The Effect of Orally Administered Iron-Saturated Lactoferrin on Systemic Iron Homeostasis in Pregnant Women Suffering from Iron Deficiency and Iron Deficiency Anaemia

Ahmed M Rateb, Ahmed M Mamdouh, Khaled M Balsha
Obstetrics and Gynecology Department - Faculty of Medicine – Ain Shams University
Corresponding author: Khaled M Balsha; **Mobile:** 01114657946; **Email:** balcca@hotmail.com

ABSTRACT

Background: Anemia is a common medical disorder affecting a lot of women in pregnancy in the developing countries. Anemia is the second indirect obstetric cause of death after cardiac causes.

Aims: To compare the safety, tolerability, efficacy and hematological response of lactoferrin in treatment of iron deficiency anemia during pregnancy versus ferrous sulfate capsules. **Methodology**: Hematological Response to lactoferrin versus ferrous sulfate in Treatment of Anemia with Pregnancy". Study site: Ain Shams University hospital. Study design: A double blind clinical trial. Study population: The study was included Two-hundred pregnant females with iron deficiency anemia attending the outpatient clinics of Ain shams university maternity hospital for routine antenatal care. For each pregnant woman, age, parity and gestational history were taken before treatment. All pregnant women took their allocated treatment regularly for eight weeks after diagnosis of iron deficiency anemia with hemoglobin level and serum ferritin level and followed up after four and eight weeks. Also, epigastric pain, diarrhea, constipation, nausea, vomiting or gastric distress reported to assess tolerability of the drugs. **Results:** The study included 200 pregnant women in a double blind study: Group I (lactoferrin): 100 cases were received 100mg of bovine lactoferrin (Pravotin sachets, Hygint, Egypt) twice a day. Group II (ferrous sulfate): 100 cases were received 150mg of dried ferrous sulphate + folic acid (vitamin B9) 0.50mg (Ferrofol, E.I.P.I.C.O, Egypt) three capsules per day. **Conclusion:** lactoferrin is more tolerable than ferrous sulphate. It has lesser GIT side effects and seems to icrease both hemoglobin and serum ferritin more than iron salts.

Recommendations: Lactoferrin is recommended for patients with iron deficiency anemia.

Keywords: Hematological response, lactoferrin, ferrous sulphate, iron deficiency anemia in pregnancy.

INTRODUCTION

Iron deficiency (ID) and iron deficiency anemia (IDA) are the most common iron disorders throughout the world. ID and IDA, particularly caused by increased iron requirements during pregnancy; represent a high risk for preterm delivery, fetal growth retardation, low birth weight, and inferior neonatal health. These pregnancy complications are thought to occur as a consequence of an increased iron requirement, related to enhanced blood volume and development of the fetoplacental unit [(1)].

ID and IDA are still a major health problem in pregnant women. To cure ID and IDA, iron supplements are routinely prescribed. The preferred treatment of ID/IDA, consisting of oral administration of iron as ferrous sulphate, often fails to exert significant effects on hypoferremia and may also cause adverse effects [(1)].

The World Health Organization (WHO) defines anemia in pregnancy as a hemoglobin (Hb) concentration of < 11 g/dl. Iron deficiency anemia (IDA) is the most common type of anemia in pregnancy. The iron content of the body is normally kept constant by regulating the amount absorbed to balance the amount lost [(2)].

The WHO estimates that 46% of pregnant women in African region, 38% in Eastern Mediterranean region, 25% in European region and 24% in the region of the Americas are anemic mainly because of iron deficiency [(2)].

Anemia is a common medical disorder affecting a lot of women in pregnancy in the developing countries [(3)].

Anemia is the second indirect obstetric cause of death after cardiac causes [(4)].

Iron deficiency anemia is 1.8% in the 1st trimester, 8.2% in the 2nd trimester [(5)], and 27.4% in the 3rd trimester. Hb levels of < 10g/dL are observed in up to 30% of women, with more sever anemia (Hb <8g/dL) seen in 10% [(6)].

Anemia may antedate conception, is often aggravated by pregnancy, and the accidents of labor may perpetuate it [(7)].

Anemia during pregnancy and its management remain an important issue in prenatal medicine. Correct diagnosis and treatment leads to effective management of fetal and maternal risk and improved prenatal outcome [(8, 9)].

Diet alone can't supply the 30-40 mg iron that is required for absorption of 4-6mg iron per day needed during the later stage of pregnancy so iron supplementation is strongly recommended for all females in developing countries [(10)].

