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Analysis of Lactoferrin vs. Intravenous Iron Sucrose in Treating Iron Deficiency Anemia during Pregnancy

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ABSTRACT

Background and Objective: The most common dietary deficiency and the primary cause of anemia is iron deficiency. When the hemoglobin level in peripheral blood is less than 11 grams per 100 milliliters during pregnancy, iron deficiency anemia (IDA) is detected to compare the cost-effectiveness of treating IDA in pregnant women with lactoferrin against intravenous (IV) iron sucrose, as well as to assess the clinical effectiveness and financial effects from a pharmacy perspective.

Material and Methods: This prospective, randomized, open-label, parallel-group study was conducted at a tertiary care hospital at Suez Canal University Hospital from January till October 2023 and performed on a total number of 88 pregnant women who presented with IDA.

Results: Adherence to time of doses was non-significantly more frequent in the iron sucrose group than in the lactoferrin group. Constipation, nausea, vomiting, gastric upset, and black stool were less frequent in the iron sucrose group; the differences were statistically significant only in constipation, gastric upset, and black stool. Lab cost was equal in either group. The cost of further research was not considerably greater in the lactoferrin group than in the iron sucrose group. Compared to the lactoferrin group, the iron sucrose group's drug cost was significantly lower.

Conclusion: Given their similar ability to increase hemoglobin and blood iron levels, lactoferrin and IV iron sucrose are both effective treatments for IDA in pregnant women. Lactoferrin provides an effective oral option that minimizes clinical visits, though with a higher risk of gastrointestinal side effects.

KEYWORDS: Iron Deficiency Anemia, Lactoferrin, Intravenous Iron sucrose.

1. INTRODUCTION

Iron deficiency is the most common dietary deficiency and the primary cause of anemia. When the quantity of hemoglobin or red blood cells in the blood decreases, it is an indication of a pathologic process that is occurring below. Pregnancy-related IDA is characterized by a peripheral blood hemoglobin content of less than 11 grams per 100 milliliters [1]. Iron loss from bleeding or inadequate food intake and absorption are the causes [2]. An important ingredient for living cells, iron is especially important for the growing fetus during pregnancy due to maternal iron transfer, as well as for the newborn via nursing and for the child through nutrition during infancy. The combined effects of hemodilution and increased iron requirements are the cause of the high prevalence of anemia during pregnancy [3]. Depending on the severity of the anemia and the gestational age, oral iron therapy can be used to treat mild IDA during pregnancy, but parenteral iron therapy or blood transfusions are required for moderate and severe anemia [4]. Iron sucrose, a mixture of polynuclear iron (III) hydroxide and sucrose, is absorbed by the reticuloendothelial system and is separated into iron and sucrose after being given intravenously [5]. One significant disadvantage of total dose infusion (TDI) should be the need for hospitalization or, at the very least, an outpatient setting with

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close monitoring, where drugs and equipment for cardiac resuscitation are available throughout infusion. Additionally, greater caution needs to be exercised. To avoid chemical phlebitis at the infusion site and the need for a test dosage before the infusion starts, it should be given in a peripheral vein, unlike other parenteral irons that do not require that. TDI of low molecular weight (LMW) iron dextran is quite costly in comparison to oral iron therapy [1].

Both human and cow milk include the protein lactoferrin. Colostrum, the first milk produced after a baby is born, has high levels of lactoferrin, around seven times that of milk produced later [6, 7]. Lactoferrin, formerly known as lacto transferrin, is a glycoprotein that is a member of the transferrin family, which also comprises proteins that can bind and transfer iron [8]. The fluids of the nose, eyes, respiratory system, and colon also contain lactoferrin. It is used to treat hepatitis C, diarrhea, and stomach and intestinal ulcers. Additionally, it serves as an antioxidant and a defense against viral and bacterial diseases [9]. Moreover, lactoferrin appears to be able to strengthen the body's defense (immune) system and regulate bone marrow activity (myelopoiesis). Lactoferrin is a multifunctional protein with both dependent and independent biological activity based on its capacity to bind iron [10]. Thus, the study's objective is to evaluate the therapeutic effectiveness and financial implications from a pharmacy standpoint, as well as the cost-effectiveness of using lactoferrin in conjunction with IV iron sucrose to treat IDA in pregnant women.

2. PATIENTS AND METHODS

2.1. Patient Grouping

This prospective, randomized, open-label, parallel-group study was carried out at the tertiary care hospital at Suez Canal University Hospital with written consent from the patients. From January to October 2023, 88 pregnant women who presented with IDA were randomly selected from pregnant women attending the antenatal outpatient clinic. The participants were split into two randomized groups, the iron sucrose group and the lactoferrin group. Initially, 106 patients were screened for eligibility, but 14 were excluded due to unmet inclusion criteria, and 4 declined participations. The final analysis was therefore conducted on the 88 enrolled participants, with 44 assigned to each treatment group Fig. 1.

