

RESEARCH ARTICLE

Oral lactoferrin versus ferrous sulphate and ferrous fumerate for the treatment of iron deficiency anemia during pregnancy

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A prospective, randomized, parallel-group, multi-center study was conducted in the Department of Obstetrics and Gynecology at Menoufia University Hospital and central hospitals at Menoufia governorate, Egypt including 300 pregnant women in the second trimester diagnosed with iron deficiency anemia (IDA) who were divided into three groups, the first received lactoferrin capsules, the second received ferrous sulphate capsules and the third received ferrous fumerate capsules daily for two months. There was a highly significant difference between the three groups ($p < 0.001$) regarding increments in Hb after one and two months and overall increase in Hb in the lactoferrin group, there was a highly significant difference between the three groups ($p < 0.001$) with gastrointestinal adverse effects being the least in the lactoferrin group, there was a highly significant difference between the three groups ($p < 0.001$) with the best compliance, acceptability and overall satisfaction in the lactoferrin group. According to the results obtained in this clinical trial, oral lactoferrin was better tolerated and more acceptable with higher increase in mean hemoglobin when compared to oral iron therapy over two month treatment. Oral lactoferrin can be used as a good substitute to oral iron therapy in mild to moderate IDA during pregnancy.

Keywords: Lactoferrin; ferrous sulphate; ferrous fumerate; pregnant women; iron deficiency anemia

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Introduction

Iron deficiency anemia (IDA) is the condition in which there is anemia due to a lack of iron. IDA develops when available iron is insufficient to support normal red cell production and is the most common type of anemia^[1].

Anemia has a significant impact on the health of the fetus as well as that of the mother. It impairs the oxygen delivery through the placenta to the fetus and interferes with the normal intrauterine growth, leading to fetal loss and perinatal deaths. Anemia is associated with increased preterm labor (28.2%), preeclampsia (31.2%), and maternal sepsis^[2,3].

The oral route is 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^[3,4].

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^[5].

This study was conducted to evaluate the effectiveness, safety and acceptability of lactoferrin in comparison to

ferrous sulphate and ferrous fumarate for the treatment of IDA during pregnancy.

Materials and Methods:

This prospective, randomized, parallel-group, multi-center study was conducted in the Department of Obstetrics and Gynecology at Menoufia University Hospital and central hospitals at Menoufia governorate, Egypt in the period between February 2014 and end of February 2015. The study protocol was reviewed and approved by the institutional review boards and ethics committees of both institutions and informed consent was obtained from all participants prior to commencing the study.

Seventy-five patients was required in each group for the study to have 90% power to detect 10% difference between the groups regarding success rate ($P=0.05$, 2-sided). To compensate for possible non-evaluable data, we enrolled more than 100 participants in each group.

A total of 342 pregnant women were enrolled and randomly assigned into three study groups using a computerized random number generator in a sequence of sealed, numbered opaque envelopes, with a 1:1:1 randomization ratio. Forty two patients were dropped out (24 discontinued drug intake and 20 lost follow up). A total of 300 pregnant women completed the study (figure 1).

The patients were assigned to take the medication orally, once daily after lunch. Patients were advised to avoid the intake of tea, coffee, milk, milk products, antacids and calcium preparation within 2 hours before or after iron capsules.

Group 1 (Lactoferrin group): included 100 pregnant women received lactoferrin 250 mg capsules (Jarrow Formulas, Egypt) once daily for 8 consecutive weeks.

Group 2 (Sulphate group): included 100 pregnant women received 150 mg of dried ferrous sulphate capsules (Ferrofol capsules, EIPICO, Egypt) once daily for 8 consecutive weeks.

Group 3 (Fumarate group): included 100 pregnant women received ferrous fumarate 350 mg capsules (Haema caps, Amoun Pharmaceutical Company, Egypt) once daily for 8 consecutive weeks.

Pregnant women with single fetus, in the second trimester, with iron deficiency anemia (hemoglobin level <11 g/dL and ferritin levels <25 ng/dL) were enrolled. Women with a history of anemia due to any other causes such as chronic blood loss, hemolytic anemia, and thalassemia (including

thalassemic trait), 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.

