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Ferrous Sulfate Versus Lactoferrin in Treatment of Pregnant Females with Iron Deficiency Anemia

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Abstract

Iron preparations, of which ferrous sulphate is the most common, are utilised in a broad variety of industries across the globe. This medicine has a high risk of adverse effects, most of which are related to the digestive system, despite being effective and inexpensive. As a transferrin family member and glycoprotein, lactoferrin is one of the proteins that can bind to and transport iron. The purpose of this research was to examine the haematological response and potential adverse effects of oral ferrous sulphate and oral lactoferrin as iron supplements for the treatment of iron deficiency anaemia (IDA) in pregnant women. A total of 108 pregnant women with a diagnosis of IDA were included in this research; 54 participants from each group. Iron sulphate (Ferro sanol duodenal cap, MINAPHARM Company) and lactoferrin (Pravotin, HYGINT Company) were both given orally to one group, while the other was given lactoferrin. Both treatments lasted for 4 weeks. Pregnancy-related or preexisting maternal diseases (such as hypertension, gestational diabetes, thyroid dysfunctions, pituitary diseases, nutritional diseases, liver pathologies, and gastrointestinal disorders), foetal abnormalities (such as microcephaly, intrauterine growth restriction), and allergy to any of the given drugs (iron sulphate [Ferro sanol duodenal cap, MINAPHARM Com]; or any of the other given drugs) disqualified subjects (Pravotin, HYGINT Company). Before and after treatment, both groups were compared for differences in outcomes and side effects, such as [haemoglobin (Hb) level, serum iron, ferritin level, total iron binding capacity (TIBC)]. No significant changes were seen in baseline or post-treatment Hb level, iron, TIBC, or ferritin levels between the two groups. As an added bonus, group A had much more nausea than group B. The incidence of vomiting was much greater in group A than in group B. Group A had considerably more cases of abdominal discomfort than Group B. People in Group A had more constipation than those in Group B. The current research concludes that oral lactoferrin has less adverse effects than oral iron therapy for the treatment of IDA during pregnancy.

Key words: Ferrous sulfate, hemoglobin, iron deficiency anemia, lactoferrin, total binding capacity.

1. Introduction

To accommodate the demands of the fetoplacental unit, to increase maternal erythrocyte mass, and to compensate for iron loss after delivery, the body's iron requirements rise dramatically throughout pregnancy [1].

The fact that iron deficiency anaemia still occurs often in pregnancy in wealthy nations suggests that physiologic adaptations are often inadequate to satisfy the increased requirements and that iron intake is usually below nutritional needs [2].

Much like the incidence of other nutritional deficiencies, iron deficiency may fluctuate with environmental factors [3].

In spite of the reported 41.8% worldwide prevalence of anaemia during pregnancy, the number of women who are iron deficient but do not have anaemia remains unclear [4].

When detected and treated, iron deficiency anaemia during pregnancy greatly improves the health of both mother and child [2].

When iron deficiency develops in the first or second trimester of pregnancy, it increases the likelihood that the baby will be born prematurely or with a low birth weight. Anemia has a role in causing premature birth in pregnant women. The risk almost doubles in mild anaemia, whereas it increases by 10–40% in moderate or severe anaemia [5].

One of the most common iron compounds is ferrous sulphate. This medicine is effective and inexpensive, but it has a high incidence of adverse effects, most of which are related to the digestive system [6].

Both human and bovine milk include the protein lactoferrin. High quantities of lactoferrin are present in colostrum, the first milk produced after birth, nearly seven times the quantity seen in later-made milk [7].

Its ability to attach to other molecules, such as lipopolysaccharides, heparin, glycosaminoglycans, deoxyribonucleic acid (DNA), oxalates, carboxylates, or metallic ions, and to keep iron bound in a low pH environment are key to its capabilities [8].

ObjectivesHematological response and side effects of oral ferrous sulphate vs oral lactoferrin as iron supplementation for treatment of iron deficiency anaemia (IDA) during pregnancy were the primary research questions driving this investigation.

