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Comparison Study between Oral Lactoferrin, Amino Acid Chelated Iron and Ferrous Fumarate in Iron Deficiency Anemia during Pregnancy

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Abstract: Background: The most prevalent deficit in the world is iron insufficiency. Although it is more common in developing nations, it is still a major issue in the industrialised world. Anemia is a global problem and is related with maternal illness and humanity. **Objective:** To compare lactoferrin's effectiveness with that of amino acid chelating iron and ferrous fumarate in behavior of IDA through condition. **Patients and Methods:** This research was performed at the Obstetrics and Gynecology Department at Alazhar University Hospital (Assuit) Egypt, as a randomized, parallel-group, single-center study. Three hundred pregnant women recruited randomized in three groups, in the period 2018-2019. **Results:** Lactoferrin group which is higher in Hb rise than other the two groups (amino acid chelated iron and ferrous fumarat group) .Also The adverse effect in Lactoferrin less than the other two groups. That gives preference to Lactoferrin to be used in pregnancy to increase Hb level. **Conclusion:** The management of anemia during pregnancy in prenatal medicine, it is still very essential. Treatment that is correct leads to management that is successful. This current study shows that the efficacy of Lactoferrin is significantly more than Amino Acid Chelated Iron and Fumarate group in behavior of iron defecincy anemia during pregnancy.
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Keywords: Oral Lactoferrin, Amino Acid Chelated Iron, Pregnancy, Ferrous Fumarate, Iron Deficiency Anemia

1. Introduction

Women they are at danger of iron insufficiency throughout their reproductive years. a result of blood loss during menstruation, especially the 10% who have severe losses. (>80ml/month). It is obvious that contraceptive practice also has an important effect on the development of anemia, while the non-medicated Oral contraceptives have the opposite effect of intrauterine devices, which increase menstrual blood loss by 30-50 percent. Iron deficiency and abrupt blood loss are the two most frequent causes of anaemia during pregnancy and puerperium.

During pregnancy, iron needs rise, and failing to maintain adequate amounts of iron may have negative maternal–fetal effects (ACOG, 2012).

Pregnancy is associated with physiologic changes that may complicate the diagnosis of hematologic disorders. There is an increased iron requirement during pregnancy because blood volume expands by approximately 50% during a singleton pregnancy, the total red blood cell mass increases by about 25% (300 mL).

Hb and Hct levels are usually lower as plasma expands more. (ACOG, 2012).

Iron deficiency anaemia (IDA) is a kind of anaemia caused by a shortage of iron in the body.

The most prevalent form of anaemia, iron deficiency anaemia (IDA), occurs when obtainable iron is inadequate to sustain usual red cell synthesis (WHO, 2015).

According to WHO estimates, between 35 and 75 percent of expectant females in poor countries are anaemic. (WHO, 2014).

The management of anemia during pregnancy remains a significant problem in prenatal medicine.

Correct diagnosis and treatment lead to successful control of foetal and maternal risk and better perinatal outcome (Helmy et al., 2018; Helmy et al., 2018).

The oral method is the primary option to replenish iron reserves since this enables the usual process of absorption to be utilised, in addition to being a cheap and effective therapy (Santiago, 2012).

The amount of iron required throughout each trimester of pregnancy varies, with the first trimester's need reducing owing to the end of menses.

Iron needs begin to increase during the second trimester, and as the pregnancy continues, iron requirements for foetal development climb gradually in proportion to the fetus's weight, with the majority of the iron that builds up in the third trimester (Fisher and Nemeth, 2016).

According to the US Centers for Disease Control and Prevention (CDC), haemoglobin (Hb) values of less than 11 mg/dl during the first and third trimesters, or less than 10.5 mg/dl during the second trimester, must be used to diagnose anaemia during pregnancy (Fisher and Nemeth 2017).

Lactoferrin is a lactoferrin-like protein found in milk (formerly known as lacto transferrin) is a cationic iron binding glycoprotein with a high affinity.

Bovine Lactoferrin is a commercially available pharmaceutical preparation that has been proven in trials to be safe and effective in the treatment of ID and IDA in pregnant women (Rezk et al., 2015).