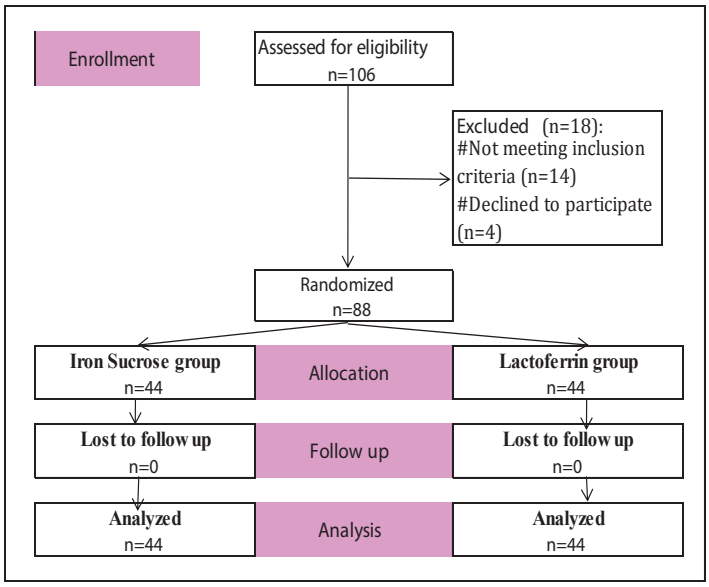

Fig. 1: Consort flow diagram for study cases

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2.2. Inclusion and Exclusion Criteria

The following inclusion criteria were used in the selection of patients: pregnant women aged 20–40 with IDA, microcytic hypochromic anemia, moderate anemia (Hb 8–9.9 g/dl), S. ferritin levels <12 ng/dl per WHO guidelines, gestational age of 13–26 weeks, and a 100% viable pregnancy. The excluded women are those with a history of anemia Bronchial asthma, severe anemia <7 g/dl requiring blood transfusion, hypersensitivity to iron preparations and treatment with any other iron preparation in the month before study entry, hemolytic anemia, chronic blood loss, thalassemia (including thalassemia trait), suspected acute infection, and a history of peptic ulcer.

2.3. Randomized Sampling Method

Using the Simple Randomization Service by Sealed Envelope Ltd. 2017 with allocation concealment, a computer-generated database of random integers was used for the randomization process. Once allocation had been done, it was not changed.

2.4. Study Procedures

Every participant had their whole medical history taken, with particular attention paid to their personal history, current pregnancy history, historical medical conditions, general examination, abdominal examination, fetal monitoring, and U/S study. While a complete blood sample (CBC) and serum ferritin were sent to a private lab, transferrin iron binding capacity (TIBC), transferrin saturation, kidney function tests, and liver function tests were done for all patients. Four weeks following the therapy, anemic pregnant women were monitored. Patients were called in between appointments to monitor any negative effects. Finding the difference in hemoglobin levels and serum ferritin levels between the two groups after four weeks is the primary outcome. Cost-effectiveness and monitoring adverse effects, such as the frequency of nausea, vomiting, upset stomach, dyspepsia, constipation, and medication compliance, were the secondary outcomes. The patient information was anonymous. Patient confidentiality was maintained, and data were presented by diagnosis rather than by name. Every participant gave their informed permission, which was verified by date and time and was in Arabic. By giving the patient's initials a number that only the researcher knew, secrecy was maintained.

2.5. Sample Size

Version 11 of the PASS program was used to determine the sample size. The statistical model NCSS, LLC (done by Hintze, 2011) was used to establish the type-1 error at 0.05 and the power at 80%.When the real difference between the hemoglobin change means is 0.04 and the standard deviation is 0.71, with equivalent limits considered to be ±0.5 gm/dL, a sample size of 40 in each group passes an equivalence test of means using two one-sided tests [1]. Assuming a drop-out rate of 25%, a total of 100 are needed to be recruited in the trial, to be randomized into one of the two groups.

2.6. Economic Evaluation

The cost-effectiveness of treating IDA during pregnancy with lactoferrin vs. IV iron sucrose was assessed using a decision tree modeling approach. The Quality-Adjusted Life Years (QALY) were the primary outcome that was taken into consideration. Both solutions' costs and effects were assessed, and the results were presented as incremental cost-effectiveness ratios, or ICRs. Options with an ICER of less than one GDP per capita may be regarded as extremely cost-effective, under WHO recommendations. An option with an ICER

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of one to three times the GDP per capita is considered cost-effective, while one with an ICER greater than three times the GDP per capita is not. To assess the model's resilience in order to input data uncertainty, a one-way sensitivity analysis was performed.

2.7. Ethical Consideration

The authors confirm that the procedures employed were in accordance with the World Medical Association's Code of Ethics (Declaration of Helsinki) and the requirements of the relevant clinical research ethics committee of the Faculty of Pharmacy, Sinai University (North Sinai, Egypt) (code #SU.REC.2024 (22 H).

3. STATISTICAL ANALYSES

The IBM SPSS Statistics software is the model used for the statistical analyses. Group quantitative data were compared using an independent t-test, while time of the paired t-test was assessed after being examined for normality using the Shapiro-Wilk test and. it was then expressed as mean±SD. For variables with tiny, anticipated numbers, the chi-square test and Fisher's exact test are used to compare qualitative data expressed as numbers and percentages. To determine the independent components influencing lab changes, linear regression is utilized. The P-value is considered significant when it is ≤ 0.05*.

3.1. Results

Baseline demographic characteristics (age, weight, parity, and gestational age) show no statistically significant differences between the groups. (p-values =0.912, 0.564, 0.522, and 0.170 respectively). The mean age of the iron sucrose group is 29.9 years (±5.8), mean weight is 72.7 kg (±9.8), and a gestational age is 19.4 weeks (±3.9). The lactoferrin group shows non-significance differences in these variables (Table 1).

Table 1: Baseline demographic characteristics between the study groups

Variables		Iron Sucrose group (Total=44)	Lactoferrin group (Total=44)	p-value
Age (years)		29.9±5.8	30.1±5.8	^0.912
Weight (kg)		72.7±9.8	71.4±10.8	^0.564
Parity (n, %)	**Primi**	23 (52.3%)	20 (45.5%)	#0.522
	Multi	21 (47.7%)	24 (54.5%)	
Gestational age (weeks)		19.4±3.9	20.5±3.5	^0.170

^Independent t-test. #Chi square test.

Primi: primigravida (first-time pregnant). Multi: multigravida (many pregnancies).

