CURRENT OPINION ON THE MANAGEMENT OF IRON DEFICIENCY ANAEMIA IN GASTROINTESTINAL DISEASES

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СОВРЕМЕННОЕ ПРЕДСТАВЛЕНИЕ О ВЕДЕНИИ ПАЦИЕНТОВ С ЖЕЛЕЗОДЕФИЦИТНОЙ АНЕМИЕЙ ПРИ ЗАБОЛЕВАНИЯХ ЖЕЛУДОЧНО-КИШЕЧНОГО ТРАКТА

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Summary

Iron deficiency is the most common cause of anaemia in the world. Despite frequently weak and masked clinical presentation of iron deficiency anaemia (IDA), this disease is very serious with complications leading to early mortality. In the developed countries IDA is predominantly diagnosed as the complication of another disease or as the result of major bleeding events. Diagnosis of IDA should be based on laboratory findings i.e. haemoglobin, mean corpuscular hemoglobin concentration and ferritin. Latter is the most sensitive marker for iron deficiency. Anaemia of chronic disease should be taken into an account as a potential differential diagnosis or coexisting state. For women in fertility age with IDA, gynaecological disorders should be ruled out first. Males and postmenopausal women with IDA should undergo upper, lower and in certain cases capsule endoscopy and/or enteroscopy to find a plausible cause of IDA. The ultimate goal of therapy is to find out and treat the primary cause of IDA. Iron body stores should be restored using either oral or parenteral iron preparations. The use of parenteral iron preparations in patients with gastrointestinal pathologies is often clinically substantiated for the treatment of IDA. Red blood cell transfusion should be administered in emergency cases only.

Keywords: iron deficiency, iron deficiency anaemia, inflammatory bowel disease, oral iron, parenteral iron.

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Резюме

Во всем мире дефицит железа является самой частой причиной развития анемии. Несмотря на слабые или замаскированные клинические проявления железодефицитной анемии (ЖДА), это заболевание очень серьёзное, которому присущи осложнения вплоть до летального исхода. В развитых странах ЖДА чаще всего диагностируется как осложнение другого заболевания или как результат кровотечения. Диагноз ЖДА должен базироваться на лабораторных данных: гемоглобин, средняя концентрация гемоглобина в эритроците и ферритин. Последний является наиболее чувствительным маркером в случае ЖДА. Анемия хронического заболевания должна рассматриваться в контексте дифференциальной диагностики или в качестве сопутствующего состояния. У женщин в репродуктивном возрасте с ЖДА, прежде всего, необходимо исключить гинекологические заболевания. У мужчин и женщин в менопаузе необходимо провести гастроскопию и колоноскопию, а в отдельных случаях также капсульную эндоскопию и/или энтероскопию для диагностики достоверной причины развития ЖДА. Конечной целью терапии является лечение первичного заболевания вызвавшего развитие ЖДА. Восстановление запасов железа в организме должно быть осуществлено с помощью пероральных или внутривенных препаратов железа. У пациентов с желудочно-кишечными заболеваниями более целесообразным является назначение внутривенных препаратов железа. Переливание эритроцитарной массы оправдано только в экстренных случаях.

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Introduction

According to the World Health Organisation there are approximately 1.6 billion patients (amounting to around 25 % of the world's population) suffering from anaemia, which is most commonly caused by iron deficiency [1]. Iron Deficiency Anaemia (IDA) is one of the most often diagnosed disorders. According to the literature data the most common cause of IDA in premenopausal women is menstrual disorders (for example, frequent and severe menstrual bleeding), whereas in men and postmenopausal women the most frequent cause of IDA is gastrointestinal bleeding [1,2,3,4,5,6,7,8,9].

Despite frequently weak and masked clinical presentation of IDA, this disease is very dangerous with complications leading to early mortality. In the developed countries IDA is predominantly diagnosed as the complication of another disease, for example, gastrointestinal, oncological, gynaecological and obstetric complication, or as the result of major bleeding events, for example, after serious surgical procedures.

