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IRON IN MEDICINE AND TREATMENT

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Abstract

Being a component of many proteins and enzymes, iron is an essential microelement for humans. However, this element can also be toxic when present in excess because of its ability to generate reactive oxygen species. This dual nature imposes a strict regulation mechanism of the iron concentration in the body. In humans, systemic iron homeostasis is mainly regulated on the level of intestinal absorption. A patient diagnosed with excess iron in the body should be treated safely and effectively. And the therapy should be consistent with the treatment of concurrent diseases.

On the other hand, iron deficiency is one of the most common disorders affecting humans. Iron-deficiency anaemia continues to represent a major public health problem worldwide, being prevalent among pregnant women, where it represents an important risk factor for maternal and infant health.

A problem detecetd relatively recently and therefore not fully clarified yet is the iron therapy in patients with restless legs syndrome (RLS). RLS is a common neurological condition defined clinically as the urge to move the legs. Reduced brain iron is strongly associated with restless legs syndrome. RLS can also be a consequence of iron deficiency in the body.

This review will focus on iron as an element whose abnormal metabolism or deficiency in the body can lead to diseases e.g. anaemia, restless legs syndrome and iron overload. Here we will describe methods of therapy, paying particular attention to the types and dosages of medications.

Key words: iron deficiency, anaemia, iron overload, restless legs syndrome, pregnancy.

ŻELAZO W MEDYCYNIE I LECZNICTWIE

Abstrakt

Żelazo jest podstawowym mikroelementem organizmu ludzkiego, stanowi bowiem istotny element wielu białek i enzymów. Jednak pierwiastek ten może wykazywać działanie toksyczne, gdy występuje w nadmiarze, ze względu na jego zdolność do generowania reaktywnych form tlenu. Ten podwójny charakter żelaza narzuca ścisłą regulację stężenia żelaza w organizmie. U ludzi homeostaza ustrojowa żelaza jest głównie regulowana na poziomie wchłaniania jelitowego. Pacjent, u którego zdiagnozowano nadmiar żelaza w organizmie, powinien być poddany bezpiecznemu i skutecznemu leczeniu, które jest zgodne z terapią współistniejących schorzeń.

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Niedobór żelaza jest jednym z najczęstszych zaburzeń dotykających ludzi. Niedokrwistość spowodowana niedoborem żelaza nadal stanowi istotny problem zdrowia publicznego na całym świecie. Szczególnie dotyczy kobiet w ciąży, stanowiąc istotny czynnik ryzyka dla zdrowia matki i dziecka.

Stosunkowo nowym i nie do końca wyjaśnionym zagadnieniem jest terapia żelazem chorych na zespół niespokojnych nóg (RLS). Jest to stan neurologiczny klinicznie określany jako przymus poruszania nogami. Z zespołem niespokojnych nóg związana jest ściśle redukcja żelaza w mózgu. RLS może być również konsekwencją niedoboru żelaza w organizmie.

W pracy omówiono nieprawidłowy metabolizm żelaza lub jego brak w organizmie, co może prowadzić do ww. jednostek chorobowych. Opisano również metody terapii, zwracając szczególną uwagę na rodzaj i wielkość dawki proponowanych leków.

Słowa kluczowe: niedobór żelaza, niedokrwistość, nadmiar żelaza, zespół niespokojnych nóg, ciąża.

IRON METABOLISM

Iron is an essential component of the human body. It is used for synthesis of haemoglobin, muscle myoglobin and enzymes. The iron daily requirements range from 1 mg to 3 mg. The requirements are met with the daily dietary intake of 12-15 mg. (Heeney et al. 2004). Under normal conditions, approximately 1-2 mg of iron per day enters the body *via* the enterocytes of the proximal small intestine. Absorption of nearly all dietary iron takes place in the proximal duodenum and includes the following steps:

1) reduction of iron from the ferric state (III) to the ferrous state (II) – this happens in the presence of ascorbic acid, cysteine and glutathione;
2) apical uptake by enterocytes followed by transcellular trafficking;
3) basolateral efflux by the ferrous iron transporter ferroportin (FPN) (Camaschella, Strati 2010).

