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Postpartum Hemorrhage and Transfusion of Blood and Blood Components

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Postpartum hemorrhage (PPH) is one of the top 5 causes of maternal mortality in developed and developing countries. The incidence of PPH is 40% after vaginal delivery and 30% after cesarean section. Criteria for PPH are based on the amount of blood loss. In clinical obstetrics, exact measurement of blood loss is often difficult. The most important treatment of PPH is red blood cell (RBC) transfusion. In the past few years, increasing concern has arisen about this treatment. Despite the introduction of several new guidelines, transfusion criteria still vary widely between clinicians. The decision whether to prescribe RBC transfusion is mostly based on postpartum hemoglobin (Hb) values. RBC transfusion should be aimed to reduce morbidity and especially to improve health-related quality of life (HRQoL). In this review, etiology, epidemiology, treatment, and prevention of postpartum hemorrhage are described. Special attention is given to the role of RBC transfusion in the treatment of PPH and the effects of RBC transfusion on HRQoL.

Target Audience: Obstetricians & Gynecologists, Family Physicians.

Learning Objectives. After completion of this article, the reader should be able to summarize the new guidelines related to transfusion criteria, explain the importance of reducing morbidity related to improving quality of life issues, and list infectious and noninfectious complications of a red blood cell transfusion.

Postpartum hemorrhage (PPH) is one of the top 5 causes of maternal mortality both in developed and developing countries. This review focuses on primary PPH in developed countries. Compared with other major causes of maternal mortality such as thromboembolism, preeclampsia, and sepsis, obstetric hemorrhage seems to be the one area where timely and appropriate intervention can make the greatest difference to a possibly disastrous outcome.

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EPIDEMIOLOGY

The average amount of blood loss postpartum is 300 to 500 mL in the first 24 hours after vaginal delivery (1–3) and 900 to 1100 mL in the first 24 hours after cesarean section (1,2,4). These amounts of blood loss do not lead to discernible changes in blood pressure. According to the World Health Organization (WHO) criteria, primary or immediate

PPH is defined as blood loss exceeding 500 mL in the first 24 hours postpartum (5).

Data from a more than 40-year-old observational study show that 40% of the patients experience more than 500 mL blood loss after vaginal delivery. Blood loss of more than 1000 mL complicates 30% of the patients undergoing an elective repeat cesarean section and 70% of the patients undergoing an elective repeat cesarean section in combination with a planned hysterectomy for sterilization (Fig. 1). The incidence of postpartum anemia necessitating red blood cell (RBC) transfusion after vaginal delivery is less than 1% (6–12) and after cesarean section 1% to 7% (6–8,10,12–16). This range might be the result of several factors such as different criteria for postpartum anemia, differences in transfusion practice between clinicians and hospitals, and differences in statistical analysis.

In addition, there is a distinct declining trend in the use of postpartum transfusions in recent years, which makes it difficult to compare all these studies. However, the incidence of PPH is not decreasing and may probably even increase as was shown in a recent Dutch study (17).

ETIOLOGY AND RISK FACTORS OF POSTPARTUM HEMORRHAGE

The etiology of obstetric hemorrhage involves several factors that can be divided into 5 groups: placental abnormalities, coagulation disorders, lacerations and trauma, uterine atony, and retained uterine contents. Another classification describes the etiology in relationship to the time of delivery: antepartum, intrapartum, and postpartum.

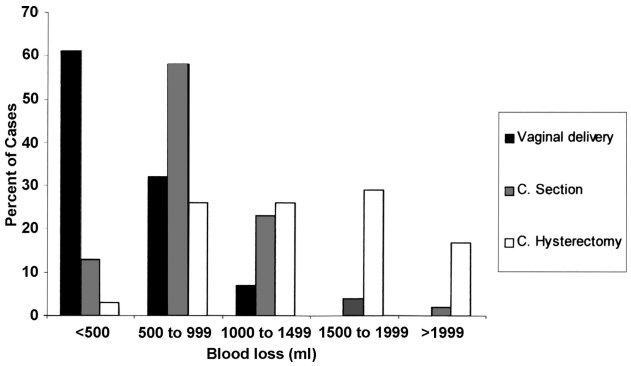

Fig. 1. Blood loss associated with vaginal delivery, elective repeat cesarean section, and elective cesarean section plus total cesarean hysterectomy for sterilization (1). Reprinted from the American Journal of Obstetrics and Gynecology, vol 84, Pritchard, et al., Blood Volume Changes in Pregnancy and the Puerperium. II. Red Blood Cell Loss and Changes in Apparent Blood Volume During and Following Vaginal Delivery, Cesarean Section, and Cesarean Section Plus Total Hysterectomy, Pages 1271–1282, Copyright ©1962, with permission from Elsevier.