Regarding baseline hemoglobin, hematocrit (%), MCV, MCH, MCHC, serum ferritin, and serum irontransferrin saturation (p-values =0.768, 0.928, 0.853, 0.500, 0.980, 0.767, 0.725, and 0.850 respectively), no statistically significant differences between the studied groups were detected. Regarding TIBC, also no statistically significant differences between the studied groups (p-value =0.852). In week 4, the iron sucrose group showed statistically non-significant higher levels of blood hemoglobin, hematocrit (%), MCV, MCH, MCHC, serum iron, serum ferritin, and transferrin saturation than found in the lactoferrin group. Blood hemoglobin levels increased from 9.1 g/dL (±0.5) to 10.8 g/dL (±0.5) in the iron sucrose group, while in the lactoferrin group, it increased from 9.0 g/dL (±0.5) to 10.6 g/dL (±0.5). Regarding hematocrit levels, in the iron sucrose group, they rose from 28.3% (±2.3) to 31.5% (±2.1), while in the lactoferrin group they rose from 28.3% (±2.2) to 31.3% (±2.2) (p-value =0.618). MCV values

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showed an increase from 77.9 fL (±9.0) to 85.4 fL (±8.0) in the iron sucrose group, while in the lactoferrin group they increased from 78.2 fL (±7.6) to 84.3 fL (±8.4) (p-value =0.538). In the iron sucrose group MCH levels also showed an increase from 25.0 gm/dL (±3.2) to 28.0 gm/dL (±3.2) , and in the lactoferrin group THEY INCREASED from 25.4 gm/dL (±3.1) to 27.8 gm/dL (±3.3) (p-value =0.760). In addition, MCHC levels showed an increase from 32.1 gm/dL (±1.9) to 34.3 gm/dL (±1.9) in the iron sucrose group, and increased from 32.1 gm/dL (±2.7) to 34.2 gm/dL (±2.5) in the lactoferrin group (p-value =0.825). As well as serum ferritin levels showed an increase from 8.3 ng/mL (±2.0) to 14.6 ng/mL (±2.2) in the iron sucrose group, and increased from 8.1 ng/mL (±2.5) to 13.8 ng/mL (±2.4) in the lactoferrin group (p-value =0.101). Serum iron also in the iron sucrose group showed an increase from 5.7 µmol/L (±1.7) to 16.6 µmol/L (±3.6), and in the lactoferrin group it increased from 5.6 µmol/L (±1.9) to 15.6 µmol/L (±3.1) (p-value =0.178). Finally, transferrin saturation percentage showed an increase in the iron sucrose group from 6.4 % (±2.1) to 24.1% (±6.9), while in the lactoferrin group it increased from 6.4% (±2.5) to 22.4 % (±5.9) (p-value =0.222). TIBC in week four showed statistically non-significant difference between the two groups. It was lower in the iron sucrose group (from 90.5 µmol/L (±12.6) to 70.9µmol/L (±12.1)) than in the lactoferrin group (from 90.0 µmol/L(±11.8) to 71.6 µmol/L(±10.4)) (p-value =0.778). Hemoglobin, hematocrit (%), Serum ferritin, Serum iron, MCV, MCH, MCHC, and transferrin saturation significantly increased in week 4 as compared to the baseline level in lactoferrin group and iron sucrose group (p-values <0.001* for all parameters). TIBC significantly decreased in week 4 as compared to the baseline level in the lactoferrin group and the iron sucrose group (p-value <0.001*). In the iron sucrose group, hemoglobin, hematocrit (%), MCV, MCH, MCHC, serum ferritin, serum iron, and transferrin saturation are non-significantly increased more than in the lactoferrin group (p-values =0.109, 0.451, 0.079, 0.072, 0.713, 0.224, 0.163, and 0.157 respectively). TIBC was non-significantly more decreased in the iron sucrose group than in the lactoferrin group (p-value =0.476) (Table 2).

Table 2: Hemoglobin, Hematocrit, MCV, MCH, MCHC, Serum ferritin, Serum iron and Transferrin saturation between the study groups.

Variables	Time	Iron Sucrose group (Total=44)	Lactoferrin group (Total=44)	^p-value (groups)	Relative effect	
					Mean±SE	95% CI
Hemoglobin (gm/dL)	Baseline	9.1±0.5	9.0±0.5	0.768	0.1±0.1	-0.2–0.2
	Week-4	10.8±0.5	10.6±0.5	0.269	0.2±0.1	-0.1–0.3
	Change	1.7±0.3	1.6±0.3	0.109	0.1±0.1	0.0–0.2
	#p-value (times)	<0.001*	<0.001*			
Hematocrit (%)	Baseline	28.3±2.3	28.3±2.2	0.928	0.0±0.5	-0.9–1.0
	Week-4	31.5±2.1	31.3±2.2	0.618	0.2±0.5	-0.7–1.1
	Change	3.2±1.3	3.0±1.0	0.451	0.2±0.2	-0.3–0.7
	#p-value (times)	<0.001*	<0.001*			
MCV (fL)	Baseline	77.9±9.0	78.2±7.6	0.853	-0.3±1.8	-3.9–3.2
	Week-4	85.4±8.0	84.3±8.4	0.538	1.1±1.7	-2.4–4.6
	Change	7.5±4.2	6.1±3.2	0.079	1.4±0.8	-0.2–3.0
	#p-value (times)	<0.001*	<0.001*			
MCH (gm/dL)	Baseline	25.0±3.2	25.4±3.1	0.500	-0.4±0.7	-1.8–0.9
	Week-4	28.0±3.2	27.8±3.3	0.760	0.2±0.7	-1.2–1.6
	Change	3.0±1.1	2.4±2.0	0.072	0.6±0.3	-0.1–1.3
	#p-value (times)	<0.001*	<0.001*			