Aim of the work

To compare the effectiveness of lactoferrin to that of amino acid chelating iron and ferrous fumarate in treatment of IDA during pregnancy.

2. Patients and Methods

Type of the study:

Randomized, controlled, double-blinded trial.

Study setting: The Obstetrics and Gynecology Department at Al Azhar University Hospital (Assiut) Egypt, performed this randomised, parallel-group, single-center research.

The examples were gathered from pregnant women who visited an outpatient clinic for prenatal care. antenatal care in the period2018-2019.

Inclusion criteria:

Patients enrolled in this study if they fulfil the following pregnant women (aged 18-40 years) with a single foetus in the second and third trimesters, with a haemoglobin level of less than 10 g/dL. (Hb level 8.00-10.5 gm. /dl). All women are allowed to follow a diet that isn't restricted in any way.

Exclusions criteria:

Anemia (Hb level 8 gm/dl) in women owing to any cause, including chronic blood loss, hemolytic anaemia, and thalassemia (including thalassemia trait).

Peptic ulcer history.

Pregnancy-related medical problems include cardiovascular, thyroid, pituitary, nutritional, renal, and liver disorders, as well as diabetes mellitus (DM) and hypertension (HTN).

Microcephaly and intrauterine growth restriction are examples of foetal abnormalities (IUGR).

Sample Size:

Three hundred pregnant women randomized in three groups. Method of randomizations closed envelop method. We were enrolling 100 participants in each group. The patients who were given the medicine to take orally.

Group 1 (Lactoferrin group):

Comprise 100 expectant females who were given 100 mg lactoferrin sachets once a day for four weeks.

Group 2 (Amino group):

Includes100 pregnant women who receiving the drug (amino acid chelated iron) for four consecutive weeks.

Group 3 (Fumarate group):

Includes 100 expectant females who received the drug (Ferrous fumarate) for four successive weeks.

One sachet of lactoferrin dissolved in 1/4 glass of water, once per day, just before lunch

Patients are recommended not to consume tea, coffee, milk, milk products, antacids, or calcium supplements for at least 2 hours before or after taking the sachet.

Data collection:

(1) The primary tested parameter the rise in hemoglobin level after 4 weeks of use.

(2) The secondary parameter was the therapy's side effects and the patient's adherence to the treatment

- During the research period, participants were asked to describe any unexpected or unpleasant symptoms.
- All of the ladies were instructed to keep track of five possible gastrointestinal adverse symptoms in a journal (Epigastric pain, nausea, vomiting and constipation).

Data from each patient collected and entered in a prepared “Data Sheet”. Data over the period of four weeks were recorded.

Statistical analysis:

The statistical programme for social sciences, version 20.0, was used to analyse the data (SPSS Inc., Chicago, Illinois, USA).

The mean and standard deviation were used to represent quantitative data (SD).

Frequency and percentage were used to represent qualitative data.

The following tests were done:

When comparing two means, an independent-samples t-test of significance was employed.

To compare proportions between two qualitative characteristics, the Chi-square (x2) test of significance was employed.

The confidence interval was set at 95%, while the acceptable margin of error was set at 5%.

The following p-value was deemed significant:

Probability is a term that describes how likely something is (P-value)

- P-value <0.05 was considered significant.
- P-value <0.001 was considered as highly significant.
- P-value >0.05 was considered insignificant.

3. Results

The study included 300 pregnant women divided to three groups each group had 100 pregnant women took certain drug to increases haemoglobin level

(Lactoferrin, Amino acid chelated iron and Ferrous Fumarate) mean age in Lactoferrin group was 23.71 with standard deviation (SD) 2.98, was 23.34 with SD 2.45 in Amino acid chelated iron group and was 24.73 with SD 2.06 in Ferrous Fumarate group. The Gestational Age mean was 25.29, 24.4 and 23.7 in Lactoferrin group, Amino acid chelated iron group and Ferrous Fumarate collection individually (Table 1).

Table (1): Demographic data and history between drug used groups.

