The Egyptian Journal of Hospital Medicine (July 2021) Vol. 84, Page 1955-1960

Ferrous Sulphate Alone Versus Combination of Ferrous Sulphate and Lactoferrin for The Treatment of Iron Deficiency Anemia during Pregnancy and Their Effect on Neonatal Iron Store: A Randomized Clinical Trial

Ibrahim Ali Seif El-Nasr*, Sayed Abdmoneim Mahmoud, Eman Mahmoud Elnaddar, Hesham Ali Ammar
Obstetrics and Gynecology Departments, Faculty of Medicine, Menoufia University Menoufia, Egypt.
***Corresponding author:** Ibrahim Seif El-Nasr, **Mobile:** (+20)01003086747, **Email:** ibrahimaliseifelnasr@gmail.com

ABSTRACT

Background: Iron deficiency anemia (IDA) is a frequent medical condition that causes disturbing pregnancies, especially in low-resource nations, and it contributes considerably to morbidity and mortality. As a result, early detection and treatment of IDA are strongly advised.

Objective: This study was conducted to evaluate the effectiveness, safety and acceptability of ferrous sulphate alone in comparison to combination of ferrous sulphate and lactoferrin for the treatment of iron deficiency anemia during pregnancy and their effect on neonatal iron store.

Patients and methods: This randomized prospective cohort study was conducted on 300 pregnant women from the second trimester with IDA who were enrolled and randomly separated on 2 groups; ferrous sulphate group: 150 pregnant women received 150 mg of dried ferrous sulphate capsules. Combined ferrous sulphate and lactoferrin group: 150 pregnant women received combined 200 mg lactoferrin and 30 mg iron once daily for eight consecutive weeks.

Results: Total increase in CBC with combined ferrous sulphate and lactoferrin was higher compared to ferrous sulfate alone (p value < 0.05). Gastrointestinal adverse effects occurred more frequently with ferrous sulphate than the combined ferrous sulphate and lactoferrin (p< 0.05). Neonatal iron store significantly increased in combined ferrous sulphate and lactoferrin than in ferrous sulphate alone (p value < 0.001).

Conclusion: Combined ferrous sulphate and lactoferrin was more effective than ferrous sulfate in pregnant women with IDA, with fewer gastrointestinal adverse effects and better effect on neonatal iron store.

Keywords: Combined ferrous sulphate and lactoferrin, Ferrous sulphate, Iron deficiency anemia.

INTRODUCTION

IDA is the most common type of anemia**,** it is more prevalent during pregnancy due to high iron requirements during gestation due to the increase in maternal red cell mass, and for development of the fetus and placenta **(1).**

Anemia affects maternal and fetal health. It affects the general wellbeing of the mother (i.e. fatigue, dyspnea, palpitations, headaches and irritability) and increases the risk of maternal morbidity and mortality, preterm birth, fetal growth retardation, low birthweight and perinatal death and decrease neonatal iron store **(2).** There are different routes in treatment of IDA in pregnancy **(3).**

The oral route as ferrous iron preparations are the first choice to replace iron stores as this allows the normal mechanism of absorption to be used, in addition to being an inexpensive and effective treatment **(4).** Unfortunately, gastrointestinal side effects such as epigastric discomfort, nausea, vomiting, diarrhea, constipation, abdominal colicky pain and dark stools are frequently associated with ferrous iron supplements and up to 30% of patients' experience dose limiting side effects **(5).**

Oral bovine lactoferrin is an alternative to ferrous sulphate for treatment of IDA in pregnancy with minimal gasterointestinal side effects **(6).**

This study was conducted to evaluate the efficacy and safety of combined ferrous sulphate and lactoferrin in comparison to ferrous sulphate for the treatment of IDA during pregnancy and their effect on neonatal iron store.

PATIENTS AND METHODS

This randomized prospective cohort study included 300 pregnant women suffering from iron deficiency anemia, conducted in the Department of Obstetrics and Gynecology at Menoufia University Hospital and General Menouf Hospital from October 2019 to April 2020.

Ethical approval:

The study protocol was approved by Hospital Local Medical Ethical Committee, Faculty of medicine, Menoufia University.

An informed consent was obtained from all study participants after explanation nature and scope of the study.

