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Iron-Deficiency Anemia Management in Gynecological Surgery: A Review of Current Evidence and Best Practices

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Abstract

Purpose: Due to the high prevalence of iron deficiency anemia in women undergoing gynecological surgeries and its association with worse postoperative results, it is necessary to identify and treat anemia preoperatively. However, although anemia and iron deficiency are significant global health problems, there are still disparities in the recognition and implementation of "Patient Blood Management" (PBM) as a comprehensive approach to mitigating the risks associated with these diseases. The purpose of the study is to review best practices for the treatment of anemia based on the Enhanced Recovery After Surgery (ERAS) protocol and PBM recommendations. **Methods**: This study reviewed the literature on preoperative iron deficiency anemia in patients undergoing gynecological surgery. We identified references through searches in PubMed using relevant search terms. **Results**: Among the various strategies used in PBM, perhaps the most important is the early detection and management of anemia. In gynecological surgery, there are several approaches to reducing perioperative blood loss, highlighting the use of gonadotropin-releasing hormone (GnRH) agonists (aGnRh) and antifibrinolytics. Oral and intravenous iron supplementation can be performed in addition to blood transfusion to treat anemia. **Conclusion**: Addressing preoperative and postoperative anemia through systematic correction, following the guidelines of the ERAS protocol and PBM guidelines, is essential to improving perioperative outcomes in women undergoing gynecological surgery.

Keywords

Anemia, Gynecological Surgery, Iron Supplementation, Iron Deficiency

1. Introduction

Anemia and iron deficiency are significant global health issues affecting about one-third of the world's population [1]. Iron deficiency anemia is more prevalent in women of reproductive age and preschool-age children compared to the general population, an observation independent of geographic factors or financial diversity [2]. Moreover, women in most age groups have a higher risk of anemia than men, regardless of geographic region [3]. The World Health Organization (WHO) reports that 30% of menopausal women have iron-deficiency anemia, and this prevalence may be higher among women undergoing gynecological surgeries [4]-[9]. Post-menopause, the primary cause of anemia is daily losses through bleeding from the gastrointestinal tract, uncompensated by the intestinal mucosa's increased absorption of dietary iron [8].

The occurrence of anemia in patients with indications for surgical treatment is higher than in the general population, reaching up to 75% in some populations undergoing major surgery [6] [10]. Preoperative anemia is associated with worse perioperative outcomes, including increased morbidity, mortality, blood transfusion, length of hospital stay, and increased complication rates [6]. Some surgical techniques can have a positive impact on preventing or improving perioperative anemia, such as minimally invasive techniques, which are associated with clinical benefits for the patient, such as reduced estimated blood loss (EBL), decreased blood transfusion requirements, shorter length of stay (LOS), reduced peri-operative pain and analgesic requirement [11]. Nonetheless, despite its preventability, many surgical patients experience hospital-acquired anemia, with an incidence ranging from 35% to 74% and reaching 100% in patients with an ICU stay > 7 days. Approximately 80% - 90% of patients will become anemic post-surgery [1].

According to numerous guidelines, including the British Committee for Standards in Hematology, the Enhanced Recovery After Surgery (ERAS) program, the National Institute for Health and Care Excellence (NICE), the British Society for Haematology (BSH), the Society for the Advancement of Patient Blood Management (SABM), the European Association for Cardio-Thoracic Surgery (EACTS), the National Blood Authority Australia, the American College of Obstetricians and Gynecologists (ACOG) and the International Federation of Gynecology and Obstetrics (FIGO), tracking and treating anemia is crucial to minimize unfavorable events during the perioperative period [12]. Anemia has been associated with a higher rate of transfusion, increased risk of postoperative complications, prolonged hospital stays, delayed recovery, and reduced quality of life [8]. This can result in a four-fold increase in the risk of renal injury, three times the risk of mortality, double the risk of infection, and four times the need for transfusion [13] [14]. To optimize perioperative management, the ERAS program recommends preoperative treatment of anemia [15].

Nonetheless, there remains a disparity in the implementation of "Patient Blood Management" (PBM) as a comprehensive approach to mitigating the risks associated with iron deficiency, anemia, blood loss, and coagulopathy [1]. PBM

aims to improve patient outcomes by adopting evidence-based clinical and surgical practices to maintain hemoglobin (Hb) levels, maintain hemostasis, and reduce blood loss [16].

Considering the high prevalence of iron-deficiency anemia in women undergoing gynecological surgeries, its association with worse postoperative results, the need to identify and treat preoperative anemia, and the need to encourage the implementation of PBM, we aimed to review preoperative iron-deficiency anemia in patients undergoing gynecological surgery. The proposed approach involves the treatment of anemia, emphasizing good medical practices based on PBM recommendations.