	Drug used			One Way ANOVA test of sig.	
	Lactoferrin group	Amino group	Fumarate group		
	Mean ± SD	Mean ± SD	Mean ± SD	P-Value	Sig.
Age (years)	23.71 ± 2.98	23.34 ± 2.45	24.73 ± 2.06	<0.001 (A1)	S
Gestational Age (Weeks)	25.29 ± 4.69	24.4 ± 1.94	23.7 ± 1.81	0.002 (A2)	S

(A) Post hoc Bonferroni test was significant at: (A1) Fumarate group Vs. (Lactoferrin and Amino groups).
(A2) Lactoferrin group Vs. Fumarate group.

Rise in Hb mean 1.74 with SD 0.35 in Lactoferrin group which is higher in Hb rise than other the two groups 1.6 SD 0.28 and 1.58 SD 0.27 for Amino acid chelated iron group and Ferrous Fumarate group respectively. P-Value was <0.001 which indicate significant difference between three groups. Post-hoc Bonferroni test was used to detect the significance between the three groups and was significant between Lactoferrin group Vs. (Ferrous Fumarate and Amino acid chelated iron groups). Rise in HCT mean 5.19 with SD 1.05 in Lactoferrin group which is higher in Hb rise than other the two groups 4.81 SD 0.87 and 4.79 SD 0.83 for Amino acid chelated iron group and Ferrous Fumarate group respectively. P-Value was <0.001 which indicate significant difference between three groups. Post-hoc Bonferroni test was used to detect the significance between the three groups and was significant between Lactoferrin group Vs. (Ferrous Fumarate and Amino acid chelated iron groups) (Table 2).

So, it gives preference to Lactoferrin to be used in pregnancy to increase Hb level.

Table (2): Hb investigation between drugs used groups.

	Drug used			One Way ANOVA test of sig.	
	Lactoferrin group	Amino group	Fumarate group		
	Mean ± SD	Mean ± SD	Mean ± SD	P-Value	Sig.
Hb(g/dl)	10.09 ± 0.33	10.14 ± 0.26	10.12 ± 0.27	0.54	NS
Haemoglobin after	11.85 ± 0.39	11.76 ± 0.33	11.7 ± 0.37	0.013 (A2)	S
Rise in HB	1.74 ± 0.35	1.6 ± 0.28	1.58 ± 0.27	<0.001 (A1)	S
RISE in HCT	5.19 ± 1.05	4.81 ± 0.87	4.79 ± 0.83	0.003 (A1)	S

(A) Post hoc Bonferroni test was significant at: (A1) Lactoferrin group Vs. (Ferrous Fumarate and Amino acid chelated iron groups). (A2) Lactoferrin group Vs. Ferrous Fumarate group.

The adverse effect in group A Lactoferrin as follows: 6% had epigastric pain, 6% had constipation, 1% had nausea and 16% had vomiting and 71% had no side effects. In Group B Amino acid chelated iron 18% had epigastric pain, 16% had constipation, 15% had nausea and 26% had vomiting and 25% had no side effects. In Group C ferrous fumarate 17% had epigastric pain, 13% had constipation, 27% had nausea and 27% had vomiting and 16% had no side effects. P-Value <0.001 indicates significant difference between the three groups as Lactoferrin had less side effects than other two groups (Table 3).

Table (3): Side effects of drug used between drugs used groups.

		Drug used			Chi-Square test of sig.	
		Lactoferrin group	Amino group	Fumarate group		
		N (%)	N (%)	N (%)	P-Value	Sig.
Side Effect	Nil	71 (71%)	25 (25%)	16 (16%)	<0.001	S
	Epigastric Pain	6 (6%)	18 (18%)	17 (17%)		
	Nausea	1 (1%)	15 (15%)	27 (27%)		
	Vomiting	16 (16%)	26 (26%)	27 (27%)		
	Constipation	6 (6%)	16 (16%)	13 (13%)		

4. Discussion

When oral iron preparations are used at therapeutic dosage levels, nausea, vomiting, and epigastric pain are common side effects. These effects are thought to be caused by Mucosal irritation and gastrointestinal motility are both affected by the presence of labile iron in the lumen.

As the dosage is raised, a greater proportion of patients are impacted (Nappi et al., 2010).

