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Lactoferrin efficacy versus ferrous sulfate in curing iron deficiency and iron deficiency anemia in pregnant women

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Abstract Iron deficiency (ID) and iron deficiency anemia (IDA) are the most common iron disorders throughout the world. ID and IDA, particularly caused by increased iron requirements during pregnancy, represent a high risk for preterm delivery, fetal growth retardation, low birth weight, and inferior neonatal health. Oral administration of ferrous sulfate to cure ID and IDA in pregnancy often fails to increase hematological parameters, causes adverse effects and increases inflammation. Recently, we have demonstrated safety and efficacy of oral administration of 30% iron saturated bovine lactoferrin (bLf) in pregnant women suffering from ID and IDA. Oral administration of bLf significantly increases the number of red blood cells, hemoglobin, total serum iron and serum ferritin already after 30 days of the treatment. The increasing of hematological values by bLf is related to the decrease of serum IL-6 and the increase of serum hepcidin, detected as prohepcidin, whereas ferrous sulfate increases IL-6 and fails to increase hematological parameters and prohepcidin. bLf is a more effective and safer alternative than ferrous sulfate for treating ID and IDA in pregnant women.

Keywords Iron deficiency · Iron deficiency anemia · Lactoferrin · Pregnant women · Inflammation

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Introduction

Iron deficiency (ID) and iron deficiency anemia (IDA) are the most common iron disorders throughout the world. When iron requirement is higher than that absorbed, a negative iron balance occurs and iron store decrease. In ID without anemia, total serum iron concentration decreases, while hemoglobin levels remain normal. In IDA, the deficit of iron is so severe that iron stores are absent or unavailable resulting in abnormally low hemoglobin and red blood cells. ID and IDA, particularly caused by increased iron requirements during pregnancy, represent a high risk for preterm delivery, fetal growth retardation, low

birth weight, and inferior neonatal health (Scholl 2005). However, the degree of fetal ID is not always as severe as maternal ID (Harris 1992) to cause of iron transfer from the mother to the fetus through the placenta (Bradley et al. 2004). At the maternal-placental interface placental syncytiotrophoblasts acquire ferric iron bound to maternal transferrin at the apical membrane through transferrin receptors (Cheng et al. 2004; Bastin et al. 2006), which are noticeably increased in pregnant women suffering ID and IDA (Cheng et al. 2004). After the 30th week of gestation, most fetal iron transfer occurs, also involving placental expression of hepcidin and ferroportin (Bastin et al. 2006), two proteins known to modulate systemic iron homeostasis in adults (Ganz 2006; De Domenico et al. 2008).

Iron homeostasis is tightly regulated through iron absorption, storage and transport (Bothwell 2000). Iron absorption occurs in the proximal duodenum and includes in the apical site of enterocytes the reduction of ferric ions by a ferrireductase (duodenal cytochrome B, DCYTB), the apical uptake and the transcellular trafficking via divalent metal transporter 1 (DMT1), the storage into ferritin and finally, the basolateral efflux by the iron transporter ferroportin (De Domenico et al. 2008). Ferroportin, the only known cellular iron exporter from tissues into blood, has been found in all cell types involved in iron export, including enterocytes, hepatocytes, placental cells (Donovan et al. 2005) and macrophages which recycle 20 mg of iron daily from lysed erythrocytes for erythropoiesis (Nemeth and Ganz 2006a).

Another important component of systemic iron homeostasis is hepcidin, a circulating peptide hormone synthesized by hepatocytes in iron loading conditions and secreted in plasma (Krause et al. 2000) and urine (Park et al. 2001). Hepcidin regulates the entry of iron into plasma through ferroportin (Ganz 2005; Loreal et al. 2005). Binding of hepcidin with ferroportin causes the formation of a hepcidin–ferroportin complex resulting in ferroportin phosphorylation, internalization and degradation in lysosomes (Nemeth et al. 2004a; De Domenico et al. 2007). Consequently, iron export is hindered and cytosolic iron storage in ferritin is enhanced. Iron homeostasis disorders appear to arise from hepcidin and/or ferroportin dysregulation (Nemeth et al. 2004b; De Domenico et al. 2007, 2008). Similarly to the regulation of maternal systemic iron homeostasis, fetal hepcidin controls transfer of maternal iron across the placenta to the fetus. Enhanced placental-fetal iron transport is related to increased expression of ferroportin on placental basal fetal-facing membranes, consistent with unidirectional mother-fetus iron transport (Bastin et al. 2006; Collard 2009).