Newly absorbed iron is released into the circulation and binds to the serum protein transferrin. Most absorbed iron is transported in the bloodstream bound to the glycoprotein transferrin. Transferrin is a carrier protein that plays a role in regulating the transport of iron from the site of absorption to virtually all tissues. The proper level of serum transferrin is 20-120 μg l^{-1} for women and 30-300 μg l^{-1} for men. Transferrin binds only two iron atoms. Normally, 20-45% of transferrin binding sites are filled. Approximately 3 mg of iron circulates bound to transferrin. Transferrin-bound iron is taken up by cells by transferrin receptor 1 (TfR1)-mediated endocytosis. Most of the transferrin-bound iron in the circulation is destined for developing erythrocytes of the bone marrow, where it is taken up at a rate of approximately 21 mg of iron per day, and used in the production of haemoglobin. About 65–70% of body iron exists in this form in circulating red blood cells. Old or damaged red blood cells are removed from the circulation by the macrophages of the reticuloendothelial (RE) system, where iron is released from haemoglobin and either stored in the intracellular iron storage protein ferritin, or released back into the circulation as transferrin-bound iron. The

cells of the RE system release about 21 mg of iron per day, thus replacing the amount taken up by the bone marrow (Anderson et al. 2007).

The main systemic regulator of iron absorption and macrophage release is hepcidin. This 25 amino acid liver peptide negatively interacts with and degrades ferroportin in response to iron overload and inflammation. In this way, iron absorption and macrophage release are blocked to reduce circulating iron (Camaschella, Strati 2010).

Approximately 10–15% of body iron is present in such proteins, with up to 80% of this element found in muscle cell myoglobin. The remaining 20% of body iron is present as storage iron, predominantly located in the macrophages of the RE system and the hepatocytes of the liver (Anderson et al. 2007). The liver is a major storage organ of iron, in which excess iron is stored as ferritin and hemosiderin (Kahgo et al. 2008)

The iron turnover is extremely limited. Iron metabolism occurs largely in a closed system, because the losses are small. Under physiological conditions, the daily turnover of iron is 35 mg, meanning that this amount of iron leaves plasma: 32 mg leaves the pool of erythropoietic iron, 1 mg of iron is lost in urine, sweat, bile, exfoliating the epidermis and intestinal epithelium, 1 mg of iron is incorporated into myoglobin and heme enzymes. Simultaneously, 35 mg of iron returns to the plasma during the day: 21 mg of iron from the erythrocytes which broke up, 11 mg comes from erythropoietic iron pool, 1 mg comes from the extravascular space, 1 mg comes from storage and 1 mg is absorbed from the gastrointestinal tract (Pasternak 2000)

The proper concentration of iron in the blood plasma is 12.5-26.6 µmol l^{-1}. Under physiological conditions, normal parameters for iron excretion from the body are: 3.58 μmol^{-1}day for urine and 17.9 μmol^{-1} day^{-1} for stool (Pasternak 2000).

TREATMENT OF IRON DEFICIENCY

Iron deficiency is one of the most common disorders affecting approximately 2 billion people all over the world. Iron-deficiency anaemia represents a major public health problem worldwide. It is especially common among women of childbearing age because of pregnancy and menstrual blood loss. Another groups of patients include those with other sources of blood loss, malnutrition, or gut malabsorption (Alleyne et al. 2009).

Alleyne et al. (2009) classified the causes of iron deficiency anaemia into 4 different categories related to the consumption or loss of iron. This classification is presented in Table 1. In the majority of cases, iron-deficiency causes anemia is avoidable and reversible by increasing iron supplementation or reducing iron loss (Alleyne et al 2009).

