

DOI: <http://dx.doi.org/10.18203/2320-1770.ijrcog20200336>

Original Research Article

A randomized controlled trial on lactoferrin versus ferrous sulphate for the treatment of mild to moderate iron deficiency anaemia in pregnancy

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Received: 29 September 2019

Revised: 27 December 2019

Accepted: 02 January 2020

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ABSTRACT

Background: One of the important factors associated with maternal and foetal complications during pregnancy is Anaemia. Various oral preparations of iron are available, and each has different bioavailability, efficacy and adverse effects. Lactoferrin is a naturally existing iron-binding multifunctional glycoprotein, and a member of a transferrin family, thus belonging to those proteins capable of binding and transferring iron. Lactoferrin has considerably less gastrointestinal side effects than ferrous sulfate and is very useful as well as promising alternative to ferrous sulphate.

Methods: Prospective randomized controlled study. Total 100 females with 24 to 36 weeks of pregnancy with haemoglobin between 8 to 10 grams were included out of which 50 patients were given ferrous sulphate 200 mg BD and 50 patients were given lactoferrin 250 mg BD daily for 8 weeks. Various haematological parameters and the adverse effects of both the drugs were studied at registration, 4 weeks and 8 weeks and compared.

Results: Thus, after this study authors can say that the rise in haemoglobin with lactoferrin was 1.58 g/dl while with ferrous sulphate it was 1.67 g/dl at 8 weeks. Adverse effects were much lesser in Group A taking lactoferrin compared to Group B.

Conclusions: Thus, lactoferrin has the advantage over ferrous sulphate in having less side effects and increasing the compliance and thus the efficacy of the drug compared to ferrous sulphate.

Keywords: Anaemia, Ferrous sulphate, Haemoglobin, Iron deficiency anaemia, Lactoferrin, Pregnancy, Serum Iron, Total iron binding capacity

INTRODUCTION

Anemia has a significant impact on the health of the fetus as well as that of the mother.^{1,2} Many preparations are available to increase haemoglobin.³ Lactoferrin is an oral preparation which is easily accepted by the patients.^{4,5} Very few studies about this are done in India. Hence, authors decided to study and compare ferrous sulphate and lactoferrin in pregnant females. Objective of this study was to compare the effectiveness and adverse effects of lactoferrin versus ferrous sulphate for the

treatment of mild to moderate Iron deficiency anaemia during pregnancy.

METHODS

Prospective randomized controlled Study was done for a period of 8 weeks from December 2018 to February 2019.

Total 100 females with 24 to 36 weeks of pregnancy with haemoglobin between 8 to 10 grams were included out of

which 50 patients were given ferrous sulphate 200 mg BD and 50 patients were given lactoferrin 250 mg BD daily for 8 weeks. Various haematological parameters like rise in haemoglobin, rise in serum iron, rise in serum ferritin, fall in TIBC and the adverse effects of both the drugs were studied at registration, 4 weeks and 8 weeks and compared. And authors found that all these indices were almost same in both the groups and the overall acceptability of ferrous sulphate was less, around 22% while of lactoferrin was 96%.

Inclusion criteria

- Pregnant women from 24-36 weeks of gestation
- Mild to moderate anemia.

Exclusion criteria

- Women with a history of anemia due to any other causes other than IDA
- Severe anemia requiring blood transfusion
- History of peptic ulcer
- Known hypersensitivity to iron preparations.

RESULTS

It was found in our study that in group A the mean haemoglobin at registration was 9.03 which increased to 9.77 at 4 weeks and 10.61 at 8 weeks. Thus, total rise in haemoglobin was 1.5 ± 0.49 grams. P-value was significant (Table 1).

Table 1: Group A: rise in haemoglobin with lactoferrin (n = 50).

	At registration	At 4 weeks	At 8 weeks
Mean	9.03	9.77	10.61
SD	0.55	0.56	0.46

F-value = 108.52 and P-value < 0.05.

In Group B, the mean haemoglobin at registration was 9.13 which increased to 9.88 at 4 weeks and 10.80 at 8 weeks. Thus, total rise in haemoglobin was 1.67 ± 0.44 grams. P-value was significant (Table 2).

