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Compliance and Efficacy of Oral Lactoferrin versus Ferrous Sulfate in Treatment of Nutritional Iron Deficiency Anemia during Second Trimester among Egyptian Ladies

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ABSTRACT

Background: Nutritional iron deficiency anemia is of a major concern in Egypt, especially during pregnancy. The most commonly used treatment is oral iron mainly as ferrous sulfate. Unfortunately, ferrous sulfate has low efficacy with many adverse effects. Lactoferrin is a glycoprotein which belongs to proteins which have the ability to bind and transfer iron. This study was done to assess the compliance, efficacy and safety of lactoferrin in comparison to ferrous sulfate.

Methods: This randomized clinical trial was conducted in outpatient clinic under supervision of Department of Obstetrics and Gynecology, Faculty of medicine, Ain Shams University, Cairo, Egypt from August 2019 to February 2020. 140 women with iron deficiency anemia in second trimester were recruited and randomly assigned to either group. First group received lactoferrin 200 mg sachets once daily and second group received 100 mg of dried ferrous sulfate capsules twice daily for 4 consecutive weeks. Compliance to treatment, efficacy and side effects were recorded.

Results: Compliance is better in lactoferrin group in comparison to ferrous sulfate group. Maternal side effects were significantly less common in lactoferrin group than in ferrous sulfate group. The increase in hemoglobin was significantly higher in lactoferrin group. Number of cases achieved Hb level ≥10.5 was more frequent in lactoferrin group.

Conclusion: Oral lactoferrin is more tolerated and effective as compared to traditional treatment by ferrous sulfate.

Key words: nutritional iron deficiency anemia, anemia in pregnancy, lactoferrin, ferrous sulphate.

INTRODUCTION

Iron deficiency anemia is the most common micronutrient deficiency that affects more than 2 billion people all over the world. Pregnant ladies and infants especially in developing countries are among the highest risk group. Also those in developed countries still have the risk [(1)]. Iron deficiency during pregnancy is caused mainly by maternal–fetal iron transfer, exacerbated by deficient maternal iron stores [(2)]. In normal pregnancy, total iron needed is about 1gm. Fetus and placenta consume about 300 to 350 mg, 500 mg for RBCs mass and during delivery an amount of 250 mg is associated with blood loss[(3)].

Anemia in pregnancy is diagnosed according to Center of Disease Control (CDC) if hemoglobin below 11 g/dl (Hematocrit;{HCT} < 33%) during the first and third trimesters and below 10.5 g/dl (HCT < 32%) in the second trimester. According to the World Health Organisation (WHO), anemia in pregnancy is diagnosed as hemoglobin level below 11 gm/dl all through pregnancy [(4,5)]. Anemia in pregnancy is not without risks. It is a risk factor for miscarriage, fetal growth restriction, prematurity, fetal mortality and neonatal anemia together with early infancy anemia due to low iron stores [(6)]. Many cellular activities depend on iron as an essential and vital nutrient. So iron is crucial for early stages of nervous system development. Therefore iron has a vital role in intrauterine and postnatal development [(7)].

In pregnancy, oral iron supplements are usually used for treatment of iron deficiency anemia. But compliance to oral iron is usually low as a result of its side effects mainly gastrointestinal as nausea, vomiting and constipation, resulting in subsequent discontinuation [(8,9)]. Lactoferrin, glycoprotein from transferrin family, is present abundantly in human's milk and other mammals. Most exocrine secretions contain lactoferrin. Also neutrophils in inflammation and infection sites synthesize lactoferrin. The iron affinity to lactoferrin is two times higher than serum transferrin. Lactoferrin chelates two Fe^{+3} ions per molecule, which is reversible [(10)].

In this study, the aim was to assess the compliance, efficacy and safety of lactoferrin and ferrous sulfate during second trimester among Egyptian ladies.

METHODS

This randomized clinical trial was conducted in outpatient clinic under supervision of Department of Obstetrics and Gynecology, Faculty of medicine, Ain

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Shams University, Cairo, Egypt from August 2019 to February 2020. Selection of participants was based on following selection criteria:

Inclusion criteria:

1. Pregnant women with singleton pregnancy.
2. Gestational age < 28 weeks.
3. Hemoglobin level between 8 to 10 gm% and serum ferritin levels <25 ng/dL).

Exclusion criteria:

1. Multiple pregnancy.
2. Age < 20 or > 40 years old.
3. Hemoglobin level < 8 or > 10 gm %.
4. Gestational age more than 28 wks.
5. Any other cause of iron deficiency anemia other than nutritional causes.
6. Hypersensitivity to iron preparations.

