

Recovery after surgery: do not forget to check iron status before

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Abstract: The perioperative period poses a risk for anemia due to the high prevalence of pre-existing anemia secondary to underlying pathologies in patients who are candidates for surgery, and as a result of the increased blood loss caused by surgery. Pre-operative anemia is an independent risk factor associated with higher risk of blood transfusion and negative surgery outcomes. Anemia and iron deficiency (ID), the main causes of pre-operative anemia, can be easily diagnosed with blood testing and are readily treated before elective surgery. However, pre-surgical screening and treatment of anemia and ID are frequently overlooked. These topics were presented and discussed at the symposium entitled "Recovery after Surgery: Don't Forget to Check Iron Status Before", held at the 11th Annual Meeting of the European Urogynaecological Association (EUGA) in October 2018 in Milan. The objectives of the symposium were to stress the high prevalence and the consequences of pre-operative anemia, illustrated with three clinical cases of women undergoing surgery, and to choose the best option for iron supplementation. In conclusion, it is essential to take time to diagnose and treat iron deficiency anemia (IDA) before surgery. The first-line treatment is oral iron when surgery can be delayed and when there is no intolerance to oral treatment or inefficient uptake, as in the case of iron sequestration or absorption disorders. Among iron preparations, ferrous sulfate in a polymeric complex (FSPC) was found to be one of the treatments of choice to improve hemoglobin iron stores and quality of life in IDA patients.

Keywords: European Urogynaecological Association, EUGA, ferrous sulfate, iron deficiency, elective surgery, tolerability, urogynecological surgery

Introduction

Iron deficiency (ID) is a widespread and common disorder, despite being easily detected with blood testing and readily treatable by iron supplementation.¹ Anemia may be encountered at any time around surgery: pre-operatively, as patients undergoing planned surgery are frequently anemic and/or iron deficient; as well as peri- and post-operatively, since most surgical procedures are associated with bleeding (expected or unexpected) and because surgery implies a number of phlebotomies for blood monitoring,^{2,3} as well as a degree of inflammation, possibly leading to iron sequestration. Therefore, the perioperative period, which includes the pre-, peri- and post-surgery periods, should be considered a risk for anemia, a pathology associated with increased risk of transfusion and negative surgery outcomes.² Recent awareness of transfusion risk due to pre-operative anemia has led to improvement of patient blood management, involving anemia management, minimization of blood loss, and appropriate use of transfusions. Iron deficiency anemia (IDA), the main cause of pre-operative anemia, can be easily diagnosed with blood

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testing and treated before elective surgery. Surprisingly, it seems that pre-surgical screening, diagnosis, and treatment of pre-operative anemia is frequently overlooked.

These topics were presented and discussed at the symposium entitled “Recovery after Surgery: Don’t Forget to Check Iron Status Before”, held at the 11th Annual Meeting of the European Urogynecology Association (EUGA) in October 2018 in Milan. The objectives of the symposium were to stress the consequences of pre-operative anemia, especially in gynecology-obstetrics, illustrated by three clinical cases of women undergoing surgery, and to discuss what type of iron supplementation would be the best choice.

Anemia in the pre-operative period Underdiagnosed and undertreated

The prevalence of preoperative anemia in gynecology conditions reported in the literature varies with the studied population and the threshold used for anemia; anemia prevalence was found to be 23.9% in patients scheduled for myomectomy or hysterectomy using hematocrit (HCT) level <36.0% for defining anemia,⁴ or 27% in heavy menstrual bleeding using hemoglobin (Hb) <120 g/L as a threshold,⁵ or 64% in women scheduled for hysterectomy using Hb <130 g/L as a threshold.⁶