Epidemiology

Iron deficiency (ID) is the most common cause of anaemia in the world. This deficiency accounts for 2–5 % of anaemia in men and postmenopausal women in the developed countries [1,2,9]. At least 10 % of the world population or more than 500 million people are diagnosed with iron deficiency anaemia [10]. This situation is somewhat worse in the less developed countries (30–70 % of the populations), where iron deficiency is caused by poor diet and frequent intestinal parasite invasion [11].

Physiology

Human body contains approximately 4000mg of iron. The largest amount of it (~65 %) is found in haemoglobin (Hb) stored in erythrocytes. Myoglobin contains ~15 %. The remaining iron is stored in so-called "iron depots' formed by the liver and monocyte / macrophages system (reticuloendothelial system), bone marrow and spleen [12].

Only small amount of iron (0.1 %) is freely circulating in plasma with assistance of transferrin. In physiological condition human body loses 0.6–1.3 mg of iron daily (predominantly in the process of skin and mucosa renewal, as well as during menstrual bleedings in reproductive age females) [13].

Duodenum and jejunum proximal part are responsible for iron absorption. The regulation of this process is dependent on the amount of iron intake, the amount of stored iron in iron depots, as well as erythropoietic regulation determined by erythropoiesis. The "free" iron is moving in the blood stream with the help of transferrin. Immediately after the delivery of iron by enterocytes to the depot, it is conjugated with ferritin. The amount of daily iron intake should be 5 mg/day in men and postmenopausal women and 15 mg/day in premenopausal women and growing children respectively [10,13,14].

Nutritional Iron

IDA develops when the amount of nutritional iron drops below 1–2 mg/day. In the developed countries the average iron intake ranges from 6 to 15–20 mg/day. However, only 15–20 % of the total nutritional iron is absorbed. Furthermore, the better-absorbed iron is a so-called "heme" iron, contained in the meat and meat products, which is bivalent and comparatively easily is absorbed by the enterocytes. A trivalent iron on the other hand (a so-called "non-heme" iron), contained in vegetables and fruit, requires a transitional cascade in order to enter the blood stream. Trivalent iron must first be reduced to bivalent iron by ferrireductases. About 20 % of heme iron (in contrast to 1 % to 2 % of non-heme iron) is absorbable [10,15, 16].

The development of IDA can also be induced by specific diets, such as vegetarian and, even more so vegan. Iron absorption could be enhanced by different acids (ascorbic, citric etc.) or inhibited by excessive use of tannates (found in tea), carbonates and phosphates. However with no clearly defined amount related to increased risk or the development of IDA. [15]

Iron Deficiency Anaemia

Iron deficiency anaemia is a haematological syndrome characterised by impaired haemoglobin synthesis during erythropoiesis caused by iron deficiency.

There following etiologic factors should be considered:

- Acute or chronic, overt or occult blood loss (most frequent cause):
  - ▹ Gastro-intestinal bleeding (the most common),
  - ▹ Benign or malign tumours,
  - ▹ Genitourinary system disorders (menstrual bleeding, urinary tract tumours etc.),
  - ▹ Toxic effects of substances (salicylates and other non-steroidal antinflammatory drugs (NSAID), alcohol),
  - ▹ Inherited hemorragical diseases:
    - Inherited vascular diseases,
    - Von Willebrand disease,
    - Defects of platelet function;
  - ▹ Blood donation.
- Impaired absorption of iron:
  - ▹ Gastrointestinal surgery,
  - ▹ Intestinal malabsorption,
  - ▹ Infectious agents and parasites,
  - ▹ Iron-refractory ID.
- Pregnancy and lactation (in some cases the severity of anaemia is equivalent to the loss of 1500 ml of blood);
- Rapid growth (in children);
- Insufficient nutritional bioavailable iron intake;
- Chronic inflammation (inflammatory cytokines influencing hepcidin);
- Renal diseases (for example, chronic renal insufficiency) [9,10,11,13,16,17,18].

