VIA MEDICA

RECOMMENDATIONS

Ginekologia Polska
2023, vol. 94, no. 5, 415–422

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.a2022.0153

Guidelines of the Polish Society of Gynecologists and Obstetricians on the diagnosis and treatment of iron deficiency and iron deficiency with anemia

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Guidelines of the Polish Society of Gynecologists and Obstetricians present the most up-to-date treatment and management recommendations, which may be modified and altered after detailed analysis of a specific clinical situation, which in turn might lead to future modifications and updates.

INTRODUCTION

According to the World Health organization (WHO), anemia affects approximately 30% of the global population. In the developing countries, anemia is diagnosed in every second pregnant woman [1]. Iron deficiency remains the most common cause of anemia in pregnancy (approximately 60–80% of the cases) [2], which in turn causes impaired iron synthesis and is characterized by the appearance of erythrocyte population with low hemoglobin count and content.

The acceptable norm for hemoglobin (Hb) concentration in healthy individuals depends on the investigated population. Obstetric and gynecologic causes of iron-deficiency anemia (IDA) in women include puberty, pregnancy and lactation (insufficient supply due to increased demand), menorrhagia, endometrial polyps, uterine myomas and uterine tumors, as well as other abnormal bleedings (increased blood loss).

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Received: 30.11.2022 Accepted: 30.11.2022 Early publication date: xx.xx.2022

The symptoms of iron deficiency and IDA include difficulty concentrating, irritability, palpitations, the Pica syndrome (cravings for clay, chalk, starch), sore, inflamed and smooth surface of the tongue, skin dryness, painful and cracked corners of the mouth, changes in the nail plate (paleness, fragility, ridges) and hair (thinning strands, brittleness, split ends, hair loss). Importantly, the spectrum of the symptoms varies between the individual cases [3].

In the absence of Polish recommendations, the Polish Society of Gynecologists and Obstetricians issued their own guidelines concerning the diagnostic process and treatment of anemia and iron deficiency in pregnant and reproductive-age women.

IRON DEFICIENCY

Iron requirements vary throughout human life and depend on age, sex, and the overall health condition. In adult females, daily requirement is 2 mg, but the demand changes during pregnancy and breastfeeding: 1–2.5 mg in the first trimester and 6.5 mg/day in the third trimester [4, 5]. Iron deficiency occurs when the iron content in the body fails to meet the current demand, but iron deficiency is not always equivalent to anemia. Iron deficiency may be pre-latent, latent and symptomatic (with anemia) [3, 6] (Tab. 1).

Ferritin serves as storage for iron, but it is also an acute-phase reactant, so ferritin levels rise as an immune response to inflammation. The lower range of normal ferritin levels in an inflammatory state is 100 mcg/L. Additionally, transferrin saturated with iron (TSAT) levels might be useful in the process of diagnosis as any result of < 20% will be indicative of iron deficiency [3].

DIAGNOSTICS

Iron deficiency is caused by significant blood loss, an increase in demand but inadequate supply, malabsorption, poor dietary intake, genetic treatment-resistant iron deficiency anemia. Complete blood count (CBC) is a simple, inexpensive and easily available test which is used as the first-choice tool in the diagnostic process of anemia.

The following iron parameters should be used to differentiate the causes of anemia:

— serum ferritin levels;
— serum iron levels;
— total iron-binding capacity (TIBC);
— transferrin saturation (TSAT), iron concentration × 100/TIBC (normal values 20–50%).

Additional recommended tests include measuring serum vit. B12 and folic acid levels.

In accordance with the Management of Physiological Pregnancy Standards based on the Ministry of Health regulation, CBC is recommended at the first prenatal visit, and at 15–20, 27–32, 33–37 and 38–39 weeks of gestation. Apart from CBC, the Polish Society of Gynecologists and Obstetricians recommends to also measure ferritin levels at the first prenatal visit, especially in case of anemia to differentiate the underlying cause. Routine CBC is recommended once a year in all healthy women [7] (Fig. 1, Tab. 2) .