Traditional therapeutic options of iron deficiency anemia during pregnancy were

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administration of oral iron shows lack of compliance and side effects and often limited intestinal absorption and bioavailability [11].

The most commonly used treatment for ID and IDA currently consists of oral administration of iron as ferrous sulphate. However, ferrous sulphate administration often fails to exert any significant effects on these pregnancy-associated pathologies, and frequently causes several adverse effects (gastrointestinal discomfort, nausea, vomiting, diarrhoea, constipation). This is likely due to the poor bio-availability of inorganic iron requiring the administration of large quantity of ferrous sulphate [12].

Lactoferrin is a multifunctional protein of the transferrin family. Lactoferrin is a globular glycoprotein with a molecular mass of about 80 kDa that is widely represented in various secretory fluids, such as milk, saliva, tears, and nasal secretions. Lactoferrin is also present in secondary granules of PMN and is secreted by some acinar cells. Lactoferrin can be purified from milk or produced recombinantly. Human colostrum (*"first milk"*) has the highest concentration, followed by human milk, then cow milk (150 mg/L) [13].

It has been suggested that lactoferrin, a major protein in human milk, has multiple biological roles: an antimicrobial protein; an inhibitor of bacteria, viruses, and yeasts; an immunostimulatory compound; a mitogenic protein; an anticancer agent; and an enhancer of iron absorption [14].

AIM OF THE WORK

To compare the safety, tolerability, efficacy and hematological response of lactoferrin in treatment of iron deficiency anemia during pregnancy versus ferrous sulphate capsules.

PATIENTS AND METHODS

This a double blind clinical trial study included a total of 188 pregnant females with iron deficiency anemia attending outpatient clinics of Ain Shams University Maternity Hospital for routine antenatal care. Approval of the ethical committee and a written informed consent from all the subjects were obtained. This study was conducted between September 2017 and March 2018.

Patients with single fetus, in the second trimester with IDA (hemoglobin level <11g/dL and ferritin level <12ng/dL) were enrolled. Patients with a history of anemia due to any other causes such as chronic blood loss, hemolytic anemia and thalassemia, Clinical and/or laboratory evidence of hepatic, renal, cardiovascular abnormalities, history of peptic disorders, esophagitis, hiatal hernia, or malabsorption syndrome were ruled out.

The study included two groups and was done through giving iron therapy to anemic pregnant women. Group I (lactoferrin): 95 cases were received 100 mg of bovine lactoferrin (Pravotin sachets, Hygint, Egypt) twice a day. Group II (ferrous sulfate): 93 cases were received 150 mg of dried ferrous sulphate + folic acid (vitamin B9) 0.50mg (Ferrofol, E.I.P.I.C.O, Egypt) three capsules per day.

For each pregnant woman, age, parity and gestational history were taken before treatment. All pregnant women took their allocated treatment regularly for four weeks after diagnosis of iron deficiency anemia with hemoglobin level and serum ferritin level and followed up after four weeks.

Iron supplementation was commenced between 14 and 30 weeks of gestation and lasted for 4 weeks. Laboratory investigations were requested (CBC & serum ferritin) at 0 wk and repeated at 4 weeks after treatment. Follow up has taken place as regard as hematological response, possible side effects (abdominal pain, constipation, nausea, vomiting), tolerability and compliance of treatment.

Statistical analysis

Descriptive statistics for measured variables were expressed as range, mean and standard deviation(for metric data) .range, median and interquartile range(for discrete data) and number and properties(for categorical data). Paired T test was used to detect differences in the same group before and after and independent T-test to compare the differences between the two groups. P value >0.05 insignificant, P value<0.05 significant and P value<0.01 highly significant [15].

RESULTS

Table (1): Demographic characteristics among the studied groups

Vatiables	Measures	Lactoferrin (N=95)	Ferrous sulphate (N=93)	P
Age (years)	**Mean±SD**	27.5±3.5	28.0±3.2	^0.330
	Range	20.0–37.0	20.0–36.0	
BMI (kg/m^2)	**Mean±SD**	27.5±1.6	27.9±1.6	^0.122
	Range	24.3–32.1	24.1–32.0	
Parity (n, %)	**PG**	28 (28.0%)	24 (24.0%)	#0.519
	MG	72 (72.0%)	76 (76.0%)	
GA (weeks)	**Mean±SD**	19.1±2.0	19.5±2.0	^0.241
	Range	14.0–24.0	14.0–23.0	

^Independent t-test, #Chi square test

Table (1) reveals the demographic characteristics among the studied groups with no significant difference.