2. Materials and Methods

This study reviewed the literature on preoperative iron deficiency anemia in patients undergoing gynecological surgery. We identified references through searches in PubMed using relevant search terms (Anemia, Gynecological Surgery, Iron Supplementation, Iron Deficiency) and through the "snowball" method, used to identify references. We also considered some relevant pages found on the internet, such as data from the World Health Organization. The research was carried out using the English language. Articles unrelated to iron deficiency anemia were excluded and a total of 62 references were ultimately reviewed.

3. Iron Metabolism and Pathophysiology of Secondary Iron-Deficiency Anemia Due to Gynecological Causes

Iron plays a vital role in maintaining human homeostasis. It is involved in the synthesis of Hb and myoglobin and is a component of various enzymes involved in cellular respiration, including catalases and oxidases [4]. The average adult human body contains approximately 3 - 4 g of iron (45 mg/kg of body weight), with most (1.5 - 3 g) bound to Hb heme, which primarily oxygenates tissues. Normal adults absorb 1 - 2 mg of iron from their diet daily, with the amount absorbed from heme iron varying from 20% to 30% and the absorption of vegetable-derived iron 1% - 7% [17].

Hepcidin, a hormone produced by the liver, plays a significant role in iron homeostasis. Its primary function is to inhibit iron release from enterocytes into the portal circulation and reticuloendothelial cells into the systemic circulation, ensuring controlled release of iron from storage sites to circulation and avoiding oxidative toxicity [18]. Hepcidin synthesis increases in inflammatory states, causing reticuloendothelial cells to have high intracellular iron stores. This leads to anemia secondary to chronic diseases such as chronic kidney disease and inflammatory bowel disease [4] [18].

In non-pregnant adult women, anemia is defined as Hb < 12 g/dL. Anemia can be classified as mild (Hb > 10 g/dL), moderate (Hb 7 - 9.9 g/dL), or severe (Hb < 7 g/dL) [3] [19]. Preoperative anemia is considered Hb levels < 13 g/dL in surgeries with significant blood loss [20]. Women with borderline anemia are

more likely to be transfused with more units of red blood cells and have a significantly longer hospital stay than non-anemic women [21].

Iron deficiency remains prevalent among women during their fertile years and those with heavy menstrual bleeding (HMB) [5]. Chronic blood loss can result in iron deficiency prior to the onset of anemia if the continuous loss exceeds absorption [22]. In adult women, menstrual losses are the main factor associated with iron-deficiency anemia [4] [7] [23].

4. Other Types of Anemia

Although iron deficiency anemia is the most common among all types of anemia, there are other types. Other substances interfere with hemoglobin synthesis and iron metabolism. Deficiencies of riboflavin (B2), pyridoxine (B6), cobalamin (B12) and folate are associated with anemia. Vitamin B12 and folate deficiencies can result in macrocytic anemia, affecting DNA synthesis and cell division in the bone marrow. Bioavailable forms of vitamin B12 are found primarily in animal-source foods and the origin of their deficiency commonly arises from inadequate dietary intake. However, deficiency can also occur due to malabsorption problems, particularly in the elderly, those with gastric atrophy, pernicious anemia, and bacterial or parasitic infections [3].

Furthermore, numerous diseases such as aplastic anemia, hereditary bone marrow failure syndromes, chronic diseases, or autoimmune disorders contribute to anemia through various mechanisms, including impaired hemolysis or erythropoiesis and the impact of inflammation on iron metabolism. A low reticulocyte count may indicate conditions related to nutritional deficiencies, decreased erythropoietin levels, aplastic anemia, or hereditary bone marrow failure syndromes. Anemia associated with chronic diseases or autoimmune disorders usually presents as normocytic and with a low reticulocyte count. In autoimmune diseases, pro-inflammatory cytokines, notably IL-6, worsen the condition by altering iron metabolism [3].

In addition, it is worth mentioning sickle cell disorders, the most prevalent genetic hemoglobin disorders. In sickle cell disease, abnormal sickle-shaped red blood cells result from defective β-globin chains. Thalassemias involve defects in the synthesis of globin chains, with α-thalassemia resulting from reduced or absent synthesis of the α-globin chain, while β-thalassemia results from reduced or absent synthesis of the β-globin chain. These autosomal recessive conditions manifest as chronic hemolytic anemia and impaired erythropoiesis, with severity ranging from asymptomatic carriers to severe cases, resulting in anemia, growth impairment, skeletal abnormalities, and potentially fatal outcomes in α or β thalassemia major [3].

5. Preoperative Diagnosis of Iron-Deficiency Anemia

The preoperative diagnosis of iron deficiency anemia is crucial for identifying potential complications [7] [24] [25]. **Table 1** shows the stages of iron deficiency and its laboratory findings [17] [22].

Table 1. Stages of iron deficiency [17] [22].