Sample Size Justification and randomization:

Using G power program, setting alpha error of 5% and power at 80% and assuming an effect size corresponding to a (w) coefficient of 0.25 on the rate of side effects between the two study groups (lactoferrin vs ferrous sulphate) produced a sample size of 70 cases per group (total 140). The study was conducted on (140) women subdivided into 2 groups according to Computer-generated random list using MedCalc© version 13.

Ethical approval:

This study was done after approval of the ethical committee of the department of obstetrics and gynecology, faculty of medicine, Ain Shams University. The approval number is FMASU M S 265/2019. Informed consent was taken from all participants before recruitment in the study.

Study procedures

Full history was taken to detect the presence of inclusion criteria and absence of exclusion criteria. Gestational age was calculated using last menstrual period providing that the woman having regular cycles, sure of date, not breastfeeding or using oral contraceptive pills or any other factors that could influence the ovulation time. This was confirmed by first trimester ultrasound (up to and including 13 6/7 weeks of gestation). Ultrasound was done to exclude any abnormalities. Also serum ferritin and hemoglobin level were measured. MCV and MCHC were recorded. Then each eligible patient was randomly allocated to one of the 2 groups:

(Lactoferrin group): 70 women received lactoferrin 200 mg sachets (Mamyvital 200 mg sachets, Dulex Lab Egypt) daily for 4 consecutive weeks.

(Ferrous Sulfate group): 70 women received 100 mg of ferrous sulfate capsules twice daily for 4 consecutive weeks.

Follow up:

Hemoglobin level was measured again after 4 weeks of therapy.

Outcomes:

1ry outcome: Compliance in both groups.

2ry outcomes:

1. Effectiveness (rise in hemoglobin level)
2. The side effects (nausea, vomiting, heart burn, abdominal pain and constipation) related to iron therapy by four weeks of treatment.

Statistical analysis

The collected data was coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 22.0, IBM Corp., Chicago, USA, 2013.

Descriptive statistics was done for quantitative data as minimum& maximum of the range as well as mean±SD (standard deviation) for quantitative normally distributed data, while it was done for qualitative data as number and percentage.

Inferential analyses was done for quantitative variables using K-S test for normality testing, independent t-test in cases of two independent groups with normally distributed data and paired t-test in cases of normality testing, independent t-test in cases of two independent groups with normally distributed data and paired t-test in cases of two dependent groups with normally distributed data. In qualitative data, inferential analyses for independent variables was done using Chi square test for differences between proportions. The level of significance was taken at P value < 0.050 is significant, otherwise is non-significant.