Pregnant women with single fetus, in the second trimester, with IDA (hemoglobin level< 10.5 g/dL and ferritin level< 12 ng/mL) were enrolled.

Received: 9/4 /2021
Accepted:5 /6 /2021

Women with a history of anemia due to any other causes, such as chronic blood loss, hemolytic anemia and thalassemia, severe anemia requiring blood transfusion, bronchial asthma, clinical and/or laboratory evidence of hepatic, renal, hematologic or cardiovascular abnormalities, history of peptic ulcer, hypersensitivity to iron preparations and treatment with any other iron preparation in the last one month before study entry and suspected acute infection were excluded from the study.

Patients were randomly divided into two study groups:

Group 1: Included 150 pregnant women received oral ferrous sulphate (Ferrofol capsules, Eipico, Egypt): Dried ferrous sulphate 150 mg at least 1 hour before or 2 hour after meals once daily after 12 weeks of pregnancy and for 8 weeks.

Group 2: Included 150 pregnant women received oral combined lactoferrin and ferrous sulphate (Complir sachets, Medicina medical ltd): 200 mg lactoferrin and 30 mg iron, 1 sachet to be dissolved in 1/4 glass of water once daily after 12 weeks of pregnancy and for 8 weeks.

All patients were subjected to complete history taking and complete general and abdominal examination. Obstetric ultrasound and laboratory investigations as CBC was done to all patients. Follow up of pregnant women was done by measuring Hb, HCT, MCV after 4, 8 weeks of treatment and at delivery. Monitoring the efficacy in the newborn iron store was done by measuring neonatal Hb level and iron stores immediately after delivery from the umbilical cord.

Outcomes:

The primary outcome measures: Increase hemoglobin level at 4 weeks, 8 weeks after treatment and at delivery.

The secondary outcome measures:

- Rates of maternal side effects during treatment period as: (epigastric discomfort, nausea, vomiting, diarrhea, constipation, abdominal pain and dark stool).
- Obstetric effects as: preterm birth (less than 37 weeks of gestation), low birth weight (less than 2500 g), intrauterine fetal death, neonatal death (within 28 days after delivery), ICU admission, neonatal weight, Apgar score and neonatal iron Store.
- Mode of delivery and associated complications (vaginal delivery or cesarean section).
- Post-partum complications as post-partum hemorrhage.

Statistical analysis

The collected data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for the Social Sciences) software version 22.0, IBM. Descriptive statistics were presented for quantitative data as mean ±SD (standard deviation) and were compared by independent t-test, while for qualitative data it was presented as number and percentage and were compared by Chi-square (X^2) test. P value less than 0.05 was considered statistically significant and less than 0.001 was considered highly significant.

RESULTS

A total number of study group included 300 pregnant women with mild to moderate anemia during the 2nd trimester of pregnancy and randomly divided into 2 groups; the first group received ferrous sulphate alone and the second group received combined ferrous sulphate and lactoferrin drug as in (Figure 1).

