis and treatment of DIC agree that the underlying cause responsible for the onset of DIC should be treated first to achieve, in most cases, its spontaneous resolution. In the case of patients with persistent major PPH, the use of transfusion therapy during DIC follows what has been said above for PPH from other causes. The predefined laboratory targets to guide the management of major haemorrhage are also the same:

1. Tlreatment of the underlying condition responsible for coagulopathy.
2. Pharmacological prophylaxis of venous thromboembolism with low molecular weight heparin as soon as the bleeding is controlled, and the coagulopathy corrected.
3. Prophylaxis by mechanical means (elastic stockings and/or intermittent pneumatic compression) if pharmacological prophylaxis of venous thromboembolism is not feasible due to too high a bleeding risk.

THIRD STAGE CARE AND PREVENTION OF POSTPARTUM HAEMORRHAGE

The most effective prophylaxis of haemorrhage in vaginal birth has been identified as active treatment of the third stage. The third stage of labour is defined as the period between expulsion of the fetus and that of the fetal annexes (placenta and membranes).

The choice of third-stage care has been confronted by two different modes: waiting and active management. The principles of wait-and-see conduct

involve a passive clinical approach, of waiting until signs of placental abruption appear. The principles of active management of the third stage are the rapid and effective promotion of contractile activity of the uterine muscle, after expulsion of the fetus and placenta, to prevent postpartum haemorrhage due to uterine atony and thus reduce blood loss.

Current scientific evidence confirms that 'active management' of the third stage of labour can reduce the incidence of postpartum haemorrhage by 40%-50% compared to 'expectant management' (26).

Active treatment of the third stage classically consists of 3 interventions:

1. Administration of uterotonic drugs.
2. Immediate clamping of the umbilical cord.
3. Controlled traction of the umbilical cord after signs of placental detachment from the uterine wall.

Early administration of oxytocin proves to be the best procedure to reduce the risk of bleeding.

The recommended dose is 10 IU intramuscularly at anterior shoulder disengagement or immediately after expulsion of the fetus, before clamping and cutting the umbilical cord and in any case before secondment.

In women at increased risk of postpartum haemorrhage, it is recommended that the 10 IU of intramuscular oxytocin be followed by a slow infusion of 8-10 IU/hour in isotonic solution for 2-4 hours.

A recent systematic review of the literature has re-evaluated the role of immediate cord clamping, which appears to be contraindicated in terms of risk/benefit for the newborn (27). Late cord cutting, in fact, in preterm infants reduces the risks of haemotransfusion, intraventricular haemorrhage (IVH) and necrotizing enterocolitis (NEC), and in term infants it increases iron stores (28,29). Based on the available evidence, in the absence of signs of fetal compromise, the umbilical cord should not be clamped until 1-3 minutes after delivery. Controlled traction of the umbilical cord may be considered optional and should only be performed after administration of oxytocin, clamping of the umbilical cord and recognition of signs of placental abruption (30).

In caesarean section oxytocin is the drug of first choice for the prevention of PPH. In women at low risk of postpartum haemorrhage, the recommended dose of oxytocin after caesarean section is 3-5 IU of oxytocin as a slow intravenous bolus, followed by a slow infusion of 8-10 IU/hour in isotonic solution for 2-4 hours. In women at increased risk of PPH, administration of tranexamic acid at a dosage of 1 g intravenously, 5-20 minutes prior to skin incision or prior to spinal anaesthesia, is recommended in combination with oxytocin prophylaxis (4).

A systematic review has shown that, in caesarean section, controlled cord traction, compared to manual removal of the placenta, is associated with less blood loss, and should therefore be preferred (31).

POSTNATAL CARE IN WOMEN WITH PPH

It is recommended that the vital parameters, uterine tone, lochia, vulvovaginal trauma, bladder function and pain of all women in the immediate postpartum period be monitored and documented in the medical record to detect clinical signs and symptoms of haemorrhage at an early stage. It is also recommended that it is recommended that the woman and her partner be offered, at a mutually

appropriate time, an interview about the events surrounding the PPH, specifying the risks for future pregnancies. It is very important to be given a discharge letter containing detailed information about the PPH and any procedures/surgeries performed.

In women affected by anaemia in the postnatal period, appropriate therapy should be initiated. Oral iron is the treatment of choice in mild to moderate postnatal anaemia (haemoglobin concentration between 8 and 10 g/dl). In the presence of a haemoglobin concentration below 7 g/dl in the postnatal period, without ongoing or threatened bleeding, the decision to transfuse should be evaluated on a case-by-case basis.

As we have already seen, pregnancy and puerperium are characterized by an increased thromboembolic risk. Risk factors for venous thromboembolism in pregnancy and puerperium are listed in the following table (Table 4).