TREATMENT

Treatment of anemia should identify its cause as anemia itself is merely a symptom. In IDA, iron replacement therapy (IRT) and, in extreme cases, transfusion therapy using erythrocyte concentrate are used. The route of administration should be modified, depending on the clinical condition, test results, and patient response to treatment. The possible routes include oral as well as parenteral (intravenous and intramuscular) IRT.

ORAL IRON REPLACEMENT THERAPY

The oral route is recommended in mild IDA, when Hb levels exceed 9 g/dL. The benefits of oral IRT include ease of

Table 1. Stages of iron deficiency in women

Parameter	Norm	Pre-latent	Latent	Symptomatic with anemia
		Lowered levels of serum ferritin and bone marrow iron stores	Significantly lowered ferritin concentration, lowered serum and bone marrow iron levels, low tsat values, but high transferrin and soluble transferrin receptor levels, hb and mcv are normal	Significantly lowered ferritin concentration, lowered serum and bone marrow iron levels, low tsat values, while transferrin and soluble transferrin receptor levels rise; hb and mcv concentrations drop
Ferritin	30–200 mcg/L	< 30 mcg/L	< 12 mcg/L	< 30 mcg/L, as in pre-latent stage
Serum iron	55–180 mcg/L	55–180 mcg/L	< 55 mcg/L	< 55 mcg/L
Hb	≥ 12 g/dL ≥ 11 g/dL in pregnancy ≥ 10g/dL postpartum	≥ 12 g/dL ≥ 11 g/dL in pregnancy ≥ 10 g/dL postpartum	≥ 12 g/dL ≥ 11 g/dL in pregnancy ≥ 10 g/dL postpartum	< 12 g/dL < 11 g/dL in pregnancy < 10 g/dL postpartum
MCV	82–92 fL	82–92 fL	82–92 fL	< 82 fL
Transferrin	2–4 g/L	> 4 g/L	> 4 g/L	> 4 g/L

Hb — hemoglobin; MCV — *mean corpuscular volume; TSAT* — transferrin saturated with iron

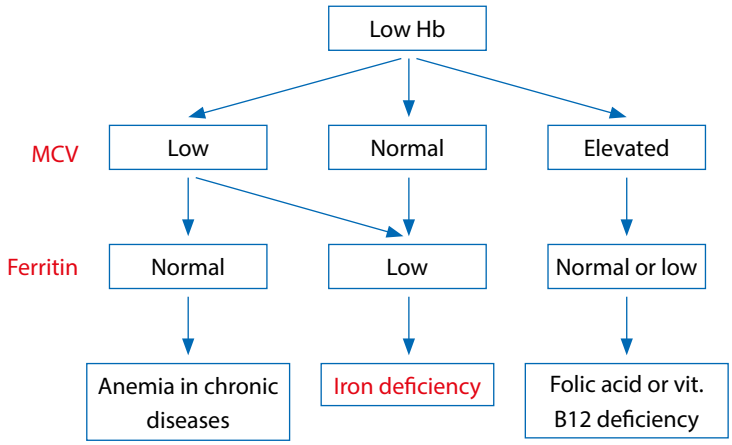

Figure 1. Algorithm for causes of anemia; MCV — mean corpuscular volume; Hb — hemoglobin

Table 2. Differentiation between iron deficiency, iron-deficiency anemia and anemia of chronic disease

Parameter	iron deficiency	iron-deficiency anemia	Anemia of chronic disease
Hb	N	↓ different levels	Hb < 9 g/dL — rarely
MCV	N	↓	N or ↓
Serum ferritin	↓	↓	↑ or less often N
TIBC	↑	↑	↓
TSAT	↓	↓	N or ↓
Serum iron	↓	↓↓	↓ or less often N

↓ decreased concentration/value, ↑ increased concentration/value; Hb — hemoglobin; MCV — mean corpuscular volume; N — normal concentration/value; TIBC — total iron-binding capacity; TSAT — transferrin saturated with iron

administration and the fact that the patient does not require assistance during administration. Oral iron preparations can be divided into iron (II) and iron (III), depending on its oxidation state.