Most important risk factors for PPH are abnormal placental lie, previous cesarean section, multiparity, high gestation, age (>35 years), obesity, a history of PPH, maternal Hispanic ethnicity, low income, prolonged third stage (>30 minutes), preeclampsia, anemia at 24 and 29 weeks gestation, anemia before delivery, coagulation disorders (9–11,13,18–21), type of anesthesia (13,14), instrumental vaginal delivery (9), and augmentation of labor (9,20).

MEASUREMENT OF BLOOD LOSS POSTPARTUM

Exact measurement of blood loss is often difficult in clinical obstetrics. This may be a result of contamination with amniotic fluid and other excreta and of blood loss on the floor or towels.

Different techniques are described to measure blood loss postpartum in the literature (4). The most practical one is the direct volumetric method, measuring the blood volume in basins and sponges. This method seems best suited for vaginal deliveries and is the only one still in use. Recently, the use of a collecting bag and even use of cholera beds is suggested to increase the estimation of postpartum bleeding (22).

However, in most deliveries, both in the delivery room and the operating room, blood loss is estimated. Techniques are visual inspection, measuring vital signs, the "tilt test," and measurement of diuresis.

Because the clinical estimation of blood loss at delivery is regarded as inaccurate (23–25), it is routine practice in many hospitals to obtain postpartum hemoglobin values. The first signs of a clinical problem are often physical complaints while laboratory results are pending. This makes the usefulness of routine postpartum hematocrit screening unclear, especially for patients without risk factors. When this screening is confined to patients with an estimated blood loss greater than 500 mL, only 1% of the remaining patients will have a discharge hematocrit less than 27% (26).

HEMODYNAMIC CHANGES DURING PREGNANCY AND POSTPARTUM

The circulating blood volume increases during pregnancy to 100 mL/kg constituting to a total blood volume of 6 to 7 L. The several blood components contribute differently to this increase: plasma in-

creases with 40%, whereas erythrocyte volume increases with 15% to 20%. Consequently, Hb level decreases with a maximum of approximately 10%. This natural process of hemodilution improves the placental circulation. In addition, the blood coagulation system will be activated, which reduces the risk of extensive blood loss during parturition and thus postpartum anemia. During the first 3 days after delivery, the redistribution of extracellular fluid induces a further decrease in Hb level. From the third day postpartum, Hb levels start to increase and return to normal values after 6 weeks postpartum.

Hb levels lower than 10.9 g/dL during pregnancy and/or postpartum are considered anemic according to the WHO criteria (27). Recently, the Dutch College of General Practitioners redefined the criteria for anemia during pregnancy as follows: until week 18, a Hb level below 10.9 g/dL and after week 18, a Hb level below 10.5 g/dL (28). During pregnancy and the postpartum period, Hb levels were found to be 0.4 to 0.6 g/dL lower for black patients than for white patients (29,30). An Hb level below 10.5 g/dL indicates an increased risk of low birth weight and preterm delivery independent of ethnicity (31). Symptoms of anemia are classified as compensated (palpitations, dizziness, tachycardia), mild (weakness, sweating, tachycardia), moderate (restlessness, pallor, oliguria), and severe (collapse, air hunger, anuria) (32). Maternal complications of PPH vary from none to hypovolemic shock, disseminated intravascular coagulation (DIC), renal failure, hepatic failure, adult respiratory distress syndrome, and maternal death.

TREATMENT OF POSTPARTUM HEMORRHAGE

Treatment of primary PPH includes medical, mechanical, and surgical methods and combinations of these methods.