Globally, the prevalence of pre-operative anemia was found to vary between 5% in hip surgery patients to up to 76% in patients with advanced colon cancer undergoing colectomy.² ID is one of the most common causes of this anemia.⁷ Munoz et al⁶ analyzed data from 3,342 patients scheduled for different kind of surgery (elective orthopedic, cardiac, colorectal cancer resection, radical prostatectomy, gynecological surgery, or resection of liver metastases). For both sexes, anemia was defined as a Hb level <130 g/L. The overall prevalence of anemia was 36% and higher (64%) in patients undergoing gynecological surgery.⁶ Among anemic patients, 69% were women, 62% presented with absolute iron deficiency and 10% with iron sequestration. Over half of all non-anemic patients presented with absolute iron deficiency or inadequate iron stores. Peuranpää et al⁵ revealed that in 236 women referred for heavy menstrual bleeding and randomized to treatment with hysterectomy or a levonorgestrel-releasing intrauterine system, 27% were anemic at baseline and 60% were iron deficient, with a ferritin level <15 µg/L. Among the total population only 6% had taken iron supplements. El Halabi et al⁸ reported that in a population of

patients hospitalized for gastrointestinal (GI) bleeding, less than a third had undergone evaluation of their anemia to detect IDA. Around half of them had laboratory-proven IDA but less than two thirds of the patients with proven IDA received iron supplementation.

The high prevalence of anemia in patients scheduled for gynecological surgery should prompt healthcare professionals to investigate the iron status in all surgical procedures especially when blood loss is expected; the members of the surgery team; gynecologists, surgeons, anesthesiologists and nurses should make sure that the basic biological parameters such as Hb, HCT, ferritin are systematically measured as soon as the surgery is planned.

Definition

Anemia is defined by the World Health Organization (WHO) as a Hb concentration <130 g/L for men, <120 g/L for non-pregnant women¹ and for pregnant women as a Hb concentration of <110 g/L in the first and third trimesters of pregnancy and 105 g/L in the second trimester.⁹

However, the same surgical procedure performed in men or women will result in comparable amounts of blood loss, and as women have lower circulating blood volumes, blood losses will be proportionally higher in women. Therefore, the same Hb threshold, <130 g/L for pre-operative anemia, should be adopted for women and men.¹⁰

Consequences

Pre-operative anemia itself is an independent risk factor for post-operative complications, longer hospital stays, infection and increased mortality.^{2,11} A meta-analysis of 24 studies¹² concluded that pre-operative anemia, which was identified in 39.1% of patients, is associated with poor outcomes after surgery and that red cell transfusion is much more frequent among anemic patients.

Low Hb or HCT values are significant risk factors for blood transfusion,² which increases the risk for worsened outcomes. Compared with patients who were not transfused, surgical patients with anemia receiving only one or two units of erythrocytes were more likely to have post-operative complications and had a higher risk of mortality and morbidity, such as infectious complications. Transfused patients are also more susceptible to allergic reactions, immunomodulation, alloimmunization, and circulatory overload in cases with greater volumes of blood. This increase in risk is dose-dependent.^{13–15}

Considering the documented serious consequences of pre-operative anemia, adequate measures should be taken

to target a hemoglobin concentration ≥ 130 g/L for women too.

Anemia and gynecological surgery

In patients undergoing gynecological surgery, Richards et al⁴ demonstrated that pre-operative anemia (HCT $<36.0\%$), diagnosed in 23.9% of women, was an independent factor associated with an increased risk of 30-day mortality and morbidity. These effects increased with declining HCT levels. Blood transfusion did not appear to ameliorate these risks and may be independently associated with an increased risk of 30-day mortality and morbidity.

Intraoperative bleeding will worsen the situation of anemic patients. Looking more specifically at urogynecological surgical procedures, increased bleeding was reported to occur in 2.7% of mid-urethral sling (MUS) procedures.¹⁶ The risk of blood transfusion was found to be 3.7% in uterosacral ligament suspension surgery, 2.2% in sacrospinous ligament fixation¹⁷ and 5.5% in abdominal sacrocolpopexy.¹⁸ In a retrospective cohort of 54,387 women who underwent pelvic reconstructive surgery, a low pre-operative HCT $<30\%$, a history of coagulopathy, and concomitant hysterectomy were found to be independently associated with the risk of blood transfusion.¹⁹