Oral iron preparations which are available in Poland include:

— complex of iron(III) hydroxide and poli-isomaltose;
— iron (II) sulphate;
— iron (II) fumarate;
— iron (II) gluconate;
— iron (III) protein succinylate.

Iron is absorbed in the duodenum and the small intestine, mainly as reduced iron (II). The acidic environment of the gastric and ascorbic acid prevents earlier iron oxidation. On entering the enterocyte, iron is translocated to blood plasma, where it binds to transferrin. Part of the iron binds with apoferritin in the intestinal mucosa epithelium, forming ferritin, which is the circulating iron reserve. Iron (III) is transported and stored, while iron (II) is contained in hemoglobin [8–10].

Pregnant women

According to the WHO criteria, hemoglobin concentration of < 11 g/dL in each of the trimesters and < 10 g/dL during the puerperium is considered anemia in pregnancy [11]. Similar criteria have been suggested by the Centers for Disease Control and Prevention (CDC), which define iron-deficiency anemia in pregnancy as Hb concentration of 11 g/dL in the first and third trimester and 10.5 g/dL in the second trimester [12].

Likewise, the Polish Society of Gynecologists and Obstetricians recommends establishing the threshold value for anemia at 11 g/dL in all trimesters and 10 g/dL in the puerperium.

Since 12 weeks of gestation, plasma volume expansion achieves a 40–60% increase, even 70–100% in multiple pregnancy, which is the cause of physiological anemia of pregnancy (relative expansion of the plasma volume in comparison to hematopoietic cells). The levels of hemoglobin and hematocrit drop by 3–5% to 36 weeks of gestation [13, 14].

Iron deficiency may increase the risk for premature labor, infection, low birthweight and perinatal complications [1, 15].

In non-anemic pregnant women, with ferritin concentrations < 60 mcg/L after 16 weeks of gestation, it is recommended to replace iron at a maximum daily dose of up to 30 mg. The rationale behind it is that iron overload is detrimental to the human body as it generates reactive oxygen species [7]. The probability of IDA is lower if ferritin concentration ranges from 60 to 70 mcg/L.

Women with non-anemic iron deficiency are recommended a daily dose of 65 mg elemental iron. In IDA, a daily dose of 60–200 mg elemental iron is recommended [9]. Hemoglobin and ferritin levels should be measured two weeks after therapy commencement to evaluate patient response to treatment – absorption of that form of iron in the body.

Once normal Hb level is achieved, the treatment needs to be continued for three months and for at least six weeks postdelivery to replace iron deficiency. Preparations with higher bioavailability and differential diagnosis to detect the cause for anemia are recommended in patients who are non-responsive to oral IRT.

Unfavorable consequences of iron overload include:

— development of insulin resistance and decreased insulin secretion by pancreatic β-cells [16, 17];
— increased risk for developing preeclampsia, especially in women supplementing iron before 16 weeks of gestation without decreased hemoglobin levels (Hb > 13.2 g/dL at the beginning of the second trimester) [18, 19];
— development of gestational diabetes [20, 21] (Tab. 3).

Non-pregnant women

Anemia in non-pregnant women, regardless of their age, is defined as Hb levels of < 12 g/dL [22, 23]. Routine CBC is recommended in healthy women at least once a year.

Table 3. Consequences of iron deficiency and iron overload

iron deficiency — increased risk for:
— premature labor — infection — low birthweight — perinatal complications — central nervous system abnormalities in the fetus
iron overload — increased risk for:
— insulin resistance and decreased insulin secretion by pancreatic β-cells — preeclampsia — gestational diabetes

Special steps should be taken to address iron deficiency in women who are about to undergo surgery due to gynecological reasons (*e.g.*, uterine myomas, endometrial hyperplasia, gynecologic malignancy, *etc.*), to avoid transfusions during the postoperative period and improve healing and convalescence.

