

Heme-bound iron in treatment of pregnancy-associated iron deficiency anemia

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ABSTRACT

Background: The iron requirements increase during the second and third trimesters of pregnancy. Maternal anemia is a leading cause of adverse perinatal outcome. **Objectives:** This study was designed to evaluate the efficacy of the heme-bound iron in treatment of pregnancy-associated iron deficiency anemia (IDA). **Materials and Methods:** In all, 122 women with IDA during pregnancy and hemoglobin ≤ 10 g/dL were studied. The studied women were treated with heme-bound iron tablets for ≥ 3 months. Pretreatment hemoglobin, ferritin, mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH) were compared with the posttreatment values to detect the efficacy of heme-bound iron (Optifer[®]) in treatment of IDA during pregnancy. **Results:** The mean pretreatment hemoglobin significantly increased from 8.4 ± 2.7 to 11.2 ± 2.1 g/dL and the mean pretreatment ferritin level significantly increased from 22.6 ± 5.6 to 112.8 ± 4.8 $\mu\text{g/L}$ ($P < 0.003$ and 0.04 ; respectively) 3 months after heme-bound iron treatment. In addition, the mean pretreatment red blood cells' MCV and MCH significantly increased from 74.2 ± 4.8 fL and 24.2 ± 7.8 pg, respectively, to 92.0 ± 4.1 fL and 32.6 ± 6.2 pg ($P = 0.04$ and 0.007 , respectively) 3 months after heme-bound iron treatment. **Conclusion:** Heme-bound iron (Optifer[®]) is an effective oral iron preparation to treat IDA during pregnancy and to replace the depleted iron store.

Keywords: Deficiency, heme-bound, iron, pregnancy

Introduction

Hemoglobin < 11 g/dL is defined as anemia, and iron deficiency anemia (IDA) is the commonest type of nutritional deficiencies.^[1,2] The iron requirements during pregnancy are high and increase furthermore during the second and third trimesters.^[3]

In addition, blood loss during vaginal and cesarean deliveries increases maternal anemia and increases the need for blood transfusion.^[4,5] Maternal anemia is a leading cause of adverse perinatal outcome.^[6-9] Recently, Froessler *et al.* reported that iron

deficiency and its related anemia are associated with adverse outcomes such as reduced maternal cognitive activities and increased maternal depressive disorders. While they reported preterm labor (PTL), intrauterine growth retardation, intrauterine fetal death, and neonatal infection as adverse neonatal outcomes for iron deficiency and IDA.^[10]

Peripartum anemia increases the need for red blood cells' (RBCs) transfusion, which is independently associated with increased morbidity.^[11,12] In addition, RBCs' transfusion corrects hemoglobin temporarily and not the underlying condition.^[13] Adequate and effective iron supplementation is crucial during pregnancy to reduce the adverse perinatal outcome related to IDA.^[14]

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How to cite this article: Abdelazim IA, Abu-Faza M, Shikanova S, Zhurabekova G, Maghrabi MM. Heme-bound iron in treatment of pregnancy-associated iron deficiency anemia. J Family Med Prim Care 2018;7:1434-8.

Access this article online

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DOI:
10.4103/jfmpc.jfmpc_271_18

Oral iron therapy is effective in treatment of IDA. The conventional non-heme iron salts are associated with gastric discomfort and constipation which adversely affect the compliance.^[15,16]

Heme iron is a tolerable, effective oral iron preparation, improves the compliance, and ensures continuous iron intake.^[15-17] Nissenson *et al.* concluded that the use of heme iron preparations in patients undergoing hemodialysis was effective in treatment of IDA and replaced the intravenous iron preparations.^[18]

Abdelazim *et al.* concluded that heme iron is tolerable, effective, and replaces the intravenous iron for treatment of IDA during pregnancy.^[17,19] In addition, Hoppe *et al.* concluded that heme iron dietary-based treatment can improve the reproductive age women's iron store.^[20]

Heme-bound iron (Optifer[®]) is a new genuine heme-bound iron supplement made under Hazards Analysis and Critical Control Points (HACCP) and Good Manufacturing Practice (GMP) standards in Sweden. This study was designed to evaluate the efficacy of new heme-bound iron (Optifer[®]) in treatment of pregnancy-associated IDA.

Materials and Methods

This was a prospective comparative study conducted in Ahmadi Hospital, Kuwait Oil Company, for a period of 1 year from August 2017 to August 2018, after approval of the study by the Ethical Committee of the Department of Obstetrics and Gynecology.