Medical treatment consists of administration of oxytocin, methylergometrine, and prostaglandin analogues. Rectal misoprostol in a dose of 800 μg could be a useful "first-line" drug for the treatment of primary PPH (33). Lately, it became clear that recombinant activated factor VIIa (rFVIIa; NovoSeven; Novo Nordisk A/S, Bagsvaerd, Denmark) might be the drug of choice in abundant bleeding of various etiologies (34). rFVIIa was originally developed for the treatment of bleeding in patients with hemophilia A or B with inhibitors to factors VIII or IX. Recently, it has been successfully used to prevent or control bleeding in several other conditions, including thrombocytopenia, platelet function disorders, impaired liver functions, extensive surgery, and severe trauma with profuse bleeding (35). rFVIIa has been assumed as a "universal pancoagulant." Recently, Ahonen et al described the possible beneficial role of the use of rFVIIa in life-threatening PPH (36). However, further clinical trials are needed to establish the cost–benefit and risk–benefit profiles, and to establish it as a standard treatment for bleeding.

Several mechanical and surgical methods to control PPH have been described in the literature. Mechanical methods comprise uterus massage, bladder catheterization, and uterine packing with gauzes or a balloon. Surgical methods include the B-Lynch suture, ligation or embolization of major arteries, and peripartum hysterectomy. The latter is considered as the ultimum refugium after failure of all other efforts to stop bleeding. Removal of uterine packings or intrauterine balloons may involve risk of further hemorrhage, necessitating appropriate planning. However, with the exception of randomized, controlled trials investigating the effect of various uterotonic agents, most of the evidence supporting other methods of treating PPH is in the form of retrospective small series or even case reports (37).

RED BLOOD CELL TRANSFUSION THERAPY

Despite the development of several techniques to reduce blood loss during labor, RBC transfusion is often necessary in the treatment of PPH. RBC transfusions are required for symptomatic treatment of shock and severe anemia (38). The easy availability and the seemingly safe use of blood and blood components in developed countries resulted in a liberal use of blood transfusion, especially in the postpartum period. However, the current awareness of transfusion-related complications (bloodborne infections, transfusion reactions, immunologic effects) and the cost prompted a reevaluation of this transfusion practice.

Various national health care organizations introduced new guidelines for RBC transfusion policy (39–43). Starting in the 1970s, there is a decline in the amount of RBC transfusions in obstetrics and gynecology (47–77%) (7,15,44,45). This decline continues in the 1990s and the new millennium despite the worldwide increase in cesarean section rates (46). Despite the introduction of guidelines, a great variance between physicians' attitudes toward blood transfusions in patients undergoing cesarean section is described (47).

PPH may be treated with standard RBC products. Although in most European countries universally, leukocyte depletion of blood products is introduced, this is not indicated in the treatment of PPH.

TRANSFUSION TRIGGERS FOR RED BLOOD CELL TRANSFUSION

The possible risks of RBC transfusion caused a reconsideration of transfusion policy in a number of clinical fields (48–50). Some authors introduced a restrictive transfusion policy by lowering the hemoglobin transfusion trigger. In these studies, no cardiovascular events occurred (51,52). In obstetrics, the optimal postpartum hemoglobin level is not clear (47). A hemoglobin level of at least 8.0 g/dL is recommended after RBC transfusion. Hemoglobin values below 8.0 g/dL may lead to a worse hemostasis (eg, lower platelet adhesion capacity and a higher velocity) (53–56).

HEALTH-RELATED QUALITY OF LIFE

The postpartum Hb level is the most important parameter for the decision to prescribe RBC transfusions (57). The acute treatment of PPH is to prevent the consequences of cardiovascular shock. The most important subacute clinical feature of obstetric hemorrhage is anemia, with severe fatigue as the most important symptom. This fatigue is not an isolated physical symptom but rather involves lethargy, decreased mental alertness, physical weakness, and poor concentration. However, RBC transfusions are not primarily intended to increase postpartum Hb level, but should reduce this subacute morbidity and particularly improve health-related quality of life (HRQoL), especially fatigue. HRQoL covers the physical, psychologic, and social domains. Conceptually, HRQoL domains can be measured in terms of "objective" functioning (what the patient is able to do) and, complementary, in the patient's subjective evaluation. It is common practice to combine generic measures, allowing for comparison of HRQoL scores across disease stages and diagnostic groups with condition-specific and/or domain-specific measures.

