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Intravenous Iron versus Oral Iron in Correction of Iron Deficiency Anemia during Third Trimester of Pregnancy

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ABSTRACT

Background: Iron deficiency anemia is a common problem during pregnancy and affects about 50% of pregnant women in developing countries. **Objective:** The aim of the current study was to compare hematological responses to intravenous and oral iron supplementation in the correction of iron deficiency anemia during third trimester of pregnancy. **Patients and methods**: This clinical trial included 70 pregnant women during third trimester who were recruited from those attending the Antenatal Care Clinic of Zagazig University Hospitals with iron deficiency anemia. The participants were divided into 2 groups: *Group 1* received oral iron supplementation (ferrous fumarate), and *Group 2* received intravenous iron supplementation (ferric hydroxide sucrose complex).

Results: Hb level increased by 1.11 g/dl among oral iron treatment group, while the increase was 1.33 g/dl among *Group 2*. Also HCT increased by 4% of pretreatment value among *Group 2* cases versus 2% increase from pretreatment level of *Group I* cases. The serum ferritin increased 6 times of the pretreatment level after oral iron intake and about 9 times increase after intravenous iron infusion, and iron level elevated about 2 times pretreatment level in both groups, but was more in intravenous iron therapy. Also, TIBC increased after iron supplementation by 13% of the original levels among *Group I* versus 20% increase among *Group II* (P-value <0.001).

Conclusion: Intravenous iron although its cost and its need for hospitalization is a safe and effective alternative to oral iron in correction of iron deficiency anemia of pregnancy during the third trimester.

Keywords: Oral iron, Anemia, Third Trimester, Pregnancy, Clinical trial, Zagazig University.

INTRODUCTION

The most prevalent hematological condition that affects pregnant women is anemia. The WHO states that a shortage of iron is the main cause of anemia during pregnancy. About 80% of pregnant women in some populations are anemic [(1)].

The woman will eventually become anemic as a result of the pregnancy's dilution of the blood. The dilution of blood during pregnancy is a normal process that begins around the eighth week of the pregnancy and lasts until the 32nd or 34th week [(2)].

Anemia in pregnancy affects between 40 and 80 percent of pregnant women in tropical nations. It falls between the 10–20% range in wealthy nations. In underdeveloped nations, it causes 20% of maternal deaths. By impacts on immunological function and an increased susceptibility to or severity of infections, iron deficiency may contribute to maternal morbidity [(3)].

Anemia causes an increase in peripartum blood loss, placental abruption, premature births, low birth weights, children's cognitive development being hindered, postpartum hemorrhage, and perhaps placental abruption [(4)].

Most pregnant women can get enough iron from oral supplements. However for certain women, oral iron supplements may be insufficient due to intolerance to iron, irregularities in absorption, and non-compliance; in these cases, parenteral iron supplementation may be beneficial [(5)].

The aim of the current study was to compare hematological responses to intravenous and oral iron supplementation in the correction of iron deficiency anemia during third trimester of pregnancy.

PATIENT AND METHODS

This clinical trial was conducted on 70 pregnant women during the third trimester recruited from those attending the Antenatal Care Clinic (ANC) of Zagazig University Hospitals with iron deficiency anemia, from April 2022 to October 2022.

Inclusion criteria were pregnant women who were aged 18- 40 years with singleton pregnancy, gestational age at 3rd trimester between 29th – 40th weeks gestation , no prior intravenous iron supplements in the current pregnancy and (hemoglobin level Hb >8, and <10 g/dL).

Exclusion Criteria: History of allergy to intravenous iron. History suggestion of a cause for anemia other than iron deficiency anemia: Hemolytic anemia (e.g., Thalasemia), chronic renal disease, liver disease, chronic peptic ulcer and malabsorption syndromes.

METHODS

All patients underwent thorough **History Taking** of symptoms of iron deficiency anemia e.g., Feeling of weakness, exhaustion, loss of appetite, Palpitation, and dyspnea, in addition, taking history about the intake of iron containing foods, or foods inhibits iron absorption, previous treatment, and past medical, obstetric and menstrual history to rule out anemia of chronic disease.