If anemia is diagnosed, oral IRT with a single (or split in two) daily dose of 60–200 mg elemental iron is recommended.

An increase in the reticulocyte count after 7 days and in Hb concentration by app. 2 g/dL after 2 weeks since therapy commencement is indicative of treatment efficacy. The treatment should be continued until normal Hb and ferritin concentrations are achieved, typically for min. 3 months after normalization of Hb levels.

General comments

Iron preparations should be taken on an empty stomach, if possible, and not combined with other medicines such as antacids calcium supplements, H_2 receptor antagonists, or tetracyclines as these drugs lower iron absorption. The longest possible time interval between administration of these medicines and iron IRT is recommended.

According to Campbell, a daily dose of 250 mg vit. C might improve absorption from the digestive system as iron absorption is more effective in acidic environment [24]. Still, the effects of IRT combined with vit. C to improve iron absorption remains to be fully elucidated [25].

Attention should be paid to differences in elemental iron content in the available preparations.

Resistance to treatment with iron (II) oral preparations is defined as lack of an increase in Hb concentration by > 1 g/dL after 4–6 weeks of IRT with a daily dose of 100 mg iron. Resistance may be the result of chronic bleeding, malabsorption, misdiagnosis, or patient non-compliance [3]. If the response to oral IRT is poor, other factors which might contribute to the anemia — folate deficiency, vitamin B12 deficiency, anemia of chronic diseases or low-iron anemia caused by iron loss from the digestive tract (*e.g.*, IBD) which are often observed in pregnancy — should be investigated.

Iron preparations for oral IRT have adverse effects mainly on the gastrointestinal system and include nausea, emesis and constipation. In order to avoid the abovementioned side effects, a smaller (gradually increasing) dose or change of iron preparation is recommended.

The presence of side effects is not an indication to discontinuation of IRT. Contraindications to IRT include iron overload, other types of anemia without iron deficiency, or acute infection.

Interactions between certain groups of medicines with oral iron supplements are presented in Table 4.

Table 4. Interactions between certain groups of medicines with oral iron supplements

Medicines	Interactions	Recommendations
Antacids	↓ iron absorption	The longest possible time interval between these medicines is advised
Calcium supplements	↓ iron absorption	The longest possible time interval between these medicines is advised (min. 2 hours)
H_2 receptor antagonists	↓ iron absorption	At least 1 hour interval between oral iron preparation and H_2 receptor antagonist
Tetracyclines	↓ iron and tetracycline absorption	Tetracycline should be administered 3 hours after or 2 hours before oral iron preparation
Intravenous iron preparations	↑ iron toxicity	Concurrent administration of oral and intravenous preparations is not advised
Methyldopa	↓ methyldopa absorption, decreased hypotensive activity	BP should be monitored
Penicillamine	↓ penicillamine absorption	A min. 2 hour-interval is advised
Thyroxine	↓ thyroxine absorption	A min. 2 hour-interval is advised; thyroid function should be monitored
Vitamin C	↑ iron absorption	Concurrent supplementation with vit. C and iron preparations may be beneficial

INTRAVENOUS IRON REPLACEMENT THERAPY

Intravenous IRT is recommended in cases when oral supplementation proves to be ineffective and iron content cannot be replaced over 1–3 months (malabsorption, iron loss which exceeds absorption capacity, intolerance of oral preparations, non-compliant patients), and if Hb levels are 7–9 g/dL in pregnancy, in the second and third trimester, and in non-pregnant women.

Parenteral route should be considered since the second trimester of pregnancy and during the puerperium in women with IDA who are not responsive to oral IRT, are intolerant of the oral route, or in cases when Hb levels range from 7 to 9 g/dL.

Intravenous iron preparations available in Poland include:

— iron (III)-hydroxide sucrose complex (ferric gluconate);
— iron (III)-hydroxide dextran complex;
— ferric carboxymaltose;
— iron (III)-derisomaltose.

