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Comparison Study of Liposomal Iron versus Iron Fumarate in Pregnant Women with Mild Anemia

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ABSTRACT

Background: In nations with weaker economies, women of reproductive age and young children of growing age are particularly vulnerable to iron deficiency anemia (IDA), a very painful illness. Traditional oral iron salts have adverse effects on the gastrointestinal tract and low absorption. Increased absorption is linked to liposomal iron without having any notable negative consequences.

Objective: This study aimed to assess liposomal iron versus iron fumarate in pregnant women with mild anemia.

Patients and methods: A randomized control study included 100 pregnant females with mild anemia (Hb 9 - 11 mg/dl) randomized to either the liposomal iron group or iron fumarate group.

Results: In this study, Hb at 28-32 weeks was significantly higher in the liposomal iron group (11.18 ± 0.44) than in the ferrous iron group (10.70 ± 0.39). There wasn't significant difference among the studied groups regarding Hb before treatment and Hb at 20 weeks. ($p > 0.05$).

Conclusion: Liposomal carriage of iron is linked to targeted delivery of iron and enables lower doses to be administered due to direct absorption into the bloodstream without the need for protein carriers. It is also associated with reduced exposure to gastric contents, decreased interaction with food contents, and no exposure to various digestive juices. Clinical research suggests that liposomal iron dramatically raises hemoglobin and ferritin levels in both pregnant women and women with iron insufficiency. Compared to standard dosages of ferrous sulphate, using smaller quantities of liposomal iron proved to be successful.

Keywords: Anemia, Ferrous sulphate, Gastrointestinal, Iron fumarate, Liposomal iron.

INTRODUCTION

About 1.24 billion people globally are impacted by IDA, making it a global burden. 32 million women globally have it, making pregnant women more likely to have it [(1)]. Because iron is preferentially allocated to the growing baby over the pregnant person, pregnancy raises physiologic iron needs [(2)]. Throughout pregnancy, fetal hepcidin controls the placental transfer of iron from maternal plasma to the fetal circulation [(3)].

When hepcidin levels are low, iron enters the plasma more quickly. When hepcidin levels are high, iron is trapped in hepatocytes, enterocytes, and macrophages [(4)]. In addition to having reduced iron reserves to assist compensatory erythropoiesis after severe blood loss, women who enter labor with IDA are more likely to experience postpartum hemorrhage [(2)]. The manner of delivery should be determined by obstetric indications [(5)]. However, the following should be taken into consideration: Active treatment of the third stage of labor, availability of a group and screen, suitable intravenous access, and delivery in an obstetrician-led unit [(6)].

Greater maternal Hb concentrations and a lower risk of IDA, as well as greater birth weight and a lower risk of low birth weight babies, have all been linked to iron supplementation [(7)]. Iron protein succinylate, ferrous gluconate, ferrous fumarate, ferrous sulfate with or without mucoproteose, and ferrous sulphate (glycine) are examples of traditional iron supplements. Insufficient adherence to therapy because of unavailability and anxiety about adverse effects, especially gastrointestinal symptoms as nausea, vomiting, constipation, and metallic taste [(8)].

Additionally, the majority of these salts harm the GI tract's mucosal lining and result in additional adverse consequences including constipation [(9)]. Of these supplements, ferric pyrophosphate's pharmacokinetics were significantly altered by liposomal technology, which reduced its local toxicity and enabled three times more absorption and bioavailability [(10)]. However, little data is available about its use during pregnancy. The primary endpoint was the comparative efficacy of liposomal iron versus iron fumarate in pregnant women with mild anemia.

SUBJECTS AND METHODS

Study design: A randomized control study included 100 pregnant females with mild anemia (Hb 9 - 11 mg/dl) randomized to either the liposomal iron group or the iron fumarate group. We used block randomization with randomly mixed block sizes.

Subjects grouping: All women got the same dietary advice during enrollment, as required by study protocols. All patients were split into two groups, the liposomal iron group included 50 pregnant women who received oral tablets (180 mg/per day) and the iron fumarate group included 50 pregnant women who received oral tablets (180 mg per day).

Inclusion criteria: Pregnant women in the second trimester, and hemoglobin level of 9 - 11 g/dl.

