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Postpartum Hemorrhage: Risk Factors and Preventive Strategies

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Abstract: Background: Postpartum hemorrhage is considered the leading cause of pregnancy related deaths worldwide, with an estimated 140,000 women dying annually from this complication. Aim: Postpartum hemorrhage is defined as the loss of more than 500 ml of blood after delivery or more than 1000 ml of blood after cesarean section. However, there are variations in its definition between societies and clinical practice guidelines. Findings: The incidence of postpartum hemorrhage is generally estimated between 4% and 6% and some studies report that identifiable risk factors can only be found in 39% of patients, so at least 2/3 of the women could have postpartum hemorrhage without any identifiable risk factor. Discussion: Today there is still an upward trend in the incidence of postpartum hemorrhage, some authors believe that it may be due to the change in maternal characteristics or assisted reproductive techniques but there is little evidence to support it, instead it seems that it may be due to a delay in identification and treatment. Conclusion: it is important to take action without delay at the onset of postpartum hemorrhage that includes the implementation of established protocols and patient fluid management, with a trained team in the identification, reducing maternal morbidity and mortality due to this complication.

Keywords: Postpartum Hemorrhage, Risk Factors, Threatment Protocols, Preventive Strategies, Placenta, Bledding

1. Introduction

Postpartum hemorrhage (PPH) is considered the leading cause of pregnancy related deaths worldwide, [1] with an estimated 140,000 women dying annually from this complication. PPH is the leading cause of death regardless of age group and kills those women living in low resource countries. [1]

Postpartum hemorrhage is defined as the loss of more than 500 ml of blood after delivery or more than 1000 ml of blood after cesarean section. However, studies using chromate-tagged red blood cells have found that the average blood loss at vaginal delivery typically exceeds 500 mL. [2], The American College of Obstetricians and Gynecologists also suggests as criteria to take into account: a 10% decrease in hematocrit, a subsequent need for transfusion and the hemodynamic instability of the patient. [3]

PPH can be classified according to the time of onset: early, if it occurs within the first 24 hours of delivery and late if it occurs after 24 hours and up to 6 weeks postpartum.

Three guidelines: the American College of Obstetricians and Gynecologists (ACOG); the Royal College of Obstetricians and Gynecologists (RCOG) and the Society of Obstetricians and Gynaecologist of Canada (SOGC), remark the subjectivity when quantifying the volume of blood lost with methods such as estimating bleeding in pads or drapes, and there seems to be no consensus regarding which method would be the most indicated for estimating blood loss. [4]

The incidence of postpartum hemorrhage is generally estimated between 4% and 6% and some studies report that identifiable risk factors can only be found in 39% of patients, so at least 2/3 of the women could have postpartum hemorrhage without any identifiable risk factor.

The importance of identifying risk factors in pre-delivery settings and taking rapid action at the onset of PPH are

crucial points for the appropriate management of these events.

2. Epidemiology

The incidence of PPH varies depending on the criteria taken into account for its definition, but it is generally estimated to be 4% to 6%. [5, 6] and there is some evidence of an increasing trend in rates of PPH [7, 8]. Cameron and colleagues [9] found in a study in New South Wales, Australia, that the rate of PPH increased from 8.3% of deliveries in 1994 to 10.7% of deliveries in 2002. This rate was adjusted for maternal age and type of delivery, obtaining similar results. They also found a 6- fold increase in maternal transfusions for PPH over the same period. In the United States, PPH is the fifth cause of maternal mortality and causes approximately 11-12% of all maternal deaths. The data show that between 1994 and 2006, PPH rates increased by 26% and there has been a 50% increase in cases caused specifically by uterine atony [10].

Carroli and colleagues performed a systematic review from different regions around the world [11]. They found that the prevalence of PPH greater than 1000 ml was 1.86% (95% CI, 1.82-1.90) and its prevalence was almost double when the blood loss was measured objectively (3.04%; 95% CI, 2.90-3.17).

A prospective cohort study carried out in two Latin American countries (Uruguay and Argentina), [12] analyzed 11,323 vaginal deliveries, objectively measuring blood loss, established that mild PPH (> 500 ml of blood loss) occurred in 10.8% and severe PPH (> 1000 ml of blood loss) in 1.9% of the cases.

There is little evidence or studies regarding the incidence of late PPH. In a retrospective study carried out by Hoveyda and Mackenzie it is estimated that it occurs in 1% of deliveries. [13].

3. Risk Factors and Causes

Several risk factors associated with postpartum hemorrhage have been described, summarized in Table 1. (See Table 1) [4, 14].