Many various kinds of iron salts, such as ferrous sulphate, ferrous fumarate, ferrous gluconate, ferric polymaltose, and ferrous bisglycinate, amino acid chelated iron, and Lactoferrin, are now available in iron preparations.

Furthermore, the pharmacokinetics of the different formulations varies (e.g. Immediate versus slow release). Although it is well acknowledged that iron's adverse effects are dose-dependent, the impact of iron salt on the rate of side effects remains unknown (Nocerino et al., 2014).

Aim of our study to compare the effectiveness of lactoferrin in the treatment of IDA during pregnancy to amino acid chelating iron and ferrous fumarate The study included 300 pregnant women divided to three groups each group had 100 pregnant women took certain drug to increases haemoglobin level (Lactoferrin, Amino acid chelated iron and Ferrous Fumarate) mean age in Lactoferrin group was 23.71 with standard deviation (SD) 2.98, was 23.34 with SD 2.45 in Amino acid chelated iron group and was 24.73 with SD 2.06 in ferrous fumarate group.

In my current study gives preference to Lactoferrin to be used in pregnancy to increase Hb level ,as Rise in Hb mean 1.74 with SD 0.35 in Lactoferrin group which is higher in Hb rise than other the two groups 1.6 SD 0.28 and 1.58 SD 0.27 for Amino acid chelated iron group and Ferrous Fumarate group respectively P-Value was <0.001 This indicates that there is a substantial difference between the three groups. Post-hoc Bonferroni test was used to detect the significance between the three groups and was significant between Lactoferrin group Vs. Ferrous Fumarate and Amino acid chelated iron groups).Rise in HCT mean 5.19 with SD 1.05 in Lactoferrin group which is higher in Hb rise than other the two groups 4.81 SD 0.87 and 4.79 SD 0.83 for Amino acid chelated iron group and Ferrous Fumarate group respectively. P-Value was <0.001 which indicate significant difference between three groups.

Post-hoc Bonferroni test was used to detect the significance between the three groups and was significant between Lactoferrin group Vs. (Ferrous Fumarate and Amino acid chelated iron groups).The adverse effect in group A (Lactoferrin) as follows: 6% had epigastric pain, 6% had constipation, 1% had nausea and 16% had vomiting and 71% had no side effects. In Group B(Amino acid chelated iron) 18% had epigastric pain, 16% had constipation, 15% had nausea and 26% had vomiting and 25% had no side effects. In Group C (Ferrous Fumarate) 17% had epigastric pain, 13% had constipation, 27% had nausea and 27% had vomiting and 16% had no side effects. P-Value <0.001 indicates significant difference between the three groups as Lactoferrin had less side effects than other two groups.

Oral use of ferrous sulphate produces gastrointestinal pain, nausea, vomiting, diarrhoea, and constipation, among other things.. Bovine

Lactoferrin is a commercially available pharmaceutical preparation that has been shown in studies to be safe and effective in the treatment of ID and IDA in pregnant women (Rezk et al., 2015).

Rezk et al. (2015) conducted a study to compare Lactoferrin vs Treatment of iron deficiency anaemia (IDA) during pregnancy with ferrous sulphate: efficacy and safety

The Department of Obstetrics and Gynecology at Menoufia University Hospital in Egypt recruited 200 pregnant women with IDA in the second trimester and randomly allocated them to receive either 150 mg dried ferrous sulphate capsules or 250 mg lactoferrin capsules once day for eight days. days in this prospective, randomised, parallel group, single centre study.

The amount of rise in haemoglobin concentration at 4 and 8 weeks, the adverse effects related with iron therapy, and patient compliance with the treatment were the key efficacy criteria.

Lactoferrin caused a greater overall rise in Hb (2.26 0.51 g/dL) than ferrous sulphate (1.11 0.22 g/dL) after 2 months (p 0.001).

The ferrous sulphate group had more gastrointestinal adverse events than the lactoferrin group (p 0.001). In the ferrous sulphate group, the number of women seeking a change in medication was greater (p 0.001).

Lactoferrin was shown to be more efficacious than ferrous sulphate in pregnant women with IDA, resulting in less gastrointestinal side effects and higher treatment acceptance.