General Examination: Signs of iron deficiency anemia e.g., pallor of the skin and mucous membranes, glossitis and stomatitis, and soft systolic murmur can be heard in the mitral area due to hyperdynamic circulation, together with complete abdominal examination.

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Laboratory Investigations: Pre-iron supplementation to confirm that the included patient has iron deficiency anemia, degree of anemia, other abnormalities as leucopenia and thrombocytopenia, and also repeated after treatment to show the effect of iron taken on the parameters of laboratory investigation performed included; Complete blood count, serum ferritin, serum iron, serum total iron binding capacity, and iron supplementation.

Estimation of transferrin-saturation was calculated from the equation: Saturation = Iron/TIBC x100. Normal level is between 20% and 50%.

Eligible cases were divided into two equal groups according to planned iron therapy:

Group 1 included 35 cases who received oral iron supplementation (ferrous fumarate). It was given twice daily after meals by 2 hours with full glass of water or juice for 4 weeks, each capsule contains ferrous fumarate 73mg equal to 24mg elemental iron.

Group 2 included 35 cases who received intravenous iron supplementation (ferric hydroxide sucrose complex) each ampoule (5ml) contained 100 mg iron sucrose for intravenous infusion. Total dose is 600 mg elemental iron given on 2 divided doses, 300 mg at day 0 on 500 ml 0.9 % normal saline and 300 mg at day 15 on 500 ml 0.9 % throughout the course of 30 to 50 minutes, normal saline after sensitivity test dose.

Outcomes: We compared the safety, tolerability, efficacy and hematological responses to iron supplementation between two groups by any symptoms related to oral or intravenous iron intake e.g. nausea, vomiting, constipation, hypotension, bowel disturbances, abdominal pain, drug reaction, and hyper-sensitivity were recorded. Laboratory investigations included CBC, serum iron, serum ferritin and total iron binding capacity (TIBC). They were repeated after 2 weeks from the end of the treatment in the 2 groups.

Sampling for estimation of CBC 2 ml of venous blood was collected in EDTA tubes. Another 2ml venous sample for determination of serum iron, serum total iron binding capacity and serum ferritin was collected in a tube without EDTA, stand up to coagulate and serum was separated by centrifugation at 5000 rpm.

Ethics Considerations:

This study was ethically approved by the Institutional Review Board of the Faculty of Medicine, Zagazig University. Written informed consent was obtained from all participants. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.

Statistical Analysis

Microsoft Excel software was utilized to code, enter, and analyze historical data, basic clinical evaluations, laboratory investigations, and outcome assessments. The Statistical Package for the Social Sciences (SPSS version 20.0) Programme was then used to import and analyze the data. Qualitative data were defined as numbers and percentages. Chi-Square test and Fisher's exact test were used for comparison between categorical variables as appropriate. Quantitative data were tested for normality by Kolmogorov-Smirnov test. Normal distribution of variables was described as mean and standard deviation (SD), and independent sample t-test/Paired t test was used for comparison between groups. P value ≤0.05 was considered to be statistically significant.

RESULTS

During intravenous iron infusion, 5 cases suffered of anaphylaxis and were excluded from the study; only the results of 30 cases were analyzed.

Hb level increased by 1.11 g/dl among oral iron treatment group while the increase was 1.33 g/dl among *Group II* cases, also HCT increased by 4% of pretreatment value among *Group II* cases versus 2% increase from pretreatment level of *Group I* cases with statistical significant difference between both groups. RBCs raised post treatment (iron supplementation) by 23% of the original value among *Group II* versus 8% increase among *Group I* (P<0.001) (**Table 1**).

Table (1): Hematological parameters before and after 4 weeks of supplementation in both groups.