Exclusion criteria: All subjects who refused to consent, pre-existing impaired kidney functions, pre-existing impaired liver functions, intolerance to iron

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supplements, any other maternal complications**,** and any possible fetal complications.

Measuring outcome: Full history data were selected from all subjects under study as, age, gestational age, body mass index, number of gestation, parity, and laboratory measurements as serum iron, hematocrit, transferrin levels, hemoglobin, and ferritin level before treatment and after 20 weeks and 28-32 weeks, Hb, RBC, MCV, plasma ferritin, plasma iron, and plasma transferrin (Tf) were among the iron indicators measured in maternal fasting venous blood. These samples were taken at enrollment (11-13 weeks of gestation), 20, and 28-32 weeks of gestation.

Study outcomes:

Primary outcome: The primary goal of our experiment was comparing liposomal and traditional ferrous iron formulations on maternal iron reserves during pregnancy after three months.

Secondary outcomes: To compare the side effects of iron supplementation in both groups.

Sample size estimation: A prior research demonstrated that the mean birth weight was 3253 ± 323.8 and 3499.3 ± 464.1 in ferrous and liposomal iron groups respectively [(7)]. So, the sample size was obtained using the following equation: n-(X^2 x P x Q)/D2 at CI95% Assuming = 0.05 (standard value of1.96), at least 50 pregnant women in each group with a minimal total sample size 100 women to achieve a power of 80% (0.8).

Ethical approval: After being approved by The Local Ethics and Research Committee of Menoufia University (7/2024OBSGN 10-2). All women participants were given the option to reject to participate in the study. Participants might potentially withdraw from the research by telling the prescribing doctor. The Helsinki Declaration was followed throughout the course of the investigation.

Statistical Analysis

The findings were tabulated and statistically analyzed using SPSS version 25.0. The descriptive statistics used were mean ± SD, and median. The X^2-test, standard student-t test (t), Mann-Whitney U test, and paired t test were all used in the analysis. A P value of ≤ 0.05 was judged statistically significant.

RESULTS

A flowchart of the study population is shown in figure (1)**.** Of the 109 women at Menoufia University Hospitals, 9 women were excluded from the study (3 declined consent, 6 did not meet the inclusion criteria), and 100 pregnant women in the study, which were divided into liposomal iron group included 50 patients who received oral tablet (180 mg/per day) and iron fumarate group included 50 patients who received oral tablet (180 mg/per day).