RESULTS

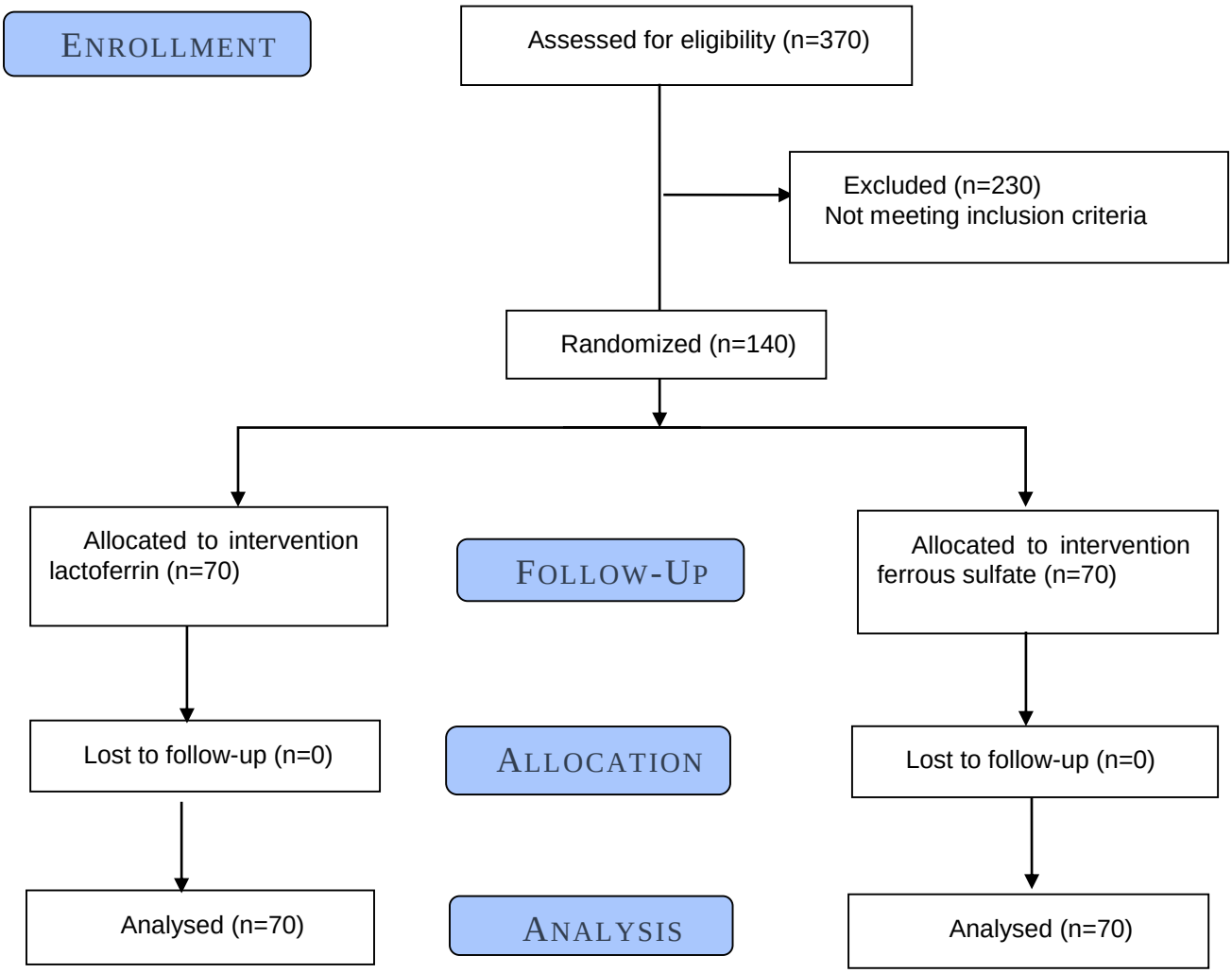

Figure (1): Patients flow chart

As regard the demographic data no significant difference between the lactoferrin and ferrous sulphate groups.

Table (1): Demographic data of both groups

Items	Measure	Lactoferrin (N=70)	Ferrous sulphate (N=70)	P-value
Age (years)	Mean±SD	26.4±4.2	27.4±4.5	>0.05
	Range	20.0–34.0	20.0–35.0	
Parity	Median(1st–3rd IQ)	1.0 (0.0–2.0)	1.0 (0.0–3.0)	>0.05
	Range	0.0–4.0	0.0–4.0	
Parity	Primi	20 (28.6%)	21 (30.0%)	>0.05
	Multi	50 (71.4%)	49 (70.0%)	
GA (in weeks)	Mean±SD	19.3±2.7	19.0±2.5	>0.05
	Range	12.0–25.0	14.0–24.0	

No significant difference between the studied groups regarding basal laboratory findings **(**table 2).

Table (2): Basal laboratory findings

Items	Measure	Lactoferrin (N=70)	Ferrous sulphate (N=70)	^ P-value
HCT (%)	Mean ±SD	28.5±2.2	28.1±2.7	>0.05
	Range	22.6–34.0	21.3–34.3	
MCV	Mean ±SD	72.1±6.5	71.1±5.6	>0.05
	Range	54.6–88.6	54.0–82.0	
MCHC	Mean ±SD	23.3±2.8	23.5±2.8	>0.05
	Range	17.6–30.4	18.0–32.1	
Serum ferritin	Mean ±SD	10.8±3.3	10.7±3.2	>0.05
	Range	4.0–23.0	4.0–17.0	

Follow up hemoglobin and hemoglobin elevation were higher in lactoferrin group than in ferrous sulfate group (table3 and figure 2).

Table (3): Basal and follow up Hemoglobin (gm/dL)

Time	Measure	Lactoferrin (N=70)	Ferrous Sulfate (N=70)	^P-value (groups)
Basal	Mean ±SD	9.0±0.6	9.1±0.6	>0.05
	Range	8.0–9.9	8.0–9.9	
Follow up	Mean ±SD	10.2±0.6	9.6±0.6	<0.001*
	Range	9.1–11.2	8.3–10.6	
Change (after-before)	Mean ±SD	1.2±0.2	0.5±0.2	<0.001*
	Range	0.2–1.3	-0.5–0.8	
P-value (time)		<0.001*	<0.001*	
Value of lactoferrin over ferrous sulfate				
Items		Mean ±SE	95% CI	
Hemoglobin elevation		0.7±0.0	0.6–0.8	