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MCHC (gm/dL)	Baseline	32.1±1.9	32.1±2.7	0.980	0.0±0.5	-1.0–1.0
	Week-4	34.3±1.9	34.2±2.5	0.825	0.1±0.5	-0.8–1.1
	Change	2.2±1.3	2.1±1.0	0.713	0.1±0.3	-0.4–0.6
	#p-value (times)	<0.001*	<0.001*			
Serum ferritin (ng/mL)	Baseline	8.3±2.0	8.1±2.5	0.767	0.2±0.5	-0.8–1.1
	Week-4	14.6±2.2	13.8±2.4	0.101	0.8±0.5	-0.2–1.8
	Change	6.4±2.8	5.7±2.4	0.224	0.7±0.6	-0.4–1.8
	#p-value (times)	<0.001*	<0.001*			
Serum iron (µmol/L)	Baseline	5.7±1.7	5.6±1.9	0.725	0.1±0.4	-0.6–0.9
	Week-4	16.6±3.6	15.6±3.1	0.178	1.0±0.7	-0.5–2.4
	Change	10.9±3.0	10.0±2.5	0.163	0.9±0.6	-0.3–2.0
	#p-value (times)	<0.001*	<0.001*			
TIBC (µmol/L)	Baseline	90.5±12.6	90.0±11.8	0.852	0.5±2.6	-4.7–5.7
	Week-4	70.9±12.1	71.6±10.4	0.778	-0.7±2.4	-5.5–4.1
	Change	-19.6±7.1	-18.4±8.2	0.476	-1.2±1.6	-4.4–2.1
	#p-value (times)	<0.001*	<0.001*			
Transferrin saturation (%)	Baseline	6.4±2.1	6.4±2.5	0.850	0.0±0.5	-0.9–1.1
	Week-4	24.1±6.9	22.4±5.9	0.222	1.7±1.4	-1.0–4.4
	Change	17.6±5.7	16.0±4.7	0.157	1.6±1.1	-0.6–3.8
	#p-value (times)	<0.001*	<0.001*			

^Independent t-test (comparison between study groups). #Paired t-test (comparison between baseline and week-4 within each group). *Significant. Change = Week-4 – baseline. Relative effect: The effect in Iron Sucrose group relative to the effect in Lactoferrin group. SE: Standard error. CI: Confidence interval.

Table 3: Compliance to treatment and medications' side effects between the study groups.

Items	Iron Sucrose group (Total=44)	Lactoferrin group (Total=44)	p-value (groups)	Relative effect	
				RR	95% CI
Receiving medication	44 (100.0%)	44 (100.0%)	NA	NA	NA
Adherence to time of doses	39 (88.6%)	33 (75.0%)	#0.097	1.18	0.97–1.44
Constipation	1 (2.3%)	10 (22.7%)	**#0.004***	0.10	0.01–0.75
Nausea	5 (11.4%)	7 (15.9%)	#0.534	0.71	0.25–2.08
Vomiting	2 (4.5%)	7 (15.9%)	§0.157	0.29	0.06–1.30
Gastric upset	3 (6.8%)	11 (25.0%)	**#0.020***	0.27	0.08–0.91
Black stool	0 (0.0%)	6 (13.6%)	**§0.026***	NA	NA
Liver function impairment	0 (0.0%)	0 (0.0%)	NA	NA	NA
Kidney function impairment	0 (0.0%)	0 (0.0%)	NA	NA	NA
Allergy	0 (0.0%)	0 (0.0%)	NA	NA	NA

NA: Not applicable. #Chi square test. Relative effect: The effect in Iron Sucrose group relative to the effect in Lactoferrin group. RR: Relative risk. CI: Confidence interval.

All cases in either group received the allocated medication. Adherence to dosage timing was not significantly greater in the iron sucrose group compared to the lactoferrin group (p-value =0.097). Constipation, nausea, vomiting, stomach upset, and black stool were less common in the iron sucrose group. Changes were only statistically significant for constipation, gastric upset, and black stool (p-values =0.004*, 0.020*, and 0.026* respectively). Liver function impairment and kidney function impairment, and allergy did not occur in all cases of

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either group (Table 3). Lab cost was equal in either group (p-value =0.999). the cost of further research would not be that higher in the lactoferrin group than in the iron sucrose group (p-value =0.093). The iron sucrose group's drug cost was lower than that of the lactoferrin group (p-value <0.001*). Compared to the lactoferrin group, the iron sucrose group's administration costs were much greater (p-value <0.001*). Compared to the lactoferrin group, the iron sucrose group's cost of the medication used to treat side effects was not statistically lower (p-value =0.054). Compared to the lactoferrin group, the iron sucrose group's overall cost was much greater (p-value <0.001*). The iron sucrose group's treatment efficiency (measured in Egyptian pounds per gram of hemoglobin increase) was not statistically greater than that of the lactoferrin group (p-value =0.409) (Table 4).

Table 4: Cost (Egyptian pound) and Treatment efficiency (cost in Egyptian pound per gram hemoglobin elevation) among the studied groups.

Measures	Iron Sucrose group (Total=44)	Lactoferrin group (Total=44)	^p-value	Relative effect	
				Mean±SE	95% CI
Lab cost	240.0±0.0	240.0±0.0	0.999	0.0±0.0	0.0–0.0
Other investigations cost	36.1±64.3	17.5±34.0	0.093	18.6±11.0	-3.2–40.4
Drug cost	256.8±43.4	361.7±33.1	<0.001*	-104.9±8.2	-121.2–-88.5
Administration cost	150.0±0.0	0.0±0.0	<0.001*	150.0±0.0	150.0–150.0
Cost of drug used to treat side effects	5.9±10.7	10.6±11.9	0.054	-4.7±2.4	-9.5–0.1
Total cost	688.8±72.4	629.8±42.4	<0.001*	59.0±12.6	33.9–84.2
Treatment efficiency	415.7±77.2	402.7±69.9	0.409	13.0±15.7	-18.2–44.