Clinical symptoms

Clinically iron deficiency can be divided into three stages:

1. Latent iron deficiency
2. Erythropoiesis iron deficiency
3. Iron deficiency anaemia

Latent iron deficiency develops when the iron reserves are depleted and there is a deficiency in iron depots. There are no clinical signs during this stage. Usually, such patients coming to medical attention only because of abnormalities noted on laboratory tests [11].

This stage is commonly associated with reduced ferritin, however normal "free" iron amount in the serum.

Erythropoiesis iron deficiency is characterised by reduced activity of tissue enzymes (cytochromes, catalases, etc.), due to depletion of iron-containing enzymes in cells, with possible skin, nail, hair changes and muscle weakness (due to distorted myoglobin metabolism). Unusual craving for certain non-nutritional substances — pica, which is unique to iron deficiency, could rarely be observed (pagophagia, geophagia, amylophagia). Pica is developed due to the depletion of iron from the central nervous system [10,15].

Blood analyses reveal the reduction of ferritin, increase of transferrin, reduced serum iron, increased total iron binding capacity and reduced transferrin saturation (in physiological state approx. 30 %, in this stage less than 20 %).

IDA produces the signs and symptoms common to all anemias, which are general weakness, malaise, fatigue, palpitations, shortness of breath, fainting and drowsiness. As well as any of the signs and symptoms mentioned in previous chapter could be presented in patients with IDA. The severity of these symptoms usually depends on the degree of anaemia. In some cases generalised rash and dysphagia (Plummer-Vinson syndrome) due to an esophageal stricture have been reported. Plummer-Vinson syndrome is characterized by IDA, esophageal dysphagia and glossitis. Others potential consequences of IDA are depressed immunity, reduced tolerance to work performance and neuropsychologic abnormalities [10,11,13,15,19].

Diagnosis

History

In order to determine the daily nutritional iron intake, dietary peculiarities of the patient should be established, especially if the patient favours specific diets. The use of aspirin and/or NSAIDs and other potentially toxic substances (alcohol etc.) should be noted. A family history of IDA can indicate inherited malabsorption syndrome, telangiectasia and frequent bleeding episodes. A history of blood donation or any other source of blood loss should be obtained [9,20].

Laboratory evaluation

Perhaps mean haemoglobin concentration in red blood cells (MCH) is the most accurate indicator of IDA because it is less affected by the method of determining. Reduced MCH indicates on hypochromia and reduced mean corpuscular volume (MCV) — on microcytosis. Both microcytosis and hypochromia are sensitive indicators of IDA in the absence of chronic disease or coexistent conditions (vitamin B12 or folate deficiency etc.) [9,21,22]. Initial screening (blood count) usually includes hemoglobin level, MCV, MCH, mean cell hemoglobin concentration (MCHC), erythrocyte and reticulocyte count.

The most reliable serum marker of iron deficiency is ferritin level, which reflects total body iron stores. Other conditions that may lower the plasma ferritin concentration independently of a decrease in iron stores are hypothyroidism and ascorbate deficiency. However, such conditions solely cause problems in clinical practice in very rare cases [9,11,23,24]. Other markers, like transferrin saturation, serum iron, and total iron binding capacity (TIBC) may not be unfailing indicators of IDA because they are abnormal in the anaemia of chronic disease as well. However, in the absence of inflammatory condition, chronic infection or malignancies, they could be worthwhile additional markers. In case of IDA, level of transferrin saturation and serum iron usually is decreased and TIBC level — increased [9,10,11]. Serum iron concentration and transferrin saturation reflect current iron supply to tissues. Transferrin saturation less than 16 % could be used as a marker for impaired (deficient) erythropoiesis [9,11]. However, if IDA and chronic inflammation, leading to anemia of chronic disease (ACD) coexist, transferrin saturation could be dramatically low [25]. Ferritin borderline value ranges from 12 to 15 mg/l, depending on the employed test method. However, this only applies to patients with no inflammatory diseases. Otherwise, even a higher ferritin concentration can be interpreted as iron deficiency [9,26,27]. Soluble transferrin receptor (sTFR) concentration could be used as a marker in differential diagnosis between patients with solely ACD and combination of IDA and ACD [25,28].