Iron deficiency stage	Pathophysiological mechanism	Laboratory findings
Depletion of reserves	Initially, iron stored in the liver and in reticuloendothelial cells is mobilized into the systemic circulation, allowing for a normal level of iron in the blood. There is still no impairment of erythropoiesis.	↓ Ferritin (<30 ng/mL) ↓ Bone marrow iron (absent)
Mild iron deficiency	With the reduction of iron stores, the iron transport in the blood will be reduced, leading to a mild impairment of erythropoiesis. There is a reduction in cell size, but not yet a reduction in hemoglobin.	↓ Serum iron (<50 mcg/dL) ↓ Ferritin (<30 ng/mL) ↓ TSI (Transferrin saturation index) (<20%) ↑ TIBC (Total Iron Binding Capacity) (>450 mcg/dL) ↓ MCV (Mean Corpuscular Volume) (<80 fL) ↑ RDW (*Red cell distribution width*) (>14%)
Iron deficiency anemia	In the last stage of iron deficiency, there is a significant impairment of erythropoiesis, leading to a reduction in the size and number of red blood cells as well as a reduction in hemoglobin levels.	All previous finds ↓ Hematocrit (<35%) ↓ Hemoglobin (<12 g/dL)

A transferrin saturation below 20% and a ferritin level below 30 ng/mL indicate iron deficiency. However, ferritin is an acute-phase protein that increases during inflammation, and thus, evaluating C-reactive protein levels can help identify these situations [26].

Iron deficiency anemia is typically hypochromic and microcytic. Differential diagnosis with traits of thalassemia, which also present with microcytic and hypochromic anemia, must be considered in populations where these traits are prevalent [26]. When there is a suspicion of an association between minor thalassemia and iron-deficiency anemia, it is recommended first to correct the iron deficiency and anemia, then quantify Hb A2. Another differential diagnosis is chronic disease anemia, which is associated with normochromic and normocytic anemia and is caused by inflammatory, infectious, or neoplastic diseases [17].

6. "Patient Blood Management" (PBM)

PBM is a comprehensive care paradigm designed to control anemia, which is being utilized for various patient groups. PBM's main objective is to improve patient outcomes while conserving health resources and reducing costs, dependence on blood transfusions, and associated risks and complications [27]. In 2010, PBM was endorsed by the World Health Assembly Resolution WHA63.12 [28].

The core principle of PBM is using measures that preserve and protect a patient's blood. The "three pillars of PBM" are the detection and treatment of ane-

mia and iron deficiency, minimization of blood loss and optimization of coagulation, and optimization of the patient's tolerance to anemia (**Figure 1**) [29]. Other principles include patient education, shared decision-making, multi-professional protocols, and integration among primary care physicians, family physicians, specialists, and hospital health professionals [30].

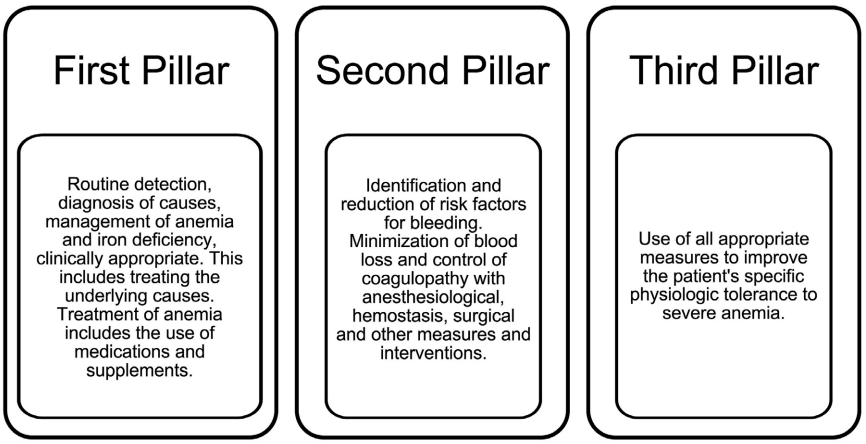

Figure 1. The three pillars of "Patient Blood Management" (PBM) [29].

PBM leads to better outcomes for surgical patients, including lower morbidity and mortality, shorter hospital and ICU stays, and fewer complications [1]. For healthcare professionals, PBM results in better clinical outcomes, improved clinical performance, more satisfied patients, and reduced costs associated with transfusions [1] [27].

Despite the scientific and economic evidence supporting PBM and its endorsement by the WHO, its adoption is still limited. Barriers to implementing PBM include a lack of awareness among patients and health professionals, a need for cultural and behavioral change, and structural adjustments in health services delivery. It is recommended that healthcare systems worldwide adopt PBM as a standard of care to improve patient outcomes and use health resources [1].

The early detection and management of anemia is an essential strategy of PBM. However, preoperative anemia is often overlooked, with indiscriminate use of allogeneic transfusion as a "quick fix" [10]. **Figure 2** shows a suggested algorithm for detecting and treating iron-deficiency anemia in the pre-surgical context.