2. Patients and Methods

2.1The study population

Specifically, it was a prospective randomised controlled trial. Following permission from the Benha University School of Medicine's Local Ethic Committee, all study participants were culled from the Benha Maternal Care centre A's outpatient clinic between January 2020 and January 2021. Two groups

of 54 pregnant women with IDA were studied in this research. Iron sulphate (Ferro sanol duodenal cap, MINAPHARM Company) and lactoferrin (Pravotin, HYGINT Company) were both given orally to one group, while the other was given lactoferrin. Both treatments lasted for 4 weeks. Each participant gave their informed permission before starting the research. Pregnancy-related or preexisting maternal diseases (such as hypertension, gestational diabetes, thyroid dysfunctions, pituitary diseases, nutritional diseases, liver pathologies, and gastrointestinal disorders), foetal abnormalities (such as microcephaly, intrauterine growth restriction), and allergy to any of the given drugs (iron sulphate [Ferro sanol duodenal cap, MINAPHARM Com]; or any of the other given drugs) disqualified subjects (Pravotin, HYGINT Company). For four weeks, those in Group A took 100 mg of oral lactoferrin (Pravotin, HYGINT Company). For four weeks, participants in Group B took 100 mg of elemental iron in the form of ferrous sulphate (Ferro sanol duodenal cap, MINAPHARM Company) by oral capsule. Before and after treatment, patients had their complete medical and obstetric histories taken, as well as a thorough examination for signs of anaemia (such as paleness, rapid heart rate, sore tongue, angular cheilitis, and koilonychia) and for any adverse reactions (by measuring HB levels, serum iron levels, ferritin levels, and TIBC) (abdominal pain, nausea, vomiting, diarrhoea and constipation).

2.2Statistical Analysis

SPSS v.25 was used for the data management and statistical analysis (IBM, Armonk, New York, United states).

Statistical information was summarised using means and standard deviations. Quantitative and percentage summaries of the categorical data were generated. The t test for independent samples was used to compare numerical data from the two sets. We used the Chi-square test to compare categorical variables.

P-values were always two-tailed. When the probability of a random event was less than 0.05, it was deemed significant.

3. Results

No significant differences between both groups as regard Hb level pre and post treatment **(Table 1).**

Table (1) Hemoglobin level in both groups

		Group A (n = 54)	Group B (n = 54)	P value
Pre	Mean ±SD	9.5 ±0.6	9.6 ±0.7	0.683
Post	Mean ±SD	10.5 ±0.7	10.6 ±0.7	0.542

No significant differences between both groups as regard iron level pre and post treatment **(Table 2).**

Table (2) Iron level in both groups

		Group A (n = 54)	Group B (n = 54)	P value
Pre	Mean ±SD	21.6 ±2.9	21.6 ±2.9	0.898
Post	Mean ±SD	28.3 ±5.2	28.4 ±5.5	0.856

No significant differences between both groups as regard TIBC pre and post treatment **(Table 3).**

Table (3) TIBC level in both groups

		Group A (n = 54)	Group B (n = 54)	P value
Pre	Mean ±SD	464.8 ±43.2	469.2 ±9.1	0.457
Post	Mean ±SD	441.6 ±36.1	446.2 ±22.9	0.432

No significant differences between both groups as regard ferritin pre and post treatment **(Table 4).**

Table (4): Ferritin levels in both groups

		Group A (n = 54)	Group B (n = 54)	P value
Pre	Mean ±SD	10.4 ±1.3	10.8 ±2.9	0.335
Post	Mean ±SD	15.2 ±4	15.8 ±4.4	0.513

Nausea was significantly higher in group A (79.6%) compared to group B (55.6%), vomiting was significantly higher in group A (51.9%) compared to group B (27.8%), abdominal pain was significantly higher in group A (31.5%) compared to group B (7.4%), and constipation was significantly higher in group A (81.5%) compared to group B (55.6%) **(Table 5).**

Table (5) Frequency of side effects in both groups

		Group A (n = 54)	Group B (n = 54)	P value
Nausea	Yes	43 (79.6)	30 (55.6)	0.008
Vomiting	Yes	28 (51.9)	15 (27.8)	0.011
Abdomen pain	Yes	17 (31.5)	4 (7.4)	0.002
Constipation	Yes	44 (81.5)	30 (55.6)	0.004

4. Discussion

There is a higher chance of developing IDA during pregnancy because to the increased iron requirements that occur during this time. Half or more of all pregnant women in the world's poorest countries are at risk [9]. An examination of many research revealed that children born to women with IDA during pregnancy had a greater prevalence of iron insufficiency than those delivered to mothers with normal iron status. Children with a lack of iron at birth are more likely to have impairments in cognitive and motor development [10].

One of the most common iron compounds is ferrous sulphate. This medicine is effective and inexpensive, but it has a high incidence of adverse effects, most of which are related to the digestive system [11].