Table 1. *PREEXISTING AND INTRAPARTUM RISK FACTORS FOR POSTPARTUM HEMORRHAGE.*

RISK FACTORS FOR POSTPARTUM HEMORRHAGE	
Preexisting factors	**Intrapartum factors**
Overdistended uterus (macrosomia, twins, hydramnios)	Prolonged labor
High parity	Rapid labor
Antepartum hemorrhage or prior History of postpartum hemorrhage	Episiotomy
Maternal anemia	Operative delivery
Maternal obesity	Prolonged rupture of membranes
Preeclampsia	Chorioamnionitis
Asian or Hispanic ethnicity	Induction of labor
Uterine anomalies (fibroid tumors) or previous uterine surgery	Cesarean delivery
Hereditary coagulopathies	Placental abruption
Fetal death	Retained placenta
Placental factors: Placenta previa, Abnormal placentation.	

Note. Risk factors for postpartum hemorrhage. Adapted from: Dahlke JD, Mendez-Figueroa H, Maggio L, Hauspurg AK, Sperling JD, Chauhan SP, et al. Prevention and management of postpartum hemorrhage: a comparison of 4 national and Mousa HA, Blum J, Abou El Senoun G, Shakur H, Alfirevic Z. Treatment for primary postpartum haemorrhage. The Cochrane database of systematic reviews. 2014 (2): CD003249.

Many of these factors are commonly found in pregnant women today, which makes it possible to intuit the difficulty of predicting PPH when there is a combination of several of them. [15, 16]. Some studies report that identifiable risk factors can be found in only 39% of patients who experience PPH [17]. This difficulty in predicting or calculating the individualized risk for each patient, makes it difficult to establish institutional policies that asses personal risk efficiently and therefore designs an effective preventive strategy for each patient. [18]

Kramer MS, et al in a US study [19] found the following risk factors in order of importance: uterine rupture (adjusted odds ratio [aOR], 11.6; 95% CI, 9.7-13.8), cervical laceration (aOR, 94.0; 95% CI, 87.3-101.2), placenta previa or abruption (aOR, 7.0; 95% CI, 6.6-7.3), preeclampsia (aOR, 3.1; 95% CI, 2.9-3.3), amnionitis (aOR, 2.9; 95% CI, 2.5-3.4), multiple pregnancy (aOR, 2.8; 95% CI, 2.6-3.0), fibroids (aOR, 2.0; 95% CI, 1.8-2.2), maternal age ≥35 years (aOR, 1.5; 95% [CI], 1.5-1.6), instrumental vaginal delivery (aOR, 1.5; 95% CI, 1.4-1.6), and cesarean delivery (aOR, 1.4; 95% CI, 1.3-1.5). However, we see that some of the most significant risk factors become evident at the time of delivery or near the end of it, creating the need to establish protocols for immediate action at the time of their appearance.

In study carried out in multiple Latin America countries, the risk factors more strongly associated to PPH were: retained placenta ([aOR] 6.02, 95% [CI] 3.50-10.36), multiple pregnancy (aOR 4.67, CI 2.41-9.05), macrosomia (aOR 2.36, CI 1.93-2.88), Episiotomy (aOR 1.70, CI 1.15-2.50), and need for perineal suture (aOR 1.66, CI 1.11-2.49).

Ford and colleagues [20] studied the occurrence and recurrence of PPH in 125,295 women in labor, reporting that PPH occurred in 5.8% of women in their first delivery, and a three-fold increase in the risk of PPH in their second consecutive delivery with 14.8% (RR, 3.3; 95% CI 3.1-3.5). In addition, in their third consecutive delivery, women who had experienced PPH in their two previous deliveries had a recurrence in 21.7% of the cases.

The California Maternal Quality Care Collaborative (CMQCC) developed a toolkit for obstetric bleeding in 2010. One of the objectives of this toolkit was to categorize patients according to the PPH risk in high, medium, and low risk groups [21]. In a validation study, they found that 22% of the women who had PPH were classified as high risk. In a posterior validation study in 2011 [22], 10,134 deliveries were evaluated, of which 139 experienced PPH and required blood transfusion, but only 22% of those were classified as high risk. Then the authors developing a modified high risk scale obtained an increase of 87% of prediction. So we understand again that some women experience PPH without having recognizable risk factors. [23]

4. Causes of PPH

4.1. Uterine Atony

Uterine atony is the most frequent cause of PPH, it is estimated that it produces more than 70% of cases.

The uterus is an organ with a large muscular wall, the myometrium, and once delivery occurs with the expulsion of the fetus and the placenta, it requires an effective contraction for the ligation of the blood vessels that nourish the placental bed. Another mechanism by which bleeding is prevented is clot formation in these vessels.