7. Preoperative Treatment of Iron Deficiency Anemia

Dietary modifications alone are insufficient to fully resolve iron-deficiency anemia. Iron supplementation, either oral or intravenous (IV), is crucial to correct the deficiency and is considered the first-line treatment [31].

7.1. Oral Iron Supplementation

The recommended dose of elemental iron for oral supplementation is 2 to 5

mg/kg/day until normalization of Hb levels (1 to 2 months) and serum ferritin levels (2 to 6 months). The daily dose may range from 100 to 200 mg of elemental iron, and the duration will vary based on the degree of iron depletion, age, time, side effects, and the underlying cause of anemia [17]. **Table 2** provides an overview of the various oral iron compounds available.

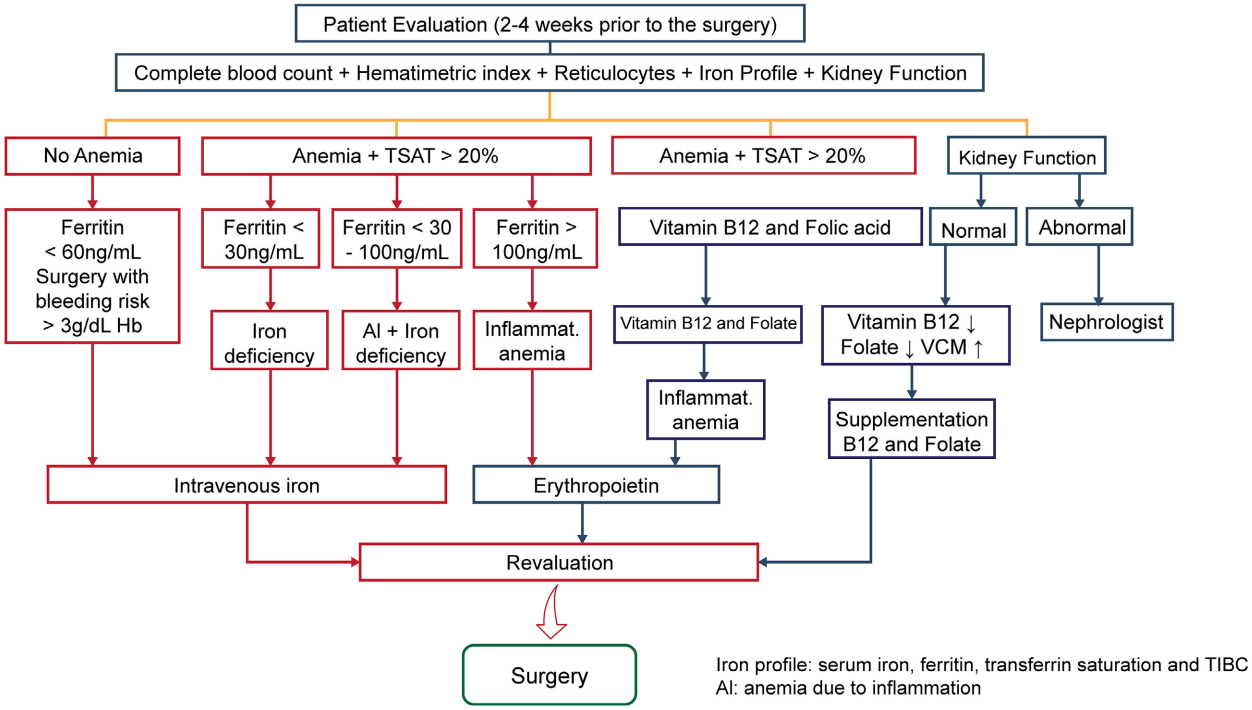

Figure 2. Algorithm for the detection and treatment of iron-deficiency anemia in the pre-surgical context [10].

Table 2. Main presentations of oral iron [36] [61].

Compound	Total iron (mg)	Elemental iron (mg)
Ferrous sulfate	190	40, 60
Ferric glycinate	150, 300, 500	30, 60, 100
Ferripolimaltose	333, 33/337	100

It is crucial to avoid administering high doses of iron, as this may induce a decrease in iron absorption through the negative feedback mechanism of hepcidin production [32] [33]. In the past, oral iron supplementation was typically given in multiple doses. However, the swift rise in hepcidin levels had a detrimental impact on the absorption of subsequent iron doses. An alternative and more effective strategy involves taking iron supplements every other day [18].

Gastrointestinal adverse effects are more frequent when using oral iron than IV iron because of unabsorbed iron, which can harm the gastrointestinal system, considering its oxidative attributes. IV administration is recommended in cases of intolerance or refractoriness to oral therapy, poor intestinal absorption, and the need for a rapid increase in Hb [18].

7.2. Intravenous Iron Supplementation

There has been a suggestion to utilize IV iron as an alternative to rectify anemia and minimize the need for blood transfusions. Ideally, patients should undergo assessment and treatment before surgery [18].