Preexisting factors	Obstetrical factors of the current pregnancy	Transient factors
previous episode congenital thrombophilia high risk (deficiency of AT III, protein C, protein S) low risk (factor V Leiden heterozygosity, prothrombin G20210A gene mutation) acquired thrombophilia: antiphospholipid antibodies, persistent lupus anticoagulant, persistent anticardiolipin or beta2 glycoprotein antibodies. family history in non-estrogen-related first-degree relatives concomitant diseases: heart failure, cancer, SLE, polyarthropathy, inflammatory bowel disease, nephrotic syndrome, sickle cell anaemia, type 1 diabetes mellitus with nephropathy, intravenous drug abuse age > 35 years obesity (BMI > 30) parity > 3 smoking varices above the knee or symptomatic (phlebitis, oedema, skin changes) - paraplegia	multiple pregnancy assisted reproduction pregnancy. pre-eclampsia caesarean section rotational or mid-section operative deliveries prolonged labour (> 24 hours) post-partum haemorrhage (> 1 l) preterm delivery (< 37 weeks of amenorrhoea) stillbirth	surgical procedures in pregnancy or puerperium excluding repair of the perineum. hyperemesis dehydration ovarian hyperstimulation syndrome immobility (≥ 3 days in bed) systemic infection (requiring hospitalization and intravenous antibiotic therapy) prolonged travel (> 4 hours)

Table 4 - Risk factor for venous thromboembolism

The assessment of risk factors allows patients to be stratified and to start proper thromboembolic prophylaxis in puerperium (Table 5).

previous thromboembolic episode high-risk thrombophilia low-risk thrombophilia with family history any indication for prenatal prophylaxis	**High risk** postpartum prophylaxis with LMWH for 6 weeks
Caesarean section in labour BMI > 40 prolonged hospitalization (≥ 3 days) in puerperium surgical procedures in pregnancy or puerperium excluding repair of the perineum. concomitant chronic diseases	**Intermediate risk** post-partum prophylaxis with LMWH for at least 10 days the persistence or presence of more than 3 risk factors indicates a longer duration of prophylaxis
age > 35 years obesity (BMI > 30) parity > 3 smoking elective caesarean section family history in first-degree relatives low-risk thrombophilia varices systemic infections immobility pre-eclampsia multiple pregnancy preterm delivery (< 37 weeks of amenorrhoea) stillbirth rotational or mid-section operative deliveries prolonged labour (> 24 hours)	**Intermediate risk** in the presence of at least 2 risk factors (see above) **Low risk** in the presence of < 2 risk factors early mobilization and avoidance of dehydration

Table 5 - Risk definition of postpartum thromboembolism and thromboprophylaxis

In the case of VTE associated with other pre-existing or obstetrical venous thromboembolism risk factors, pharmacological VTE prophylaxis with low-molecular-weight heparins should be performed once the bleeding has been controlled. Prophylaxis should also be continued after delivery, after excluding the presence of secondary VTE.

CLINICAL RISK MANAGEMENT

Risk management in healthcare is a tool to improve the quality of care. Clinical risk management must include the involvement of both clinicians and non-clinical practitioners and must be part of the continuing education of specialists (18). Risk management includes proactive actions, such as periodic simulations to reduce the incidence of sentinel events, and reactive actions, such as incident reporting aimed at risk identification. Obstetrics is a discipline that is particularly exposed to high clinical risk situations, and birth centers should be constantly prepared for their management through adequate planning of their management, based on collaboration between the various professionals involved and on adequate allocation of human and technological resources. The ACOG recommends the adoption of procedures that, considering the local context and available resources, provide standardized interventions for different obstetric emergencies, because the prompt identification of the critical situation and the speed of response of the care team increase safety and reduce the severity of outcomes (45). Each delivery room must have all the drugs and supplies necessary for the management of an PPH emergency, and their availability and location must be known and shared by all the staff involved in the care, to facilitate communication between professionals and the rapidity and

appropriateness of care interventions. The material required for emergency management must be conveniently organized so that it is readily available, always accessible, and periodically checked.