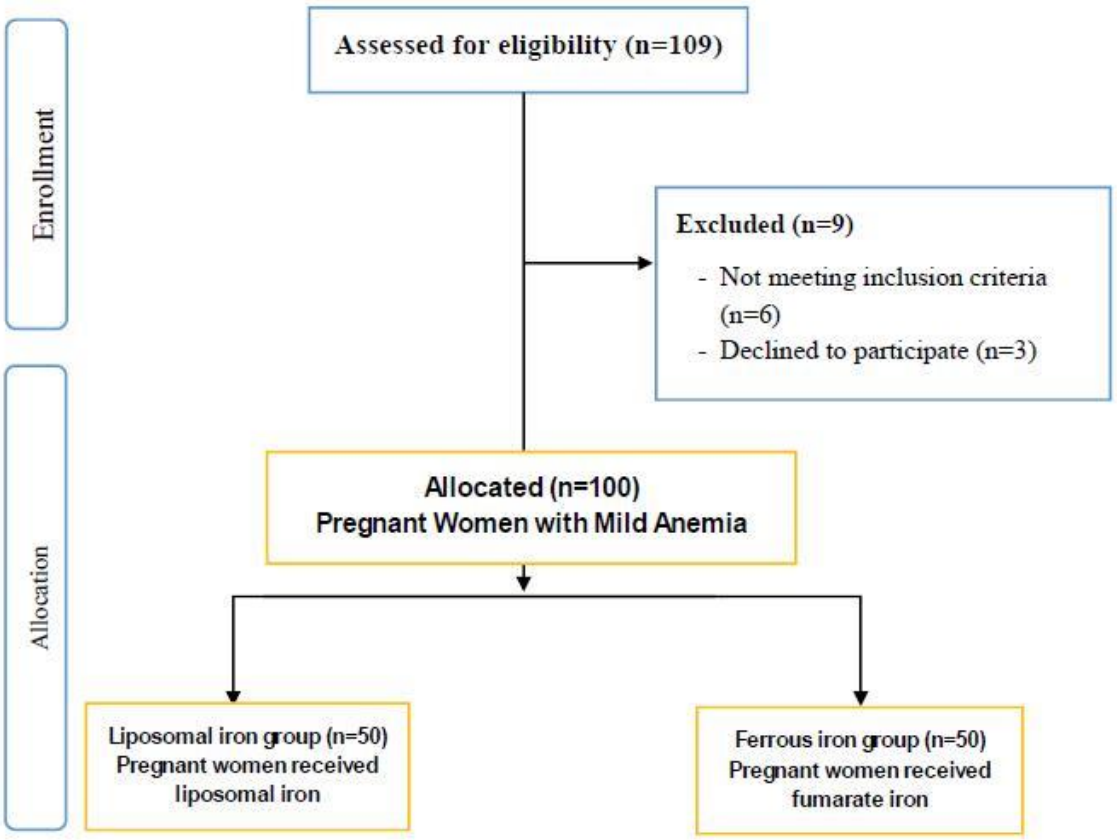

Figure (1): Flowchart of the studied pregnant women

There was no significant difference among the studied groups regarding age, BMI, gestational age, No. of gestations and parity. (p>0.05), (Table 1).

Table (1): Demographic data among the studied groups

Variables	Liposomal iron (n=50)	Ferrous iron (n=50)	t	*P value*
Age (years)				
Mean ± SD.	27.42± 5.89	28.64± 5.01	1.116	0.267
Range	19.00-40.00	19.00-38.00		
BMI (kg/m^2)				
Mean ± SD.	29.64±4.35	29.24±3.92	0.484	0.630
Range	21.00-39.00	20.00-35.00		
Gestational age/weeks				
Mean ± SD.	22.44±2.82	22.16±2.74	0.504	0.615
Range	16.00-27.00	16.00-26.00		
No. of gestation				
Mean ± SD.	1.28±0.57	1.20±0.49	0.747	0.457
Range	1.00-3.00	1.00-3.00		
Parity				
Mean ± SD.	1.56±0.64	1.42±0.76	0.995	0.322
Range	1.00-4.00	1.00-4.00		

There was a significant difference among the studied groups regarding transferrin basal (g/l) and serum iron basal (mcg/dl), (p<0.05). There was no significant difference among the studied groups regarding MCV basal (Fl) and hematocrit basal (p>0.05) (Table 2).

Table (2): Basal laboratory measurements performed among the studied groups

Variables	Liposomal iron (n=50)	Ferrous iron (n=50)	U	*P value*
Transferrin basal (g/l)				
Mean ± SD.	3.67± 0.43	3.91± 0.42	884.000	**0.011***
MCV basal (Fl)				
Mean ± SD.	69.38± 4.69	67.38± 4.62	998.500	0.082
Hct basal (%)				
Mean ± SD.	28.98± 1.73	29.44± 1.75	1064.500	0.195
Serum iron basal (mcg/dl)				
Mean ± SD.	51.06± 3.48	49.50± 2.88	907.000	**0.017***

In our study, there was a significant difference among the studied groups regarding Hb at 28-32 weeks. (p<0.001). Hb at 28-32 weeks was significantly higher in the liposomal iron group (11.18 ± 0.44 gm/dl) than in the ferrous iron group (10.70 ± 0.39 gm/dl). There was no significant difference among the studied groups regarding Hb before treatment and Hb at 20 weeks (p>0.05) (Figure 2a). There was a significant difference among the studied groups regarding ferritin at 28-32 weeks. (p<0.001). Ferritin at 28-32 weeks was significantly higher in the liposomal iron group (36.12 ± 6.96 ng/ml**)** than the ferrous iron group (31.36 ± 3.67 ng/ml). There was no significant difference among the studied groups regarding ferritin before treatment and ferritin at 20 weeks. (p>0.05) (Figure 2b).