ID and IDA up regulate DMT1 (Gunshin et al. 1997; Mims and Prchal 2005) as well as DCYTB (Zoller et al. 2003), while down regulate hepcidin expression. It has been reported that in animal models its production is decreased by anemia (Nicolas et al. 2002).

Even if the molecular mechanisms of hepcidin regulation by iron and anemia are still unclear (Nemeth and Ganz 2006b), it is well known that iron loading and Interleukin-6 (IL-6) increase hepcidin gene transcription in hepatocytes (Nemeth et al. 2004b). In inflammatory and infectious disorders, excessive hepcidin contributes to development of anemia of inflammation, characterized by ID and IDA, despite adequate iron stores (Nemeth and Ganz 2006b). As matter of fact, iron is stored in host cells when its export is inhibited. However, inflammation may contribute to ID and IDA by hepcidin-independent mechanism(s) such as the down regulation of ferroportin (Weinstein et al. 2002). Independent of hepcidin synthesis, high levels of serum IL-6 appear to down regulate ferroportin mRNA expression, thus blocking iron flow into plasma by sequestering iron inside cells (Weinstein et al. 2002; Ludwiczek et al. 2003). The inability to export iron leads to hypoferremia, decreased serum transferrin-Fe (III) and iron-limited erythropoiesis (Ganz 2006; De Domenico et al. 2008).

Discovery of the hepcidin–ferroportin complex has greatly clarified the enigmatic mechanism underlying systemic iron homeostasis. Notwithstanding this advance in understanding iron homeostasis disorders, ID and IDA are still routinely treated with large quantities of oral ferrous sulfate due to its exceptionally poor bio-availability. Ferrous sulfate often fails to restore iron homeostasis in subjects suffering ID and IDA, and frequently causes many adverse effects: gastrointestinal discomfort, nausea, vomiting, diarrhea, and constipation (Kadiiska et al. 1995; Oldenburg et al. 2000; Reifen et al. 2000).

Recently, in the clinic, significant decreases of total serum iron and serum ferritin combined with increases of serum IL-6 have been observed in

pregnant women (Paesano et al. 2009, 2010) and in haemodialysis patients (Provenzano et al. 2009) treated with oral ferrous sulfate. These results strongly support the possibility that iron supplemented via ferrous sulfate is not exported from cells to circulation, but it is accumulated inside host cells resulting in inflammatory conditions (Kadiiska et al. 1995; Oldenburg et al. 2000; Reifen et al. 2000). This evidence and our previous clinical experience (Paesano et al. 2009, 2010) has raised serious questions regarding the safety/efficacy of oral ferrous sulfate, resulting in new approaches for treating ID and IDA and avoiding toxicities associated with iron overload.

Lactoferrin (Lf), a high-affinity cationic iron-binding glycoprotein (Baker and Baker 2005), is emerging as an important regulator of systemic iron homeostasis (Paesano et al. 2006, 2009, 2010). Lf is synthesized by exocrine glands and neutrophils in inflammation and infection sites. In humans, Lf in tissues and secretions and transferrin in serum ensure that free iron does not exceed 10^{-18} M thereby avoiding iron precipitation, microbial growth and formation of reactive oxygen species (Weinberg 2009).

Lf is a multifunctional protein exhibiting both dependent and independent biological activity based upon its iron binding capacity (Valenti and Antonini 2005). In our clinical trials on bovine Lf (bLf) oral administration, we have demonstrated that this natural compound is safe and effective in treating pregnant women suffering from ID and IDA (Paesano et al. 2006, 2008, 2009, 2010; Valenti et al. 2008)

Influence of ferrous sulfate oral administration on hematological parameters, serum IL-6 and prohepcidin in pregnant women suffering of ID and IDA

In spite of the recent discovery of the hepcidin–ferroportin complex (Nemeth et al. 2004b) and the efforts to develop better treatment strategies for treating ID and IDA, oral ferrous sulfate is still widely used. Few papers have explored the underestimated problems of side effects subsequent to this therapy (Paesano et al. 2006, 2009, 2010; Schümann et al. 2007; Provenzano et al. 2009). Recently, it has been reported that use of oral ferrous sulfate in inflammatory bowel disease decreases the quality of life (Dejaco and Gasche 2002; Belluzzi et al. 2007). By any standard of care, current options for treating anemia are unsatisfying and represent a large unmet medical need. In particular, anemic pregnant women treated with ferrous sulfate oral administration did not show significant improved hematological parameters, including number of red blood cells, hemoglobin, total serum iron, serum ferritin concentrations. In Table 1, the mean hematological values deriving from all clinical trials on pregnant women receiving ferrous sulfate are reported (Paesano et al. 2006, 2008, 2009, 2010; Valenti et al. 2008).