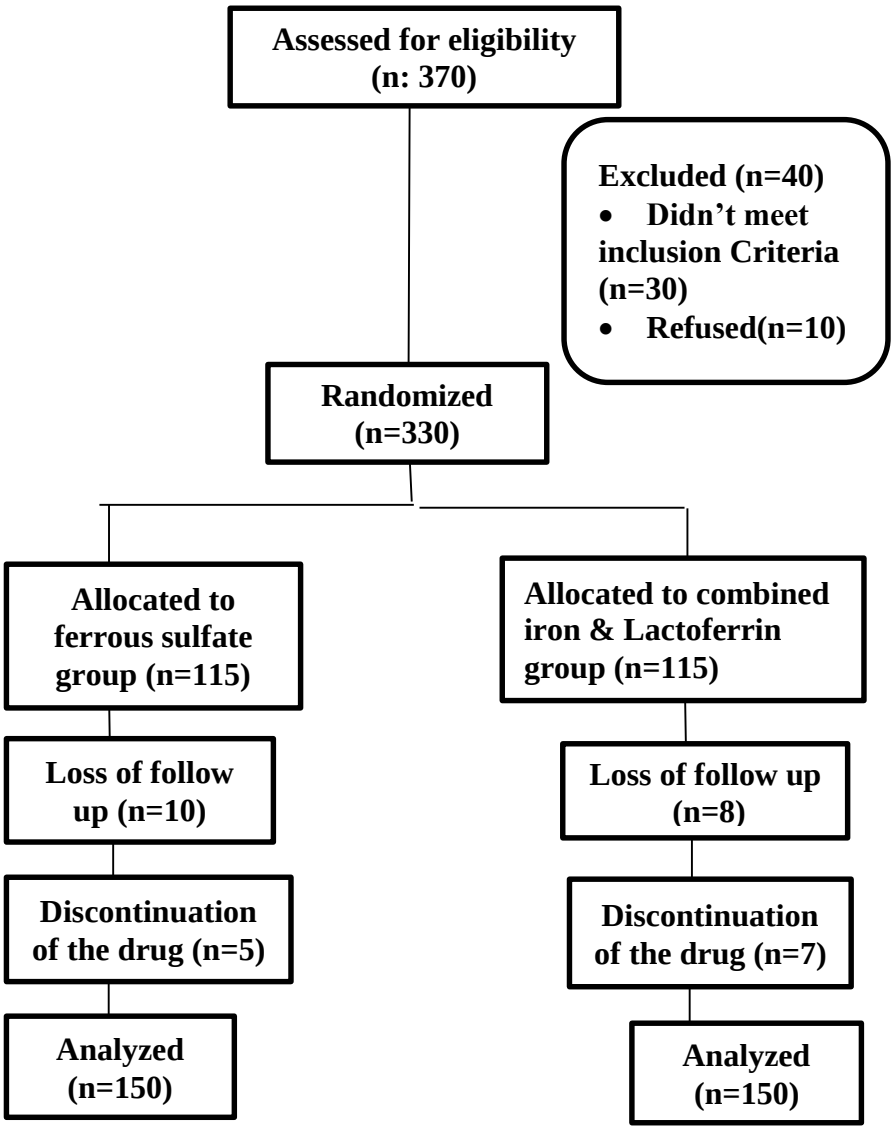

Figure (1): Patient flow chart.

The 2 study groups were homogenous in the maternal demographic data regarding age, parity, BMI, GA at start of study as in (Table 1).

Table (1): Demographic data among the studied groups

		Group 1 N=150	Group 2 N=150	P value
Age (years) Mean ±SD		26.95±6.64	27.14±6.32	>0.05
BMI (kg/m^2) Mean ±SD		27.42±2.75	26.95±2.23	>0.05
GA at start of study (weeks) Mean ±SD		12.84±0.69	12.71±0.71	>0.05
Parity	**PG (N, %)**	43 (28.6%)	50 (33.3%)	>0.05
	Multipara (N, %)	107 (71.3%)	100 (66.6%)	

SD: standard deviation, Kg/m^2: kilogram/ meter^2, BMI: body mass index, GA: gestational age, PG: primigravida, N: number

(Delete the column of t-test from each table)

Table (2) shows maternal CBC (gm/dL), the total increase in Hb, HCT, MCV were higher in combined ferrous sulphate and lactoferrin compared to ferrous sulphate alone.

Table (2): CBC among the studied groups

		Group 1 N=150	Group 2 N=150	P value
Hb (g/dL) (Mean ±SD)	**Basal**	8.79±0.86	8.84±0.85	>0.05
	After 1m	9.42±0.87	9.82±0.84	<0.001
	After 2M	10.02±0.91	10.78±0.84	<0.001
	At 36 week	11.14±1.04	12.77±0.96	<0.001
	Total increase of Hb level	2.25±0.80	3.87±0.91	<0.001
HCT (Mean ±SD)	**Basal**	29.39±2.27	28.99±1.87	>0.05
	After 1m	31.42±2.40	32.23±1.85	<0.001
	After 2M	33.09±2.53	34.94±1.73	<0.001
	At 36 week	35.18±2.47	37.46±1.79	<0.001
	Total increase of HCT level	5.66±1.68	8.31±2.01	<0.001
MCV (Mean ±SD)	**Basal**	69.36±2.46	68.84±2.095	>0.05
	After 1m	71.78±2.60	72.44±2.05	0.016
	After 2M	73.59±2.67	75.27±2.09	<0.001
	At 36 week	76.04±2.72	78.69±2.22	<0.001
	Total increase of MCV	6.34±1.39	9.87±2.03	<0.001

CBC: complete blood count, Hb: hemoglobin, HCT: hematocrit, MCV: mean corpuscular volume, M: month, SD: standard deviation

There was statistically a significant difference between ferrous sulphate alone and combined ferrous sulphate and lactoferrin group regarding gasterointestinal side effects as in table 3.