Additional tests for diagnosis of iron deficiency are optional and not very commonly employed. The histochemical method of determining of iron concentration in bone marrow can provide information about body stores of iron. However, this method is rather subjective and very rarely necessary [9,21]. Other possibility is a therapeutic trial of oral or parenteral iron. Nevertheless it depends on compliance and treatment tolerance [9].

Examination

Examination protocol for IDA with unclear aetiology should consist of rather broad spectrum of investigations.

In female patients gynaecological pathologies must first be excluded (gynaecologic bleedings, myoma, etc.).

Urinalysis should be performed in all patients with IDA. Approximately 1 % patients with IDA could have renal tract malignancy (i.e. one-third renal carcinoma patients will have anaemia due to haematuria and hemosiderin deposits in the tumour) Further investigations are necessary only in case of positive haematuria finding [8,9,29].

Celiac disease commonly cause IDA. Serological coeliac disease screening — tissue transglutaminase antibody or endomisial antibody — should be performed in all the patients with IDA and no signs of bleeding [9,30]. Antigliadin antibodies (IgA and IgG) are less reliable due to lower sensitivity and specificity. Due to that fact, they could not be used as a primary test [31]. Biopsy from post bulbar part of duodenum during upper endoscopy in addition to coeliac serology is justified in following cases: 1) patients with a high probability of celiac disease; 2) patients with positive celiac serology (to confirm the diagnosis); 3) patients with negative celiac serology, but with classic (i.e. diarrhea etc.) celiac disease clinical features.

Upper and lower endoscopy is essential for patient (especially postmenopausal female and all male patients) with gastrointestinal blood loss. However, the presence of erosions and even peptic ulcer disease should not be accepted as the reason of IDA until the rest part of the gastrointestinal tract is evaluated properly [9]. It is recommended to take biopsy from terminal ileum during colonoscopy for Crohn's disease screening. Capsule endoscopy and/or enteroscopy could be valuable for detection of small bowel angiodysplasia, Crohn's enteritis, different types of enteropathies and small bowel carcinoma in cases when upper and lower gastrointestinal endoscopy did not reveal a plausible cause of IDA [9,32,33,34,35].

Mesenteric vascular imaging techniques are commonly used in patients with IDA, which are dependent on transfusions for evaluation of vascular malformations or presence of other hidden vascular problems. Usually, these techniques are used, if all the endoscopic modalities (upper and lower endoscopy, capsule endoscopy and/or enteroscopy) were failed to establish the source of bleeding [9]. Other methods of investigation, including liver and kidney functional tests etc., have no diagnostic value with respect to IDA, unless there is a history or indication of systemic disease. Similarly, faecal occult blood test has no diagnostic value in IDA patients due to its low sensitivity and specificity [3,9,36,37,38].

Screening for *Helicobacter pylori* infection should be performed in case of unexplained IDA. Studies show that *Helicobacter pylori* colonisation can decrease iron

absorption and increase the loss of iron, which can potentially cause IDA. Several studies show that *Helicobacter pylori* eradication can improve the condition of patients diagnosed with IDA [9,39,40,41,42,43,44,45,46].

Autoimmune gastritis has been reported as potential cause of IDA in approximately 25 % of patients. However the clinical significance and value of these findings in terms of treatment is relatively low [9,47,48]. As it was mentioned previously, ascorbic acid at a low pH starts the biochemical cascade, which converts nonheme iron into ferrous form. In its turn, ferrous form latter is absorbed in a proximal part of small bowel. Several studies have shown that up to 30 % of patients with IDA have gastric atrophy and therefore do not produce an acid environment that contributes to iron absorption [18,48,49,50,51].