Table 2: Group B: rise in haemoglobin (g/dl) with ferrous sulphate (n = 50).

	At registration	At 4 weeks	At 8 weeks
Mean	9.13	9.88	10.80
SD	0.58	0.50	0.41

F-value = 141.87 and P-value < 0.05.

Table 3: Group A: rise in serum iron (mcg/dl) with lactoferrin (n = 50).

	At registration	At 4 weeks	At 8 weeks
Mean	39.83	60.6	79.73
SD	5.92	7.53	7.07

F-value = 413.03, P-value < 0.05.

When serum iron was studied, it was found that at registration the value was 39.83 which rose to 60.6 at 4 weeks and 79.73 AT 8 weeks. The total rise in serum iron was found to be 39.90. P-value was significant (Table 3).

Table 4: Group B: rise in serum iron (mcg/dl) with ferrous sulphate (n = 50).

	At registration	At 4 weeks	At 8 weeks
Mean	40.08	60.25	77.29
SD	4.61	4.96	5.37

F-value = 710.735, P-value < 0.05.

In Group B it was found that at registration the value was 40.08 which rose to 60.25 at 4 weeks and 77.29 at 8 weeks. The total rise in serum iron was found to be 37.21. P-value was significant (Table 4).

Table 5: Group A: rise in serum ferritin (mcg/dl) with lactoferrin (n = 50).

	At registration	At 4 weeks	At 8 weeks
Mean	9.37	11.25	13.16
SD	0.87	0.93	1.04

F-value = 195.27, P-value < 0.05.

In Group A, serum ferritin was 9.37 at registration, 11.25 at 4 weeks and 13.16 at 8 weeks. The total rise was found to be 3.79 which was significant and proven by P-value (Table 5).

Table 6: Group B: rise in serum ferritin (mcg/dl) with ferrous sulphate (n = 50).

	At registration	At 4 weeks	At 8 weeks
Mean	9.49	11.64	13.63
SD	0.84	0.86	0.87

F-value = 297.859, P-value < 0.05.

In Group B, serum ferritin was 9.49 at registration, 11.64 at 4 weeks and 13.63 at 8 weeks. The total rise was found to be 4.14 which was significant and proven by P-value (Table 6).

In Group A, TIBC was 407.31 at the registration which decreased to 382.04 at 4 weeks and 348.12 at 8 weeks.

Table 7: A Group A: fall in TIBC (mcg/dl) with lactoferrin (n = 50).

	At registration	At 4 weeks	At 8 weeks
Mean	407.31	382.04	348.12
SD	36.15	31.44	25.01

F-value = 9.90, P-value < 0.05.

Total fall in TIBC was 59.19. P-value was significant (Table 7).

In Group B, TIBC was 421.62 at the registration which decreased to 382.92 at 4 weeks and 345.45 at 8 weeks.

Total fall in TIBC was 76.17. P-value was significant (Table 8).

Table 8: Group B: fall in TIBC (mcg/dl) with ferrous sulphate (n = 50).

	At registration	At 4 weeks	At 8 weeks
Mean	421.62	382.92	345.45
SD	32.46	29.90	27.01

F-value = 82.90, P-value < 0.05.

Thus, on comparing the adverse effects of both the drugs, constipation was seen in 92% of pregnant females taking ferrous sulphate while those taking lactoferrin only 14% had constipation. Next more common adverse effect was darkening of stool which was seen in 90% of population taking ferrous sulphate while it was not seen with lactoferrin at all i.e. Zero percent. gastric up set was seen in 84% of population on ferrous sulphate and 30% in women with lactoferrin. Vomiting was seen in 62% with ferrous sulphate and 18% with lactoferrin. Abdominal pain was seen in 24% of women having ferrous sulphate and 10% of women taking lactoferrin.

Table 9: Adverse effects.

	Lactoferrin (Group A) N = 50	Ferrous sulphate (Group B) n = 50
Gastric upset	15	42
Acceptability	48	11
Vomiting	9	31
Constipation	7	46
Dark stools	0	45
Abdominal pain	5	12

The overall acceptability of ferrous sulphate was less, around 22% while of lactoferrin was 96% (Table 9).