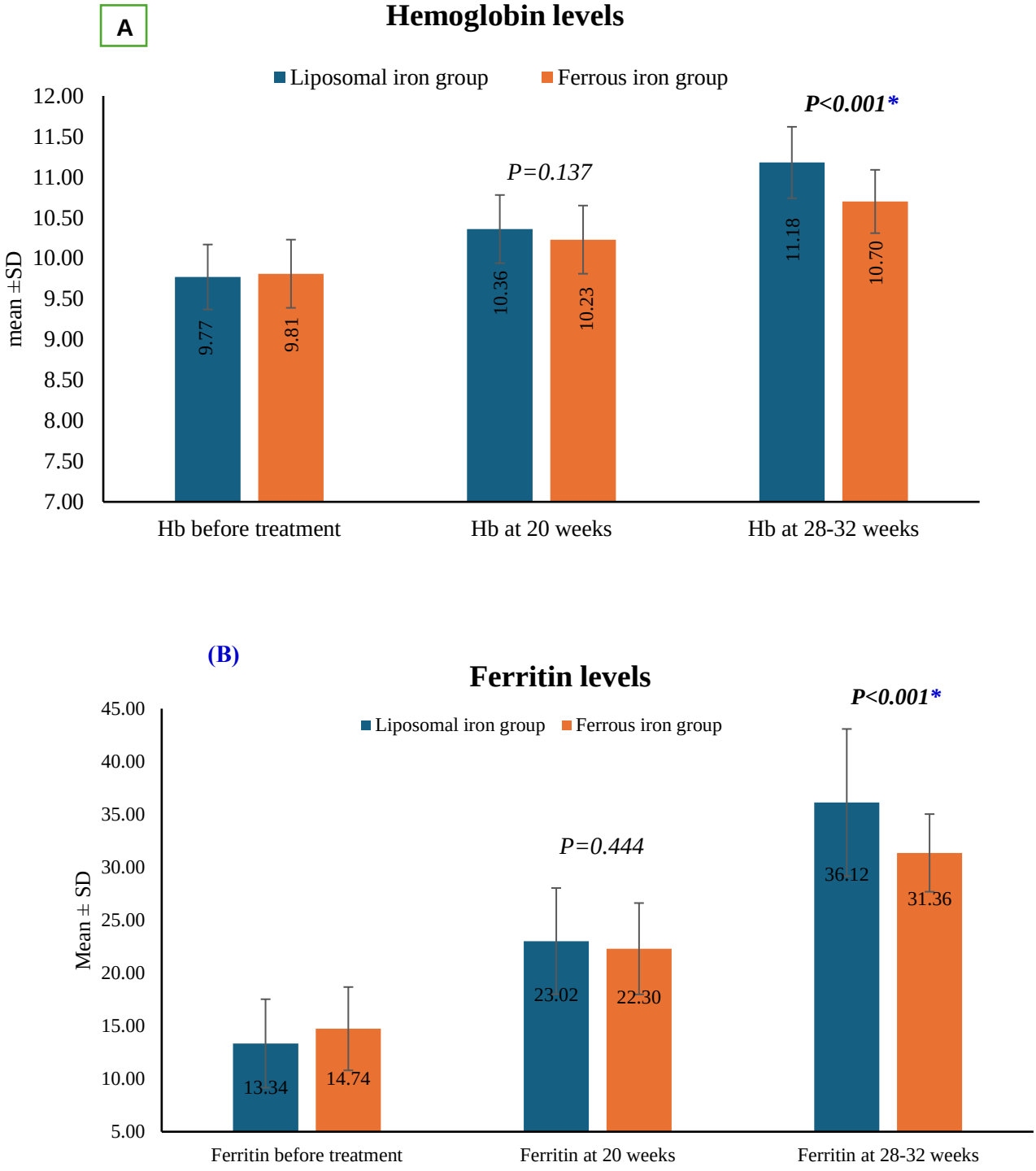

Figure (2): Comparison of hemoglobin levels (a) and ferritin levels (b) among the studied groups.

Among the liposomal iron group, mean changes of hemoglobin levels were significantly increased after 28-32 weeks of treatment compared to before therapy with mean change of 1.41 ± 0.46 ($p < 0.001$). However, among ferrous iron group, the mean changes of hemoglobin levels were significantly increased after 28-32 weeks of treatment compared to before therapy with mean change of 0.89 ± 0.33 ($p<0.001$) (Figure 3a). Regarding mean changes of ferritin levels, they were significantly increased after 28-32 weeks of treatment compared to before therapy with mean change of 22.78 ± 6.63 ($p<0.001$). Among the ferrous iron group, the mean changes of ferritin levels were significantly increased after 28-32 weeks of treatment compared to before therapy with mean change of 16.62 ± 3.71 ($p<0.001$) (Figure 3b).