In all, 122 women with pregnancy-associated IDA and hemoglobin ≤ 10 g/dL (8–10 g/dL) were studied after informed consent. The studied women were treated with heme-bound iron (Optifer[®]) tablets for correction of pregnancy-associated IDA twice daily for ≥ 3 months.

The inclusion criteria included pregnant women ≥ 20 years old and 14–26 weeks' gestation with hemoglobin ≤ 10 (8–10 g/dL). Pregnant women with anemia other than IDA and/or received blood transfusion during current pregnancy were excluded from this study.

Diagnosis of IDA was based on hemoglobin concentration (g/dL), serum ferritin ($\mu\text{g/L}$), mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH).^[7-9,21] The heme-bound iron (Optifer[®]) tablets (MediTec NutriCare Division, MediTec Intern, FairLife Group, Sweden; L'Avenir Med., Kuwait and Qatar) contain 18 mg of heme-bound iron. The heme iron content of the Optifer[®] tablets has unique intestinal carrier receptors Heme Carrier Protein-1 (HCP-1).

The studied women received heme-bound iron (Optifer[®]) tablets twice daily (one tablet morning and one tablet evening) not related to meals for ≥ 3 months till hemoglobin level of 11–12 g/dL

(according to the manufacturer's instructions) and then one tablet daily as maintenance dose.^[18]

The iron content of the Optifer[®] tablets absorbed by the HCP-1 receptors of the intestine and each tablet of Optifer[®] increases the serum iron by 3.15 mg.^[9] The studied women received oral folic acid with Optifer[®] to avoid folic deficiency, and the participants were asked during each antenatal care visit for the side effects related to Optifer[®] such as metallic taste, constipation, and/or intolerance.

Pretreatment hemoglobin, ferritin, and RBCs' MCV and MCH were compared with the 3 months' posttreatment values to detect the efficacy of Optifer[®] in treatment of pregnancy-associated IDA.^[22,23]

Primary outcome measures the efficacy of the Optifer[®] in treatment of pregnancy-associated IDA. While the secondary outcome measures the tolerability and the side effects related to the Optifer[®].

Sample size calculation

The required sample size was calculated using data from previous studies^[18,19] and G*Power software for sample size calculation (Heinrich Heine Universität, Germany). An effective sample of ≥ 120 women was needed to produce a statistically acceptable figure.

Statistical analysis

Collected data were analyzed using Statistical Package for Social Sciences (SPSS) version 20 (Chicago, IL, USA). The mean and standard deviation (\pm SD) were used to present the numerical values, while the number (*n*) and percentage (%) were used to present the categorical values. Student's *t*-test was used to compare the pretreatment hemoglobin, ferritin, and RBCs' MCV and MCH with the 3 months' posttreatment values to evaluate the efficacy of heme-bound iron in treatment of pregnancy-associated IDA. *P* value < 0.05 was considered significant.

Results

A total of 122 women with pregnancy-associated IDA and hemoglobin ≤ 10 g/dL (8–10 g/dL) were included in this prospective comparative study and treated with heme-bound iron tablets for ≥ 3 months. Five women were excluded from the final statistical analysis of this study due to PTL (three women) and (traveling two women), and the study was completed with final analysis of data from 117 pregnant women with IDA. Table 1 shows the demographic data of the studied pregnant women with IDA.

The mean pretreatment hemoglobin significantly increased from 8.4 ± 2.7 to 11.2 ± 2.1 g/dL and the mean pretreatment ferritin level significantly increased from 22.6 ± 5.6 to 112.8 ± 4.8 $\mu\text{g/L}$

($P < 0.003$ and 0.04 , respectively) 3 months after heme-bound iron treatment.

In addition, the mean pretreatment RBCs' MCV and MCH significantly increased from 74.2 ± 4.8 fL and 24.2 ± 7.8 pg, respectively, to 92.0 ± 4.1 fL and 32.6 ± 6.2 , pg) ($P = 0.04$ and 0.007 , respectively) 3 months after heme-bound iron treatment [Table 2].

Only 1.7% (2/117) of the studied women developed intolerance and gastric upset to heme-bound iron tablets (insignificant difference using Chi-square (χ^2) test) and no other side effects were recorded with heme-bound iron tablets.

Discussion

IDA is the third leading cause for years lived with disability since 1990.^[24] In addition, IDA ranked 13 for disability-adjusted life-years.^[25] IDA affects more than 40% of women globally.^[26,27]

IDA in the context of peripartum hemorrhage increases the maternal mortality and morbidity.^[28] In addition, blood loss during vaginal and cesarean deliveries increases maternal anemia and increases the need for blood transfusion.^[29]

In all, 122 pregnant women with pregnancy-associated IDA and hemoglobin ≤ 10 g/dL were studied and received heme-bound iron tablets for ≥ 3 months for correction of pregnancy-associated IDA. Five women were excluded from final statistical analysis of this study, and the study was completed with final analysis of data from 117 pregnant women with IDA.