Table (3): Maternal side effects among the studied groups

	Group 1 (N=150)	Group 2 (N=150)	P value
Gastric upset (N, %)	93 (83.0%)	19 (17.0%)	<0.001
Abdominal pain (N, %)	98 (74.2%)	34 (25.8%)	<0.001
Diarrhea (N, %)	30 (83.3%)	6 (16.7%)	<0.001
Vomiting (N, %)	70 (85.4%)	12 (14.6%)	<0.001
Constipation (N, %)	107 (81.7%)	24 (18.3%)	<0.001
Dark stool (N, %)	117 (86.7%)	18 (13.3%)	<0.001

N: number

Regarding obstetric outcome of the two groups, there was no significant difference between the two groups regarding GA at delivery, mode of delivery, preterm birth, IUFD, neonatal death, ICU admission and postpartum hemorrhage as in table 4.

Table (4): Obstetric outcomes among the studied groups

	Group 1 (N=150)	Group 2 (N=150)	P value
GA at delivery (weeks) (Mean ±SD)	38.38±1.133	38.45±1.01	>0.05
Mode of delivery **SVD (N, %)** **CS (N, %)**	 117 (48.8%) 33 (55%)	 123 (51.2%) 27 (45%)	>0.05
Preterm birth (N, %)	3 (75%)	1 (25%)	>0.05
IUFD (N, %)	0	0	--
Neonatal death (N, %)	1 (100%)	0	>0.05
ICU admission (N, %)	5 (62.5%)	3 (37.5%)	>0.05
Postpartum Hge (N, %)	3 (60)	2 (40)	>0.05

GA: gestational age, SVD: single vaginal delivery, CS: cesarean section, IUFD: intrauterine fetal death, ICU: intensive care unit, Hge: hemorrhage, N: number

Neonatal iron stores (neonatal Hb, serum ferritin level, serum iron, TIBC and transferrin saturation) significantly increased with combined ferrous sulphate and lactoferrin group than ferrous sulphate alone as shown in table 5.

Table (5): Neonatal iron store among the studied group

	Group 1 (N=150)	Group 2 (N=150)	P value
Neonatal Hb (g/dL)- Mean ±SD	15.90±2.01	17.34±1.46	<0.001
Serum ferritin level (ng/mL) Mean ±SD	136.65±4.02	161.87±30.34	<0.001
Serum iron (mcg/dL)-Mean ±SD	159.29±35.74	182.27±30.062	<0.001
TIBC (mcg/dL)- Mean ±SD	342.59±52.90	368.68±45.34	<0.001
Transferrin saturation (µg/dL) Mean ±SD	33.50±4.77	38.56±4.71	<0.001

Hb: hemoglobin, SD: standard deviation, TIBC: total iron binding capacity.

DISCUSSION

Hemoglobin (Hb) less than normal during pregnancy is defined by the WHO as <11 g/dl in the first trimester, <10.5 g/dl in the second trimester, and <11 g/dl in the third trimester [(7)]. Anemia has a detrimental influence on maternal and fetal health because it inhibits oxygen transport to the fetus through the placenta, raising the risk of preterm birth, fetal growth retardation, low birthweight, perinatal mortality, and a decrease in neonatal iron stores [(8)].

The most extensively used iron preparation in the world is ferrous sulphate. Despite its effectiveness and inexpensive cost, however, this medicine is linked to a significant number of adverse effects, most of which involve the gastrointestinal system [(9)].

Lactoferrin (previously lactotransferrin) is a glycoprotein that belongs to the transferrin family, which includes proteins that may bind and transfer iron [(10)]. Lactoferrin levels in cow milk and human milk colostrum are roughly seven times higher than lactoferrin levels in milk produced later [(11)].