Thus, lactoferrin has the advantage over ferrous sulphate in having less side effects and increasing the compliance and thus the efficacy of the drug compared to ferrous sulphate.

DISCUSSION

One of the important factors associated with maternal and foetal complications during pregnancy is Anaemia.^{1,2} The World Health Organization (WHO) defines anaemia in pregnant women as Hb < 11.0 g/L.

Anemia has a significant impact on the health of the fetus as well as that of the mother.^{1,2} Anemia is common pregnancy due to increased demand of iron for the growing fetus and placenta; and increased red blood cell mass (with expanded maternal blood volume in the third trimester), which is further aggravated with other factors such as childbearing at an early age, repeated pregnancies, short intervals between pregnancies and poor access to antenatal care and supplementation.³

It impairs the oxygen delivery through the placenta to the fetus and interferes with the normal intrauterine growth, leading to fetal loss and perinatal deaths⁴. Anemia is associated with increased preterm labor preeclampsia and maternal sepsis.

Iron deficiency anaemia (IDA) is the most common cause of anaemia in pregnancy.^{1,5,6} IDA develops when available iron is insufficient to support normal red cell production. The daily requirement of iron is around 1.5 mg in nonpregnant women. This requirement increases dramatically during pregnancy to reach 6-7 mg/day (total 1000 mg) with advanced gestational age.⁷ Pregnancy causes a twofold to threefold increase in the requirement for iron and a 10- to 20-fold increase in folate requirement. The increase in demand for iron is mainly due to fetal requirement, placenta, blood volume, tissue accretion, and the intra-partum potential for blood loss⁴. Iron absorption takes place in the apical site of proximal duodenum through its reduction by duodenal cytochrome B followed by trans-cellular trafficking via divalent metal transporter I, and its storage into ferritin. Iron efflux occurs in basolateral sites via Ferroportin, the only known cellular iron exporter from tissues into blood, has been found in enterocytes, hepatocytes, placental cells and macrophages. Another pivotal component of systemic iron homeostasis is hepcidin, a circulating peptide hormone synthesized by hepatocytes in iron loading conditions and secreted in plasma and urine. The binding of hepcidin with ferroportin resulting in ferroportin phosphorylation, internalization and degradation in lysosomes, hinders iron export. Iron homeostasis disorders appear to arise from hepcidin and/or ferroportin dysregulation. Dietary changes are not sufficient to correct iron deficiency in pregnancy. Oral iron supplements are still considered as the first choice, with a therapeutic dose of 100 to 200 mg elemental iron daily. Management of iron deficiency anemia with ingestion of iron medications will allow the hemoglobin levels to increase in a slow pattern, around after 1-2 weeks of therapy, will eventually increase roughly 2 g/dL. The Hb concentration should increase by around 20 g/L over 3 to 4 weeks and iron should be continued for 3 months after the Hb returns to normal (and at least 6 weeks postpartum) to replenish iron stores.⁴ Many women are intolerant to oral iron because of gastric irritation and diarrhoea or constipation.² If a reduction in oral iron dose is not effective, then treatment with parenteral iron is required. Lactoferrin forms a very good and promising alternative to oral iron preparations and help in avoiding parenteral iron and associated complications. In pregnant women, oral administration of bovine lactoferrin, 30% iron saturated, significantly improved hematological parameters, including number of red blood cells, hemoglobin, total serum iron, serum ferritin concentrations with lesser adverse effects compared to those observed in pregnant women treated with ferrous sulfate. Lactoferrin (formerly known as lactotransferrin) is a glycoprotein, and a member of a transferrin family, thus belonging to those proteins

capable of binding and transferring iron.^{4,5} Lactoferrin is a naturally existing iron-binding multifunctional protein; it is present at high concentrations in human milk and in the milk of other mammals.⁵ It is also present in other body fluids such as tears, saliva, bile, pancreatic juice, genital and nasal secretions as well as in circulating neutrophils.⁵ Therefore, oral administration of bovine lactoferrin as an iron-supplying molecule is an appealing therapeutic strategy. The molecular composition of lactoferrin is composed of a single polypeptide chain which is folded into two lobes (N and C lobes).⁵ Both lobes are connected by a α -helical residue, making Lactoferrin a structurally flexible molecule in character.