^Independent t-test (comparison between study groups). *Significant. Relative effect: The effect in Iron Sucrose group relative to the effect in Lactoferrin group. SE: Standard error. CI: Confidence interval.

Maternal age and gestational age were significant independent factors that decreased hemoglobin elevation in the lactoferrin group (p-values =0.021*, and 0.033* respectively). Gestational age was a significant independent factor that decreased hematocrit elevation in the lactoferrin group (p-value =0.009*). Weight was a significant independent factor that increased MCH elevation in the lactoferrin group (p-value =0.013*). No baseline demographic characteristics in the study was a significant independent factor that cab affect the level of hemoglobin, hematocrit, MCV, MCH, MCHC, serum iron, serum ferritin, transferrin saturation and TIBC (Table 5).

Table 5: Multiple linear regressions for independent factor affecting change of hemoglobin in each of Iron Sucrose group and Lactoferrin group.

	Group	Factors	β	SE	p-value	95% CI	R^2
Change of hemoglobin	Iron Sucrose group (Total=44)	**Constant**	1.23	0.39	**0.003***	0.44–2.03	0.098
		Age	0.00	0.01	0.909	-0.01–0.02	
		Weight	0.00	0.00	0.705	-0.01–0.01	
		Multipara	-0.06	0.09	0.509	-0.24–0.12	
		Gestational age	0.02	0.01	0.062	0.00–0.04	
	Lactoferrin group (Total=44)	**Constant**	3.12	0.35	**<0.001***	2.41–3.83	0.349
		Age	-0.02	0.01	**0.021***	-0.03–0.00	
		Weight	-0.01	0.00	0.108	-0.01–0.00	
		Multipara	-0.09	0.08	0.251	-0.24–0.07	
		Gestational age	-0.02	0.01	**0.033***	-0.05–0.00	
Change of	Iron Sucrose group (Total=44)	**Constant**	3.31	1.91	0.090	-0.54–7.17	0.035
		Age	0.00	0.03	0.987	-0.07–0.07	

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		Weight	-0.02	0.02	0.484	-0.06–0.03	
		Multipara	0.03	0.44	0.950	-0.86–0.92	
		Gestational age	0.05	0.05	0.322	-0.05–0.16	
	Lactoferrin group (Total=44)	**Constant**	7.54	1.46	**<0.001***	4.58–10.49	
		Age	-0.05	0.03	0.053	-0.11–0.00	
		Weight	0.00	0.02	0.937	-0.03–0.03	0.233
		Multipara	-0.20	0.32	0.525	-0.85–0.44	
		Gestational age	-0.12	0.05	**0.009***	-0.22–-0.03	
Change of MCV	**Iron Sucrose group (Total=44)**	**Constant**	8.01	6.41	0.219	-4.96–20.98	
		Age	0.06	0.12	0.601	-0.17–0.29	
		Weight	0.02	0.08	0.815	-0.14–0.17	0.027
		Multipara	-0.53	1.48	0.724	-3.52–2.46	
		Gestational age	-0.15	0.17	0.399	-0.50–0.20	
	Lactoferrin group (Total=44)	**Constant**	4.14	4.93	0.406	-5.83–14.11	
		Age	0.09	0.09	0.344	-0.10–0.27	
		Weight	0.03	0.05	0.544	-0.07–0.14	0.051
		Multipara	-0.85	1.07	0.435	-3.01–1.32	
		Gestational age	-0.08	0.15	0.619	-0.39–0.23	
Change of MCH	**Iron Sucrose group (Total=44)**	**Constant**	1.76	1.64	0.291	-1.56–5.08	
		Age	0.05	0.03	0.096	-0.01–0.11	
		Weight	0.00	0.02	0.975	-0.04–0.04	0.094
		Multipara	-0.39	0.38	0.309	-1.16–0.38	
		Gestational age	0.01	0.04	0.743	-0.08–0.10	
	Lactoferrin group (Total=44)	**Constant**	0.99	2.94	0.737	-4.95–6.94	
		Age	-0.04	0.05	0.432	-0.15–0.07	
		Weight	0.08	0.03	**0.013***	0.02–0.14	0.169
		Multipara	-0.10	0.64	0.881	-1.39–1.20	
		Gestational age	-0.14	0.09	0.136	-0.32–0.05	
Change of MCHC	**Iron Sucrose group (Total=44)**	**Constant**	0.22	2.06	0.916	-3.96–4.39	
		Age	0.01	0.04	0.809	-0.07–0.08	
		Weight	0.02	0.02	0.383	-0.03–0.07	0.026
		Multipara	-0.16	0.48	0.741	-1.12–0.80	
		Gestational age	0.02	0.06	0.773	-0.10–0.13	
	Lactoferrin group (Total=44)	**Constant**	2.20	1.59	0.174	-1.01–5.40	
		Age	0.00	0.03	0.890	-0.06–0.05	
		Weight	-0.01	0.02	0.457	-0.05–0.02	0.045
		Multipara	-0.12	0.35	0.734	-0.82–0.58	
		Gestational age	0.05	0.05	0.306	-0.05–0.15	
Change of Serum ferritin	**Iron Sucrose group (Total=44)**	**Constant**	5.24	3.94	0.191	-2.73–13.20	
		Age	-0.01	0.07	0.925	-0.15–0.14	
		Weight	0.09	0.05	0.059	0.00–0.19	0.144
		Multipara	-1.15	0.91	0.213	-2.99–0.69	
		Gestational age	-0.19	0.11	0.089	-0.40–0.03	
	Lactoferrin group (Total=44)	**Constant**	6.35	3.77	0.100	-1.28–13.99	
		Age	0.01	0.07	0.875	-0.13–0.15	
		Weight	0.00	0.04	0.925	-0.08–0.08	0.039
		Multipara	0.59	0.82	0.474	-1.07–2.26	
		Gestational age	-0.11	0.12	0.374	-0.34–0.13	
Change of Serum iron	**Iron Sucrose group (Total=44)**	**Constant**	7.00	4.52	0.129	-2.14–16.14	
		Age	0.07	0.08	0.403	-0.10–0.23	
		Weight	0.04	0.05	0.494	-0.07–0.15	0.043
		Multipara	-0.99	1.04	0.347	-3.10–1.12	
		Gestational age	0.03	0.12	0.814	-0.22–0.28	