Table (2): Hemoglobin (g/dL) among the studied groups

Time	Measures	Lactoferrin (N=95)	Ferrous sulphate (N=93)	^P
Basal	**Mean±SD**	9.4±0.9	9.5±0.8	0.604
	Range	7.2–10.9	7.1–10.8	
After	**Mean±SD**	10.9±1.0	10.3±0.8	**<0.001***
	Range	8.8–13.5	7.9–12.3	
Elevation	**Mean±SD**	1.5±0.5	0.8±0.4	**<0.001***
	Range	0.3–2.7	0.2–1.7	
	#P	**<0.001***	**<0.001***	
Impact of lactoferrin over ferrous sulphate in Hb				
Items		**Mean±SE**	**95% CI**	
Hb elevation		0.7±0.1	0.5–0.8	

^Independent t-test, #Paired t-test,*Significant, **CI:** Confidence interval

Table (2) reveals the change in hemoglobin level after treatment; there was a significant difference between the two groups, being higher in the lactoferrin group.

Table (3): Serum ferritin (ng/dL) among the studied groups

Time	Measures	Lactoferrin (N=95)	Ferrous sulphate (N=93)	^P
Basal	**Mean±SD**	9.2±1.3	9.3±1.2	0.648
	Range	6.5–11.9	6.5–11.9	
After	**Mean±SD**	13.7±1.4	10.6±1.2	**<0.001***
	Range	10.1–17.3	7.6–14.0	
Elevation	**Mean±SD**	4.5±0.5	1.3±0.5	**<0.001***
	Range	3.3–5.7	0.6–2.4	
	#P	**<0.001***	**<0.001***	
Impact of lactoferrin over ferrous sulphate in serum ferritin				
Items		**Mean±SE**	**95% CI**	
Ferritin elevation		3.2±0.1	3.0–3.3	

^Independent t-test, #Paired t-test,*Significant, **CI:** Confidence interval.

Table (3) reveals the change in serum ferritin level after treatment; there was a significant difference between the two groups, being higher in the lactoferrin group.

Table (4): Maternal side effects among the studied groups

Side effects	Lactoferrin (N=95)	Ferrous sulphate (N=93)	^P	RR (95% CI)
Abdominal pain	20 (21.1%)	60 (64.5%)	**<0.001 ***	0.352 (0.238–0.521)
Nausea	10 (10.5%)	59 (63.4%)	**<0.001***	0.210 (0.121–0.367)
Vomiting	8 (8.4%)	42 (45.2%)	**<0.001***	0.267 (0.145–0.492)
Constipation	17 (17.9%)	52 (55.9%)	**<0.001***	0.374 (0.245–0.570)

^Chi square test, RR: Relative risk (in lactoferrin relative to ferrous sulphate),*Significant, **CI:** Confidence interval.

Table (4) reveals the adverse effects of treatment; there was a significant difference between the two groups, being the least among the lactoferrin group.

DISCUSSION

Iron deficiency (ID) and iron deficiency anemia (IDA) are the most common iron disorders throughout the world. ID and IDA, particularly caused by increased iron requirements during pregnancy; represent a high risk for preterm delivery, fetal growth retardation, low birth weight, and inferior neonatal health. These pregnancy complications are thought to occur as a consequence of an increased iron requirement, related to enhanced blood volume and development of the fetoplacental unit [(1)].

ID and IDA are still a major health problem in pregnant women. To cure ID and IDA, iron supplements are routinely prescribed. The preferred treatment of ID/IDA, consisting of oral administration of iron as ferrous sulphate, often fails to exert significant effects on hypoferremia and may also cause adverse effects [(1)].

The World Health Organization (WHO) defines anemia in pregnancy as a hemoglobin (Hb) concentration of < 11 g/dl. Iron deficiency anemia (IDA) is the most common type of anemia in pregnancy. The iron content of the body is normally kept constant by regulating the amount absorbed to balance the amount lost [(2)].

The WHO estimates that 46% of pregnant women in African region, 38% in Eastern Mediterranean region, 25% in European region and 24% in the region of the Americas are anemic mainly because of iron deficiency [(2)].