The aim of our study was to evaluate the effectiveness, safety and acceptability of ferrous sulphate alone in comparison to combination of ferrous sulphate and lactoferrin for the treatment of iron deficiency anemia during pregnancy and their effect on neonatal Iron store.

In our study, the results showed that total increase in Hb, HCT, MCV after 2 months with combined ferrous sulphate and lactoferrin was higher compared to ferrous sulfate. This is in agreement with the study conducted by **Paesano *et al.* [(12)];** who designed a study to compare the efficacy and tolerability of oral bovine lactoferrin (100 mg twice a day) and ferrous sulphate (520 mg once a day). In all treated women, the hemoglobin and total serum iron values showed a significant increase (P < 0.001) after 30 days of treatment. However, in pregnant women receiving ferrous sulphate, the increase in mean values of hemoglobin and total serum iron (0.9 g/dL and 8.0 ug/dL, respectively) were lower than those observed in women receiving lactoferrin (1.5 g/dL and 54.2 ug/dL respectively). Also our study is consistent with **Hashim *et al.* [(13)]** systematic review and meta-analysis study that aimed to evaluate the efficacy of daily oral bovine lactoferrin versus daily oral ferrous iron preparations for treatment of IDA during pregnancy. The study included 4 eligible trials (600 women) and estimated for change in hemoglobin levels at 4 weeks with daily oral lactoferrin versus daily oral ferrous sulphate. Pooled estimates for change in hemoglobin levels at four weeks favored daily oral lactoferrin over daily oral ferrous sulphate (mean difference 0.77; 95% confidence interval [CI] 0.04-1.55; P = 0.04, 4 trials, 600 women). The present study is also in agreement with the study conducted by **Rateb *et al.* [(14)].** It was a double blind clinical trial that aimed to compare the safety, tolerability, efficacy and hematological response of lactoferrin in treatment of iron deficiency anemia during pregnancy versus ferrous sulfate capsules on 200 pregnant women for 8 weeks. The results showed that the total increase in hemoglobin after 2 months with lactoferrin was higher (1.5±0.5g/dL) compared to ferrous sulphate (0.8±0.4g/dL) (P <0.001).

However the study conducted by **Nappi *et al.* [(15)]**; which was a prospective, randomized, controlled, double blind trial to compare the effects of bovine lactoferrin with ferrous sulfate on iron nutritional status and to evaluate their tolerability in 100 pregnant women with iron deficiency anemia, concluded that bovine lactoferrin has the same efficacy as ferrous sulfate in restoring iron deposits, the results showed Hb before therapy was 10.1± 0.5 g% and after therapy by ferrous sulfate for 4 weeks Hb increased to11.5±0.6 g% and by lactoferrin for 4 weeks Hb increased to 11.2 ± 0.5 g% (p value >0.05).

According to the present study gasterointestinal side effects increase with ferrous sulphate alone than combined ferrous sulphate and lactoferrin group. This is in agreement with **Hemeda *et al.* [(16)]** who did a prospective open label randomized clinical trial to compare ferrous fumarate and bovine lactoferrin as regard treatment of anemia in 146 pregnant patients with iron deficiency anemia. The study concluded that gastrointestinal side effects occurred more frequently with ferrous sulphate than lactoferrin group (P<.0.001).

In the present study there was no significant difference between ferrous sulphate group and combined ferrous sulphate and lactoferrin group

regarding obstetric outcome. This is consistent with **Rezk *et al.* [17]** study that concluded that there was no significant difference between ferrous sulphate and lactoferrin regarding gestational age at delivery, mode of delivery, postpartum complications, neonatal death, IUFD, preterm birth and ICU admission (p value > 0.05).

Our study shows significant increase in combined iron and lactoferrin group than in ferrous sulphate group regarding neonatal iron store.

CONCLUSION

Oral combined ferrous sulphate and lactoferrin was better tolerated and more acceptable with higher increase in mean hemoglobin, neonatal weight, neonatal iron store and less gastrointestinal side effects when compared to oral iron therapy.

Strength of this study:

- Large sample size.
- The study involves effects and side effects of the drug.
- The study involves intrapartum and postpartum complications.
- The study involves neonatal outcome.

Limitation of this study: It includes pregnant women with single viable fetus during 2nd and 3rd trimester of pregnancy complains with mild to moderate anemia. No history of maternal medical disorder.