IV iron is generally superior to oral iron supplementation in effectiveness, tolerance, and ability to enhance quality of life [34]. IV iron supplementation, both in a general context and preoperatively, should be prioritized in cases of severe anemia, intolerance to oral iron, failure of oral treatment, gastric surgery, and chronic diseases such as inflammatory bowel disease, kidney disease, celiac disease, Crohn's disease, ulcerative colitis and atrophic gastritis [20] [34]. IV iron is also a priority in patients experiencing repeated bleeding episodes, where the amount of iron absorbed through oral supplementation falls short of meeting requirements due to substantial iron loss [17].

New IV iron carbohydrate complexes have recently been developed to optimize iron supply. Table 3 outlines the main IV iron-based formulations available and their recommended forms of administration [35]. The delivery of large iron doses, even up to 1 g, through a single infusion can fulfill the necessary total iron levels. This method facilitates the correction of Hb deficiency and the swift reestablishment of iron reserves [18]. Recently, three new formulations have been approved: ferumoxytol, ferric carboxymaltose, and iron isomaltoside. These formulations gradually release elemental iron, enabling the total replacement dose to be administered over 15 to 60 minutes [36]. All these iron products have consistently demonstrated a strong track record of safety [37].

Table 3. Main intravenous iron formulations [36] [61] [62].

Compound	Concentration	Dosage	Infusion
Ferric Hydroxide Saccharate	20 mg/ml	100 to 200 mg 1 to 3 times a week. Maximum 200 mg/day.	Depending on the dose. Maximum dose of 200 mg should be taken in 30 minutes.
Ferric Derisomaltose	100 mg/ml	Hb < 10 g/dL: 1500 mg if weight 35 - 70 kg; 2000 mg if weight > 70 kg Hb > 10 g/dL: 1000 mg if weight 35 - 70 kg; 1500 mg if weight > 70 kg Maximum 500 mg/day up to 3× per week	Depending on the dosage. 500 mg bolus up to three times per week at a delivery rate of up to 250 mg. iron/minute. ≤1000 mg: More than 15 minutes. >1000 mg: 30 minutes or more.
Ferric Carboxymaltose	50 mg/ml	Hb < 10 g/dL: 1500 mg if weight 35 - 70 kg; 2000 mg if weight > 70 kg Hb > 10 g/dL: 1000 mg if weight 35 - 70 kg; 1500 mg if weight > 70 kg Maximum 1000 mg per day, up to 1× per week	>200 to 500 mg: 6 minutes >500 to 1000 mg: 15 minutes

Ferumoxytol, one of the first IV iron agents used after iron dextran to decrease the occurrence of anaphylactic reactions, reduces the release of free iron into the bloodstream in contrast to sodium ferric gluconate and iron sucrose [38]. Iron isomaltoside is combined with a carbohydrate component, with the

iron securely enclosed within a structured matrix. This arrangement enables a regulated and gradual release of iron to iron-binding proteins, mitigating the risk of potential toxicity associated with the release of unstable iron [34].

Ferric carboxymaltose comprises ferric oxyhydroxide enveloped and securely bound by carboxymaltose, forming a stable compound that minimizes the release of unstable iron during administration. This characteristic makes applying a larger, single dose possible, which makes the medication cost-effective. It is also a complex that does not contain dextran and, therefore, has a low rate of hypersensitivity and adverse effects. It can be regarded as a safe medication and a viable choice for delivering substantial iron doses rapidly in a single infusion, facilitating the swift replenishment of iron stores [35] [38]. Ferric carboxymaltose permits a weekly administration of as much as 1000 mg of elemental iron, with a minimum infusion duration of 15 minutes, and is phagocytosed and subsequently directed towards erythropoiesis through plasma transferrin [17].

For over ten years, ferric carboxymaltose has been employed to address iron-deficiency anemia in various clinical scenarios. In a study examining the effects of iron therapy, two groups of patients were examined, one receiving oral iron therapy (ferrous sulfate) and the other IV iron sucrose, compared with ferric carboxymaltose. The assessment focused on increased Hb levels from day 0 to day 35. In the first group (cohort 1), the administration of 1500 mg of ferric carboxymaltose led to an average Hb level increase of 1.57 g/dL, while oral ferrous sulfate resulted in a smaller increase of 0.80 g/dL ($P < 0.001$). In the second group (cohort 2), 1500 mg of ferric carboxymaltose raised the Hb level by an average of 2.90 g/dL, while 1000 mg of iron sucrose increased it by 2.16 g/dL ($P < 0.001$). It is noteworthy that severe adverse events did not significantly differ between ferric carboxymaltose and the other studied compounds [38] [39].