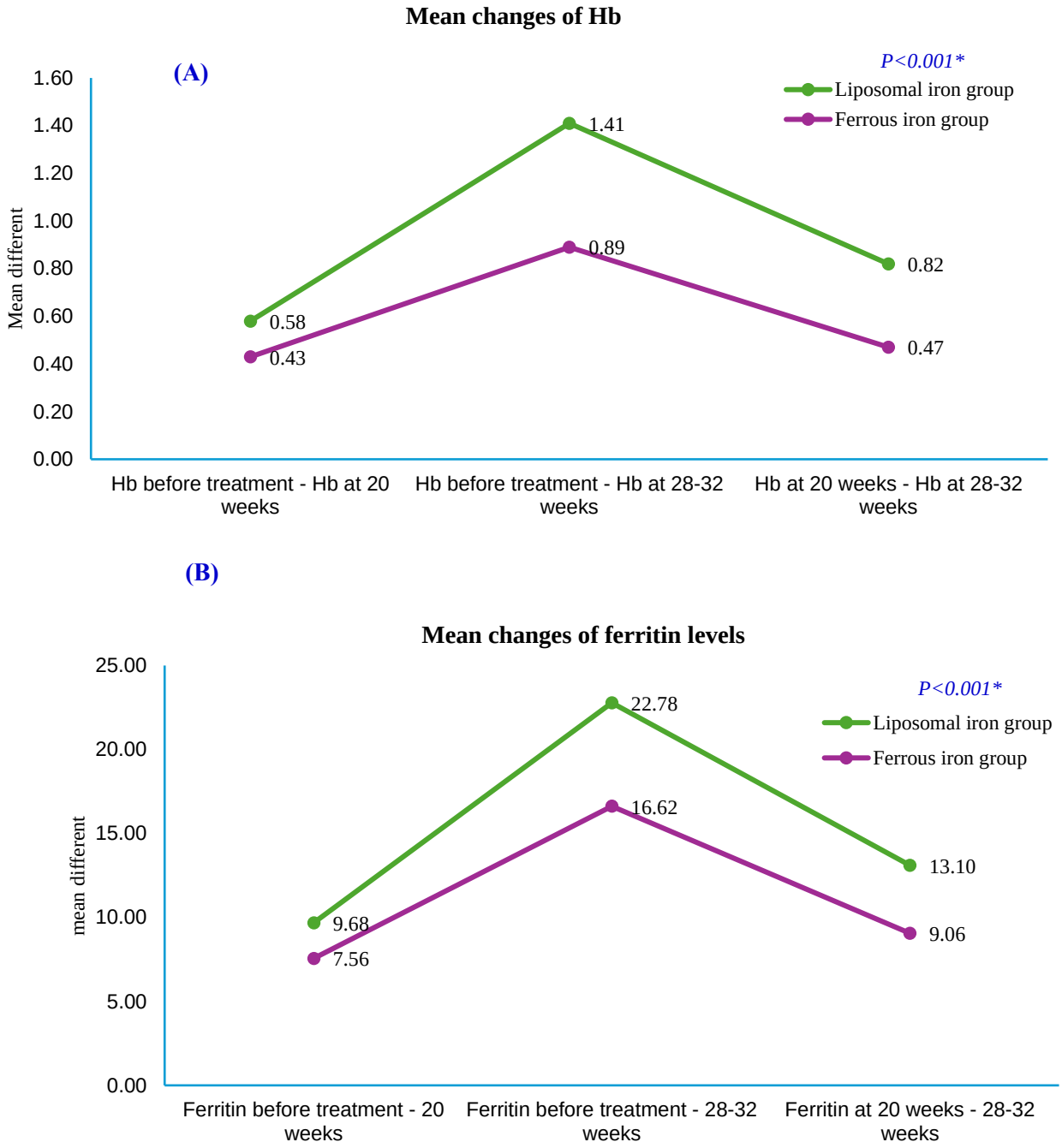

Figure (3): Mean changes in hemoglobin (a) and ferritin levels (b) after treatment compared to before therapy among the studied groups.