All the above mentioned intravenous iron preparations are equally effective in treating IDA and have a similar safety profile. The main differences are associated with the number of injections and time required to administer the full dose, as well as administration costs (Tab. 5).

Several authors have presented their experience with parenteral iron therapy to treat IDA and reported faster increase of Hb levels and better repletion of the iron storage as compared to oral administration. Satisfactory effects of intravenous iron preparations were demonstrated especially in the case of iron sucrose [28] and ferric carboxymaltose (III) [29]. A large retrospective study reported a lower number of postdelivery transfusions in women receiving intravenous IRT [30].

Possible complications of intravenous IRT include:

— anaphylactic reaction,
— hypophosphatemia — as a result of increased urinary phosphate excretion caused by elevated serum FGF-23 (fibroblast growth factor 23) levels, followed by decreased levels of circulating 1,25-dihydroxyvitamin D [31],
— non-allergic reactions to the infusion (manifesting as self-limiting urticaria, palpitations, dizziness, neck and back spasms in < 1% of the affected individuals) typically do not lead to more serious reactions [32],
— complement activation-related pseudo-allergy (CARPA), manifesting as facial redness, chest and back pains, known as the Fishbane reactions [33, 34]. Intravenous IRT in patients with active infection should be delayed until symptom resolution [35].

INTRAMUSCULAR IRON REPLACEMENT THERAPY

Intramuscular IRT offers an alternative to intravenous route, but it is not the method of choice as far as iron supplementation is concerned. Iron (III)-hydroxide dextran complex is the only intramuscular iron preparation available in Poland. The injections are painful and associated with high risk for permanent skin discoloration, so intramuscular route is not recommended [36]. If it is necessary, the Z-track method for intramuscular injections is recommended to minimize the risk for iron transmission to the skin. The Z-track method is used to avoid injection or seeping of the injected

Table 5. Comparison of intravenous iron supplements available in Poland* [27]

	Iron (III)-hydroxide dextran complex	Iron (III)-hydroxide sucrose complex	Ferric carboxymaltose	Iron (III)-derisomaltose
Test dose	Before every intravenous administration; one time before intramuscular administration	Only once, in new patients	Not necessary	Not required
Route of administration	Slow infusion	Slow infusion	intravenous administration over 15 min.	Slow infusion
Total daily dose	Up to 20 mg/kg of body weight for 4–6 hours	Single dose, not more than 200 mg, may be repeated 3 times/week	Up to 20 mg/kg (max. 1000 mg/week)	Up to 20 mg/kg for 1 hour
Half-life	5 hours	20 hours	7–12 hours	24–96 hours
Dosing	100–200 mg 2–3 times/week, depending on Hb concentration (up to the max. dose — 20 mg/kg)	Single dose, not higher than 200 mg, may be repeated 3 times/week	1.Intravenous injection of non-diluted solution. The maximum single dose: 15 mg iron/kg body weight. 2. Intravenous infusion diluted in 0.9% m/V sterile sodium chloride. The maximum single dose: 20 mg iron/kg weight	1. Bolus iv injection at a dose of up to 500 mg up to 3 times/ week. 2. IV drip infusion : — single infusion at a dose of up to 20 mg iron /kg body weight / week — directly into the venous limb of the dialyzer, the same procedure as iv bolus injection
Pregnancy	Contraindicated in the first trimester	Contraindicated in the first trimester	Contraindicated in the first trimester	Contraindicated in the first trimester
Lactation	Unknown risk	Transfer into breast milk is unlikely, no clinical trials	< 1% transfers to breast milk, insignificant	Unknown risk
Adverse effects	5% of patients — min. adverse effects, Risk of anaphylaxis < 1/10000. Risk of allergic reaction > 1/1000 < 1/100	0.5–1.5% of patients – adverse effects, Risk of anaphylaxis > 1/10000 < 1/1000	3% of patients — adverse effects; hypersensitivity: > 1/1000 to < 1/100; pseudo-anaphylactic/ anaphylactic reactions: > 1/10000 to < 1/1000	> 1% of patients — adverse effects; Risk of anaphylaxis ≥ 1/10 000 to < 1/1000; Risk of allergic reaction ≥ 1/1000 to < 1/100

*based on the Summary of Product Characteristics (SmPC)

substance into the subcutaneous tissue. During the procedure, the skin and tissue are pulled in the direction away from the site of the injection.