Moreover, in pregnant women the mean values of serum IL-6 are higher than that observed in non pregnant women (30 ± 10 respect to 2.0 ± 1), while the mean values of hepcidin levels detected as hepcidin precursor prohepcidin in pregnant and non pregnant women are similar (100 ± 30) (Paesano et al. 2010). In anemic pregnant women, after 30 days of ferrous sulfate oral administration, the mean values of serum IL-6 significantly increased ($P = 0.0015$) and serum prohepcidin decreased without reaching statistical significance ($P = 0.05$) (Table 1) (Paesano et al. 2009, 2010).

Influence of bovine lactoferrin oral administration on hematological parameters, serum IL-6 and prohepcidin in pregnant women suffering of ID and IDA

Bovine Lf represents an attractive and promising alternative to ferrous sulfate oral administration. In pregnant women, oral administration of bLf, 30% iron saturated, significantly improved hematological parameters, including number of red blood cells, hemoglobin, total serum iron, serum ferritin concentrations compared to those observed in pregnant women sub-optimally treated with ferrous sulfate (Table 1) (Paesano et al. 2006, 2008, 2009, 2010; Valenti et al. 2008).

Differently from oral ferrous sulfate administration, already after 30 days of bLf administration, serum IL-6 concentrations significantly decreased ($P < 0.0001$), while serum prohepcidin increased ($P = 0.007$) (Table 1) (Paesano et al. 2009, 2010).

Unlike ferrous sulfate standard therapy, oral administration of bLf is well tolerated and demonstrates an excellent safety profile. In particular, no

Table 1 Mean values of hematological parameters in pregnant women suffering of ID and IDA before and after bovine lactoferrin or ferrous sulfate therapy

Parameters	Before therapy[a]	After therapy	
		bLf[b]	Ferrous sulfate[c]
Red blood cells ($\times 10^3$)	≤4.000	4.250 ± 229	3,730 ± 226
Hemoglobin (g/dl)	≤11	12.7 ± 0.9	11.5 ± 0.6
Total serum iron (mg/dl)	≤30	84 ± 16	47 ± 9
Serum ferritin (ng/ml)	≤12	29 ± 7	5 ± 2
Serum IL-6 (pg/ml)[d]	33 ± 10	12 ± 10	52 ± 13
Serum prohepcidin (ng/ml)[e]	102 ± 27	150 ± 32	92 ± 28

[a] The reported values of red blood cells, hemoglobin, total serum iron and serum ferritin values defined ID and IDA; pregnant women were enrolled when at least one of these parameters was positive for ID or IDA

[b] bLf (100 mg) was orally administered before meals twice a day for 30 days

[c] Ferrous sulfate (520 mg) was orally administered during meals one time a day for 30 days. The mean values are calculated on 339 and 228 anemic pregnant women treated with bLf or ferrous sulfate, respectively (Paesano et al. 2006, 2008, 2009, 2010; Valenti et al. 2008)

[d,e] The mean values of serum IL-6 and prohepcidin are calculated on 30 and 30 anemic pregnant women treated with bLf or ferrous sulfate, respectively (Paesano et al. 2010)

adverse effect has been recorded in all anemic pregnant women treated with bLf in the clinical trials (Paesano et al. 2006, 2008, 2009, 2010; Valenti et al. 2008).

Conclusion

The pathophysiology of iron homeostasis disorders, as iron overload in tissues and iron deficiency in blood, has remained enigmatic until the recent discovery of the hepcidin–ferroportin complex (Nemeth et al. 2004a). Yet in spite of this important contribution to the understanding of systemic iron homeostasis and attempts to develop better therapy strategies for treating ID and IDA, oral ferrous sulfate is still widely used. Notwithstanding its known side effects, few papers have explored the underestimated problems with this therapy (Dejaco and Gasche 2002; Paesano et al. 2006, 2009, 2010; Belluzzi et al. 2007). By any standard of care current options for treating anemia are unsatisfying and represent a large unmet medical need.

Bovine Lf represents an attractive and promising alternative to ferrous sulfate oral administration. Unlike standard therapy using ferrous sulfate, anemic pregnant women receiving bLf did not experience any adverse effects. Although the amount of iron supplied by 30% iron saturated bLf was lower than that supplied by ferrous sulphate (Paesano et al. 2006), oral bLf significantly improved the number of red blood cells, hemoglobin, total serum iron, and serum ferritin concentrations compared to those detected in pregnant women sub-optimally treated with ferrous sulfate (Paesano et al. 2006, 2008, 2009, 2010; Valenti et al. 2008). We have also recently shown that in pregnant women the potent effect of bLf administration in curing ID and IDA is related to the significant decreasing serum IL-6 concentrations, and to the increasing serum prohepcidin synthesis. Conversely, oral ferrous sulfate induced an increase of serum IL-6 synthesis and a further decrease of serum prohepcidin levels consistent with its failure to cure ID and IDA in the study population (Paesano et al. 2009, 2010).