The necessary dose of IV iron can be estimated using the Ganzoni formula [40]: Iron requirement = Body weight × (Desired hemoglobin − Actual hemoglobin) × 2.4 + Iron reserves [mg of iron] [kg] [g/dL] [mg of iron]. Regarding iron reserves, 500 mg is typically used for adults and children over 35 kg, and 15 mg/kg is used for children under 35 kg. Alternatively, the simplified **Table 4** can be used to calculate the iron dose to be administered, considering the actual Hb and the patient's weight [41].

Table 4. Simplified table of venous iron supplementation dosage [45].

Hb (g/dL)	Patient body weight > 35 kg and <70 kg	Patient body weight ≥ 70 kg
≥10	1000 mg	1500 mg
<10	1500 mg	2000 mg

However, there are specific contraindications to its use, including anemia not related to iron deficiency, transferrin saturation greater than 50%, active/septicemia infection, severe liver or heart dysfunction, a history of severe hypersensitivity to the iron carrier molecule, and being in the first trimester of pregnancy [26]. The relationship between ferritin and IV iron infusion is debat-

ed. Still, in patients with chronic kidney disease, IV iron infusion with ferritin up to 700 ng/mL has been demonstrated to be safe [42]. The primary adverse effect associated with IV iron treatment is infusion reactions. Research indicates mild reactions occur in around 1 in 200 cases, while severe reactions affect only 1 in 200,000 individuals. These are not typical allergic responses but rather result from the trigger of the complement system. This is referred to as "complement activation-related pseudoallergy." In mild reactions, the infusion is halted temporarily and then restarted at a slower rate when symptoms have subsided. In more severe reactions, the approach may involve administering fluids and steroids [37].

Table 5 presents the laboratory parameters and possible treatments for correcting iron deficiency and iron deficiency anemia using oral or intravenous iron.

Table 5. Treatment of iron deficiency and iron-deficiency anemia in the PBM context [17].

Iron status	Laboratory findings	Initial treatment	Adjuvant treatment
Normal	Ferritin: 30 - 300 ng/mL TSAT: 20% - 50% PCR < 5 md/L	None	None
Low iron	Ferritin < 100 ng/mL	Oral iron 40 - 30/day 800 - 100 once daily 6 - 8 weeks	If intolerance, contraindication or short-term surgery = IV iron
Iron deficiency	Ferritin < 30 ng/mL	Oral iron 40 - 30/day 800 - 100 once daily 6 - 8 weeks	If intolerance, contraindication, no response, or short-term surgery = IV iron Investigation of chronic gastrointestinal, gynecological, or urological loss.
	Ferritin 10 - 30 ng/mL + TSAT < 20% + PCR > 5 mg/L	IV iron	Treat underlying cause EPO if no response to iron
Functional iron deficiency	Ferritin 100 - 500 ng/mL TSAT < 20%	IV iron	Vitamin B_{12} and folic acid
Iron kidnapping	Ferritin > 100 ng/mL TSAT < 20% and/or PCR > 5 mg/L	EPO, if anemia	IV iron if iron deficiency

TSAT: transferrin saturation.

7.3. Blood Transfusion

In cases of anemia, prior therapeutic interventions should be explored when feasible. However, allogenic blood component transfusions remain the standard therapy. Studies have shown that blood transfusions are independently and dose-dependently associated with adverse outcomes, including increased morbidity, mortality, and hospital and ICU stays. Randomized controlled trials have demonstrated no benefit and possible harm from transfusions. Adverse transfusion outcomes are believed to be caused by immunomodulation and storage lesions [1]. Serious adverse events related to transfusions occur in 1 in every 21,413 bags transfused, while the risk of iron IV anaphylaxis is less than 1 in

200,000 infusions [43] [44].

By following the principles of PBM, blood transfusions can be reduced by valuing the patient's blood as a resource. This results in decreased red blood cells, fresh frozen plasma, and platelet transfusions while maintaining or improving outcomes such as reduced mortality and morbidity, decreased incidence of complications, reduced hospital and ICU stays, reduced costs, and resource utilization [1].

Generally, anemias with Hb levels higher than 10 g/dL are well tolerated and rarely require transfusions. However, when Hb falls below 7 g/dL, there is an increased risk of tissue hypoxia and compromised vital functions. Red blood cell concentrate (RBC) transfusions provide benefits in such cases. For Hb values between 7 and 10 g/dL, the need for transfusions depends on the patient's clinical status [45] [46].

Early treatment of preoperative anemia is crucial to reduce the need for erythropoiesis stimulants or blood transfusions. The recent guideline from the British Committee of Hematology found no strong evidence supporting the use of preoperative transfusions to improve surgical outcomes. If they are deemed necessary, there is no evidence to suggest any advantages of preoperative transfusions over intraoperative transfusions. The focus should be on preventing blood loss during the intraoperative period whenever possible [25].

Historically, preoperative transfusion was standard practice until Hb 10 g/dL and a hematocrit above 30% were reached. However, numerous observational studies and randomized clinical trials have highlighted the associated risks with this practice, including perioperative infection, thromboembolism, multi-organ dysfunction, immunological adverse events, hemolysis, lung injury, anaphylaxis, iron overload, graft versus host reaction, increased transmission risk of hepatitis B, C and HIV and prolonged hospitalization time [47].