The primary efficacy parameter was the amount of increase in Hemoglobin concentration by 4 and 8 weeks of treatment. The adverse effects (patients were asked to report any unusual or unpleasant symptoms during the study period) related to iron therapy and the patient acceptability (in terms of compliance, overall satisfaction of treatment & the probability of reuse in subsequent pregnancy or advice to other women) were recorded as a secondary outcome.

Hemoglobin concentration was measured by spectrophotometry^[6]. Serum ferritin was measured using the human ferritin enzyme immunoassay test kit (Bio Plus, Inc; South San Francisco, California) with cut-off value of 25 ng/dL^[7].

Statistical analysis

Data were collected, tabulated, statistically analyzed by computer using SPSS version 16, two types of statistics were done:

1-Descriptive statistics

Quantitative data are expressed to measure the central tendency of data and diversion around the mean, mean (\bar{x}) and standard deviation (SD).

Qualitative data expressed in number and percentage.

2- Analytic statistics

ANOVA was used for comparison of more than two groups of normally distributed variables; chi-square (χ^2) tests were used to compare categorical outcomes with the Scheffe' test is the degrees of freedom for the between variance times the critical value for the one-way ANOVA test.

All these tests were used as tests of significance at

P value > 0.05 was considered statistically non significant.

P value ≤ 0.05 was considered statistically significant.

value ≤ 0.001 was considered statistically highly significant.

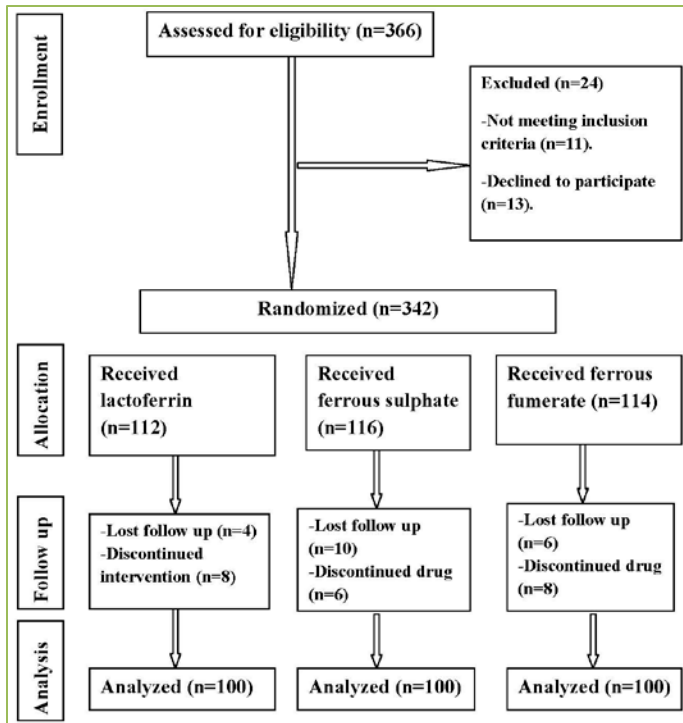


Figure 1.The flow Diagram

Results

Table (1) reveals the maternal characteristics with no significant difference between the three groups.

Table (2) shows the changes in hemoglobin (Hb) concentration after treatment, there was a highly significant difference between the three groups regarding increments in Hb after one and two months and overall increase in Hb in the lactoferrin group.

Table (3) reveals the adverse effects of treatment, there was a highly significant difference between the three groups with gastrointestinal adverse effects being the least in the lactoferrin group.

Table (4) shows the maternal acceptability parameters, there was a highly significant difference between the three groups with the best compliance, acceptability and overall satisfaction in the lactoferrin group.

Discussion

Several international organizations recommend oral iron supplementation during pregnancy [8]. For the treatment of iron deficiency anemia, current guidelines recommend the dose of 60 to 120 mg of elemental iron of ferrous sulphate per

day for a minimum duration of 3 months in pregnant women [9].