Acknowledgement: The authors would like to acknowledge the contribution of patients, residents and nursing staff at Obstetrics and Gynecology Department and Outpatient Clinic of Menoufia University Hospital.

Conflict of interest: The authors declare that they have no conflict of interest.

Funding source: None.

REFERENCES

1. **Paidas M, Hossain N, Shamsi T *et al.* (2011):** Hematologic changes in pregnancy. Hemostasis and Thrombosis in Obstetrics and Gynecology, 3: 1-11.
2. **Pavord S, Myers B, Robinson S *et al.* (2012):** UK guidelines on the management of iron deficiency in pregnancy. British Journal of Hematology, 156(5): 588-600.
3. **Auerbach M, Adamson J (2016):** How we diagnose and treat iron deficiency anemia. American Journal of Hematology, 91(1): 31-38.
4. **Pereira I, Couto Irving S, Lomer C *et al.* (2014):** A rapid, simple questionnaire to assess gastrointestinal symptoms after oral ferrous sulphate supplementation. BMC Gastroenterology, 14: 103.
5. **Lopez A, Cacoub P, Macdougall I *et al.* (2016):** Iron deficiency anaemia. The Lancet, 387(10021): 907- 916.
6. **Rezk M, Kandil M, Dawood R *et al.* (2015):** Oral lactoferrin versus ferrous sulphate and ferrous fumerate for the treatment of iron deficiency anemia during pregnancy. Advancd Nutrition and Human Metabolism Journal, 2: 740-45.
7. **WHO (2011):** Haemoglobin concentrations for the diagnosis of anemia and assessment of severity. Vitamin and Mineral Nutrition Information System. Geneva, World Health Organization. https://www.who.int/vmnis/indicators/haemoglobin/en/
8. **Rahman M, Abe K, Rahman S *et al.* (2016):** Maternal anemia and risk of adverse birth and health outcomes in low- and middle-income countries: systematic review and meta-analysis. American Journal of Clinical Nutrition, 103:495–504.
9. **Tolkien Z, Stecher L, Mander A *et al.* (2015):** Ferrous sulphate supplementation causes significant gastrointestinal side-effects in adults: a systematic review and meta-analysis. PIoS One, 10(2): 117383.
10. **Karav S, German J, Rouquié C *et al.* (2017):** Studying lactoferrin N-glycosylation. International Journal of Molecular Sciences, 18(4): 870-75.
11. **Kochhar P, Kaundal A, Ghosh P (2013):** Oral iron in treatment of iron deficiency anemia in pregnancy: A randomized clinical trial. J Obstet Gynaeco Res., 39: 504-510.
12. **Paesano R, Pietropaoli M, Gessani S *et al.* (2009):** The influence of lactoferrin, orally administered, on systemic iron homeostasis in pregnant women suffering of iron deficiency anemia. Biochimie., 91(1): 44-51.
13. **Hashim H, Foda O, Ghayaty E (2017):** Lactoferrin or ferrous salts for iron deficiency anemia in pregnancy: A meta-analysis of randomized trials. European Journal of Obstetrics & Gynecology and Reproductive Biology, 219: 45-52.
14. **Rateb A, Mamdouh A and Balsha K (2018):** The effect of orally administered iron-saturated lactoferrin on systemic iron homeostasis in pregnant women suffering from iron deficiency and iron deficiency anaemia. The Egyptian Journal of Hospital Medicine, 71(4): 2851-2857.
15. **Nappi C, Tommaselli A, Morra I *et al.* (2009):** 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 Scandinavica, 88(9): 1031-1035.
16. **Hemeda H, Mohamed A, Islam B *et al.* (2018):** Effectiveness of bovine lactoferrin versus ferrous fumarate in the management of iron deficiency anemia in pregnancy: Randomized clinical trial. International Journal of Reproductive Medicine & Gynaecology, 4(1): 006-011.
17. **Rezk M, Dawood R, Abo-Elnasr M *et al.* (2016):** Lactoferrin versus ferrous sulphate for the treatment of iron deficiency anemia during pregnancy: a randomized clinical trial. J Matern Fetal Neonatal Med., 29: 1387-1390.