Recently, the relation between anemia and HRQoL has been investigated in patients with myelodysplastic syndromes (MDS) who experience chronic anemia and in patients with acute anemia such as in PPH (58,59). The HRQoL questionnaires, used in these studies, showed a high feasibility, reliability, and validity. Patients with MDS had worse HRQoL scores than the age- and sex-matched general population, and a positive correlation between Hb level and HRQoL was found. Also, patients with PPH scored lower on the HRQoL questionnaires than the controls. In both patient groups, Hb value and HRQoL are complementary variables for evaluation of the severity of chronic and acute anemia. However, further longitudinal research is needed to assess the effect of RBC transfusion on HRQoL and to confirm the role of HRQoL in the decision whether RBC transfusion is necessary. The measures that were used in these studies are complementary and seem to be useful tools in future clinical trials.

COMPLICATIONS OF RED BLOOD CELL TRANSFUSION

Since the 1990s, guidelines and directives from national and European health authorities require hospitals to institute a hemovigilance system. The objective of this hemovigilance system is to collect and assess information concerning unexpected and undesirable effects arising from the therapeutic use of labile blood products and to prevent the recurrence of such incidents. Results of the systems in France, The Netherlands (Transfusie Reacties In Patiënten [TRIP]), and the United Kingdom ("Serious Hazards Of Transfusions" [SHOT]) showed a transfusion complication rate of 0.1 to 2.3 per 1000 blood products administered (60–62). The real incidence will probably be higher because incidents stay unrecognized and/or are unreported. Complications of RBC transfusions, however rare, can be divided into noninfectious and infectious complications.

Noninfectious Complications

Noninfectious complications represent approximately 99% of the reported incidents. They can be divided into: incorrect blood component ("wrong blood") transfused, with potential risk of RhD sensitization in a female of childbearing potential; acute transfusion reaction; delayed transfusion reactions; transfusion-associated graft-versus-host disease; transfusion-related acute lung injury; posttransfusion purpura (thrombocytopenia arising 5–12 days after transfusion of red cells associated with the presence of antibodies directed against the HPA [human platelet antigen] systems); and formation of red cell antibodies.

One of the risks of RBC transfusion is the formation of primary RBC alloimmunization. The incidence after elective surgery is approximately 8% (63). Multitransfused patients have a risk varying from 12% to 22% to develop RBC alloantibodies

(63–66). RBC alloantibodies during pregnancy may lead to hemolytic disease of the newborn resulting in intrauterine anemia, hydrops, and death of the fetus. Possible perinatal complications are anemia of the newborn and elevated neonatal bilirubin concentrations, necessitating phototherapy or exchange transfusion. Although formation of Rhesus D alloantibodies is the most frequent cause of hemolytic disease of the newborn, also nonRhesus D alloantibodies play an important role. Since July 1998, all pregnant women in The Netherlands are screened for RBC alloantibodies. The prevalence of RBC alloantibodies during pregnancy varies from 0.09% to 0.9%. In The Netherlands, the frequency of nonRhesus D alloantibodies was approximately 0.25% (67). Different studies showed that 17% to 30% of primary detected red cell alloantibodies were caused by RBC transfusion (67,68). Clinical relevance is different for nonRhesus D alloantibodies. Of these antibodies, anti-c, anti-Kell, and anti-E antibodies are the most frequent and most likely to cause hemolytic disease of the newborn. To prevent this complication, all women should receive ABO-Rhesus D-compatible RBC transfusions and women under 45 years of age also Kell-negative RBC concentrates (40).

Infectious Complications

Although rare, infectious complications, especially bacteria-associated transfusion reactions, are identified as the most frequent cause of death in transfusion incidents. Transfusion-transmitted infections can be caused by bacterial, viral, fungal, and parasitic infections. The onset of symptoms related to a transfusion-transmitted viral infection may occur from several weeks to years after the transfusion. Most common viral infections include human immunodeficiency virus (HIV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), human T-cell lymphotrophic virus (HTLV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), Parvo B19, and lately in the United States, West Nile virus (69). More recently, there is an increase in parasitic infections like *Trypanosoma cruzi*, especially in the southern states of the United States and in Spain (70). No transfusion-transmitted viral infections of HIV, HBV, HCV, or HTLV were reported to the SHOT (1996–2003) or the TRIP (2003). The chance of HIV infection by RBC transfusion is estimated as one in 2 million transfusions. Risk of infection from allogeneic donors is decreasing as a result of the improved viral screening methods (including NAT testing) of donors, and in some countries, the introduction of routine leukocyte depletion for prevention of CMV infection. Recently, photochemical treatment (PCT) methods have been developed for inactivation of pathogens in cellular products. Platelet components prepared with PCT offer the potential to further improve the safety of platelet transfusion using technology compatible with current methods to prepare buffy coat platelet components (71). For RBC transfusions, this technique is not yet available for clinical use.