Iron absorption is a reliable process. Under normal conditions, the loss of 1 mg of iron through the microbleeding or sloughing of intestinal epithelial

Table 1

Causes of iron deficiency in adults

Causes	Examples
Increased iron loss	acute hemorrhage alimentary respiratory urinogenital dermal chronic or occult hemorrhage menstruation inflammatory cancer hemolysis blood donation
Decreased iron in diet	vegetarian diet malnutrition dementia psychiatric illness
Decreased iron absorption	antacid therapy or high gastric pH celiac disease inflammatory bowel disease partial gastrectomy
Increased iron requirements	pregnancy lactation

cells is precisely balanced by the absorption of the same amount. Importantly, iron absorption can increase severalfold after iron depletion. However, when the absorptive capacity of the small intestine (which increases to a maximum of 2-4 times above normal) is exceeded by iron loss over a prolonged period of time, the result is iron deficiency anaemia. The fact that iron deficiency anaemia occurs only after depletion of total iron contained in the body is also relevant (Rimon et al. 2006).

Iron therapy is recommended to nearly all patients with anaemia caused by iron deficiency. Iron is available in many different doses and formulations and there are various ways of its administration. Various iron preparations are available in the forms of tablets, capsules, drops, and syrups in different dose sizes. Slow release iron reduces the side effects of iron therapy. Iron salts such as sulphate, gluconate, lactate, fumarate and succinate are absorbed to about the same extent. Iron carbonate, phosphate and citrate are poorly absorbed. Iron preparations generally contain 1 of 3 iron salts (Beutler 2006). The amount of elemental iron available in different formulations varies greatly, e.g. ferrous sulphate involves 20% elemental iron, i.e. a 325 mg tablet contains about 65 mg of elemental iron. The recommended daily dose of elemental iron for adults suffering from iron deficiency ranges from 150 to 200 mg. This approach entails prescribing 1 ferrous sulphate tablet three times daily because each tablet contains approximately 60 mg of elemental iron (Alleyne et al. 2009).

The recommended daily dose of elemental iron for patients with iron deficiency anaemia ranges from 120 mg to 200 mg. Oral iron preparations are best taken on an empty stomach or between meals to increase absorption. If patients suffer from symptoms from the gastrointestinal tract, the formulations may be administered after a meal, though it may reduce its absorption. There are multiple variables that may enhance or inhibit the absorption of iron. Differences in absorption are caused by the requirement of acidity in the duodenum and upper jejunum for iron solubility. For iron released beyond these sites, the alkaline environment reduces absorption. The products inhibiting iron absorption are coffee, tea, milk, cereals, dietary fiber, multivitamin or dietary supplements containing calcium, zinc, manganese, or copper, antacids, H2 blockers, and proton pump inhibitors, quinolones and tetracycline antibiotics. The products facilitating iron absorption include vitamin C, acidic foods, eg, tomato sauce, nonenteric, coated iron tablets, fasting ingestion of iron supplements (Alleyne et al. 2009).

The second important issue is administration of this element to patients with iron deficiency anaemia for a longer period of time. Typically, therapy should take 2-3 months for haemoglobin to return to normal levels. However, in patients with anaemia, iron levels in the body are low and should be supplemented. Iron supplementation usually requires 4-6 months (Rimon et al. 2006).

Iron is most often given orally, although for those with serious absorptive abnormalities, it can be administered intravenously (Rimon et al. 2006). The role of intravenous iron in clinical medicine is poorly understood and underused in the treatment of iron deficiency and anaemia in chronic diseases. Iron administered parenterally was considered dangerous and used only in extreme situations, or when oral iron was not tolerated. It was mainly based on poorly characterized anaphylactic reaction to the high-molecular-weight dextran preparation (Imferon), which was the only formulation available for intravenous administration. It is now known that intravenous iron, as opposed to oral iron, increases erythropoiesis in dialysis patients, therefore it is routinely used (Auerbach et al. 2007).