Differential diagnosis

Anaemia of inflammation and chronic disease (also known as anemia of chronic disease (ACD) or "anemia of inflammation"). ACD is determined by a wide variety of diseases (chronic and acute infections, malignancies, inflammatory conditions etc.). This is the second most common iron deficiency anaemia etiologic factor and most common amongst hospitalized patients [15,25,52,53,54]. ACD is usually mild or moderate (with haemoglobin levels 8–9 g/dl), normochromic, normocytic, with decreased serum iron level, normal-low transferrin level with normal or increased ferritin. Latter indicates on retention of iron within the reticular endothelial system and immune system activation. ACD often asymptomatic due to its chronic progression and the dominant symptoms are those of the underlying disease [15]. In case of combination of ACD and IDA, significant reduction of transferrin saturation could be observed [26]. Additionally to the signs of anaemia, there is also an increase in inflammatory mediators. Whilst usually presenting as normochromic and normocytic, in some 20–50 % of cases it also seen as microcytic anaemia. The development of ACD is related to the following:

1. Disorders in erythropoietin homeostasis. Accelerated red blood cells destruction and retarded formation due to decreased erythropoietin levels; [25]
2. Impaired iron metabolism due to increased synthesis of hepcidin. Hepcidin is a small liver acute phase protein, which regulates iron transport and reacts hypoxia and inflammation. Hepcidin inhibits ferriportin function in macrophages and reduces the transfer of iron from the storage pool to developing erythroid precursors in the bone marrow, which in its turn cause precursors to "starve" for iron. Furthermore, hepcidin inhibits iron transfer from the enterocyte to blood stream. As a result, iron molecules become entrapped in the duodenal cells and later — lost, when the cells are sloughed off [15,25,5 0,55,56,57,58,59,60,61];

The diagnosis of ACD often is difficult. Due to the fact that ACD develops in wide range of patients with broad spectrum of acute and chronic illness there is no gold standard for diagnostic test. The co-existance of IDA and ACD should be concerned. However, in case of chronic or acute inflammation, it is rather tricky to establish a correct diagnosis, because ferritin and transferrin are acute phase proteins, which respond to inflammation. In ACD serum ferritin level usually is normal or elevated. Nevertheless in case of combination of IDA and ACD, it is usually lower than 50ng/ml. Soluble transferrin receptors and serum hepcidin level could help in differential diagnosis [25]. In case of isolated ACD, both markers are increased. Nonetheless measurement of hepcidin level still is not approved in clinical practice [25].

Thalassemia

Thalassaemia or thalassaemia syndromes is a group of congenital anaemias. Main defect occurs in the synthesis of globin chain subunit in haemoglobin tetramer [11]. Clinical presentations are various and are based on combination of effects, namely insufficient haemoglobin production and dysbalanced accumulation of globin subunits. Hypochromia and microcytosis develop as a result, causing ineffective erythropoiesis. Thalassemia diagnosis should be ruled out in patients coming from Mediterranean basin and tropical or subtropical regions of Asia and Africa [11].

Therapy

Specific diets should be taken into account with sufficient nutritional iron in the patient's diet always to be established. Some patients, even those non-vegetarians, eat meat on relatively rare occasions and often not beef or liver, but rather poultry meat. In these cases the correct patient history would be determining a correct and effective treatment.

The major goal of therapy is to find out and treat the primary cause of IDA. Otherwise iron substitution with oral or parenteral iron or red blood cell transfusion will have an impermanent effect.