Thus, the risks and benefits of blood transfusion must be carefully weighed. Transfusion should only be used in severe iron deficiency anemia cases or patients with immediate, acute symptoms requiring correction. The minimum number of units necessary for clinical stability should be transfused [47]. In an adult of average height, one unit of RBC typically increases the hematocrit by 3% and Hb by 1 g/dL. The infusion time for each unit of RBC in adult patients should be between 60 to 120 minutes. The therapeutic response to RBC transfusion should be evaluated by re-testing Hb or hematocrit 1 to 2 hours post-transfusion, considering the patient's clinical response [48] [49]. A proposed approach to preoperative anemia is shown in **Figure 3**.

8. Strategies to Reduce Perioperative Blood Loss in Gynecology

The preoperative approach should include strategies for correcting anemia and reducing perioperative blood loss. Among the possible interventions with this goal, gonadotropin-releasing hormone (GnRH) agonists (aGnRh) and antifibri-

nolytics stand out.

aGnRh's are drugs similar to the hypothalamic GnRH, with a molecular structure similar to the endogenous hormone but with chemical alterations that prolong its half-life. The continuous presence of aGnRh in the pituitary initially leads to increased gonadotropin secretion, which can increase uterine bleeding. However, with constant stimulation, there is desensitization and downregulation of GnRH receptors, leading to a reduction in follicle-stimulating hormone (FSH) and luteinizing hormone (LH) production and induction of a hypogonadotropic hypogonadal state, causing anovulation and amenorrhea [50].

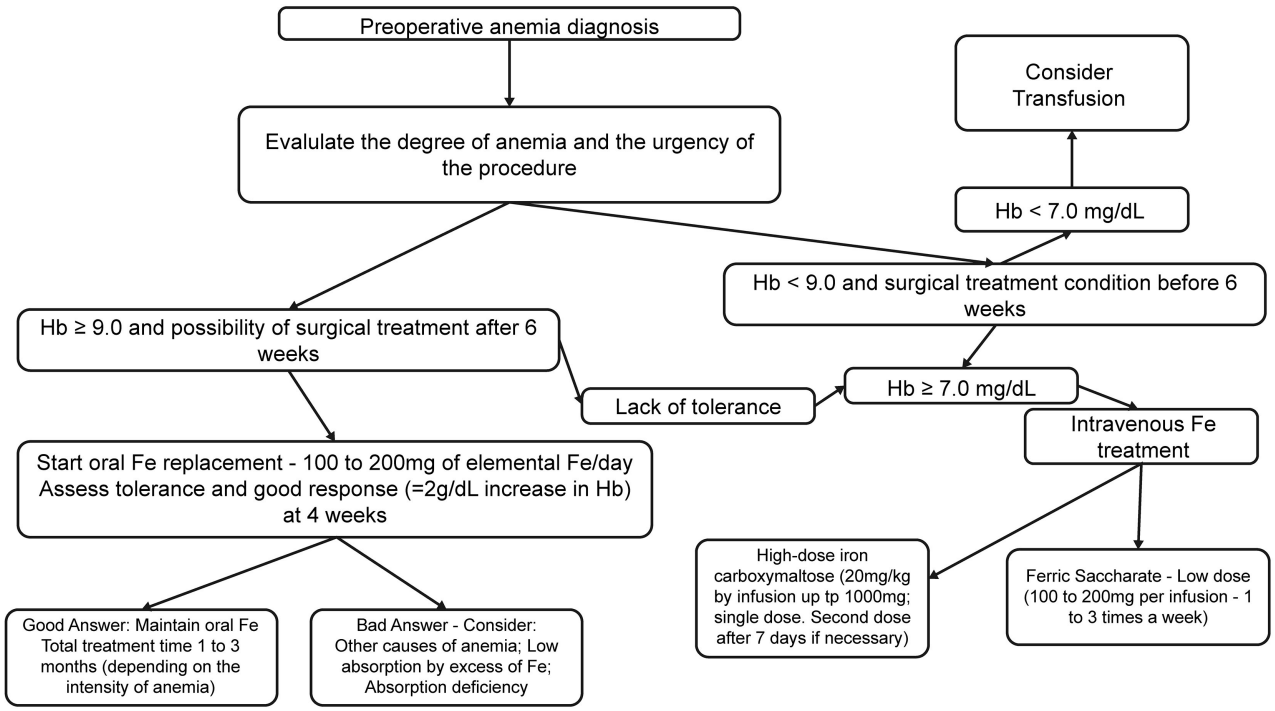

Figure 3. General representation of ways according to the diagnosis of preoperative anemia.

aGnRh is well established as a preoperative strategy for fibroids (myomectomies and hysterectomies), especially when there is a significant increase in uterine volume or iron-deficient anemia that is not responsive to iron treatment [50]. The reduction in uterine size occurs mainly in the first three months of treatment [51]. A Cochrane review showed that women with fibroids treated preoperatively with 3 - 4 months of aGnRh had significantly reduced uterine volume and size, improved preoperative hemoglobin, and reduced surgical and hospitalization times [52]. Furthermore, due to the volumetric reduction of fibroids, aGnRh may also increase the rate of patients who are eligible for a vaginal approach. Its use may be limited due to the short and medium-term adverse effects related to hypoestrogenism, such as vasomotor symptoms and urogenital syndrome [50].