Almost all cases of iron deficiency anemia respond readily to treatment with iron supplementation, patients do not always respond adequately to oral iron therapy because of noncompliance due to side effects. Gastrointestinal disturbances characterized by colicky pain, nausea, vomiting, constipation, diarrhea and gastric distress may occur in patients taking iron preparations [(16)].

The most commonly used treatment for ID and IDA currently consists of oral administration of iron as ferrous sulphate. However, ferrous sulphate administration often fails to exert any significant effects on these pregnancy-associated pathologies, and frequently causes several adverse effects (gastrointestinal discomfort, nausea, vomiting, diarrhoea, constipation). This is likely due to the poor bio-availability of inorganic iron requiring the administration of large quantity of ferrous sulphate [(12)].

For pregnant women the WHO recommends that all pregnant women should be supplemented with 60mg iron daily in pill that also contain 400µg folic acid given after eight weeks of pregnancy and for six months. If the six months duration cannot be achieved in pregnancy, supplement is to be continued during the postpartum period for 6 months or increase the dose to 120 mg iron in pregnancy. Women should continue the prophylaxis for three months in the postpartum period [(17)].

Treatment of iron deficiency anemia with oral iron preparations will make the hemoglobin concentration rise slowly, usually after approximately one to two weeks of treatment, and will rise approximately 2 g/dL over the ensuing three weeks. The hemoglobin deficit should be halved by approximately one month, and the hemoglobin level should return to normal by six to eight weeks [(18)].

Therefore, our study was conducted to evaluate the efficacy and tolerability of lactoferrin versus ferrous ferrous sulphate.

The selection of the second trimester pregnancy was made upon the fact that the iron demand increases remarkably in the second trimester as there is no extra fetal iron demand

required in the first trimester, Furthermore, the fetal blood is not well formed from the erythropoietic system. Iron would be very irritant to the stomach especially if emesis gravidarum exists [19].

Paesano *et al.* [1], *Rezk et al.* [21] and Darwish *et al.* [22] used lactoferrin preparation to the participants of one group in their studies.

***Kambar et al.* [16]** used ferrous sulphate as the form of iron provided to the participants of one group in their studies.

The results of our study revealed that there was No significant difference between ferrous sulphate and lactoferrin groups regarding basal hemoglobin (P > 0.05), while there was a significant increase in Hb level in both groups after 4 weeks of treatment (P < 0.01) as therapeutic iron supplementation stimulates erythropoiesis in iron deficient states.

The rate of hemoglobin rise in our study was significantly higher in lactoferrin group (2.7 g/dl) than in ferrous sulphate group (1.7 g/dl) at 4 weeks.

S. ferritin level was not significantly different between group A (Lactoferrin) and group B (Ferrous sulphate) at 0 wk (P > 0.05)

Serum ferritin significantly increased in ferrous sulphate and lactoferrin groups after treatment (P <0.01).

The increase in the level of s. ferritin in group A (Lactoferrin) at 4 weeks was (3.3–5.7 **ng/dL**) while in group B (ferrous sulphate) the increase in the level of s. ferritin was (0.6–2.4 **ng/dL**) at 4 weeks and this shows that the rate of s. ferritin rise was higher in group A (lactoferrin) than group B (ferrous sulphate).

The incidence of adverse effects of course of treatment including constipation, abdominal pain, nausea and vomiting was higher in group B (ferrous sulphate) than group A (lactoferrin) as there was statistically a significant difference between both groups (P < 0.01).

The cost of 4 weeks treatment with lactoferrin was 120 LE for every pregnant woman and this cost was much more expensive than the cost of 4 weeks treatment with ferrous sulphate which was only 7 LE for every pregnant woman.

Paesano *et al.* [20] 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), the pregnant women (n=205) were divided into 2 groups independently of the trimester of pregnancy, the ferrous sulphate group (n=98) and lactoferrin group (n=107). In all treated women, the hemoglobin and total serum iron values showed a significant increase (P < 0.01) 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 of 8.0 ug/dL, respectively) were lower than those observed in women receiving lactoferrin (1.5 g/dL and 54.2 ug/dL respectively).

With respect to side effects of 98 women receiving ferrous sulphate, 95% had abdominal pain and constipation, 2% had diarrhea. By contrast, no side effects were observed in those who received lactoferrin. The study concluded that oral bovine lactoferrin for 30 days showed higher hemoglobin values, higher compliance among treated women and lesser side effects than those of ferrous sulphate. It is likely that lactoferrin inhances intestinal iron delivery better than ferrous sulphate and could influence iron homeostasis.