Many times the lack of contraction can be due to situations that produce uterine over distention, such as polyhydramnios, fetal macrosomia, or multiple gestations. Also a precipitous labor with vigorous contractions or a very prolonged labor (as in the case of inductions) can cause exhaustion of the uterine muscle fibers and finally cause uterine atony and PPH. [24]

4.2. Genital Tract Trauma

During delivery, trauma can occur at any level of the birth canal, involving lacerations and tears at the perineum, vaginal walls, cervix or uterine corpus, either spontaneous or intentional during an episiotomy. In instrumented deliveries such as vacuum, spatulas or forceps there is an increased risk of lacerations and PPH. It is also known that during caesarean sections there is an average blood loss greater than in a vaginal delivery.

4.3. Retained Placenta and Clots

After delivery the placenta and membranes must be completely expelled. Retention of placental tissue can cause a deficiency in uterine contraction and PPH.

4.4. Inherited or Acquired Coagulation Defects

Situations such as placental abruption, massive blood loss, amniotic fluid embolism, intrauterine fetal demise, or sepsis can cause disseminated intravascular coagulopathy.

There are other factors inherent to the patient such as coagulopathies, like Von Willebrand disease, thrombocytopenia or the use of anticoagulation therapy that can cause excessive bleeding during childbirth. [24)]

4.5. Uterine Inversion

Uterine inversion occurs mainly due to strong traction of the cord before separation of the placenta. The bleeding occurs due to a difficulty in the proper contraction of the uterus and can lead to significant hemorrhage and shock. Its incidence is rare but it is a situation that can be life-threatening. [21]

5. Prevention and Treatment of PPH

Preventive measures for PPH should be taken when assisting all deliveries in all patients, since predictive models of PPH are not discriminatory and there are patients without identifiable risk factors at the time of delivery, that develop a life-threatening hemorrhage. [15-17]. Active management of the third stage of labor (AMTSL) used to be based on the execution of three actions: prophylactic administration of uterotonic drugs immediately after delivery of the fetus, early cord clamping and cutting, and controlled cord traction (CCT).

In a Cochrane review, AMTSL in women with mixed risk factors for bleeding was compared with expectant management and it was evidenced that active management reduces the rate of SPPH > 1000 ml ((RR) 0.34, 95% confidence interval (CI) 0.14 to 0.87) and hemoglobin (Hb) < 9 g/dL (average RR 0.50, 95% CI: 0.30 to 0.83). There was also evidence of a reduction in mild PPH and the need for maternal transfusion as well as the use of therapeutic medication in the third stage or in the first 24 hours. [25]

In a 2013 meta-analysis [26], the efficacy of prophylactic administration of oxytocin was evaluated, indicating that it reduces bleeding after delivery greater than 500 ml in 50% of the cases and the risk of bleeding greater than 1000 ml in 40% of the patients. In regard to controlled cord traction (CCT), there was no significant impact on the prevention of PPH in both, low-resource settings and those with optimal resources, according to two randomized controlled trials. [27, 28]. Early cord clamping is generally no longer included in AMTSL. [29, 30], Conversely, there is evidence that late cord clamping after 1-3 minutes can benefit the newborn [31-33].

For this paper, we have taken into consideration the results of recent studies and reviews as well as a comparison of the recommendations form clinical practice guidelines for management PPH elaborated by the American College of Obstetricians and Gynecologists (ACOG); the Royal College of Obstetricians and Gynecologists (RCOG), United Kingdom; the Society of Obstetricians and Gynecologist of Canada (SOGC) the Royal Australian and New Zealand College of Obstetricians and Gynecologists (RANZCOG).

The principal uterotonics recommended in PPH are oxytocin, ergot derivatives, misoprostol, and carbetocin, however oxytocin remains the first line uterotonic [4]. SOGC guidelines recommend administering 10 units oxytocin intramuscularly or 5-10 units intravenously, after de

expulsion of the anterior fetal shoulder, if available, over 1-2 minutes for low-risk vaginal deliveries. There is evidence to support the use of oxytocin even later, if it is not available at the time of anterior shoulder expulsion or after placental expulsion. [34]

Ergot derivatives reduce the incidence of PPH compared with placebo in mild and severe cases (RR 0.49 95% CI 0.26-0.90) and SPPH (RR 0.32 95% CI 0.04-2.59) but is associated with important adverse effects, especially hypertension (RR 2.60 95% CI 1.03- 6.57) [35]. SOGC guideline recommends Ergonovine as a second-line drug or suggests its use in situations where oxytocin is not available. RCOG guideline recommend it as a second line agent for PPH prophylaxis, suggesting the use of a combination of 5 IU of oxytocin and 0.5 mg of ergometrine (Syntometrine) and emphasizes the side effects.