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	Lactoferrin group (Total=44)	Constant	14.27	3.97	**0.001***	6.24–22.31	0.045
		Age	-0.06	0.07	0.398	-0.21–0.08	
		Weight	-0.02	0.04	0.575	-0.11–0.06	
		Multipara	-0.36	0.86	0.680	-2.11–1.39	
		Gestational age	-0.01	0.12	0.950	-0.26–0.24	
Change of TIBC	Iron Sucrose group (Total=44)	Constant	-21.28	10.30	**0.045***	-42.11–-0.45	0.116
		Age	0.00	0.19	0.999	-0.38–0.38	
		Weight	-0.08	0.12	0.534	-0.32–0.17	
		Multipara	-2.03	2.37	0.398	-6.83–2.77	
		Gestational age	0.53	0.28	0.065	-0.03–1.09	
	Lactoferrin group (Total=44)	Constant	-23.55	12.95	0.077	-49.74–2.64	0.026
		Age	0.16	0.24	0.507	-0.32–0.64	
		Weight	0.07	0.13	0.582	-0.20–0.35	
		Multipara	-1.62	2.82	0.568	-7.32–4.07	
		Gestational age	-0.12	0.40	0.767	-0.94–0.70	
Change of Transferrin saturation	Iron Sucrose group (Total=44)	Constant	15.52	8.66	0.081	-2.00–33.05	0.027
		Age	0.06	0.16	0.681	-0.25–0.38	
		Weight	0.05	0.10	0.658	-0.16–0.25	
		Multipara	0.35	2.00	0.863	-3.69–4.39	
		Gestational age	-0.19	0.23	0.421	-0.67–0.28	
	Lactoferrin group (Total=44)	Constant	24.89	7.04	**0.001***	10.64–39.13	0.127
		Age	-0.08	0.13	0.561	-0.34–0.18	
		Weight	-0.10	0.07	0.173	-0.25–0.05	
		Multipara	-1.58	1.53	0.308	-4.68–1.52	
		Gestational age	0.15	0.22	0.491	-0.29–0.60	

β: Regression coefficient. SE: Standard error. CI: Confidence interval. *Significant. R^2: Coefficient of determination

3.2. Discussion

Pregnant women frequently suffer from iron deficiency anemia (IDA), which has a serious negative influence on the health of the maternal and the fetus. Preterm delivery, low birth weight, and higher mother morbidity are among the unfavorable pregnancy outcomes that are linked to it. The primary approach to treating IDA involves iron supplementation, which can be administered either orally or intravenously. However, the choice of treatment is often influenced by factors such as efficacy, side effects, patient adherence, and overall cost. IV iron sucrose is widely used for rapid correction of anemia, particularly in cases where oral iron is poorly tolerated or ineffective. On the other hand, lactoferrin, a naturally occurring iron-binding glycoprotein, has gained attention as a potential alternative due to its role in enhancing iron absorption and modulating immune function [11]. This condition is a significant contributor to both disability and mortality on a global scale. Although most cases of IDA are effectively managed with iron supplementation, oral iron therapy is often met with poor adherence due to side effects. These adverse reactions, including diarrhea, colicky pain, vomiting, nausea, constipation, and general gastric discomfort, can deter patients from continuing treatment [2]. Given the frequent gastrointestinal side effects associated with oral iron therapy, particularly in pregnant women, there is interest in evaluating alternatives. Studies have specifically contrasted the hematological outcomes, tolerability, and safety of lactoferrin and iron dextran in the treatment of IDA during pregnancy [1]. In this regard, the current study sought to evaluate the effectiveness of lactoferrin in treating IDA in pregnant women in comparison to IV iron sucrose. This study compared the cost-effectiveness and clinical outcomes of lactoferrin with intravenous iron sucrose in treating IDA in pregnant women. The patients were similar in terms of age, weight, parity, and gestational age after being divided

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into two randomized groups. The iron sucrose group and the lactoferrin group had similar baseline metrics, demonstrating statistical non-significance in these variables. Regarding hematological outcomes, over a four-week period, the two groups showed significant improvements in hematological markers from baseline. Additionally, although the difference between the groups was not statistically significant, both the lactoferrin and iron sucrose groups displayed an increase in hemoglobin levels. Likewise, hematocrit and MCV levels increased in the lactoferrin and iron sucrose groups. These results, though non-significant between groups, confirmed that both treatments effectively improved anemia indicators.