OTHER BLOOD COMPONENTS

RBC concentrate is the most frequently prescribed blood component. Other blood components are platelet concentrates and plasma products.

Platelet Transfusion

Platelet transfusions are indicated to control or prevent bleeding in patients with thrombocytopenia or platelet dysfunction. A platelet count of more than 50×10^9/L is recommended for patients scheduled for surgery (eg, lumbar puncture, epidural anesthesia, laparotomy) and for patients with acute bleeding. Patients undergoing a vaginal delivery should have a platelet count of 30×10^9/L to 50×10^9/L. The most important complications of platelet transfusion are development of alloantibodies to platelets and the risk of bacterial transmission (as a result of storage of platelet concentrates at room temperature).

Patients exposed to foreign platelet antigens may develop alloantibodies that cause alloimmunization resulting in platelet refractoriness. Alloimmunization is most often the result of patient antibodies against donor HLA class I antigens present on the leukocyte and platelet surface. To assess platelet response, a 1-hour corrected count increment (CCI) is performed:

$$\text{CCI} = (\text{post-/preplatelet count } [\times 10^9/\text{L}] \times \text{the body surface area of the patient [m2]})/\text{the number of platelets transfused } (\times 10^{11})$$

A CCI of <7.5 at 1 hour is likely to be the result of an immunologic cause. A normal 1 hour CCI followed by a worse CCI after 16 to 24 hours may be the result of a nonimmunologic cause.

Plasma Transfusion

More rarely, plasma transfusions are given in the obstetric setting. Fresh-frozen plasma (FFP) should

only be used in massive hemorrhage treatment or to replace single inherited clotting factor deficiency for which no virus-safe fractionated product is available. FFP involves mostly factor V. FFP and platelets are indicated in case of demonstrable multifactor deficiencies associated with severe bleeding and/or DIC. DIC without evidence of bleeding is not an indication for a FFP transfusion.

FFP contains near-normal levels of many plasma proteins, including procoagulant and anticoagulant components of the coagulation cascades, acute-phase proteins, immunoglobulins, and albumin.

MASSIVE HEMORRHAGE

In The Netherlands, triggers for infusion of platelet concentrates or plasma in massive hemorrhage are based on the following laboratory values: an activated partial thromboplastin time (APTT) and a prothrombin time (PT) of more than 1.5 times the reference value for the laboratory, a platelet number of less than 50×10^9/L, and a fibrinogen concentration lower than 0.8 g/L.

There is no consensus for the correct transfusion policy in hypovolemic shock. Most guidelines recommend "blind" transfusion of RBCs and plasma. Recently, Frölke et al published an example of a transfusion algorithm, which can be used in the situation of massive bleeding with a hemodynamically unstable patient (Fig. 2) (72).

Patients who have received massive RBC transfusion are best managed in a high-care or intensive care unit. Prophylactic anticoagulation is mandatory because of the increased risk of pulmonary embolism with massive transfusion.