***Rezk et al.* [21]** Conducted a study to evaluate the efficacy and side effects of lactoferrin and ferrous sulphate, A total of 200 pregnant women with single fetus in their second trimesters were enrolled and divided into 2 groups, Lactoferrin group(n=100); received 250 mg capsules (Jarrow Formulas, Egypt) once daily for 8 weeks and Ferrous sulphate group(n=100); received 150 mg of dried ferrous sulphate (Ferrofol, Eipico, Egypt) once daily for 8 weeks, The results showed that the total increase in hemoglobin after 2 months with lactoferrin was higher (2.26±0.51g/dL) compared to ferrous sulphate (1.11±0.22g/dL) (P <0.001). The gastrointestinal side effects occurred more frequently with ferrous sulphate than lactoferrin group (P<.0.001). Also the number of women requesting change the drug was higher in ferrous sulphate group (P<0.001).

***Darwish et al.* [22]** conducted a study to test the efficacy and safety of oral lactoferrin plus health education versus total dose infusion (TDI) of low molecular weight (LMW) iron dextran for treating iron deficiency anemia in the second and third trimester of pregnancy. A total of 120 cases were divided into 2 groups, lactoferrin group (n=60) receiving lactoferrin oral sachets (MamyVital, Duplex Lab, Cairo, Egypt) 100 mg two times per day for 4 weeks accompanied with health education given by a nurse, and TDI of LMW iron dextran group (n=60) receiving (Cosmofer – iron (III) hydroxide dextran complex, Pharmacosmos A/S, Denmark) equivalent to 50 mg of iron per ml. However, only 33 cases in group B completed the study and the rest refused hospital admission and parenteral iron infusion. This study results showed that the TDI group had a better rise in hemoglobin (25.2%) compared to lactoferrin group (19.1%), Similarly, MCV expressed a better percent change in TDI group (16.9%) versus (5.1%) and the same applies for MCH (24.5% in

TDI group versus 7.58% in lactoferrin group). Contrarily, increased serum iron and the decrease of TIBC were better in lactoferrin group than TDI group (89.1% versus 57%) and (-38.8% versus -29.8%) respectively. It should be mentioned that a great disadvantage of TDI is the need of hospitalization for close monitoring where equipment and drugs for cardiopulmonary resuscitation are available during infusion. Another disadvantage of TDI is the cost of therapy when compared to oral iron preparation (6 times the cost of oral lactoferrin), this represent a real limitation of its liberal use on a wider scale.

The study concluded that lactoferrin can be widely used as an alternative to TDI of iron dextran supplementation due to clinical as well as laboratory improvement of IDA during pregnancy after one month of treatment [(22)].

A systematic review and meta-analysis was done by **Abu Hashim *et al.*** [(23)] and aimed to evaluate the efficacy of daily oral bovine lactoferrin versus daily oral ferrous iron preparations for treatment of iron deficiency anemia (IDA) during pregnancy.) included 4 eligible trials (600 women). Pooled estimates for change in hemoglobin levels at 4 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) and a significant increase favoring lactoferrin was reported in moderate anemia (mean difference 0.68; 95%; CI 0.53-0.83; P<0.00001, one trial, 228 women). Significantly less gastrointestinal side effects were reported with lactoferrin treatment. They concluded that daily oral lactoferrin is just as good as ferrous sulfate in improving hematological parameters with fewer gastrointestinal side effects and thereby, lactoferrin should be the iron replacement agent of choice for treatment of IDA in pregnancy [(23)].

CONCLUSION

Lactoferrin seems to increase Hb and serum ferritin levels more than ferrous sulphate and also seems to produce less adverse effects than ferrous sulphate as regards constipation, nausea, vomiting and abdominal pain. Thus, in pregnant women with iron deficiency anemia, lactoferrin may be considered as a more effective alternative treatment with fewer side effects than traditional ferrous sulphate treatment but with a more expensive cost.

REFERENCES

1- **Paesano R, Berlutti F, Pietropaoli M, Pantanella F, Pacifici E, Goolsbee W, Valenti P (2010):** Lactoferrin efficacy versus ferrous sulphate in curing iron deficiency and iron deficiency anemia in pregnant women; Biometals review,23(3):411-7.

2- **WHO (2011):** World Health Organization, Geneva. The global prevalence of anemia**.** www.who.int/nutrition/publications.