The majority of the prior literature compared oral lactoferrin versus oral ferrous sulphate, or infusion of low molecular iron dextran versus oral ferrous sulphate, which is a strength of our study. As far as we are aware, there aren't many studies comparing the acceptability, safety, and efficacy of lactoferrin to IV iron sucrose for the treatment of IDA during pregnancy. These results are consistent with earlier research. Darwish *et al*. [1] recruited 120 pregnant women with IDA in a prospective interventional randomized controlled trial to assess the safety and efficacy of oral lactoferrin versus TDI of low-molecular weight (LMW) iron dextran for managing IDA in the second and third trimesters of pregnancy. Four weeks following treatment, the data demonstrated significant clinical improvement in anemia in both groups. Both the TDI of LMW iron dextran therapy and the pineapple-flavored lactoferrin oral sachets significantly raised hemoglobin levels, MCH, and MCV. Both groups saw a significant reduction in TIBC as well as serum iron and ferritin indices. The efficacy of both parenteral iron preparations is demonstrated by our finding that iron sucrose and low molecular weight iron dextran are equally effective in treating IDA during pregnancy. Tariq *et al*. [12] performed a randomized controlled experiment with 198 pregnant women who had IDA in order to assess the safety profile and efficacy of split doses of IV iron sucrose with TDI of low molecular weight iron dextran for the management of IDA during pregnancy. Additionally, Mohamed *et al*. [2] assessed the safety and effectiveness of lactoferrin vs. ferrous sulphate for the management of IDA during pregnancy in a prospective study involving 200 expectant mothers. According to the findings, in months one and two after therapy, the lactoferrin group's serum ferritin and hemoglobin rise were significantly greater than those of the ferrous sulphate group.

Our findings were in line with those of Paesano *et al*. [13], who showed that bovine lactoferrin therapy is noticeably more successful in reestablishing iron storage. Rezk *et al*. [14] also reported that women treated with lactoferrin had higher hemoglobin and total serum iron values than women treated orally with ferrous sulfate for 30 days, regardless of the trimester of pregnancy. Furthermore, in order to evaluate the safety and efficacy of TDI of low molecular weight iron dextran for the treatment of IDA in contrast to oral iron replacement during pregnancy, Ayub *et al*. [15] recruited 100 pregnant women in a non-randomized controlled experiment. According to the study, while treating IDA during pregnancy, TDI of low molecular weight iron dextran significantly boosted hemoglobin more quickly. In a prospective study with 100 pregnant women, Kriplani *et al*. [16] assessed the response and impact of IV iron sucrose complex administered to pregnant women with IDA. They found that after eight weeks of treatment, the mean hemoglobin increased from 7.63 ± 0.61 to 11.20 ± 0.73 g% (p-value <0.001*), and that serum ferritin levels significantly increased as well (from 11.2 ± 4.7 to 69 ± 23.1 µg/l) (p-value <0.001*). After two weeks of beginning treatment, the reticulocyte count rose significantly (from 1.5 ± 0.6 to 4.6 ± 0.8%). Significant improvements were also seen in other metrics, such as red cell indices and serum iron levels. Paesano *et al*. [17] designed a prospective study that included 205 pregnant women who were split into two groups, independent of the trimester of pregnancy (the lactoferrin group (n=107)

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and the ferrous sulphate group (n=98)) in order to compare the efficacy and tolerability of oral bovine lactoferrin (100 mg twice a day) and ferrous sulphate (520 mg once a day). All treated women experienced a significant increase in mean hemoglobin and total serum iron levels (p-value < 0.001*) after 30 days of treatment; however, pregnant women receiving ferrous sulphate experienced a smaller increase (0.9 g/dL and 8.0 ug/dL, respectively) than those receiving lactoferrin (1.5 g/dL and 54.2 ug/dL, respectively). In the end, hemoglobin levels improved in every case involving lactoferrin or parenteral iron infusion. These were the women who began with very low Hb levels and very weak iron reserves, even if some of them do not seem to have attained the target Hb of 10.5 gm/dl [15]. Unfortunately, pregnant women's adherence to iron-supplementation programs is low, partly because of the adverse effects of these preparations [18]**.** High GIT side effects that were reported served as the impetus for this investigation. We looked for a substitute to get around the typical negative effects of oral iron treatment. Regarding side effects and compliance, our study results demonstrated that the iron sucrose group had a higher rate of adherence to treatment (88.6% of participants consistently followed dosing schedules) than the lactoferrin group (75.0%), although this variation was not statistically significant. Constipation was a significant adverse effect, occurring in 2.3% of the iron sucrose group and 22.7% of the lactoferrin group. Black stool incidence (13.6% in the lactoferrin group versus 0% in the iron sucrose group) and gastric distress were also significantly more common in the lactoferrin group (25.0%) than in the iron sucrose group (6.8%). Although they did not achieve statistical significance, other adverse effects, such as nausea and vomiting, were more common in the lactoferrin group. Only two cases in the lactoferrin group reported poor sachet palatability, according to Darwish *et al*. [1]**.** In contrast, one case in the TDI group experienced mild urticaria and immediate hypersensitivity to TDI of iron, which was treated quickly and had no effect on the treatment plan. Furthermore, iron sucrose complex IV treatment produced very few adverse effects, according to Kriplani *et al*. [16].