Currently, four parenteral iron preparations are available: low-molecular -weight iron dextran, iron saccharate, ferric glucontate and high-molecular -weight iron dextran. The most serious adverse events have been associated with the high-molecular-weight iron dextran (Imferon, which is no longer available and the current preparation, Dexferrum) and are rare (<1:200 000) with low-molecular-weight iron dextran or the two iron salts: gluconate and citrate (Chertow et al. 2004, 2006). A single infusion of the total dose of low-molecular-weight iron dextran is most convenient and cost effective in patients with uncomplicated iron deficiency. The replacement dose is calculated, diluted in normal saline and infused over 4 hours. The dose, in mg of iron, is calculated as follows:

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$$D_{Fe} = 0{,}136 \cdot m \cdot \left[\left(\frac{C_{Hb} \cdot 100}{14{,}8} \right) - 100 \right],$$

where:

m – body weight (kg),

C_{Hb} – haemoglobin concentration (g dL^{-1}).

An intravenous test dose of 25 mg of the diluted solution is required. If no adverse events occur within 1 h, the remaining solution can be administered. The administration of methylprednisolone before the test and after the infusion decreases the incidence of myalgias and arthralgias. The total intravenous dose is most appropriate for iron deficiency because of pregnancy, menometrorrhagia, surgical blood loss, and gastric bypass and for those patients with uncomplicated iron deficiency who are non-compliant with or intolerant of oral iron (Rimon et al. 2006).

Unfortunately, one of the main problems in the iron treatment is a reaction from the digestive system. The reported side effects include abdominal pain, nausea, vomiting, abdominal pain, diarrhoea and constipation. These ailments can cause a decrease in food intake. Abdominal discomfort, nausea, vomiting, changes in bowel movements, black stools are much more common in patients taking large doses of iron (150 mg elemental iron).

This problem can be eliminated by administering smaller doses of iron for an extended period of time. Rimon et al (2005) argue that this type of therapy is equally effective. Moreover, they speculate that low doses of iron can replace the commonly used higher doses (Rimon et al. 2005).

Another important question concerns controlled release of iron from the preparation. Controlled-release formulations were given for several, large groups of patients and their actions were compared with that of ferrous sulphate. The findings demonstrated fewer side effects in patients receiving controlled-release formulations of iron. However, there is a theoretical contraindication for the use of controlled-release iron preparations. It is associated with the place of iron absorption - iron is absorbed in the early parts of the duodenum and not in the final one, where it is released from sustained-release preparations (Alleyne et al. 2009).

IRON THERAPY IN RESTLESS LEGS SYNDROME

Restless legs syndrome (RLS) is a common neurological condition clinically defined by an urge to move the legs, improvement during movement, worsening while at rest, and worsening in the evening and night (Allen 2003). Reduced brain iron is strongly associated with restless legs syndrome (RLS). The most consistent pathologic finding in RLS is reduced brain iron and alterations in iron related proteins (Connor et al. 2003, 2008).

RLS is also considered to be a consequence of systemic iron deficiency (Allen 2003).

Recent research suggests that the underlying pathophysiology of RLS involves the central nervous system iron homeostatic deregulation. Cerebrospinal fluid ferritin is lower in RLS cases, and imaging studies show reduced iron stores in the striatum and red nucleus. Most importantly, pathologic data in RLS-autopsied brains show reduced ferritin staining, iron staining, and increased transferrin stains, but also show reduced transferrin receptors. No pathology aside from iron abnormalities has been identified. It is important to find the reduced transferrin receptor, because globally reduced iron stores would normally upregulate transferrin receptors. Therefore, it appears that primary RLS has reduced intracellular iron indices secondary to a perturbation of homeostatic mechanisms that regulate iron influx and/or efflux from the cell (Ondo 2005).

The mechanisms by which low intracellular iron subsequently manifests RLS symptomatology are not well understood. Dopaminergic systems are strongly implicated in RLS. Dopamine agonists (DA) most robustly treat RLS symptoms, and dopaminergic functional brain imaging studies inconsistently show modest abnormalities. There are several potential interactions between iron and dopamine systems:

- iron is a cofactor for tyrosine-hydroxylase, which is the rate-limiting step in the production of dopamine,
- iron is a component of the dopamine type-2 (D2) receptor,
- iron is necessary for Thy1 protein regulation.

