УДК 618.3:616.155.194

# Several new concepts in managing iron deficiency anemiain high risk pregnancy cohort

***Iu. Davydova, L. Butenko, A. Limanskaya, A. Ogorodnyk***
**SI «Institute of Pediatrics, Obstetrics and Gynecology National Academy of Medical Sciences of Ukraine»**

**There are represented some new concepts for early diagnostics and treatment options for iron deficiency anemia taking into consideration the issues of pregnancy period and outcome in high risk group cohort.**
***Key words:*** *pregnancy, iron deficiency anemia, diagnostics, treatment.*

The approach for managing the iron deficiency anemia has been changed and some new options appeared during the last three decades. The diagnosis and management of iron deficiency anaemia (IDA) remains a challenge nevertheless the new biomarkers and medications had been suggested [2, 5, 10].

The mechanism of iron absorption is upregulated by iron deficiency and increased erythropoiesis, and downregulated in inflammation and iron repletion, mediated by the recentlyfound regulator of iron homeostasis, hepcidin, which blocks iron release from enterocytes and macrophages, body iron stores are regulated through iron absorption [1, 5, 8].

Commonly, most body iron (2.6 g of 3–4 g) circulates as haemoglobin (Hb), which is recycled when red cells senesce. One gram of iron is stored in the liver, and 0.4 g in myoglobin and cytochromes. Small amounts (3 mg) of iron circulate bound to plasma transferrin. Non-menstruating women lose about 1 mg of body iron per day; menstruating women may lose an additional 1 mg daily on average. Full-term babies are born with 180 mg iron, but must double their red cell mass within 12 months (low birth weight infants need to more than double their red cell mass). The requirements of iron escalate rapidly during adolescence with increasing blood volume and lean body mass, compounded in females by the onset of menstruation, and in pregnancy by increases in maternal red cell mass and fetal erythropoiesis [1, 3, 4, 7]. All this indicates the additional attention for IDA detection in these groups because of the negative influence of iron deficiency on female reproductive health and pregnancy outcomes.

It is important to emphasize that IDA is associated with impaired cognitive development in preschool-aged children and diminished work productivity and cognitive and behavioural problems in adults.

As to pregnant women, IDA has been associated with increased risks of low birth weight, preterm birth and maternal morbidity (post partum depression, inflammatory complications). The non-anaemic tissue iron deficiency may cause impairment in both adults and children. What is important for high risk pregnancy patients, that in a recent randomised trial, patients with heart failure and iron deficiency (both with and without anaemia) treated with intravenous (IV) iron carboxymaltose experienced improvements in symptoms, functional capacity and quality of life, independent of Hb concentrations [6, 11].

During last two decades it was suggested the new options in IDA detection and treatment as the division on functional and absolute iron deficiency.

Thus, functional iron deficiency (FID) is considered as a state in which there isinsufficient iron incorporation into erythroid precursors in the face of apparently adequate body iron stores, as defined by the presence of stainable iron in the bone marrow together with aserum ferritin value within normal limits. So, this definition could encompass the partial block in iron transport to the erythroid marrow seen in patients with infectious, inflammatory diseases and cancer, andis a major component of the anaemia of chronic disease (ACD) [1–3].

FID may also lead to anaemia in patients with inflammatory diseases such as rheumatoid arthritis [2, 4].

In clinic for high risk pregnancy the main attention should be paid to the one form of FID, stated in some patients treated with erythropoiesis-stimulating agents (ESAs), especially in patients with chronic kidney disease (CKD).

There are represented the conditions, which are commonly linked with ESA treatment:

– significant increasein RBC production, Hb, and Hct due to ESA;

– iron uptake by erythroid cells isincreased to meet demand of increased RBC production;

– reticuloendothelial cells are unable to release stores of iron fast enough to meet demand;

– despite adequate levels of stored iron (ferritin), insufficient iron is available for epoetin-stimulated RBC production

– further iron deficiency erythropoiesis develops; the RBCs produced are small and have low Hb content;

– iron deficiency limits the response to epoetin therapy, and higher doses of epoetin are required to reach target Hb and Hct levels [2, 4].

The laboratory values used for differentiation between functional and absolute iron deficiency are represented in table 1.

The «Guide line for the laboratory diagnosis of functional iron deficiency» (2013, United Kingdom) contains there commendation for the proper assessment of iron stores [8].