Lactoferrin could sustain binding of iron in variable pH array. Specific receptors mediate and influence the physiological action, by directly altering the cell membrane, by competitive mode of absorption for the iron ions or via its enzymatic action.⁸ Its molecular and physiological behavior and features are augmented by its capability of sustaining the iron binding feature at low pH. The raised haematological values by lactoferrin is related to decreased serum interleukin 6 and increased hepcidin detected as prohepcidin whereas ferrous sulphate has raised interleukin 6. Data and results of research studies display and reveal that bovine lactoferrin has considerably less gastrointestinal side effects than ferrous sulfate (Table 9).² The rise in RBC cellular mass is associated by a rise in maternal physiological requirements and demand of iron by an additional 500 mg during gestation and additional 300 mg transferred to the developing fetus and 200 mg that are necessary for physiologically normal daily iron loss, making total iron demands in total gestational period is about 1 g.⁷

In our study which was done for 2 months duration from 11th December 2018 to 11th February 2019 total of 100 patients were included and 2 groups of 50 in each group were formed randomly. One group was given ferrous sulphate 200 mg bd and other group was given lactoferrin 250 mg bd and various haematological parameters were studied in each group at 4 weeks and 8 weeks respectively. In our study authors found that the rise in haemoglobin with lactoferrin was 1.58 g/dl (Table 1) while with ferrous sulphate it was 1.67 g/dl (Table 2) at 8 weeks. In serum iron the total rise by lactoferrin is 39.90 mcg/dl (Table 3) while with ferrous sulphate it is 37.21 mcg/dl (Table 4). Rise of serum ferritin was 3.79 mcg/dl (Table 5) at 8 weeks with lactoferrin while it was 4.14 mcg/dl (Table 6) with ferrous sulphate. The fall in TIBC with lactoferrin and ferrous sulphate are 59.19 mcg/dl (Table 7) and 76.17 mcg/dl (Table 8).

Thus, authors can very well conclude that lactoferrin is more effective and safer alternative to oral iron preparations and should be advised in pregnant females with iron deficiency anaemia as it will increase the compliance due to minimal adverse effects as compared to ferrous sulphate.^{9,10}

CONCLUSION

Ferrous sulphate and Lactoferrin both are efficient in management of iron deficiency anemia in pregnancy. Lactoferrin displayed an excellent safety profile and improved compliance compared to ferrous sulphate with comparable efficacy. Thus, after this study authors can say that the rise in haemoglobin with lactoferrin was 1.58 g/dl (Table 1) while with ferrous sulphate it was 1.67 g/dl (Table 2) at 8 weeks. In serum iron the total rise by lactoferrin is 39.90 mcg/dl (Table 3) while with ferrous sulphate it is 37.21 mcg/dl (Table 4). Rise of serum ferritin was 3.79 mcg/dl (Table 5) at 8 weeks with lactoferrin while it was 4.14 mcg/dl (Table 6) with ferrous sulphate. The fall in TIBC with lactoferrin and ferrous sulphate are 59.19 mcg/dl (Table 7) and 76.17 mcg/dl (Table 8) respectively. Adverse effects were much lesser in Group A taking lactoferrin compared to Group B (Table 9). Most of the adverse effects were gastric upset, constipation, nausea, vomiting, darkening of stools etc. which were more associated with ferrous sulphate compared to lactoferrin (Table 9). Thus, it can be said that though the haematological parameters are showing slightly more improvement amongst Group B having ferrous sulphate but the difference is not much and the adverse effects with lactoferrin are negligible as compared to ferrous sulphate. Hence, compliance was better with lactoferrin. The acceptability of lactoferrin is more in pregnancy due to less gastric effects making it preferred drug in pregnancy compared to ferrous sulphate (Table 9).

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Gawai S, Fonseca M, Kapote D. 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* 2020;9:562-6.