Anemia and delivery

Anemia itself can be a risk for bleeding. As mentioned in the recommendations of the Royal College of Obstetricians and Gynecologists on the Prevention and Management of Postpartum Hemorrhage, an association between antenatal severe anemia (Hb <90 g/L) and greater blood loss at delivery and postpartum has been reported in a population-based study.^{20,21} Indeed, women with moderate to severe anemia at enrollment had a significantly greater total blood loss average compared to non-anemic women ($p < 0.01$). Decreased uterine blood flow or low uterine muscle strength may contribute to inefficient uterine contractions and increased blood loss, potentially mediated by low body iron stores and IDA.²² IDA at delivery was found to be associated with an increased risk for Cesarean section and adverse maternal and neonatal outcomes.²³

To summarize, pre-operative anemia remains underdiagnosed and the beneficial role of iron supplementation seems to be insufficiently considered in surgical settings whenever surgery is not urgent. Therefore, the diagnosis and management of pre-operative anemia appears to be essential in the preparation and pre-optimization of patients before surgery. For women too, the target Hb concentration should be 130 g/

L or higher, prior to the surgical procedure which should be postponed if needed.

Practical cases of surgical gynecological-obstetrics patients with iron deficiency anemia

The patients corresponding to the three following clinical cases have provided both written and informed consent for the case details to be published, however they are anonymous and not recognizable. Therefore, the institutional approval was not necessary.

A woman with menorrhagia and lower urinary tract symptoms

A 44-year-old woman who had had three pregnancies with two vaginal deliveries and one miscarriage complained of fatigue. She did not suffer from any comorbidities and did not receive any long-term treatment. The frequency of menstruation was normal; however, the patient reported menorrhagia for two years. One year ago, symptoms of dry overactive bladder (OAB) developed: urgency and frequency, without urgency incontinence but associated with asthenia, insomnia, and low mood.

The symptoms encountered by this patient can be related to different kinds of disorders: detrusor overactivity, which can disturb emotional state and increase the risk of depression; hypo-estrogenism, which could explain her low mood and urinary disorders; depression, as OAB can be responsible for depression and vice versa; or uterine myoma with IDA. A complete assessment revealed an intramural anterior myoma of approximately eight centimeters associated with a low Hb level of 89 g/L. The urodynamic evaluation diagnosed a detrusor activity due to extrinsic compression of the bladder. Koch et al²⁴ found an association between the presence of anterior and/or fundal leiomyoma and OAB syndrome, probably explained by the anatomic proximity of the uterus to the urinary bladder, as illustrated by this clinical case. The decision was made to surgically remove the large myoma of this pre-menopausal woman. However, her IDA had to be treated (Hb reaching 130 g/L) first and surgery was postponed until her anemia was corrected by iron supplementation.

A woman with post-partum anemia

A 30-year-old woman, primiparous, with a normal vaginal delivery and a non-complicated episiotomy complained of asthenia and continuous bleeding two months after delivery.

A blood test prescribed by her general practitioner revealed a low level of Hb, at 108 g/L, and a low ferritin level, confirming the diagnosis of IDA. The etiologic investigation hypothesized several causes: hyperthermia, which lasted nearly two hours during delivery and which could have revealed a chronic infection or at least a chronic inflammation possibly responsible for iron sequestration and functional ID; placental material retention; hematoma; or a very rare subacute uterine rupture. Ultrasound examination revealed retained placental material. Surgical removal of the placental material was performed by hysteroscopy and oral iron therapy was prescribed for three months. The treatment was continued for three months after Hb normalization in order to restore her iron stores.