The main biomarker for iron stores evaluation is serum ferritin. The serum ferritin assay is considered as an essential in the assessment and management of patients with all forms of iron-restricted erythropoiesis (IRE) including FID. Values <12 μg/l indicate absent iron stores.The values as high as 1200 μg/l in CKD patients may testify for the possibility of FID and some

*Table 1*

| Parameter | Functional Iron Deficiency | Absolute Iron Deficiency |
|---|---|---|
| Hb | v | v |
| Ferritin | Normal/^ | v |
| TSAT | v | v |

*Table 2*

**Laboratorybloodtest used toassessironstatus**

| Diagnosis | Hemoglobin | Meancellvolum eandmeancell-hemoglobin | Serumferritin µg/L | Transferrinor totalironbind-ingcapacity | Transferrins aturation (TSAT) | Solubletrans ferrinrecep-tor (sTfR) | Seru-miron |
|---|---|---|---|---|---|---|---|
| Tissueirondefi ciencywith-outanaemia | Normal | Normalorlow | < 15-30 | Normalorhigh | Low-nor-malorlow | High-nor-malorhigh | Low |
| Irondeficiency anaemia (IDA) | Low | Low (ornormalin-early IDA) | < 15-30 | High | Low | High | Low |
| Anaemiaofchr onicdisease-orinflamma-tion (ACD) | Low | Normal (maybe-mildlylow) | Normaloreleva ted (elevated-ferritindoes-notimplyele-vatediron-stores) | Normal | Low | Normal | Low |
| IDA withcoex-istentchron-icdiseaseorin-flammation | Low | Low | Lowornormal, butusually< 60-100 µg/L | Normalorhigh | Low | High | Low |
| Ironoverload | Normal | Normal | Elevated (cor-relateswith-bodyiron-stores) | Normaltolow | High | Normal | Normalto elevated |

such patients may benefit from intravenous iron therapy. No recommendation as to the highest serum ferritin concentration beyond which it is unsafe to give a trial of intravenous iron therapy can be given. A serum ferritin concentration <100 µg/l in nondialysed patients or <200 µg/l in chronic haemodialysis patients is associated with a high likelihood of iron deficiency and testify for a potentially good response to intravenous iron therapy. The values above the suggested cut-offs should not be used to implement iron therapy. The serum ferritin values >1200 µg/l should be used to decide whether investigation of potential iron overload should be undertaken. It was stated that the serum ferritin concentration is not useful in predicting ESA responsiveness in cancer-related anaemia [8].

It is worth saying that ferritin is an acute-phase protein and is elevated in cases of inflammation, infection, liver disease and cancer. This can result in elevated ferritin levels in iron-deficient patients with coexisting systemic illness [1–3].

As to the soluble transferrin receptor (sTfR) biomarker it is considered like relatively expensive, not widely available, and is not used for the external quality assessment (EQA) in the UK. An International Standard may improve assay standardization. The treatment of renal anaemia with ESAs, which increase sTfR, is a complicating factor. The assay may have a role, either alone or in combination with the ferritin assay, if automated measures such as %HRC, CHr or Ret-He are unavailable. The soluble transferrin receptor (sTfR) concentration is elevated in tissue iron deficiency and not sensitive to inflammation; the sTfR/log ferritin ratio is highly correlated with body iron stores [8].

The serum iron, total iron-binding capacity (TIBC) and transferrin saturation (TSat) are not recommended as a predictors of responsiveness to intravenous iron therapy in patients with CKD. TSAT may be used to monitor response to ESA and/or iron therapy in CKD. If used with either the serum ferritin concentration or measurement such as % HRC and CHr it may be useful in the diagnosis of FID [2, 8].

The approach for the evaluation of different variants of IDA are represented in table 2.

If there is no effect of the routine treatment of IDA in pregnant from high risk group it is necessary to pay attention to the following reasons [6, 9–11]:

**Inadequate iron intake:**

• *Patient not taking oral iron therapy*

• *Patient taking an iron supplement or multivitamin tablet with insufficient iron content (multivitamin tablets should not be recommended for IDA treatment due to low iron content)*

**Inadequate iron absorption:**

• *Concomitant consumption of inhibitors of iron absorption (eg, tea, calcium, antacids, tetracycline, within 2 hours of iron ingestion)*

• *Coexisting inflammation with functional iron deficiency*

• *Intestinal mucosal disorders (coeliac disease, inflammatory bowel disease)*

• *Impaired gastric acid secretion (including use of proton pump inhibitors)*

• *Gastric/intestinal bypass procedures*

• *Helicobacter pylori* colonisation

• *Controlled-release iron formulations may contribute (potential for limited iron absorption in some patients)*

**Ongoing iron losses or need in excess of dose absorbed:**

• *Occult, undiagnosed or recurrent gastrointestinal blood loss (peptic ulcer, cancer, angiodysplasia, small bowel lesion, parasites)*

• *Other source of recurrent blood loss (inherited bleeding disorder such as von Willebrand disorder)*

• *Multiple sources of recurrent blood loss (hereditary haemorrhagic telangiectasia)*

• *Ongoing urinary iron losses (significant valve haemolysis)*

• *Renal failure responding to ESAs*

**Coexisting condition interfering with bone marrow response:**

• *Superimposed infection, inflammation,cancer or renal failure*

• *Concomitant B12 or folate deficiency*

• *Coexisting primary bone marrow disease or suppression*

**Incorrect diagnosis or more than one cause of anaemia:**

• *ACD or renal failure*

• *Haemoglobinopathy*

• *Other causes of anaemia ( haemolysis, myelodysplastic syndromes, congenital anaemia, endocrine disorders)*

In cases of ineffective IDA treatment by oral iron medications there three main options: to reassess the IDA diagnosis considerably to the abovementioned issues; to change the ionic iron medication (non-organic salt) to the non-ionic (iron polymaltose); to consider the intravenous (IV) iron medications in case of revealing the specific indications [6, 9].