*: Significant difference

Hb ≥10.5 was significantly more frequent in lactoferrin group than in ferrous sulfate group **(**table 4 and figure 3**).**

Table (4): Hemoglobin grade in second trimester

Grade	Lactoferrin (N=70)	Ferrous sulfate (N=70)	P-value
Hb ≥10.5	26 (37.1%)	4 (5.7%)	<0.001*
Hb <10.5	44 (62.9%)	66 (94.3%)	
Value of Lacoferrin over ferrous sulfate in getting Hb ≥10.5			
Items		Value	95% CI
Rate elevation		31.4%	17.4%–39.0%
Efficacy		84.6%	74.2%–95.6%
Relative Rate		6.50	2.36–21.43
Number needed to treat		3.2	2.6–5.8

Compliance was significantly higher in lactoferrin group than in ferrous sulfate group (table 5 and figure 4).

Table (5): Compliance to treatment

Status	Lactoferrin (N=70)	Ferrous sulfate (N=70)	P-value	RR (95% CI)
Compliant	65 (92.9%)	54 (77.1%)	0.009*	1.20 (1.04–1.39)
Not compliant	5 (7.1%)	16 (22.9%)		

#Chi square test, RR: Relative risk,*Significant, CI: Confidence interval

Maternal side effects were significantly more common in lactoferrin group than in ferrous sulfate group (table 6 and figure5).

Table (6): Maternal side effects

Side effects	Lactoferrin (N=70)	Ferrous sulfate (N=70)	P-value	RR (95% CI)
Abdominal pain	13 (18.6%)	43 (61.4%)	<0.001*	0.30 (0.18–0.51)
Constipation	13 (18.6%)	42 (60.0%)	<0.001*	0.31 (0.18–0.52)
Heart burn	12 (17.1%)	36 (51.4%)	<0.001*	0.33 (0.19–0.59)
Nausea	10 (14.3%)	33 (47.1%)	<0.001*	0.30 (0.16–0.57)
Vomiting	6 (8.6%)	23 (32.9%)	<0.001*	0.26 (0.11–0.60)

RR: Relative risk,*Significant, CI**:** Confidence interval

DISCUSSION

The main cause of iron deficiency anemia (IDA) in pregnancy is related in particular to increased iron requirements due to increased RBCs production and development of the fetoplacental unit. Both iron deficiency (ID) and IDA are associated with many adverse outcomes as premature labor, fetal growth retardation, low birth weight and poor health of the neonate [(11)].

This randomized clinical study aimed to assess the compliance, efficacy and safety of lactoferrin in comparison to ferrous sulfate for management of iron deficiency anemia during pregnancy in second trimester among Egyptian ladies. Patients were randomly allocated to two equal groups. First group included 70 women received lactoferrin 200 mg sachets once daily for 4 consecutive weeks and Second group included 70 women received 100 mg of dried ferrous sulphate capsules twice daily for 4 consecutive weeks.

Maternal adverse effects as nausea, vomiting, abdominal pain, constipation and heart burn were significantly less frequent in lactoferrin group than in ferrous sulfate group. Therefore, compliance with lactoferrin treatment was significantly higher than in ferrous sulphate group. In addition, there was significant increase in hemoglobin level above baseline value in both groups. Hemoglobin elevation and number of cases achieved Hb level ≥10.5 were significantly higher in lactoferrin group than in ferrous sulfate group.

This result was comparable with the results of ***Rateb et al.***who conducted a study in Ain Shams University. Their study aimed to compare lactoferrin and ferrous sulphate capsules in treatment of iron deficiency anemia during pregnancy as regard safety, tolerability and efficacy. Their study was carried out on 200 pregnant ladies with iron deficiency anemia divided into two groups. Group I: received 100 mg of bovine lactoferrin (Pravotin sachets, Hygint, Egypt) twice a day. Group II: received 150 mg of dried ferrous sulphate + folic acid (vitamin B9) 0.50 mg (Ferrofol, E.I.P.I.C.O, Egypt) three capsules per day. Both group received treatment for 4 weeks. As regard basal hemoglobin there was no significant difference between both groups, while there was a significant increase in hemoglobin level in both

groups after 4 weeks of treatment (P < 0.01). The increase in both hemoglobin level and serum ferritin level in their study was significantly higher in lactoferrin group (2.7 g/dl) than in ferrous sulphate group (1.7 g/dl). Also, they found that, the side effects of treatment including constipation, abdominal pain, nausea and vomiting were more frequent in group B (ferrous sulphate) than group A (lactoferrin) as there was statistically a significant difference between both groups (P < 0.01) [12].