A woman with a pelvic organ prolapse

A 59-year-old woman with a history of recurrent pelvic organ prolapse had undergone three previous surgical anti-prolapse procedures in the last ten years: a hysterectomy with concomitant anterior wall repair, then a high uterosacral ligament suspension to correct a vaginal wall prolapse, and one year ago a sacrocolpopexy for the same problem of vaginal wall prolapse. She complained of pelvic pressure and a sensation of heaviness, as well as light continuous bleeding and voiding dysfunction. Clinical examination revealed a severe anterior prolapse stage IV (Ba +6), and an apical prolapse stage IV (C +8), according to the POP-Q system,²⁵ with visible ulcerations on the vaginal wall. Urodynamic evaluation diagnosed a severe voiding dysfunction with relevant post-voiding residual volume of 200 mL and a high detrusor pressure. Blood testing diagnosed anemia, probably secondary to bleeding, with a low Hb level of 99 g/L. Therefore, iron supplementation was requested, and it was discussed if iron therapy should be started before or after surgery. Evidently, the surgery could be postponed, the oral iron treatment was started immediately, and the surgery planned after some weeks.

Management of iron deficiency anemia pre-surgery: which iron?

General health is related to the good functioning of cells, for which the first nutrient is oxygen, delivered by blood transport through Hb. Iron, a key element of Hb, is mainly involved in oxygen delivery but is also needed in many processes, such as cell growth and survival.³ Absorption of iron varies with diet, factors influencing GI absorption,

and the type of iron. Pathologies of the genital tract can lead to increased iron losses and IDA in menstruating women and also after menopause. This higher risk is well known by gynecologists; however, they rarely think about IDA as an independent risk factor for surgery outcomes. A recent international consensus statement¹⁰ on the perioperative management of anemia and ID gave useful guidelines for the management of perioperative anemia. Three of the nine experts' recommendations are of particular interest. Firstly, pre-operative anemia and ID should be considered as an indication for a "perioperative care pathway" and its management should be a concern throughout the perioperative period, from the decision to operate until complete recovery from surgery. Secondly, "major, non-urgent surgery should be postponed" in order to identify and solve the problem of anemia and ID. Thirdly, the target Hb concentration should be ≥ 130 g/L for women also, since the surgical risk of bleeding is the same in both sexes.

This recent consensus, as well as other publications,^{4,6} were a motivation to analyze the criteria to be satisfied for selecting an iron adapted to our practice in gynecology. Intravenous irons were not discussed during the symposium and this information is available elsewhere.^{26–29} The high number of available iron-containing products precluded a thorough analysis and comparison of the oral supplements.^{30,31}

Similarly to a pregnant woman before delivery, a patient should not be anemic when presenting for surgery. To reach this goal, the choice of iron should meet several requirements; efficacy in restoring normal Hb and ferritin; tolerability, notably with low GI adverse effects; and patient compliance, which is closely related to tolerability and a prerequisite for efficacy.³¹ Oral iron therapy remains the first-line treatment. In case of intolerance, or non-response to oral iron, or if surgery cannot be postponed, intravenous iron may be more appropriate.^{5,28} One important point concerning efficacy is to choose an iron that is well-absorbed. Iron supplements vary in dosage, salt, chemical state (ferrous and ferric) and galenic forms (immediate or prolonged release). Ferric iron formulations show poor solubility in alkaline media and need to be transformed into ferrous iron before being absorbed. Delivering iron as a ferrous salt allows the step of reduction to be bypassed and improves the absorption rate of iron.³² The bioavailability of ferric irons is three to four times less than that of ferrous iron. Ferrous sulfate irons are recommended by the WHO, particularly the prolonged

release formulations. As a result of the prolonged release formulation, there is only a small amount of iron in contact with the duodenal mucosa at any given time, which can explain both their improved absorption and better GI tolerance.³³ Hence, the same therapeutic effect is obtained with a smaller dose, which is associated with better compliance because of fewer side-effects.

Among all iron formulations, the prolonged release ferrous sulfate in polymeric complex (FSPC), marketed as Tardyferon[®] (or Tardyfer[®] in Italy) by Pierre Fabre laboratories, Castres, was designed to release free iron in the optimal intestinal absorption zones: the duodenum and jejunum. The polymeric complex surrounds Fe^{2+} ions, forming a matrix that controls the availability of Fe^{2+} ions to the individual sections of the gastrointestinal tract in conformity with their absorptive capacity. Several studies have been performed in women, pregnant or not pregnant or before surgery. A kinetic study³⁴ in women with IDA confirmed elevated serum levels of iron up to 12 hrs after intake of a single oral dose of FSPC. The median time to maximum serum concentrations (Tmax) occurred four hours post-dosing. When looking at the individual curve of serum concentration, all patients displayed a similar shape in their iron concentration profiles, showing very low intervariability.