BLOOD TRANSFUSION

In patients with life-threatening (Hb levels < 7 g/dL) anemia due to causes other than iron deficiency causes, transfusion of compatible erythrocyte concentrate is recommended. The decision to transfuse erythrocyte concentrate should not be based solely on the hemoglobin level but also on the clinical condition of the patient (*e.g.*, risk for further bleeding). In the case of acute blood loss and hypovolemic shock, timely red blood cell transfusion is a life-saving procedure. In such cases, hemodynamic disturbance is the indication for the transfusion and the decision needs to consider the actual and potential future blood loss. Such management aims to quickly restore the erythrocyte volume of the circulating blood.

Transfusion-related complications include:

— anaphylactic reaction,
— life-threatening hemolysis,
— transfusion-related acute lung injury (TRALI),
— febrile reactions,
— urticaria and other skin reactions [3].

The risk of red blood cell alloimmunization and the potential clinical benefits of red blood transfusion should be considered. Women deemed eligible for erythrocyte concentrate transfusion need to be fully informed about the indications for transfusion and the available alternatives. Written informed consent must be obtained from the patient and the entry about blood transfusion should be made in the patient medical records.

Table 6. Threshold Hb values to determine the route of administration in pregnant and non-pregnant women

Oral preparation	Intravenous preparation	Blood transfusion
Hb < 12 g/dL in women Hb < 11 g/dL in pregnancy Hb < 10 g/dL in puerperium	Hb 7–9 g/dL Hb in pregnancy 7–9 g/dL in the second and third trimester	Hb ≤ 7 g/dL

Hb — hemoglobin

ALTERNATIVE METHODS OF TREATING ANEMIA

Erythropoietin preparations

In case of persistent anemia — despite treatment — in pregnant women with chronic renal disease (diabetic nephropathy or history of renal transplant), administration of erythropoietin preparations might be considered as these women present with renal anemia. The available preparations include recombinant human erythropoietin or darbepoetin. Darbepoetin alpha is a unique erythropoiesis-stimulating protein, which may be administered at prolonged intervals as compared to recombinant human erythropoietin as its serum half-life is app. 3-fold longer [37].

SUMMARY

- Oral iron administration is the first-line of treatment in mild IDA, when Hb concentration exceeds 9 g/dL.
- Iron supplementation in pregnant women at the daily dose of up to 30 mg should be recommended only to non-anemic women, with ferritin levels over 60 mcg/L after 16 weeks of gestation.
- Women with non-anemic iron deficiency should receive a daily dose of 65 mg elemental iron. In IDA, the initial daily dose of 60–200 mg elemental iron is recommended.
- Intravenous IRT is recommended in cases with Hb concentrations of 7–9 g/dL in pregnancy in the second and third trimester, and of < 10 g/dL during the puerperium, as well as in the absence of patient response to oral IRT.
- Most adverse effects in intravenous IRT are not in fact anaphylactic reactions (*e.g.*, Fishbane reactions).
- Intramuscular route may be considered as an alternative to intravenous IRT, but it is not the preferred route due to the possible complications.
- Erythrocyte concentrate transfusion is recommended in cases of life-threatening anemia or when Hb levels are < 7 g/dL (Tab. 6).

CONCLUSIONS

- Iron deficiency is a global health problem.
- Symptoms of iron deficiency anemia may appear in cases of non-anemic iron deficiency.
- Route of administration of the iron preparations in cases with anemia should depend on test results (Hb concentration, ferritin, TSAT) and clinical state of the affected patients.

Conflict of interest

All authors declare no conflict of interest.

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