3- **Sunitha, Satyanarayana, Shaik M, Mobina S, Lakshmi KB, Kathi MC and Pradeep B (2010):** Hematological responses to oral administration of iron polymoltose complex in anemic and normal pregnant women. Journal of College of Medical Sciences Nepal., 6(3): 1-7.

4- **Hamza S (2005):** The maternal mortality: Egyptian National Maternal Mortality Study. Ain Shams J The Current Annals of Obstetrics and Gynecology (ASJOG®), 2: 306-307.

5- **Scholl TO (2005):** Iron status during pregnancy setting the stage for mother and infant. Am J Clin Nutr; 81: 121: 12185-225.

6- **Mumtaz A and Farooq F (2011):** Comparison for effects of intravenous versus oral iron therapy for post-partum anemia. Pakistan J the Current Nal of Medical and Health Sciences, 5(1): 113-115.

7- **Thirunavukkarasu S and Bhandary A (2009):** A novel short-course regimen of intramuscular iron therapy for anemic pregnant women. Trop Doct ., 39(4): 227-8.

8- **Lynch SR (2000):** The potential impact of iron supplementation during adolescence on iron status in pregnancy. J Nutr; 71: 12803-12845.

9- **Christian B (2002):** Iron deficiency and: modern aspect of diagnosis and therapy. Blood Cell Molecules and Diseases, 29(3): 506-516.

10- **Jai BS (2004):** A prospective partially randomized study of pregnancy outcome and hematological response to oral and intramuscular iron treatment in anemic pregnant women. Am J Clin Nutr., 79: 116-2231.

11- **Sifakis S and Pharmakides G (1999):** In. Anemia in pregnancy. In hematological problems pregnancy.first edition, Science, New York.

12- **Schumann K, Ettle T, Szegner B, Elsenhans B, Solomons N(2007):** On risks and benefits of iron supplementation recommendations for iron intake revisited, J. Trace Elem. Med. Biol., 21: 147e168.

13- **Sánchez L, Calvo M, Brock JH (1992):** "Biological role of lactoferrin". Archives of Disease in Childhood, **67** (5): 657–61.

14- **Lönnerdal B, Iyer S (1995):** Lactoferrin; molecular structure and biological function. Annu Rev Nutr., 15:93–110.

15- **De Smith MJ (2015):** Statistical Analysis Handbook: A comprehensive handbook of statistical concepts, techniques and software tools. WWW.STATSREF.COM. The Winchelsea Press, Winchelsea, UK.

16- **Kambar C, Zahedabano A and Meenakumari A (2013):** Comparative study of efficacy and safety of Iron polymaltose complex with ferrous sulphate in antenatal women with moderate anemia. Journal of Dental and Medical Sciences**, 9: 9-13.**

17- **WHO (2006):** World Health Organizaton. Sickle-cell disease and other haemoglobin disorders. www.who.int/iris/handle/10665/20890.

18- **Cancelo-Hidalgo MJ, Castelo-Branco C, Palacios S, Haya-Palazuelos J, Ciria-Recasens M, Manasanch J, Pérez-Edo L (2013):** Tolerability of different oral iron supplements: a systematic review, 29(4):291-303.

19- **Weinberg ED (2010):** Can iron be teratogenic? Biomatals,23(2):181-4.

20- **Paesano R, Torcia F, Berlutti F, Pacifici E, Ebano V, Moscarini M and Valenti P (2009):** Oral administration of lactoferrin increases hemoglobin and total serum iron in pregnant women. Bio Chem Cell Biol., 84: 377-80.

21- **Rezk M, Dawood R, Abo Elnasr M, Al Halaby A, Marawan H (2015):** Lactoferrin versus ferrous sulphate for the treatment of iron deficiency anemia during pregnancy. The Journal of Maternal-Fetal& Neonatal Medicine. Doi: 10.3109/14767058.2015.1049149.

22- **Darwish AM, Fouly HA, Saied WH, Farah E (2018):** Lactoferrin plus health education versus total dose infusion (TDI) of low-molecular weight (LMW) iron dextran for treating iron deficiency anemia (IDA) in pregnancy: A randomized controlled trial, The Journal of Maternal-Fetal & Neonatal Medicine, DOI: 10.1080/14767058.2018.1429.

23- **Abu Hashim H, Foda O, Ghayaty E (2017):** Lactoferrin or ferrous salts for iron deficiency anemia in pregnancy: A meta-analysis of randomized trials, 219:45-52.