Thy1 regulates vesicular release of monoamines, including dopamine. It also stabilizes synapses and suppresses dendritic growth. This hypothesis, therefore, states that both presynaptic and postsynaptic dopaminergic anatomy is intact, but the actual junction itself is dysfunction. This is most consistent with the functional imaging studies and clinical responses seen in RLS patients (Ondo 2005).

The first study on oral iron therapy in patients diagnosed with RLS was conducted in 1994 by O'Keeffe et al. (1994). They divided the patients into three groups based on serum ferritin levels: the ferritin level <18 mcg L^{-1} (1 mcg L^{-1} = 1 µg L^{-1}), ferritin between 18 and 45 mcg L^{-1} and ferritin between 45 and 100 mcg L^{-1}. All patients (15 persons) were treated for 2 months; a single dose of ferrous sulphate was 200 mg administrated 3 times a day. The greatest benefits were reported in patients with the lowest concentration of serum ferritin (<18 mcg L^{-1}) (O'Keeffe et al. 1994). Davis et al. (2000) conducted further studies using a randomized, double-blind study protocol. The authors found no benefit of treatment with iron (Davis et al. 2000). The issues that complicated Davis and co-authors' study was related to the kinetics of iron absorption from the gastrointestinal tract. An iron absorption curve is exponential, characterized by very high absorption of iron in the lower limit of serum ferritin (<18 mcg L^{-1}). Poor absorption of iron is observed at a concentration of ferritin above 100 mcg L^{-1}.

The percentage of iron absorbed is probably less than 1-2% in patients with ferritin level in serum >100 mcg L^{-1}. Therefore, oral administration of iron in patients with RLS and with high ferritin levels (as was the case in the study by Davis et al.) requires very high doses of iron and long-term (6-12 months) treatment (Earley 2009).

Oral iron supplements are commonly recommended for RLS but are largely ineffective due to poor absorption and poor tolerability at required doses. Controlled trials of oral iron for RLS in subjects with normal serum iron indices did not show efficacy, nor did it increase serum iron level (Wang 2009). Intravenous iron dextran has been shown to increase brain iron content. Surprisingly, only a few reports have ever presented data on the clinical effect of high dose intravenous iron for RLS (Ondo 2010). However, high molecular weight iron dextran has higher rates of anaphylaxis compared to iron sucrose or sodium ferric gluconate (Chertow 2006). A low molecular iron dextran reduces the risk of anaphylaxis, but there is no data presenting its efficacy in patients with RLS. All intravenous preparations are able to increase serum iron; however, iron dextran is retained longer by macrophages compared with other preparations, which can be important, as theoretically iron therapy for RLS presumably requires the CNS (central nervous system) iron accumulation, which might take days rather than the shorter time allowed by other iron preparations. Patients usually report a delay of at least three days before observing any benefit, which would also suggest that iron requires extended transport into the brain. Iron access to the brain is extensively regulated and not completely understood (Connor 2008). It may require a large serum iron overload extended over a period of time to shunt iron into the brain, which might not be achieved with oral iron or other intravenous iron preparations. Iron dextran has been proven to increase brain iron based on imaging studies (Earley et al. 2003).

IRON OVERLOAD

Iron overload can occur in various diseases, including hereditary haemochromatosis, thalassaemia, sickle cell disease, myelodysplastic syndromes (MDS), and some rare anaemias. In these conditions, increased iron absorption and/or transfusional loading can lead to iron accumulation in the key organs, which may result in iron-toxicity-related organ damage, as well as increased morbidity and mortality. Iron overload is characterized by excessive iron deposition and subsequent injury and dysfunction of the heart, liver, anterior pituitary, pancreas and joints, and induces damage in the central nervous system (Barton 2007).

The main cause of this organ damage is due to the overproduction of ROS (reactive oxygen species) in the presence of excess iron. The production of ROS by iron is mainly through the Fenton reaction, which eventually

forms hydroxyl radicals from superoxide or hydrogen peroxide (Crichton et al. 2002). Among ROS, the hydroxyl radical is the most toxic fraction and it targets carbohydrate, protein, and nucleic acids. It is known that the reaction of hydroxyl radicals with the nucleic acid base 8-hydroxyguanine is highly correlated with teratogenicity and carcinogenicity by oxidative stresses (Kohgo et al. 2008).