Oral Iron

Currently oral iron drugs are the first line of treatment in IDA. Bivalent iron (Fe2+) drugs are most commonly used due to their good absorption. Tablets must be used 2–3 times per day for a long period of time (usually the course of treatment is at least 5–6 months). This treatment could have many side effects and lower patient compliance (up to 20 %) [11]. Side effects usually are dose related [62]. Clinical effect is usually seen already after 3 weeks, however in some cases it appears only after 9 weeks. Trivalent iron (Fe3+) drugs are less toxic and its tolerability is better; however their absorption by enterocytes (bioavailability) is lower [63]. Sometimes, the overall cost of treatment could exceed the cost of parenteral iron treatment. [64] This treatment option is practical in patients with gastrointestinal diseases when haemoglobin level is not lower than 10 g/dl (due

to increased demand, inadequate dietary intake or absorption and chronic blood loss), as well as during latent iron deficiency [62].

Despite a wide variety of different oral iron drugs being available, only few of these contain the sufficient amount of iron required for the effective treatment of IDA. Special care should be taken with combined iron preparations (for example, iron and folic acid) in order to avoid the overdose of folic acid or other compounds. Recommended dose is 100–200 mg of iron per day (respectively dividing the dose). Calculation of paediatric dose is performed based on the body mass (kg) and usually is 3–6 mg/kg/day [11]. The goal of oral iron treatment is not the level of hemoglobin, but — ferritin level. Latter should reach of at least 50–60 ng/ml to consider discontinuation of the treatment [11,14].

Parenteral Iron

For those, who not responding to oral iron therapy (i.e. malabsorption) or in patients with haemoglobin level lower than 10 g/dl, parenteral iron preparations should be considered.

The risks of this therapy include anaphylactoid reactions and iron overload due to incorrect calculation of the required amount of iron. However, in the last years this treatment option has been improved by newly developed drugs. Earlier, in order to reach the required dose, many intravenous injections were necessary resulting in increased rate of complications. Currently there are two new generation drugs available: iron isomaltoside 1000 and ferumoxytol. These medicines allow reaching the target dose after 1–2 injections. Furthermore, they are associated with a lower allergic reactions risk [65,66,67,68,69].

It should be noted that different intravenous iron preparations have different information on prescribing, administration and safety, due to which prior to and during the use of specific medicines the relevant summary of product characteristics should be referred to.

Red blood cell transfusion

This type of treatment should be administered in emergency cases only, respectively, when IDA progression endangers the life of the patient, as well as after substantial blood loss in order to rapidly reduce the symptoms (i.e. risk of cardiovascular instability) associated with iron deficiency anaemia. Several possible adverse effects of such therapy should be taken into account (including immunological and infection transmission). Furthermore, in order to replenish the sufficient iron reserves in the body, parenteral or oral iron therapy should follow after red blood mass transfusion. Despite the increased risks and high costs associated with this treatment option, blood transfusion still is widely used for IDA treatment around the world. Decrease of red blood cell in patients (especially young men and female) with chronic IDA is usually well tolerated. In those the correct treatment strategy is to use either oral or parenteral iron preparations. However, if the severe IDA goes together with ischemia (myocardial or cerebral), red blood cell transfusion should be started at once [10].

Special Cases and Increased Risk Groups

- **Inflammatory bowel disease (IBD)** (Crohn's disease and ulcerative colitis). IBD is a relatively frequent IDA cause in gastroenterological patients. Moreover, Crohn's enteritis can cause significant iron malabsorption due to inflammation in duodenum and jejunum. According to systematic review made by *Klunigg et al.*, anaemia is found in 6.2 % to 73.7 % of patients with Crohn's disease. Owing to modern treatment strategies this trend has positive dynamics [70]. Thereby, early diagnostic and appropriate treatment of IDA in such patients is a main objective.