DISCUSSION

Serious negative consequences for the mother, the fetus, or both can result from pregnancy anemia. Bad fetal outcomes can include a high fetal death rate in the third trimester, while bad maternal outcomes include postpartum hemorrhage, sepsis, pre-eclampsia, premature labor, and a higher risk of blood transfusions. Additionally, IDA can impact children's and teenagers' mental and motor development [11, 12]. When moderate IDA and iron deficiency without anemia occur during pregnancy, oral iron supplementation is the first line of treatment that is advised. Iron (II) salts, iron (III) polymaltose complex, and liposomal iron are the many forms of oral iron [13, 14].

A more recent technique is called liposomal iron, in which the iron salt is encased in a liposome, which is a term for tiny particles encased in a phospholipid bilayer similar to that found in human cell membranes. Iron is able to withstand the stomach environment because to liposomal protection, which delays early deterioration and inactivation. This allows liposomal iron to be directly absorbed through the enterocyte's cell membrane via phage-endocytosis, vesicular fusion and diffusion [15]. One of the most researched iron, 14 fortifications was ferrous fumarate, which was initially identified in 1960s. Because of its superior sensory qualities and research showing that it can raise iron status, ferrous fumarate is currently advised as a dietary supplement for babies and teenagers [16].

So, our study aimed to compare the efficacy of liposomal iron versus iron fumarate in pregnant women with mild anemia. This prospective, randomized, double-blind trial study included pregnant females with mild anemia (Hb 9 - 11 mg/dl) randomized to either the liposomal iron group or the iron fumarate group. We used block randomization with randomly mixed block sizes. All women received the same nutritional counseling at enrollment, as requested by clinical protocols. Patients were split into two groups: The liposomal iron group [Patients received oral tablet (180 mg/per day)] and the iron fumarate group [Patients received oral tablet (180 mg/per day)].

Our study showed no significant difference among the groups regarding age, BMI, gestational age, no. of gestations, and parity. In agreement with our research**, Hemeda *et al.*** [17] examined the use of bovine lactoferrin and ferrous fumarate to treat anemia in pregnant patients with IDA. Additionally, there were statistically insignificant differences between groups A and B in terms of parity (24 primigravida & 49 multi-gravida vs. 20 primigravida and 53 multi-gravida respectively), gestational age (23.47 ± 4.33 vs. 24.65 ± 4.16 respectively), and age (27.8 ± 4.04 vs. 28.6 ± 3.96 respectively). In the same line, **Helal *et al.*** [18] studied two equal groups with the planned iron therapy. Instances who got ferrous bis-glycinate supplementation were included in group 1, and instances that received microsomal iron treatment were included in group 2. Furthermore, there was no statistically significant difference in age between the two groups, according to **Helal *et al.*** [18]**.**

Our study showed a significant difference among the studied groups regarding transferrin basal (g/l) and serum iron basal (mcg/dl). There was no significant difference among the studied groups regarding MCV basal (Fl) and Hct basal. In another study, **Helal *et al.*** [18] found a notable rise in hemoglobin, RBCs, HCT%, MCV, and MCHC at end values in comparison with the matching baseline value. These results indicated that both ferrous bis-glycinate and sucrosomal iron had a beneficial effect on CBC findings in the treatment of IDA in pregnancy. Also, **Kochhar *et al.*** [19] reported that both groups showed increases in MCV, MCH, MCHC, and reticulocyte counts, however the difference was not statistically significant.