Group	Hemoglobin(g/dl)				Hematocrit (%)				RBCs (10^6 cells /µL)			
	Pre	Post	Rise (g\dl)	P§	Pre	Post	Rise (%)	P§	Pre	Post	Rise (10^6 cells\µl)	P§
Group I	8.50 ±0.38 (g/dl)	9.56 ±0.46 (g/dl)	12.5% 1.11± 0.11 (g/dl)	0.002*	28.27 ±0.60 (%)	30.60 ±1.42 (%)	2.33 %	0.003 *	$4.65*10^6$ ±0.35	$4.92*10^6$ ±0.39	**8.3% $0.27*10^6$ ±0.04**	**0.003***
Group II	8.53 ±0.48 (g/dl)	9.86 ±0.60 (g/dl)	15.5% 1.33± 0.12 (g/dl)	0.001**	27.73 ±0.57 (%)	32.11 ±1.25 (%)	4.38 %	0.004 *	$4.32*10^6$ ± 0.41	$5.31*10^6$ ±0.43	**22.9% $0.99*10^6$ ±0.02**	**<0.001 ****
T test	0.873	3.118	---		1.017	5.943	---		0.961	3.383	---	
P-value	0.386	0.003 *			0.313	<0.001 **			0.34	<0.001**		

T: Independent sample t test, P§: Paired sample t test, *P≤0.05 is statistically significant, **P≤0.001 is statistically highly significant, P for paired sample t test.

Serum ferritin increased 6 times of the pretreatment level after oral iron intake (608.7% of the original level) and about 9 times increase after intravenous iron infusion (853.3% increase from the original level) and **iron** level raised post treatment (Iron supplementation) about 2 times pretreatment level in both groups, but was more in intravenous iron therapy (increased by 105% of the original level versus 86.7% among oral treatment group) with high significant difference (P<0.001). Also, TIBC increased after iron supplementation by 12.8% of the original levels among *Group I* versus 19.6% increase among *Group II* that was of a high statistically significance (**Table 2**).

Table (2): Iron profile distribution before and after 4 weeks of treatment in both groups.

Group	Ferritin (µg/L)				Iron (µg /dl)				TIBC(µg/dL)			
	Pre	Post	Rise (ug/l)	P§	Pre	Post	Rise (ug/dl)	P§	Pre	Post	Rise (ug/dl)	P§
Group I	10.73 ±0.40 µg/L	76.04 ±5.42 µg/L	608.7% 65.3±5.01 µg/L	<0.001**	54.25 ±4.84 µg/dl	101.28 ±4.76 µg/dl	86.71% 47.03±0.1 µg/dl	<0.001 **	225.42 ±14.15 µg/dl	254.31 ±14.1 µg/dl	12.8% 28.89± 0.05 µg/dl	<0.001 **
Group II	10.91 ±0.44 µg/L	104.12 ±9.43 µg/L	854.3% 93.2±8.99 µg/L	<0.001**	53.65 ±6.21 µg/dl	110 ±9.18 µg/dl	105.0% 56.35±2.97 µg/dl	<0.001 **	227.51 ±13.45 µg/dl	272.08 ±12.24 µg/dl	19.6% 44.57± 1.12 µg/dl	<0.001 **
T	0.959	15.994	---		0.451	6.127	---		0.613	5.38	---	
P-value	0.341	<0.001 **			0.654	<0.001 **			0.55	<0.001		

T: Independent sample t test, P§: Paired sample t test, *P≤0.05 is statistically significant, **P≤0.001 is statistically highly significant, P for paired sample t test.

Nausea, vomiting, diarrhea and constipation were more in oral iron supplementation, while hypotension, fever and pain in injection site were only in intravenous iron supplementation as shown in **Table 3**.

Table (3): Therapy side effects in oral and intravenous iron administration.

Variable	Group I	Group II	Test	P-value
	n=35 (%)	n=30 (%)	χ^2	
Nausea	8 (22.9%)	4 (13.3%)	1.6	0.205
Vomiting	3 (8.6%)	2 (6.7%)	Fisher	0.64
Constipation	12 (34.3%)	4 (13.3%)	Fisher	0.082
Diarrhea	4 (11.4%)	0 (0%)	Fisher	0.114
Metallic taste	8 (22.9%)	2 (6.7%)	Fisher	0.083
Hypotension	0 (0%)	2 (6.7%)	Fisher	>0.999
Fever	0 (0%)	2 (6.7%)	Fisher	>0.999
Pain in injection site	0 (0%)	9 (30.0%)	Fisher	<0.001**

χ^2: Chi square test, *P<0.05 is statistically significant, **P≤0.001 is statistically highly significant.