Side effects of oral iron therapy are a common problem in the treatment of patients with iron deficiency. Gastrointestinal disturbances such as nausea, heartburn, pain, constipation, and diarrhoea are the most commonly reported side effects, irrespective of the type of iron preparation. Gastrointestinal adverse effects and poor compliance with oral iron was up to 30% in previous studies [10-12].

In our study, total increase in hemoglobin after 2 months with lactoferrin was higher compared to ferrous sulfate and ferrous fumarate. Gastrointestinal adverse events occurred more frequently with ferrous sulphate and ferrous fumarate than lactoferrin group.

Only one randomized trial included 300 women at different trimesters of pregnancy were allocated for oral administration of ferrous sulfate (520 mg once a day) or 30% iron-saturated bovine lactoferrin (bLf) (100 mg twice a day), reported increased hemoglobin and total serum iron values to a greater extent in women treated with bLf than those observed in women treated orally for 30 days with ferrous sulfate, independently of the trimester of pregnancy and concluded that oral administration of partially iron-saturated bLf enhances intestinal iron delivery better than ferrous sulphate with the absence of side effects resulted in very high compliance among treated women [13].

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 IDA in pregnant women [14].

Inability to design a double blind clinical trial and to record the obstetric outcome of women with IDA were a major limitation of our study. Future research should address obstetric outcome in terms of gestational age at delivery, mode of delivery, maternal complications (postpartum hemorrhage and defective lactation) and neonatal outcome (neonatal weight, admission to neonatal intensive care unit and neonatal death).

According to the results obtained in this clinical trial, oral lactoferrin was better tolerated and more acceptable with higher increase in mean hemoglobin when compared to oral iron therapy over two month treatment. Oral lactoferrin can be used as a good substitute to oral iron therapy in mild to moderate IDA during pregnancy.

Table 1. Maternal characteristics

	Lactoferrin group (n=100)	Sulphate group (n=100)	Fumerate group (n=100)	ANOVA test	P-value
Age	25.56±5.76	26.30±5.81	24.90±5.65	0.021	>0.05
Parity	1.52±1.33	1.46±1.39	1.50±1.29	0.008	>0.05
G.A. at inclusion	16.14±1.85	15.80±1.82	16.10±1.82	0.16	>0.05
BMI at inclusion	20.86±1.97	21.00±1.90	21.50±1.70	0.175	>0.05
No of ANC visits	1.31±1.69	1.20±1.08	1.29±1.76	0.019	>0.05

G.A.=Gestational age, BMI=Body mass index, ANC=Antenatal care

Table 2. Changes in hemoglobin (Hb) concentration after treatment

	Lactoferrin group (n=100)	Sulphate group (n=100)	Fumerate group (n=100)	ANOVA test	P-value	Scheffe test
Hb at enrollement	8.03±0.70	8.15±0.58	8.03±0.70	1.08	>0.05	-----
Hb after 1 month	8.65±0.71	9.33±0.37	8.65±0.71	39.35	<0.001	P1<0.001 P2>0.05 P3<0.001
Hb after 2 months	10.41±0.33	9.41±0.35	9.14±0.63	174.37	<0.001	P1<0.001 P2>0.05 P3<0.001
Total increase in Hb	2.28±0.56	1.16±0.42	1.21±0.22	357.53	<0.001	P1<0.001 P2>0.05 P3<0.001

Table 3. Adverse effects of treatment

	Lactoferrin group (n=100)	Sulphate group (n=100)	Fumerate group (n=100)	Chi square	P-value
Gastric upset	10	63	60	64.42	<0.001
Abdominal pain	20	65	60	38.38	<0.001
Constipation	17	55	60	38.38	<0.001
Dark stools	0	35	30	42.22	<0.001
Vomiting	7	40	30	23.86	<0.001

Table 4. Maternal acceptability

	Lactoferrin group (n=100)	Sulphate group (n=100)	Fumerate group (n=100)	Chi square	P-value
Poor compliance	6	27	20	15.72	<0.001
Will use in subsequent pregnancy &/or advice other women to take	93	25	20	13.74	<0.001
Overall satisfaction with treatment	94	30	41	23.86	<0.001

Conflicting interests

The authors report no conflicts of interest.

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