Misoprostol is a powerful uterotonic prostaglandin recommended by the RANZOG guideline as second-line medication for the prevention of PPH or in settings where oxytocin is not available. [4] Carbetocin is a synthetic analogue of oxytocin, with a much longer duration of action, sustaining the contraction of the uterine muscles for up to one hour. The recommended dosage by SOGC is a single dose of 100 ug administered slowly over 1 minute. It can be administered intramuscularly or intravenously and is generally recommended for prophylaxis of PPH in caesarean section when there are identifiable risk factors. [36]

When it comes to de measures to be taken in consideration when identifying a PPH, it is important to have a multidisciplinary approach, that covers fluid management and indication for blood products transfusion. The many clinical guidelines discuss some important factors but only RANZOG provides a massive transfusion algorithm in case of SPPH. The RCOG and ACOG recommend in patients with suspected placenta acreta or percreta preemptive ordering of blood products.

It is advisable to have a protocol for massive transfusion of blood derivates as well, since the recommendations vary between organizations; RCOG suggests transfusing 4 units of fresh frozen plasma (FFP) for every 6 units red blood cells (RBC). The RCOG and RANZCOG recommend PLT transfusion if the PLT count is less than $50x10^9$/L. [37]

There is currently little evidence on the use of fibrinogen in PPH. It is formally indicated in cases of patients with hypofibrinogenemia. Some data suggest that its use in PPH may decrease the need for transfusion of blood products with few adverse effects. The starting dose is 2-3 g titrated to maintain serum fibrinogen above 200 mg/dl. [38, 39] but, more studies are needed to reinforce this recommendation. A randomized controlled trial found no evidence for preventive treatment in patients with normal serum fibrinogen levels. [40]

The fibrinolytic pathway may be activated after the placenta separates from the uterine wall, and is one of the mechanisms that could contribute to PPH. Tranexamic acid (TXA) is an antifibrinolytic drug that binds to lysin residues preventing plasmin activation and thus preventing clot breakdown. [41] The WOMAN trial, found that administration of TXA within 3h of delivery in women with PPH reduces maternal mortality and the need for surgical techniques to control hemorrhage. [42]

The use of recombinant-activated factor VII (rFVIIa) may decrease the need for blood product transfusion, but a higher risk of arterial thrombosis has been described, with few overall benefits regarding reduction of maternal mortality. [43, 44]. For this reason, it is not recommended as treatment in PPH cases. [41]

ACOG, RCOG, SOGC and RANZCOG guidelines include different surgical techniques for the management of PPH such as the use of uterine packing, balloon tamponade, performing uterine curettage (aided by ultrasound if available), uterine artery ligation or hypogastric artery ligation, uterine sutures such as B-Lynch and brace suture, arterial embolization and hysterectomy. It is strongly recommended to initiate such procedures with the least invasive technique in order to preserve fertility. [4]

ACOG advocates for the employment of a balloon tamponade technique, using either a Foley catheter with instillation of 60-80 ml of saline, Sengstaken-Blakemore tube or SOS Bakri tamponade balloon, inserting it into the uterus and instilling 300-500 ml of saline.

Likewise, ACOG guidelines explain the circumstances in which arterial embolization should be indicated, as patients "with stable vital signs and persistent bleeding, especially if the loss is not excessive". Radiographic identification of bleeding vessels allows embolization with Gelfoam, coils or glue. This technique could be used if bleeding persists after performing a hysterectomy or as an alternative to preserve fertility. [3]

6. Conclusion

It is important to consider that the increase in PPH incidence, maternal morbidity and blood transfusion rates, especially in developed countries [45], maybe attributable to a better registry of cases and the availability of resources to carry out adequate treatment in time to avoid maternal deaths and morbidity.

It has come to our attention throughout this review, the great importance of identifying risk factors in pre-delivery settings to take timely and early measures, such as an anesthetic assessment before the initiation of labor, correcting levels of maternal anemia, or considering matching blood to have availability in case it becomes necessary. Likewise, taking rapid action at the onset of PPH that includes the implementation of established protocols and patient fluid management, with a trained team and directed by specialists in gynecology and anesthesia, are crucial factors for the appropriate management of these events.

There are new medication proposals for the treatment of PPH, such as the use of tranexamic acid already included in some protocols or clinical guidelines, however, more scientific evidence is needed to support its routine use and recommendation. The use of medical devices such as the

intrauterine balloon in our clinical practice has proven to be of great aid to avoid definitive surgical treatments in some cases.

It is necessary to adjust the risk stratification systems. Although there are patients who present PPH without having any predisposing factors [23], it has been reported an increase in PPH in those patients that are obese [46] or older than 35 years, probably due to assisted reproductive techniques, which significantly increase the risk for labor induction, cesarean delivery, and postpartum complications, such PPH. [47, 48]

It would be interesting to carry out new studies on possible strategies to recognize or identify individualized risk and develop protocols adapted to the population characteristics and with the resources available in each region.

Competing Interests

All the authors do not have any possible conflicts of interest.

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