The benefit of postpartum iron supplementation on red cells and iron parameters was studied in non-anemic iron deficient women in a randomized placebo-controlled study.³⁵ After delivery, 52 pregnant women received prolonged release FSPC 80 mg or placebo for 12 weeks. The Hb increase was faster in the treated group, with a statistically significant difference versus placebo as soon as the first month and up to 12 weeks. At baseline, ferritin levels were similar in the two groups and below 20 $\mu\text{g/L}$, confirming the fact that after delivery women are often depleted in iron. Ferritin levels rose steadily in the FSPC group, with a 98% increase after three months but stayed low in the placebo group. FSPC efficiency was also evidenced in the Pearl Study,³⁶ which evaluated the efficacy and safety of oral ulipristal acetate for the treatment of symptomatic uterine fibroids before surgery. Since anemia (Hb <100 g/L) was present at baseline in the three groups of the study (the 5 mg/d ulipristal, 10 mg/d ulipristal and placebo groups), FSPC, one tablet of 80 mg per day, was co-prescribed in the three groups. The reduction in bleeding was found to be significantly improved in both ulipristal groups versus placebo, and the Hb levels improved in all groups. In the placebo group, without ulipristal but

receiving FSPC, Hb increased from 95.5 to 126.1 g/L at Week 13, showing that FSPC permitted the correction of anemia despite the ongoing bleeding.

Prolonged release sulfate irons are recommended, but are they all the same? Two prolonged release sulfate irons have been compared in a clinical study³⁷ where women aged 18–50 years and diagnosed with IDA were randomized in two groups and treated either with FSPC 80 mg or a prolonged release ferrous iron 105 mg for 12 weeks. In this study FSPC 80 mg was tested under the name of V0355 corresponding to a new formula recognized as lyoequivalent by Health Authorities. FSPC 80 mg was found to be non-inferior to the ferrous sulfate 105 mg in restoring Hb levels. A similar efficacy pattern was obtained for the two products, while their ferrous sulfate content was different, as FSPC contained 80 mg elemental iron, ie 24% less than the ferrous sulfate 105 mg; this could be explained by the better absorption rate of iron from FSPC. There were fewer reports of GI disorders of moderate and severe intensity (5.6% vs 13.9%, $p=0.007$) in the FSPC group, probably as the result of the lower amount of iron, together with prolonged release, which had the effect of smoothing the peak concentration of iron and thus preventing irritation of the gut mucosa.

With respect to safety, a literature review compared the tolerability of FSPC to other ferrous and ferric iron preparations. A lower incidence of GI events was found with FSPC (3.7%) compared to other ferrous sulfate preparations (30.2%), ferrous fumarate (43.4%), ferrous gluconate (29.9%), and to preparations containing ferric iron, such as iron protein succinylate (7.0%).^{38,39} A lyoequivalence was recognized between the former and the new formula (V0355), implying that ferrous sulphate is available to the body in the same way for both formulations.³⁴ Therefore, we can consider that product safety profile of the new formula is consistent with the one analyzed in the Palacios study.³² These kinetics and clinical studies led to the choice of FSPC for oral iron therapy.

Conclusion

The take-home messages from these lectures were that we need to take time to diagnose and treat IDA with oral iron, when possible, before surgery. In that respect, not all iron supplements are equal, and we should check for efficacy, tolerability, and thus compliance. Among the different irons, studies have confirmed the efficacy of FSPC and revealed a low incidence of general and GI adverse events, favoring good compliance. FSPC thus appears to be one of

the good choices to return Hb levels, iron stores, and quality of life back to normal in IDA patients.

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