A study evaluating the use of aGnRh for preoperative treatment of patients with moderate to severe endometriosis showed a reduction in intraoperative

blood volume [53]. Another study evaluating its use in preoperative hysteroscopic metroplasties found no evidence of benefits [54]. However, a recent randomized clinical trial comparing the use of aGnRh with ulipristal acetate in preoperative laparoscopic myomectomies showed that aGnRh use was more effective in terms of reducing fibroid volume, intraoperative blood loss, postoperative decrease in hemoglobin, time to suture the first fibroid, and various subjective parameters of surgical ease [55]. Antifibrinolytic agents are increasingly used to reduce bleeding, blood transfusions, and adverse clinical outcomes. Tranexamic acid (ATX) is the most widely studied and utilized in most countries [56]. ATX is a synthetic lysine analog antifibrinolytic. Its action is to reversibly bind to the plasminogen receptor site, reducing its conversion to plasmin and the consequent reduction in fibrin degradation. It is widely used in surgeries with a high potential for bleeding and, more recently, in severe trauma and postpartum hemorrhage due to its significant reduction in blood loss not associated with an increased risk of thromboembolic events [57].

Despite concerns about the pro-thrombotic effect and potential toxicity, thrombosis has not proven to be a significant clinical concern, and adverse effects are rare [56]. In a systematic review assessing the occurrence of thrombotic events following spontaneous bleeding in individuals using ATX, the incidence rate for deep vein thrombosis or pulmonary embolism was found to be 1.9% [58]. The U.S. Food and Drug Administration and other authorities have approved oral ATX due to its remarkable safety track record in mitigating bleeding in women experiencing idiopathic HMB. This effectiveness may stem from its ability to inhibit heightened fibrinolytic action in the endometrium throughout the initial days of menstruation [56].

Several clinical trials have demonstrated the efficacy of ATX in reducing intraoperative blood loss and transfusion rates, supporting its perioperative use in gynecological surgeries, such as hysterectomies, myomectomies, and oncological gynecological surgeries. Before surgery, intravenous administration is recommended in the immediate preoperative period or at the time of incision at a dose of 1000 mg or 10 - 20 mg/kg [57].

9. Management of Postoperative Iron-Deficiency Anemia

The management of post-surgery anemia remains a subject of limited evidence and controversy [59]. To address this issue, an international consensus of experts convened to establish best practices and evidence-based statements on treating anemia and iron deficiency following surgery [60]. Patients with iron deficiency or significant drops in Hb levels after surgery should consider iron supplementation. However, there is currently no evidence to determine the best time to initiate iron supplementation in the postoperative period.

All patients undergoing major surgeries (surgeries with blood loss greater than 500 ml or a duration greater than 2 hours) who had preoperative anemia or moderate to severe blood loss during surgery should be screened for anemia

post-surgery. If iron administration is necessary, early IV iron therapy is recommended after considering contraindications. Whenever possible, it should be administered using a single high-dose preparation for rapid infusion (15 - 60 min with doses of 1000 mg or more) for iron replenishment [61] [62].

Blood transfusions should be performed in patients with severe anemia and clinical signs and symptoms. They should be considered in patients with active bleeding and severely anemic patients when bleeding has been stopped [61].

10. Summary and Conclusions

The management of preoperative anemia is crucial for ensuring optimal outcomes for women undergoing gynecological surgeries. According to the PBM guidelines and the ERAS protocol, correction of preoperative anemia should be systematic. Iron supplementation therapy is preferred, as it is more effective and safer than transfusions. As there is generally not enough preoperative time to correct anemia with oral iron, administration of IV iron should be considered. In these cases, high-dose IV iron is preferred because it provides faster correction of anemia.

Despite rapidly increasing Hb levels, transfusions are associated with increased risks for patients, such as increased postoperative morbidity and mortality. Therefore, adopting a national policy for PBM with adequate resource distribution is essential to improve the population's health status and individual patient outcomes.

In conclusion, addressing preoperative and post-operative anemia through systematic correction, following the guidelines of the ERAS protocol and PBM guidelines, is essential to improve perioperative outcomes in women undergoing gynecological surgeries. The adoption of a national PBM policy and the availability of resources will further enhance the benefits of this approach.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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