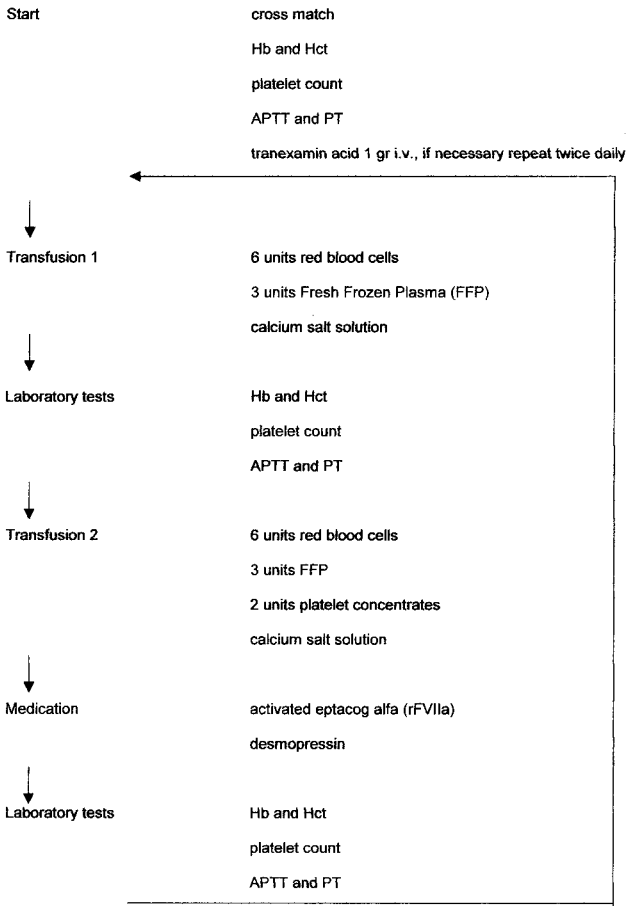

Fig. 2. Transfusion algorithm, which can be used in the situation of massive bleeding with a hemodynamically unstable patient. The protocol is repeated if the blood loss persists and the results of the laboratory tests remain abnormal (72). Hb indicates hemoglobin; Hct, hematocrit; APTT, activated partial thromboplastin time; PT prothrombin time. Reprinted from the American Journal of Obstetrics and Gynecology, vol 84, Pritchard, et al., Blood Volume Changes in Pregnancy and the Puerperium. II. Red Blood Cell Loss and Changes in Apparent Blood Volume During and Following Vaginal Delivery, Cesarean Section, and Cesarean Section Plus Total Hysterectomy, Pages 1271–1282, Copyright ©1962, with permission from Elsevier.

PREVENTION

Measures to prevent PPH can be divided in measures undertaken before, during, or after delivery.

Antepartum Strategies

The major effort of the antepartum measures is to increase Hb levels by iron and folate supplementation. Other treatments like autologous RBC donation and recombinant human erythropoietin (rhEPO) may not be justified in obstetric patients (6,73). For patients who refuse any blood products (Jehovah's witnesses), use of rhEPO is a serious option.

Perioperative and Peripartum Strategies

Perioperative and peripartum strategies to reduce allogeneic RBC transfusions are acute normovolemic hemodilution (ANH) (74,75) and perioperative red cell salvage (PCS) (76). The role of ANH in obstetrics remains unclear as a result of concerns about possible fetal effects of the acutely induced maternal anemia. PCS may be acceptable for patients with religious objections to other forms of blood administration (77–79). The role of hypervolemic hemodilution preoperative is based on a theoretical model (80) and some case reports (81,82). Other treatments, although unclear, are hypervolemic hemodilution (83) and excessive fluid intake during labor (84).

There is conflicting data about the effect of inhalation anesthesia as compared with regional anesthesia on blood loss (13,85,86) and also about the effect of the use of absorbable uterine staples on blood loss (87,88). An already old observation is that the experience of the surgeon is a significant factor in reducing blood loss (4). It seems logical that this also accounts for vaginal deliveries.

Postoperative and Postpartum Strategies

Active management of the third stage of labor (the administration of a uterotonic agent during or after delivery of the baby, the early clamping and cutting of the umbilical cord on delivery, and the delivery of the placenta by controlled cord traction) reduces the number of RBC transfusions (89). For low-risk women, neither intramuscular prostaglandins nor misoprostol are preferable over the conventional oxytocin injections (90,91). The use of the combination ergometrine and oxytocin as compared with oxytocin alone may be associated with a small reduction in the risk of blood loss more than 500 mL. No effect was observed for patients with a blood loss of 1000 mL or more. The advantage of a reduction in the risk of PPH, between 500 and 1000 mL blood loss, needs to be weighed against the adverse side effects associated with the use of ergometrine–oxytocin, eg, elevation of diastolic blood pressure, vomiting, and nausea (92).

rhEPO is not widely used in the obstetric setting as a result of costs. Also, in the acute situation, rhEPO is not a useful therapy. New intravenous iron preparations with low toxicity have been introduced. More clinical trials are needed to investigate the efficacy of intravenous iron therapy during pregnancy and the puerperium (93).

CONCLUSIONS

Postpartum anemia is still a major problem in obstetrics. Different actions, ante-, peri-, and postpartum, can be taken to minimize the amount of blood loss. RBC transfusions play an important role in the treatment of PPH. Because of the possible complications and the rising costs, a reevaluation of the present transfusion policy is necessary. The most important goal of blood transfusion is to improve HRQoL. Further clinical trials are needed to optimize the transfusion policy based on Hb level as well as HRQoL.

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