Training and preparation of staff working in the delivery room

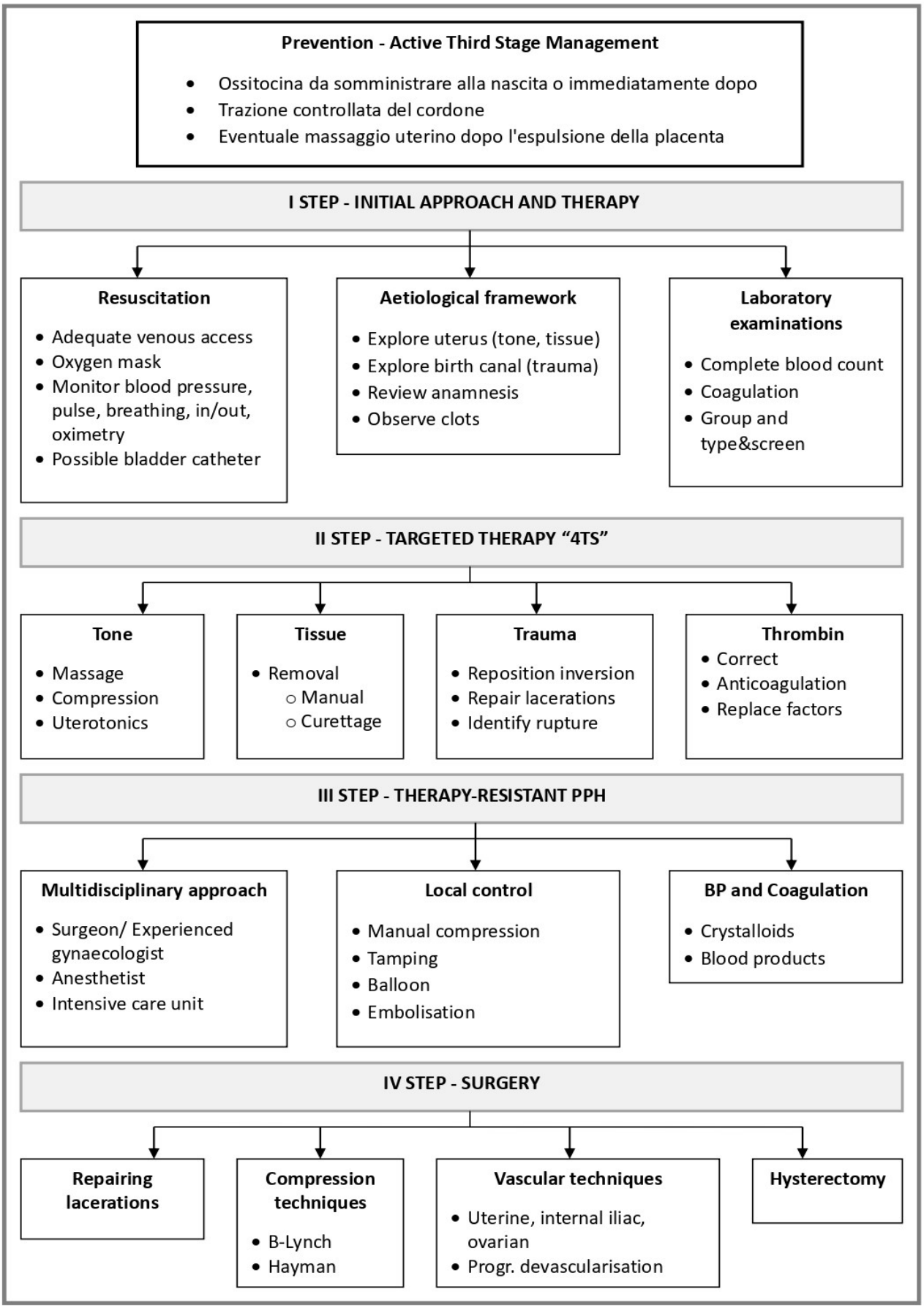
Each obstetrical unit should have multidisciplinary procedures shared by all professionals assisting the woman in a PPH emergency. Useful tools for establishing procedures include the availability of appropriate tools (check lists, prepared kits), a rapid team response scheme, the sharing of alert parameters to trigger the protocol (trigger thresholds), the use of standardized communication schemes (i.e., SBAR - Situation Background Assessment Recommendation), the development and periodic execution of skill team simulation programs. The MEOWS (Modified Early Obstetric Warning System) constitute an example of the graphic charts that should be prepared and shared in every center for the recording and timely verification, even during the emergency, of the patient's vital parameters and their trend over time in the event of EPP (21). The MEOWS (Table 6) provides that in the presence of a single markedly altered alert parameter (blue) or two simultaneously altered parameters to a lesser extent (grey), an immediate medical assessment is triggered to consider the need for intervention. The table describes the alert parameters in the MEOWS that every practitioner needs to know to use the graphic card for monitoring-alerts in the case of PPH.

	Limits marked in blue	Limits marked in grey
temperature (°C)	< 35 o > 38	35-36
systolic blood pressure (mmHg)	< 90 o > 160	150-160 o 90-100
diastolic blood pressure (mmHg)	> 100	90-100
heart rate (beats/minute)	< 40 o > 120	100-120 o 40-50
respiratory rate (acts/minute)	<10 o > 30	21-30
O2 saturation %	< 95	
neurological response	lack of response to painful stimuli	lack of response to verbal stimuli

Documentation

Accurate documentation of the management of haemorrhagic emergencies is precious for the quality and continuity of care, especially when more than one professional is involved and/or the patient is transferred. Incomplete documentation of the care pathway in the medical record not only represents a sub-standard indicator of care quality, but also exposes the patient to an increased risk of medical-legal consequences. The completeness of the documentation in the medical record involves the accurate reporting of the following aspects:

1. The practitioners involved in the assistance (including consultants from other disciplines who have been alerted) and the time of their involvement.
2. The sequence of events.
3. The administration of drugs, timing, and sequence.
4. The time of surgery.
5. The woman's condition during the entire care pathway.
6. The timing of the administration of fluids and blood products.



Appendix 1 - Algorithm to be used in the case of PPH

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