Table 4 showed that preterm labor, low birth weight was higher incidence in our selected patient (both groups) than general population, mostly due to anemia. Preterm labor in our cases was 17% *versus* 5-10% in general population. Low birth weight in our cases was 20-27% *versus* 15% in general population.

Table (4) Neonatal and maternal outcome in the two groups.

Variable	Group I	Group II	χ^2	P-value
	n=35 (%)	n=30 (%)		
Preterm labor	6 (17.1%)	5 (16.7%)	0.108	0.743
Low birth weight	7 (20%)	8 (26.7%)	0.085	0.771
IUFD/still birth	1 (2.9%)	0 (0%)	Fisher	>0.999
Postpartum hemorrhage	0 (0%)	1 (3.3%)	Fisher	>0.999
Antepartum hemorrhage	2 (5.8%)	1 (3.3%)	Fisher	>0.999

χ^2: Chi square test.

DISCUSSION

The current study showed that Hb level after 4 weeks of iron supplementation (total dose is 1344 mg elemental iron given over 4 weeks for oral group), and parenteral iron (total dose is 600 mg elemental iron given on two divided doses, 300 mg at day 0 on 500 ml 0.9 % normal saline and 300 mg at day 15 on 500 ml 0.9 % normal saline after sensitivity test dose for intravenous group) increased by 1.11 g\dl among oral iron treatment group (*Group I*) while the increase was 1.33 g/dl among intravenous iron group (*Group II*), also HCT increased by about 4-5% of pretreatment value among *Group II*, while only 2-3% increase in *Group I* with statistical significant difference between both groups (P<0.05). RBCs raised post supplementation by about 23% of the original value among *Group II* versus only 8.5 % increase among *Group I* (Highly significant P<0.001).

Which is in agreement with a study done by **Şahin and Madendağ** [6], in which iron supplementation for 4 weeks, the Hb levels were increased by 1.33 g/dl in the intravenous group (total dose is 600 mg elemental iron after 4 weeks) and 1.11 g/dl in the oral group (total dose 5600 mg elemental iron after 4 weeks of supplementation) that was statistically significant (P-value <0.001). Also, the mean MCV, MCH, and MCHC levels increased and were statistically significant different.

Agalya *et al.* [7] found that on 28th day, intravenous group (total dose was 800 mg elemental iron), while in oral group (Total dose is 2800 mg elemental iron), Hb level increased by about 1.77 g/dl in intravenous group and about 1.57 g/dl in oral group that was statistically significant with P-value <0.001.

Al *et al.* [8] found that patients with intravenously administered iron (total dose is 1000 mg elemental iron) after 4 weeks of treatment, had higher hemoglobin level than those patients with orally administered iron (total dose is 5600 mg elemental iron).

Rudra *et al.* [9] reported all hematological parameters increased in both groups following iron therapy at 2 weeks, 4 weeks, during delivery, and 3 months post-partum, with the increase in hemoglobin and other hematological indices being greater in the intravenous iron group (the total dose is 600 mg elemental iron after 4 weeks) than in oral iron group (total dose is 5600 mg elemental iron after 4 weeks of supplementation) at each point of measurement with a statistically significant difference (P-value <0.001).

Shafi *et al.* [10]**,** the difference in Hb from baseline in the intravenous group (total dose is 800 mg elemental iron after 4 weeks of supplementation), compared to oral iron (total dose is 5600 mg elemental iron after 4 weeks of supplementation) was clinically significant; higher in intravenous group.

Tigga and **Debbarma** [11] reported that Hb and hematocrit values increased in both groups after 4 weeks of iron supplementation (total dose is 5600 mg elemental iron) and the intravenous groups (total dose is 600 mg elemental iron after 4 weeks of treatment). The rise was higher in the intravenous iron group (P=0.01).