Additionally, a significant difference was found among the studied groups in our study regarding Hb at 28-32 weeks. Hb at 28-32 weeks was significantly higher in liposomal iron group (11.18 ± 0.44**)** than ferrous iron group (10.70 ± 0.39). There was no significant difference among the studied groups regarding Hb before treatment and Hb at 20 weeks. In the same line, **Hemeda *et al.*** [17] found that amongst group A (patients who received ferrous fumarate), after one and two months, serial Hb values showed a substantial improvement in both the relationship with Hb before to treatment and with each other (10.1 ± 0.49, 11 ± 0.49 vs. 10.1 ± 0.49). In another study by **Antunes *et al.*** [20] who reported a considerable rise in Hb levels (mean increase: 11.4 to 12.6 g/dL) in IBD patients who had liposomal iron replacement treatment for eight weeks, with 62% of the group having corrected IDA. Additionally, according to **Indriolo *et al.*** [21] IBD patients with IDA who received liposomal iron treatment had higher hemoglobin levels than those who received ferrous sulfate treatment (62.5% vs. 33.3% respectively). However, **Parisi *et al.*** [7] utilized 28 mg of liposomal iron in their trial, which focused on pregnant women who were not anemic and had Hb > 10.5 g/dL at 12–14 weeks of gestation. Additionally, there were no changes in hematological parameters, but ferritin and hemoglobin levels were noticeably higher at 28 weeks and during the postpartum phase. In agreement with our study **Kochhar *et al.*** [19] reported that the two groups' rates of Hb growth differed statistically significantly starting in the third week of therapy. On day 30, there was a substantial shift in hemoglobin levels (mean Hb increased by 3.1 g/dL in group A and 5.1 g/dL in group B; P=0.002). Also, **Helal *et al.*** [18] found that from the beginning of the study to its end (4 weeks), the microsomal iron group's hemoglobin level increased by 2.0 g/dl, whereas the ferrous bis-glycinate group's increased by 1.51 g/dl. This difference between the groups was significant. On day 28, however **Gupta *et al.*** [22] discovered that the ferrous bis-glycinate group's mean hemoglobin increase from baseline was 1.3 gm/dL, whereas the sucrosomal iron group's was 1.9 gm/dL.

Regarding ferritin at 28-32 weeks, ferritin at 28-32 weeks was significantly higher in the liposomal iron group (36.12 ± 6.96**)** than ferrous iron group (31.36 ± 3.67), there was no significant difference among the studied groups regarding ferritin before treatment and ferritin at 20 weeks. Additionally**, Hemeda *et al.*** [17] found that amongst group A (patients who received ferrous fumarate), compared to serum ferritin assessed before to beginning treatment mode, consecutive serum ferritin levels showed and indicated statistically significant improvements indicating improvement after one and two months (18.5 ± 1.43, 27.37 ± 1.96 vs. 10.6 ± 0.76). However, **Helal *et al.*** [18] found that there was a significant increase in serum ferritin and iron and a decrease in TIBC in group II in comparison with group I at eight weeks of evaluation time. Additionally, **Kochhar *et al.*** [19] reported that the mean ferritin levels in the ferrous bisglycinate group increased by 61.1 ng/mL, whereas the SI group's ferritin levels increased by 85.9 ng/mL. The SI group's mean hemoglobin and serum ferritin levels were 8.8 g/dL and 36.5 ng/dL, respectively, seven days after the commencement of therapy, and 12.8 g/dL and 104 ng/mL respectively thirty days later. In another study, **Bhalla and Kaushal** [23] found that women with IDA who were between weeks 11 and 13 of pregnancy and using Sideremil™ (a combination of ascorbic acid and liposomal iron pyrophosphate) between April 2018 and May 2019. By comparing the results to the baseline, there were notable improvements in hemoglobin, ferritin, sideropenia, and transferrin levels. Also, **Helal *et al.*** [18] found that there

was a significant increase in the difference between final and basal values of ferritin and iron and a decrease in TIBC. In study groups that were higher in group II, also, both ferrous bis-glycinate and microsomal iron had a beneficial effect on ferritin, iron, and TIBC in the treatment of IDA in pregnancy.

CONCLUSION

Liposomal carriage of iron is linked to targeted delivery of iron and enables lower doses to be administered due to direct absorption into the bloodstream without the need for protein carriers. It is also associated with reduced exposure to gastric contents, decreased interaction with food contents, and no exposure to various digestive juices. Clinical research suggested that liposomal iron dramatically raised hemoglobin and ferritin levels in both pregnant women and women with iron insufficiency. Compared to standard dosages of ferrous sulfate, using smaller quantities of liposomal iron proved to be successful. This lessens the gastrointestinal side effects of standard oral iron that is not capsuled.

Conflict of interest: None.
Financial disclosures: None.

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