Like other transferrin family members, lactoferrin is a glycoprotein. This means it can bind and transfer iron [12].

In the current investigation, there were no statistically significant variations in Hb levels before and after therapy between the two groups. Mohamed et al. [13] found no significant difference between the two groups in terms of baseline Hb, but they did find that following treatment, Hb in the lactoferrin group was considerably higher than in the ferrous sulphate group at both months 1 and 2. Lactoferrin was associated with a greater overall rise in Hb after 2 months compared to ferrous sulphate in studies conducted by Rezk et al. [14] and Paesano et al. [15]. While ferrous sulphate raises IL-6 and has no effect on haematological parameters or prohepcidin levels, lactoferrin's ability to boost Hb levels is linked to a reduction in serum IL-6 and a rise in serum hepcidin, detectable as prohepcidin. When it comes to treating IDA in pregnant women, lactoferrin is more effective and safer than ferrous sulphate [15]. Possible causes for the discrepancy between these findings include differences in the total number of instances, the gestational age of the subjects, and the treatment's dosage.

Our investigation showed no significant variations in baseline and post-treatment iron levels between the two groups. In contrast to our findings, Rezk et al. [14] found that women treated with lactoferrin had a larger rise in total serum iron levels than those treated with ferrous sulphate. Oral administration of partly iron-saturated lactoferrin improves intestinal iron transport during pregnancy more so than ferrous sulphate, as mentioned by the authors. Possible causes of this discrepancy include a disparity in case numbers or the gestational age, treatment dosage, or treatment duration.

No statistically significant variations in pre- and post-treatment blood ferritin levels were seen between the two groups here. In contrast to our findings, Mohamed et al. [13] found no difference in baseline serum ferritin between the ferrous sulphate and lactoferrin groups, but did find a substantial rise in ferritin in both groups at months 1 and 2. Serum ferritin increases after therapy, as shown by Nappi et al. [16].

No statistically significant variations in TIBC before and after therapy were seen between the two groups. However, Nappi et al. [16] found that TIBC actually reduced following therapy, which contradicts the results of the present investigation. Gawai [17] also discovered a reduction in TIBC after 1 month and 2 months following therapy.

The current research found that group A had much more cases of nausea, vomiting, stomach discomfort, and constipation than group B did. But when Mohamed et al. [13] looked into the gastrointestinal adverse effects of both medications, they found that lactoferrin was better tolerated than ferrous sulphate. The iron-restoring and IDA-contrasting benefits of daily lactoferrin therapy in anaemic pregnant women are greater than those of ferrous sulphate, while less gastrointestinal side effects are seen. If lactoferrin is used as an alternate method in pregnant women with IDA, it may help address one of the key issues with oral supplementation with ferrous sulphate: low compliance due to stomach upset.

Due to the compounds' distinct metabolic pathways and the need of delivering greater dosages of ferrous sulphate, the occurrence of gastrointestinal adverse effects is reduced. Taking iron orally results in absorption rates of just 10-20% at best. So, 80-90% of the iron you consume stays in the gut lumen, where it might give you some serious distress. It seems that the labile iron content in the lumen is responsible for these gastrointestinal consequences, which manifest as mucosal irritation and decreased gastrointestinal motility [13].

A person's iron intake has a direct correlation to the severity of these effects in the first region of the small intestine. However, the availability of iron ions in the colon is less proportional to the amount taken due to variances in absorption, intestinal transit duration, and binding to dietary ligands [13].

However, lactoferrin is assumed to be taken in by endocytosis. Intestinal cells breakdown lactoferrin, releasing iron from the lactoferrin-Fe complex. Transferrin carries the liberated iron over the basolateral membrane and into the bloodstream. An effective process for iron absorption is postulated, in which lactoferrin-Fe is transported from the intestinal cells' apical to basolateral membranes through a particular receptor [13].

5. Conclusion

The current study's findings suggest that lactoferrin, when taken orally, is safer than oral iron therapy for treating IDA during pregnancy.

6. Recommendations

Results from the current research should be seen in the context of its limitations, such as its small sample size. Therefore, further research is required to: Compare the effectiveness of intravenous iron therapy with that of oral lactoferrin at various stages of pregnancy. Analyze the effectiveness of iron therapy against injectable lactoferrin for the treatment of IDA during pregnancy.