Gupta *et al.* [12] reported both groups experienced an increase in Hb from baseline to 4 weeks, however the intravenous group experienced a greater increase (total dose is 600 mg elemental iron) than oral group (total dose is 5600 mg elemental iron) which was clinically significant (P-value <0.001). Moreover, a very statistically significant difference between the two groups was seen in MCV, MCH, and MCHC at 14 days (P=0.001) and 4 weeks (P=0.015) following supplementation.

The current study showed that **serum ferritin** increased 6 times of the pretreatment level after oral iron intake (608.7% of the original level) and about 9 times increase after iv iron infusion (853.3% increase from the original level) and **iron level** raised post treatment (iron supplementation) about 2 times pretreatment level in both groups, but was more in intravenous iron therapy (increased by 105% of the original level versus 86.7% among oral treatment group) with high significant difference (P<0.001). Also, TIBC increased after iron supplementation by 12.8% of the original levels among group I versus 19.6% increase among *Group II* with high statistically significant difference between both groups.

Agalya *et al.* [7] showed that the intravenous and oral groups both experienced an increase in serum ferritin levels, with the intravenous iron sucrose group experiencing the greatest increase [intravenous group had mean serum ferritin levels of 60.92 (SD 6.90) ng/ml compared to oral group's 50.68 (SD 2.64) ng/ml], and this was found to be highly statistically significant (P-value <0.001).

Shafi *et al.* [10]**,** found a significant increase in serum ferritin levels in both groups from baseline to 4 weeks, with intravenous group levels increasing higher than oral group levels at each point of testing (P=0.000).

Gastrointestinal upset as nausea, vomiting, diarrhea and constipation were more in oral iron supplementation, while hypotension, fever and pain in injection site were only in intravenous iron supplementation.

Agalya *et al.* [7] reported that 20% of intravenous group showed reactions (hypotension, fever and pain in injection site), and in oral group, 32% experienced side effects (nausea, vomiting, diarrhea and constipation), but not affect the compliance.

Mohamed *et al.* [13] reported gastrointestinal side effects in 22% of patients in the oral iron group, but not severe enough to affect the compliance. There is significant difference between oral and intravenous groups in myalgia allergic reaction; which was more in intravenous group (P-value <0.05).

Rudra *et al.* [9] reported very minor adverse events occurred, including fever (two), itching across the body

(one), swelling, redness, or discomfort at the injection site (four), arthralgia (one), and nausea. There were no significant adverse medication reactions, such as anaphylactic shock or hypotensive shock (four). In the oral group, gastrointestinal problems included nausea and vomiting (4 cases), epigastric pain and bloating (16 cases), diarrhea (4 cases), and metallic taste (4 cases). All of these symptoms were treated symptomatically, and no one stopped taking iron because of gastrointestinal symptoms.

The current study showed that preterm labor, low birth weight was higher in our selected patient (both groups) than general population, mostly due to anemia.

Gupta *et al.* [12] reported that there were no harmful medication responses. In contrast to the oral group, which had gastrointestinal tract symptoms such as 20% of patients experiencing constipation, 12% of patients experiencing metallic taste, 4% of patients experiencing nausea and vomiting, 2% of patients experiencing diarrhea, and 2% of patients experiencing abdominal pain that led to non-compliance with oral iron, there were no episodes of anaphylaxis or hypotensive shock, only 2% of patients experiencing dizziness, and 4% of patients experiencing mild allergic.

Şahin and **Madendağ** [6] reported that 69% of the mothers (total 130) experienced preterm deliveries and about 25% of babies born had lower birth weights than would be expected. Meanwhile, **Mohamed *et al.*** [13] found non-significant difference between both oral and intravenous groups as regard neonatal weight at birth (P-value >0.05).

CONCLUSION

Intravenous iron, although its needs hospitalization and expansive, is a secure and efficient alternative to oral iron for treating pregnancy-related iron deficiency anemia during the third trimester. It helps to rebuild iron stores with a rapid correction of anemia especially in advanced gestational age (near delivery), and thus avoid maternal and neonatal complication related to anemia as preterm labor, postpartum hemorrhage, and low birth weight. However, precautions as hospitalization and requirements for management of anaphylaxis if occurred are a must.

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