Another powerful ROS showing similar reactivity as the hydroxyl radical is lipid hydroxyl-peroxide: ROOH. In iron overload, lipid peroxidative products such as malondialdehyde and 4-hydroxy-2-nonenal are increased, which form the radicals ROO-(alkyl oxyradical) and RO-(alkoxyradical). These lipid-based radicals possess longer half lives than hydroxyl radicals, and also have a stronger capacity for chronic cell toxicity and DNA damage (Kohgo et al. 2008).

Pathological conditions representing body iron overload are designated as iron overload syndromes. Iron overload syndromes are classified as genetic or secondary (Kohgo et al. 2008). Hereditary haemochromatosis is the most common genetic disorder (Yen et al. 2006), and its clinical manifestation is systemic iron deposition mainly in the liver, heart, brain and endocrine organs. Damage to these organs is considered to be a result of tissue injuries by iron-induced oxidative stresses (Pietrangelo 2007). In 1996, the causative gene was identified as HFE (human hemochromatosis protein) in the human chromosome 6 (Feder et al. 1996), and approximately 85% of patients with hereditary haemochromatosis have a homologous mutation of C282Y in their HFE gene. Thereafter, other genes such as hemojuvelin (HJV), TfR2, ferroportin, and hepcidin (HAMP) gene were identified (Franchini 2006).

Iron overload is commonly observed as a secondary condition. The most common condition occurs in patients who require long-term blood transfusions due to severe anaemias. This condition includes genetic disorders such as thalassaemia and SCD (sickle cell disease), and anaemia refractory to conventional treatments. In these patients, ineffective erythropoiesis and continuous accumulation of exogenous iron by transfusion are considered to be responsible for the iron overload. The resulting organ failures such as liver failure, cardiac failure, and severe diabetes mellitus affect patients' outcome (Andrews 1999). In addition to these classical conditions, there are many diseases that show mild iron deposition or deregulation of body iron distribution. Such conditions include chronic hepatitis C, alcoholic liver disease, non-alcoholic steatohepatitis, and insulin resistance, and iron is an important cofactor that modifies these disease conditions (Kohgo et al. 2008).

Since physiologic mechanisms to excrete iron are very limited, patients with iron overload and its complications need safe, effective therapy that is compatible with their coexisting medical conditions. Three licensed iron chelation drugs: one parenteral, two oral ones, are used in the treatment of iron overload (Barton 2007). Deferoxamine (DFO) is a hexadentate siderophore derived from Streptomyces pilosus. It is a chelating drug with high affinity for iron and aluminum ions. The drug is not absorbed from the gastrointesti-

nal tract. Biological half-life in the first phase is approximately one hour, in the second phase - 6 hours. Since the half-life of DFO is very short, standard treatment involves a stringent infusion routine, which is necessary for optimal iron chelation and excretion. It is most commonly used orally in concentrations of 5-10%. Subcutaneous or intramuscular injections are performed in the doses dependent on patients` condition. Lack of patient compliance and physician dissatisfaction are major impediments to successful DFO therapy (Barton 2007).

Deferiprone (DFP; 1,2 dimethyl-3-hydroxypyrid-4-one) is an orally administered bidentate iron chelator. The drug is used to treat iron overload in patients with ß-thalassaemia, mainly when DFO is contraindicated or inadequate (Liu et al. 2002), Clinical studies have shown that a dose of 25 mg kg^{-1} body weight, administered three times a day, reduces the concentration of iron in the blood and prevents its deposition in tissues. However, the drug does not protect against damage to internal organs caused by high levels of iron. Studies have demonstrated that deferiprone, in recommended doses, is less effective than deferoxamine. DFP traverses cell membranes more readily than DFO. A standard dose of DFP is approximately equivalent to a standard dose of DFO, measured by urinary iron excretion (Wanless et al. 2002).