**IV iron should be considered in patients with confirmed IDA and one or more of the following**:

• *Significant intolerance, non-compliance or lack of efficacy with oral iron, despite modification of dose, timing and frequency;*

• *Pregnancy (beyond the first trimester) and postpartum, for the above reasons or to avoid imminent decompensation/transfusion* ***(especially in women who present late and/or display severe anaemia);***

• *Intestinal malabsorption (inflammatory bowel disease);*

• *Ongoing iron (ie, blood) losses that exceed absorptive capacity;*

• *A clinical need for a rapid iron supply (in patients where optimisation of erythroid response is important to prevent physiological decompensation/ transfusion);*

• *Chronic renal impairment receiving concomitant ESA therapy.*

## Новые концепции в лечении железодефицитной анемии в группе беременных высокого риска

***Ю. Давыдова, Л. Бутенко, А. Лиманская, А. Огородник***

В статье представлены новые подходы к ранней диагностике и лечению железодефицитной анемии, принимая во внимание аспекты течения и исходов беременности в группе беременных высокого риска.
***Ключевые слова:*** *беременность, железодефицитная анемия, диагностика, лечение.*

## Нові концепції в лікуванні залізодефіцитної анемії в групі вагітних високого ризику

***Ю. Давидова, Л. Бутенко, А. Лиманская, А. Огородник***

У статті представлено нові підходи до ранньої діагностики та лікування залізодефіцитної анемії, беручи до уваги аспекти перебігу та наслідків вагітності в групі вагітних високого ризику.
***Ключові слова:*** *вагітність, залізодефіцитна анемія, діагностика, лікування.*

### Сведения об авторах

**Давидова Юлия Владимировна** – ГУ «Институт педиатрии, акушерства и гинекологии Национальной академии медицинских наук Украины», 04050, г. Киев, ул. Платона Майбороды, 8. E-mail: juliadavyd@mail.ru

**Бутенко Людмила Петровна** – ГУ «Институт педиатрии, акушерства и гинекологии Национальной академии медицинских наук Украины», 04050, г. Киев, ул. Платона Майбороды, 8

**Лиманская Алиса Юрьевна** – ГУ «Институт педиатрии, акушерства и гинекологии Национальной академии медицинских наук Украины», 04050, г. Киев, ул. Платона Майбороды, 8

**Огородник Артем Александрович** – ГУ «Институт педиатрии, акушерства и гинекологии Национальной академии медицинских наук Украины», 04050, г. Киев, ул. Платона Майбороды, 8

### LITERATURE

1. Beutler E. Disorders of iron metabolism. In: Lichtman MA, Williams WJ, Beutler E, et al, editors. Williams hematology. 7th ed. New York: McGraw-Hill Medical, 2006: 511–553.
2. Coyne D.W. Hepcidin: clinical utility as a diagnostic tool and therapeutic target. Kidney International, 2011: 80, 240–244.
3. Department of General Medicine, Royal Children's Hospital. Oral iron preparations – iron supplementation. Melbourne: Department of General Medicine, Royal Children's Hospital, 2009.
4. Goodnough L.T., Nemeth E., Ganz T. Detection, evaluation and management of ironrestricted erythropoiesis. Blood, 2011 (116), 4754–4761.
5. Murray-Kolb L.E., Beard J.L. Iron treatment normalizes cognitive functioning in young women. Am J Clin Nutr 2007; 85: 778–787.
6. Sant-Rayn P., Flecknoe-Brown S., Allen K., Gibson P., et al. Diagnosis and management of iron deficiency anaemia: a clinical update. Med J Aust 2010; 193 (9): 525–532.
7. Sachdev H., Gera T., Nestel P. Effect of iron supplementation on mental and motor development in children: systematic review of randomised controlled trials. Public Health Nutr 2005; 8: 117–132.
8. Thomas D.W., Hinchliffe R.F., Briggs C., Macdougall I.C., Littlewood T., Cavill I., British Committee for Standards in Haematology. Guideline for the laboratory diagnosis of functional iron deficiency. Br J Haematol. 2013 Jun;161(5):639–48.
9. West A.R., Oates P.S. Mechanisms of heme iron absorption: current questions and controversies. World J Gastroenterol 2008; 14: 4101–4110.
10. World Health Organization. United Nations Children's Fund. United Nations University. Iron deficiency anaemia: assessment, prevention, and control. A guide for programme managers. Geneva: WHO, 2001.
11. Zhou S.J., Gibson R.A., Crowther C.A., et al. Should we lower the dose of iron when treating anaemia in pregnancy? A randomized dose-response trial. Eur J Clin Nutr 2009; 63: 183–190.

*Статья поступила в редакцию 19.03.2015*