In harmony with current results, ***Rezk et al.*** conducted a study to evaluate the efficacy and side effects of both lactoferrin and ferrous sulphate. Their study was done on two hundred pregnant ladies in their second trimesters. They were randomly assigned either to ferrous sulphate group (received 150 mg of dried ferrous sulphate capsules) or lactoferrin group (received 250 mg capsules once daily) for eight consecutive weeks. The results showed that the rise in hemoglobin after 8 weeks was higher in lactoferrin group than in ferrous sulphate group (2.26±0.51g/dL) and (1.11±0.22g/dL) respectively (P <0.001). The gastrointestinal side effects were higher in ferrous sulphate group (p<0.001). The poor patient compliance to iron therapy was more common in ferrous sulphate group (p<0.001). The pregnant ladies who requested to shift to other medication were more in the ferrous sulphate group (p<0.001) [13].

In line with current study, a systematic review and meta-analysis carried by ***Abu Hashim et al.*** to evaluate the efficacy of lactoferrin versus oral ferrous iron for treatment of pregnant ladies with iron deficiency anemia. The rise in hemoglobin levels after 4 weeks of treatment was more among daily oral lactoferrin intake groups. The gastrointestinal side effects were much less in lactoferrin groups. This meta-analysis recommended the use of lactoferrin as the first choice for iron deficiency anemia treatment in pregnancy [14].

Nasr et al. conducted a randomized clinical study in Al -Azhar University Hospital, Assiut, Egypt, which supported our results. 600 pregnant women in the 2nd half of pregnancy who were randomly assigned to receive one of three oral iron preparations; ferrous sulphate 150 mg or Lactoferrin 250 mg or amino acid chelated iron 15 mg once daily for 8 weeks. In their study, the clinical characteristics of the patients in all groups were comparable with no significant differences as regard to their age, parity, gestational age, and baseline hemoglobin level of the patients included in the study. After 4 weeks of therapy hemoglobin level increased in the three groups however the difference between them was statistically insignificant. The lactoferrin group (group C) showed significant increase in the RBCs level (4.3± 0.4359), followed by amino acid cheated group (group B) (4.291± 0.2092), followed by ferrous sulphate group (group A) (3.974± 0.3582) (P< 0.05). Moreover, for hematocrit value, the lactoferrin group (group C) showed significant increase in the HCT % level (42.9± 2.3), followed by ferrous sulphate group (group A) (39.22± 1.95), followed by amino acid chelated group (group B) (38.17± 2.012), (P <0.001) [15].

In addition, another randomized clinical trial by ***Mohamed et al.*** agreed with our results. The study was conducted at Al-Monira General Hospital to estimate the efficacy and the safety of both lactoferrin and ferrous sulphate in treatment of pregnant ladies with iron deficiency anemia. It included 200 women randomly assigned to one of two groups. Group 1: in which 100 pregnant women received lactoferrin 100 (Pravotin100 mg sachets, Hygint, Egypt) once daily for 2 months. Group 2: in which 100 pregnant women received 150 mg of dried ferrous sulphate capsules (Ferrofol capsules, EIPICO, Egypt) once daily for 2 months. After 2 months of treatment, the lactoferrin group showed more rise in hemoglobin compared to ferrous sulfate. The results showed that both rise in hemoglobin after 4 weeks and 8 weeks and serum ferritin were significantly higher in lactoferrin group than in ferrous sulphate group. They also reported that gastrointestinal manifestations occurrence was significantly higher in ferrous sulphate. As regard compliance and tolerability, they found that lactoferrin was much more tolerable in comparison with ferrous sulfate**.** [16].

A study by ***Nappi et al.*** agreed with our results as regard the side effects of both agents. Their results showed that lactoferrin has significantly fewer gastrointestinal side effects than ferrous sulphate. However, as regard the efficacy, our results disagreed with their results as they reported that lactoferrin is as effective as ferrous sulfate on elevation of Hb and serum ferritin [17].

CONCLUSION

Oral lactoferrin is well tolerated with much lower side effects compared to traditional treatment by ferrous sulfate. Oral lactoferrin provides significantly greater improvements in hemoglobin level compared to traditional treatment by ferrous sulfate. Oral lactoferrin may be a preferable alternative to traditional treatment (ferrous sulfate) for IDA during pregnancy.

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