Deferasirox (4-[3,5-bis(2-hydroxyphenyl)-1,2,4-triazol-1-yl] benzoic acid) is an orally administered tridentate iron chelator that is indicated for the treatment of transfusion iron overload in patients over 2 years. Its main use is to reduce chronic iron overload in patients who are receiving long-term blood transfusions for conditions such as β-thalassaemia and other chronic anemias. The half-life of deferasirox is between 8 and 16 hours. This allows the administration of this drug once a day. Two molecules of deferasirox are capable of binding to 1 ion of iron, which is subsequently eliminated by faecal excretion. Its low molecular weight and high lipophilicity allows the drug to be taken orally. Together with deferiprone, deferasirox seems to be capable of removing iron from cells (cardiac myocytes and hepatocytes) and from the blood (Barton 2007).

Chronic iron overload due to blood transfusions leads to significant morbidity and early mortality unless adequate chelation therapy is administered. Deferoxamine is recommended for chelation therapy, but the problem lies in the fact that this substance has to be administered by prolonged subcutaneous or intravenous infusion. Deferasirox with a low toxicity profile has the advantage of being administered once a day (Vermylen 2008).

IRON AND PREGNANCY

Pregnancy is characterized by an increased iron requirement. Iron deficiency anaemia is still prevalent among pregnant women and represents an important risk factor for maternal and infant health. However, the degree

of fetal iron deficiency is not always as severe as that in the mother. Iron transfer from the mother to the fetus is supported by a substantial increase in maternal iron absorption during pregnancy and is regulated by the placenta. Most iron transfer to the fetus occurs after the 30th week of gestation and likely involves placental expression of those proteins known to mediate systemic iron homeostasis (Paesano et al. 2009).

In the second and third trimesters of human pregnancy, natural dietary iron absorption is increased fivefold and ninefold, respectively. The increased iron uptake is required for physiological needs of the fetus as well as for the compensation for loss of iron in maternal bleeding at delivery. Numerous studies have recommended iron supplementation of pregnant women (Milman 2008). The awareness concerning such hazards of iron medications as upper gastrointestinal tract erosion, pre-eclampsia, oxidative stress, haemoconcentration and gestational diabetes, has been increasing (Weinberg 2010).

Supplementation has therefore been proposed to be restricted to those women who have moderate or low reserves of iron. Reserves can be determined by a serum ferritin assay either before or during early pregnancy. A value above 70 ng ml^{-1} would advise the person to forego iron supplementation. Women with values between 30 and 70 ng ml^{-1} should be recommended to take 40 mg ferrous iron daily. For those with serum ferritin below 30 ng ml^{-1}, the recommended dose would be 80 mg d^{-1} (Milman 2006).

Lactoferrin (LF) is an iron-binding glycoprotein abundantly found in exocrine secretions of mammals. LF is an important regulator of systemic iron homeostasis. Recent data suggest that this natural compound, capable of interacting with the most important components of iron homeostasis, may represent a valuable alternative to iron supplements in the prevention and cure of pregnancy-associated iron deficiency and iron deficiency anemia (Paesano et al. 2008). The results of clinical trials carried out in 2006 by Paesano et al. (2006) in pregnant woman suffering from iron deficiency and iron deficiency anaemia revealed the strong therapeutic potential of LF (Paesano et al. 2006). This natural compound represents an efficient alternative to ferrous sulphate therapy. Ferrous sulphate restores only the haemoglobin concentration,but does not significantly increase the number of red blood cells, total serum iron and serum ferritin. The failure of ferrous sulphate therapy to increase the total serum iron concentration indicates that this therapeutic regiment fails in restoring iron transport from tissues to blood, differently from that observed after LF therapy. Independently of the pregnancy trimester, oral administration of 100 mg of LF (about 30% iron-saturated) twice a day before a meal increased the total serum iron and haemoglobin concentrations to a greater extent than that observed after oral administration of ferrous sulphate. In contrast to the administration of ferrous sulphate, LF oral administration did not result in any side effect (Paesano et al. 2008).

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