The mean pretreatment hemoglobin significantly increased from 8.4 ± 2.7 to 11.2 ± 2.1 g/dL and the mean pretreatment ferritin level significantly increased from 22.6 ± 5.6 to 112.8 ± 4.8 μ g/L

($P < 0.003$ and 0.04 , respectively) 3 months after heme-bound iron treatment. In addition, the mean pretreatment RBCs' MCV and MCH significantly increased from 74.2 ± 4.8 fL and 24.2 ± 7.8 pg, respectively, to 92.0 ± 4.1 fL and 32.6 ± 6.2 ng) ($P = 0.04$ and 0.007 , respectively) 3 months after heme-bound iron treatment.

Barracough *et al.* designed a multicenter study to evaluate whether heme iron preparations effectively augment the iron stores than conventional oral iron or not.^[30] They concluded that heme iron preparations showed no clear efficacy in peritoneal dialysis patients than the conventional oral iron.^[31]

Nissenson *et al.* found that the intravenous iron was discontinued and replaced with oral heme iron preparations after 6 months of follow-up of hemodialysis patients on heme iron preparations.^[18]

In addition, this study concluded that hemoglobin, ferritin, and RBCs' MCV and MCH significantly increased 3 months after heme-bound iron treatment in pregnant women with IDA. Additionally, Abdelazim *et al.* concluded that heme iron preparations are effective to treat IDA during pregnancy.^[19]

Gastric side effects are common with oral iron and Al-Momen *et al.* found that 18 (30%) of the oral iron had gastric symptoms and 18 (30%) had poor compliance.^[32]

While in this study only 1.7% (2/117) of the studied women developed intolerance and gastric upset with heme-bound iron tablets (insignificant difference) and no other side effects were recorded with heme-bound iron Optifer[®] tablets.

Heme-bound iron represents a promising treatment option for ID and IDA due to higher bioavailability and lower gastrointestinal irritability.^[33] Superior tolerability of the heme-bound iron provides added advantage because compliance to oral iron treatment is the single most important identified obstacle to effective treatment of IDA. Thus, heme-bound iron is recommended as the first choice of iron supplementation to treat IDA during pregnancy and to maintain maternal iron stores.^[34]

Anemic pregnant women developed gastric upset when treated with intravenous iron sucrose because they cannot tolerate other oral iron preparations than Optifer[®]. To the best of our knowledge, this study was the first study conducted to evaluate the efficacy and tolerability of heme-bound iron tablets (Optifer[®]) in treatment of pregnancy-associated IDA. The limited available data about heme-bound iron (Optifer[®]) were the only limitation faced during this study. More comparative studies are needed

Table 1: Demographic data of the studied pregnant women with IDA

Variables	Studied pregnant women with IDA (n=117)
Maternal age (years)	24.4±4.3
Gravidity	5 (2-4)
Parity	4 (1-3)
Maternal weight (kg)	78.6±5.2
Maternal BMI (kg/m ²)	24.5±8.1
Gestational age at inclusion (weeks)	21.4±3.2
Pretreatment hemoglobin (g/dL)	8.4±2.1

IDA: Iron deficiency anemia; BMI: Body mass index. Data presented as mean±SD and median (range)

Table 2: Pretreatment hemoglobin, ferritin, MCV, and MCHC compared with the posttreatment values

Variables	Pretreatment values	3-months' posttreatment values	P (95% CI) significance
Hemoglobin (g/dL)	8.4±2.7	11.2±2.1	0.003* (-3.4, -2.8, -2.1)
Ferritin level (μ g/L)	22.6±5.6	112.8±4.8	0.04* (-91.5, -90.2, -88.8)
RBCs' MCV (fL)	74.2±4.8	92.0±4.1	0.04* (-18.9, -17.8, -16.7)
RBCs' MCH (pg)	24.2±7.8	32.6±6.2	0.007* (-10.2, -8.4, -6.6)

CI: Confidence interval; RBCs: Red blood cells; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin. Data presented as mean and±SD; Student's *t*-test used for statistical analysis. *Significant difference

to compare the efficacy of the heme-bound iron (Optifer[®]) in treatment of pregnancy-associated IDA with the available oral or intravenous iron preparations.

Conclusion

Heme-bound iron (Optifer[®]) is an effective oral iron preparation to treat IDA during pregnancy and to replace the depleted iron store.

Acknowledgement

The authors are grateful to women who gave consent and agreed to participate in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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