In terms of treating IDA caused by pregnancy, amino acid chelated iron and ferrous fumarate are similar; however, amino acid chelated iron has the benefit of delivering a quicker rate of haemoglobin recovery and is more tolerated by patients (Abdel Moety et al., 2017).

Our study, which was conducted in collaboration with Abdel Moety et al. (2017) in the Obstetrics and Gynecology Department, Faculty of Medicine, Cairo University, Cairo, Egypt, compared the efficacy and tolerability of iron amino acid chelate and ferrous fumarate in the treatment of iron deficiency anaemia (IDA) during pregnancy.

In this 12-week study, 150 pregnant women with iron deficiency anaemia (IDA) were randomly assigned to receive iron amino acid chelate or ferrous fumarate.

At baseline, 4, 8, and 12 weeks following therapy, haemoglobin, red cell indices, serum iron, and serum ferritin were examined. In both groups, negative consequences were questioned.

After 12 weeks of therapy, the mean values of haemoglobin, red cell indices, serum iron, and serum ferritin were not statistically different between the two groups.

The iron amino acid chelate group, on the other hand, had a much quicker increase in haemoglobin levels after 4, and 12 weeks of therapy (p = 0.001). The ferrous fumarate group had substantially greater constipation and stomach colicky discomfort (p = 0.022 and 0.031, respectively).

In the treatment of anaemia due to iron deficiency during pregnancy, both ferrous fumarate and bovine lactoferrin are effective.

Bovine Lactoferrin is more effective than ferrous fumarate in treating iron deficient anaemia in pregnant women. The use of bovine Lactoferrin to treat iron deficiency anaemia in pregnant women had a good safety profile and good case compliance (Hemeda et al., 2017).

Our findings matched those of Hemeda et al. (2017), who performed a prospective open label randomised clinical trial at the Ain Shams University Maternity Hospital outpatient clinic from February 15 to August 15, 2016. The research comprised 146 pregnant women with iron deficiency anaemia who were split into two groups. In a comparison of the two study groups (ferrous fumarate versus lactoferrin), Hb after one month, Hb after two months, serum ferritin after one month, and serum ferritin after two months were all statistically substantially higher in bovine Lactoferrin than ferrous fumarate (p 0.05).

In comparison to ferrous ascorbate, In the treatment of IDA in pregnant women, ferrous asparto glycinate is an effective iron-amino acid chelate (Kamdi and Palkar, 2015).

Kamdi and Palkar (2015) conducted a multicenter, parallel group, double-blind, prospective, randomised comparative clinical trial.

Research in three distinct Indian locations.

A total of 73 pregnant women between the ages of 12 and 26 weeks were split into two groups.

For a period of 28 days, one group was given ferrous ascorbate while the other was given ferrous asparto glycinate. On days 14 and 28, the average increase in haemoglobin and ferritin levels was assessed. Ferrous asparto glycinate therapy resulted in substantially greater levels of haemoglobin and ferritin than ferrous ascorbate treatment at both time periods.

Conclusion and Recommendations

1. The management of anemia during pregnancy remains an important in prenatal medicine. Correct treatment lead to effective management.
2. This current study shows that the efficacy of Lactoferrin is significantly more than Amino Acid Chelated Iron and Fumarate group in treatment of iron defecincy anemia during pregnancy.
3. Lactoferrin group was more beneficial, safe and effective than other groups as regard the increase in hemoglobin level and other hematological parameters.
4. As regard side effects Lactoferrin group was better than other groups, with lowest side effects.
5. Constipation, epigastric discomfort, nausea, severe stomach pain, and vomiting are the most frequent.
6. These side effects may be mitigated by taking pills after meals; however, this results in a reduction in iron absorption
7. 1. Liquid iron preparation is a superior option in this case.

Because of the coating's poor breakdown, some people have trouble absorbing the iron.

8. Oral iron treatment may cause constipation, which can be alleviated with laxatives, stool softeners, and sufficient liquid consumption. Further large studies will raise the curtain for a better understanding of the effect of different iron preparation on different types of anemia.

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