Additionally, Rezk *et al*. [14] found that a greater proportion of women in the ferrous sulphate group requested a switch to lactoferrin (p-value <0.001*), and Tariq *et al*. [12] reported that no anaphylaxis occurred during the administration of either of the parenteral iron therapies. Regarding treatment efficacy and cost, the cost study showed no variations in laboratory expenses. However, due to the requirement for IV administration, the iron sucrose group had greater administration costs but significantly lower medication prices. Although treatment efficiency, as determined by cost per gram of hemoglobin increase, did not differ significantly across groups, overall expenditures were greater in the iron sucrose group. Our results are supported by Darwish *et al*. [1], who discovered that TDI of LMW iron dextran is much more costly than oral iron treatment (6 times the cost of oral lactoferrin). This is a significant barrier to its widespread use, especially in low-resource developing nations where the majority of pregnant women have IDA. Our findings are supported by Tariq *et al*. [12], who found that because iron sucrose infusion requires several doses, it appears to be expensive and time-consuming. This becomes crucial for reducing the strain on healthcare systems in low-income nations. The requirement for hospitalization or, at minimum, an outpatient clinic for close monitoring, where medications and equipment for cardiac resuscitation should be accessible throughout infusion, should be one of TDI's primary drawbacks. Additionally, greater caution needs to be exercised. To prevent chemical phlebitis at the infusion site and the requirement for a test dosage prior to infusion initiation, it should be administered in a peripheral vein [1]**.**

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The regression analysis revealed risk variables impacting hemoglobin and hematocrit variations in relation to CBC and iron profile values. Maternal age and gestational age were also significant negative predictors of hemoglobin rise in the lactoferrin group. Hematocrit elevation in the lactoferrin group was also significantly influenced by gestational age. MCH elevation in this group was shown to be positively impacted by weight. Conversely, there were no noteworthy demographic indicators for alterations in hematological markers in the iron sucrose group. According to Tariq *et al*. [12], 60% of the women who were included had gestational ages more than 33 weeks, which indicates that the frequency of IDA rises with the length of pregnancy. The percentage of anemic women increased from 29.6% in the first trimester to 34% in the third, per a study by Habib *et al*. [19]. Similarly, the mean hemoglobin levels decreased steadily from the first to the third trimester, according to Ayub *et al*. [15]. Morasso *et al*. [20] and Dreyfuss *et al*. [21] also discovered a similar pattern. Anemia may be brought on by underlying insufficient iron storage, since these studies have shown significant iron depletion during pregnancy that worsened in the third trimester [22, 23]. Pregnancy difficulties are less likely to occur, and good reproduction is more likely when the mother is between the ages of 20 and 35. This has to do with pregnant women's physiological and mental health [24, 25]**.** However, because biological development, including reproduction, is not at its best in that age bracket, those under 20 years old are at risk for anemia. Pregnancy in the age range of 35 and higher is also considered high-risk [26]**.** Anemia is also more common in pregnant women over 35. Pregnancy-related illnesses are common as a result, and the body's strength starts to decline [27, 28].

4. CLINICAL IMPLICATIONS IN PRACTICE

From a clinical pharmacy perspective, the study underscores the importance of balancing efficacy, patient tolerance, and cost when choosing anemia treatments. Lactoferrin and IV iron sucrose both improve hemoglobin and iron levels effectively, giving pharmacists flexibility to tailor treatments based on patient needs [29, 30]. Oral lactoferrin may reduce the burden on healthcare resources by eliminating the need for IV administration, making it accessible and convenient for outpatient use [31]. However, due to the higher incidence of gastrointestinal side effects, pharmacists may need to counsel patients on managing these symptoms, possibly recommending concurrent use of supportive therapies. In contrast, IV iron sucrose, with its lower incidence of side effects, can be prioritized for patients who experience gastrointestinal intolerance with oral treatments, albeit at a higher cost due to the need for in-clinic administration [32, 33].

5. THE STRENGTHS OF THIS STUDY

The study’s prospective, randomized design is a significant strength, reducing selection bias and allowing a clear comparison of treatment effects. Additionally, using multiple indicators like hemoglobin, hematocrit, and serum ferritin provides a thorough assessment of anemia improvement. The inclusion of both clinical efficacy and cost-effectiveness measures also offers a comprehensive pharmaceutical perspective, allowing for an analysis that balances clinical benefits with economic impact, critical for pharmacists in both hospital and community settings.

6. THE LIMITATIONS OF THE STUDY

The study's short four-week follow-up period and very small sample size limit the capacity to extrapolate the results and comprehend long-term effectiveness or safety profiles.

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Furthermore, the open-label nature introduces potential bias in patient-reported outcomes, particularly side effects. Another limitation is the lack of assessment of dietary iron intake or other confounding factors that could independently affect anemia treatment outcomes. For clinical pharmacists, these limitations suggest the need for ongoing patient monitoring and individualized treatment adjustments that consider each patient's unique health and lifestyle factors.

7. CONCLUSION

Both lactoferrin and IV iron sucrose are viable treatment options for IDA in pregnant women, demonstrating comparable efficacy in raising hemoglobin and serum iron levels. Lactoferrin provides an effective oral option that minimizes clinical visits, though with a higher risk of gastrointestinal side effects. In contrast, IV iron sucrose, though requiring clinical administration, has a more favorable side-effect profile. Clinical pharmacists can leverage these findings to personalize recommendations, considering each patient's risk tolerance, likelihood of adherence, and access to in-clinic services. Clinical pharmacists should consider patient-specific needs when selecting treatments for IDA in pregnancy. For patients who tolerate oral iron, lactoferrin is recommended for its convenience and cost savings. However, for those with gastrointestinal intolerance, IV iron sucrose is a better option despite its higher cost. Pharmacists should advocate for more extensive studies and explore supportive therapies to mitigate side effects, enhancing adherence and outcomes.

8. FUTURE PERSPECTIVES

It is recommended that this study be made on a larger sample size and as a double-blind study.

AUTHOR CONTRIBUTIONS

All authors contributed significantly to the work reported. They all agreed on the journal to which the article would be submitted and accepted full responsibility.

DECLARATION

The authors used one of the AI technologies to improve the readability of the review.

CONFLICT OF INTEREST

There was no conflict of interests.

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