References

[1] **F. Parisi, C. Berti, C. Mandò, A. Martinelli, C. Mazzali, I. Cetin.** Effects of different regimens of iron prophylaxis on maternal iron status and pregnancy outcome: a randomized control trial. J Matern Fetal Neonatal Med.vol.30(15),pp. 1787-1792, 2017.

[2] **M. Blumfield, A. Hure, L. Macdonald-Wicks, R. Smith, C.** A. **Collins** systematic review and meta-analysis of micronutrient intakes during pregnancy in developed countries. Nutr Rev.vol. 71(2),pp.118-132,2013.

[3] **A. Laganà, S. Vitale, H. Ban Frangež, E. Vrtačnik-Bokal, R. D'Anna.** Vitamin D in human reproduction: the more, the better? An evidence-based critical appraisal. Eur Rev Med Pharmacol Sci.vol.21(18),pp.4243-4251,2017.

[4] **M. Goonewardene, M. Shehata, A. Hamad.** Anaemia in pregnancy. Best Pract Res Clin Obstet Gynaecol.vol. 26(1),pp.23-24,2012.

[5] **T. Scholl.** Maternal iron status: Relation to fetal growth, length of gestation, and iron endowment of the neonate. Nutrition Rev.vol.69(1),pp.23-29,2011.

[6] **Z. Tolkien, L. Stecher, A. Mander, D. Pereira, J. Powell.** Ferrous sulphate supplementation causes significant gastrointestinal side-effects in adults: a systematic review and meta-analysis. PIoS One.vol. 10(2),pp. e0117383,2015.

[7] **P. Kochhar, A. Kaundal, P. Ghosh.** Oral iron in treatment of iron deficiency anemia in pregnancy: A randomized clinical trial. J Obstet Gynaecol Res.vol. 39,pp.504-510,2013.

[8] **J. Sharma, S. Meenakshi.** Anemia in Pregnancy. JIMSA.vol.23(4),pp.253-260 ,2014.

[9] **A. Sato, E. Fujimori, S. Szarfarc, A. Borges, M. Tsunechiro.** Food consumption and iron intake of pregnant and reproductive aged women. Revista Latino-Americana de Enfermagem..vol. 18,pp.247–254, 2010.

[10] **M. Helmy, N. El Khouly, R. Ghalab.** Maternal anemia with pregnancy and its adverse effects. MMJ. 2018; 31(1): 7-11.

[11] **Z. Tolkien, L. Stecher, A. Mander, D. Pereira, J. Powell.** Ferrous sulphate supplementation causes significant gastrointestinal side-effects in adults: a systematic review and meta-analysis. PIoS One.vol.10(2),pp. e0117383,2015.

[12] **N. Nocerino, A. Fulgione, M. Iannaccone, L. Tomasetta, F. Ianniello, F. Martora, et al.** Biological activity of lactoferrin-funtionalized biomimetic hydroxyapatite nanocrystals. International Journal of Nanomedicine..vol.9,pp. 1175-1180,2014.

[13] **M. Mohamed, W. Taha, M. Farag.** Lactoferrin versus Ferrous Sulphate for the Treatment of Iron Deficiency Anemia during Pregnancy (A Randomized Clinical Trial). Al-Azhar Med J.vol. 49(1),pp. 271-282,2020.

[14] **M. Rezk, M. Kandil, R. Dawood.** Oral lactoferrin versus ferrous sulphate and ferrous fumerate for the treatment of iron deficiency anemia during pregnancy. J Adv Nutr Hum Metab.vol. 1,pp.1-5,2015.

[15] **R. Paesano, F. Berlutti, M. Pietropaoli, F. Pantanella, E. Pacifici, W. Goolsbee, et al.** Lactoferrin efficacy versus ferrous sulfate in curing iron deficiency and iron deficiency anemia inpregnant women. Biometals.vol. 23,pp.411–417, 2010.

[16] **C. Nappi, G. Tommaselli, I. Morra, M. Massaro, C. Formisano, C. Di Carlo.** Efficacy and tolerability of oral bovine lactoferrin compared to ferrous sulfate in pregnant women with iron deficiency anemia: A prospective controlled randomized study. Acta Obstetricia et Gynecologica.vol.88,pp.1031-1035,2009.

[17] **S. Gawai.** A randomized controlled trial on lactoferrin versus ferrous sulphate for the treatment of mild to moderate iron deficiency anaemia in pregnancy. Int J Reprod Contracept Obstet Gynecol.vol. 9(2),pp.562-566, 2020.