These results are also in agreement with those reported on both serum hepcidin values (Frazer and Anderson 2009) and serum prohepcidin levels (Ganz et al. 2008) as being significantly lower in IDA patients compared with healthy subjects. Interestingly, the failure in increasing of plasma iron by ferrous sulfate treatment is related to the further decrease of serum prohepcidin (Paesano et al. 2010). However, the molecular pathways underlying regulation of hepcidin are not well understood, except for anemia of inflammation (Weinstein et al. 2002; Ludwiczek et al. 2003; Nemeth et al. 2004a; Nemeth

and Ganz 2006b). Differently from that observed in anemia of inflammation, in pregnant women treated with bLf the increase of serum prohepcidin is not related with an increase of serum IL-6 levels but, conversely, with its significant decrease (Paesano et al. 2010). Therefore, our data in ID and IDA affected pregnant women, suggest that serum prohepcidin concentration can vary independent of the inflammatory state, and especially independent of serum IL-6 levels. Our data could be explained by those reported on the down regulation of ferroportin expression by IL-6 in the reticuloendothelial system (RES) (Weinstein et al. 2002; Ludwiczek et al. 2003; Theurl et al. 2006). Thus, iron sequestration in the RES that accompanies inflammation is not only caused by ferroportin internalization and degradation by high levels of hepcidin (Delaby et al. 2005) but also by down regulation of ferroportin (Weinstein et al. 2002; Ludwiczek et al. 2003; Theurl et al. 2006). Therefore, the recent advances elucidating the down regulation of ferroportin by IL-6 (Weinstein et al. 2002; Ludwiczek et al. 2003; Theurl et al. 2006) may also provide an explanation for the failure of ferrous sulfate in treating anemia in general and specifically in restoring physiological concentrations of total serum iron and serum ferritin. As described earlier, oral ferrous sulfate administration increasing IL-6 levels can result in down regulation of RES ferroportin expression, thus hindering iron export from tissues to blood. Contrary to ferrous sulfate mechanisms of action, data from previous clinical trials, demonstrate that bLf exerts a potent effect to counteract ID and IDA in pregnant women, especially in restoring physiological values of total serum iron and serum ferritin (Paesano et al. 2009, 2010). We speculate that this effect could be due to the capacity of bLf to lower serum IL-6, which in turn mitigates ferroportin down regulation, thus permitting iron export from tissues to blood. As matter of fact, in anemic subjects also including non pregnant women, bLf oral administration firstly increases the concentration of total serum iron (Paesano et al. 2010), indicating an efficient restoring of ferroportin function. Furthermore, the increase of serum hepcidin (or prohepcidin), related to an increase of hematological parameters, should be consider as signal of a regulatory mechanism to avoid an excess of iron export from cells to blood, subsequent to the restoring of ferroportin expression by bLf. Therefore, the efficacy of bLf in curing ID and IDA can be explained through its influence on systemic iron homeostasis. Conversely, unsuccessful attempts to increase total serum iron concentration using oral ferrous sulfate, suggest that the inflammatory effect subsequent to oral ferrous sulfate administration, could result in down regulation of ferroportin leading to dangerous iron overload in host cells involved in iron export from cells to blood.

A larger number of clinical trials should be carried out to fully elucidate the modulation of IL-6, hepcidin and ferroportin synthesis by bLf. In this respect, the ability of bLf to restore hematological values suggests that bLf behaves as a pivotal molecule by efficient decrease of IL-6, which in turn is able to interfere with systemic iron homeostasis. In this scenario, it is important to underline that bLf, orally administered in systemic iron disorders in pregnancy, induces several hematological changes helpful to cure ID and IDA (Table 1).

To our knowledge, the current studies are the first clinical trials describing bLf oral administration safety and efficacy in curing not only ID and IDA but also in increasing serum prohepcidin and in decreasing serum IL-6 concentrations, two important factors in systemic iron homeostasis. It is expected that administration of a compound endowed with the capacity to rescue systemic iron homeostasis and attenuate inflammation, such as bLf, should represent an extremely valid natural drug which, without any adverse effects, prevents and cures ID and IDA more effectively than ferrous sulfate.

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