  Meta-analysis of 757 publications by *Lee et al.* has convincingly shown the superiority of parenteral iron preparations in patients with IBD in comparison to oral preparations. After using intravenous iron drugs, medium haemoglobin level has increased by 6.8 g/l and ferritin — by 110 μg/l. Furthermore, the authors report better tolerance and higher clinical efficacy of this **this** treatment option [71]. *Nordfjeld et al.* have reported the use of new generation intravenous iron preparation iron isomaltoside 1000 in IBD patients. The study demonstrated high clinical efficacy and safety of the drug even when administered in high doses [72]. *Kulnigg et al.* on the other hand in meta-analysis of intravenous iron in comparison to oral iron preparations for anaemia treatment in Crohn's disease have shown higher efficacy of the earlier. According to their results oral iron therapy provides only short-term results, but up to 21 % of patients are forced to discontinue this treatment due to side effects. Furthermore, a part of studies summarised in this meta-analysis show the relationship between colorectal tumour development and intestinal inflammation in animal models [70]. *Gisbert et al.* reported that timely IDA correction in patients with inflammatory bowel disease improved the quality of life. They reported the safety of oral iron preparations and no deterioration in the progress of IBD. However, intravenous iron preparations had good tolerance and were a safe alternative especially in the event of severe anaemia [73]. *Mamula et al.* reported safe and clinically effective iron dextran use in paediatric patients with IBD and IDA, especially where oral iron preparations were not tolerated or provided no therapeutic result [74]. The study of ulcerative colitis patients treated with intravenous iron saccharate and erythropoietin performed by *Gasche et al.* has shown that isolated treatment with intravenous iron preparations is effective in most patients, and erythropoietin is beneficial only in those patients who failed to respond to isolated intravenous iron therapy [75]. The same authors in the similar study have obtained similar results in patients with Crohn's disease and IDA [76].
- **Other gastroenterological pathologies**

  Hassan in the study where paediatric patients with malabsorption and/or gastro-intestinal bleeding have received ferumoxytol, has shown good clinical

efficacy and tolerability of this drug. However further studies are required in order to confirm these results [77]. Interestingly, two studies demonstrated high efficacy of intravenous iron administration in IDA patients with total parenteral nutrition [78,79].

- **Planned surgery patients.** Timely and efficient iron substitution is important in these patients. In particular this has been shown in patients prior to joint replacement surgery. Iron substitution combined with erythropoietin has been shown effective in these patients [80,81].
- **Pregnant patients.** Mild IDA is commonly diagnosed in pregnant women. Thus, iron substitution should be initiated as soon as iron deficiency is established. Oral iron preparations are the first line of treatment. However, intravenous iron drugs should be considered where oral iron substitution is not effective / not well tolerated by the patient or severe IDA was developed. During *postpartum* period, if the patient has experienced extensive bleeding, intravenous iron preparations have shown the best results. Furthermore, if the woman is planning pregnancy in advance, ferritin level should be determined (the range of 50–60 ng/ml should be considered as a safe value for pregnancy). The level of ferritin should be monitored through the whole period of pregnancy and iron substitution should be considered, if the ferritin level starts to decrease [82,83].
- **Proton pump inhibitors**. Despite some debates in the literature there is no clear evidence that proton pump inhibitors cause IDA in humans [9].
- **Latent iron deficiency without anaemia**. Iron deficiency without anaemia is encountered three times more often than IDA [9]. In the absence of further explanation, one of the valuable options for such patients is to perform capsule endoscopy or/and enteroscopy to evaluate mucosal status of duodenum and jejunum (anatomical areas for iron absorption). If its mucosa is inflamed, it could indicate on a possible cause of latent iron deficiency.

Summary of Recommendations

1. Iron deficiency anaemia is always a secondary disease, which is caused by certain pathologic condition. The major endpoint in case of IDA is to determine the underlying cause. Treatment of the primary disease in case of IDA is essential.
2. All the treatment options for IDA mentioned above are mostly symptomatic. Correct selection of medicine is significant both from clinical efficacy and safety perspectives.
3. Gastrointestinal tract should be evaluated thoroughly in patients with unexplained IDA.
4. The use of parenteral iron preparations in patients with gastrointestinal pathologies is often clinically substantiated for the treatment of IDA.
5. Red blood cell transfusion should be administered in emergency cases only.
6. Patient monitoring strictly according to the guidelines is crucial.

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