Heme-Iron OptiFer® in the Treatment of Iron Deficiency Anemia During Pregnancy

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ABSTRACT

OBJECTIVES: This study designed to compare the efficacy, and tolerability of heme-iron OptiFer® to ferrous fumarate in the treatment of iron deficiency anemia during pregnancy.

STUDY DESIGN: Two hundred and thirty-four (234) women with iron deficiency anemia during pregnancy were included in this study; 121 women in the heme-iron OptiFer® group, and 113 women in the ferrous fumarate group. Women in the heme-iron OptiFer® group received OptiFer® tablets twice daily for ≥3 months then once daily as a maintenance dose. Women in the ferrous fumarate group received 350 mg oral ferrous fumarate once daily for ≥3 months. The pre-treatment ferritin, hemoglobin, red blood cells-mean corpuscular volume, and red blood cells-mean corpuscular hemoglobin were compared by the post-treatment values in the two studies.

RESULTS: The post-treatment hemoglobin and ferritin were significantly high in the heme-iron OptiFer® group (11.2±7.1 gm/dL and 112.8±54.8 ug/l, respectively) compared to the ferrous fumarate group (10.9 ±5.1 and 89.9±43.3, respectively; *p*=0.0002 and *p*=0.006; respectively). The post-treatment red blood cells-mean corpuscular volume and red blood cells-mean corpuscular hemoglobin were significantly high in the heme-iron OptiFer® group (92.0±4.1 fl and 31.9±6.2 pg, respectively) compared to the ferrous fumarate group (87.7±2.9 and 28.5±4.7, respectively; *p*=0.0001 and *p*=0.001, respectively). The rates of poor compliance and gastrointestinal intolerance were significantly high in the ferrous fumarate group compared to the heme-iron OptiFer® group (12.4% and 19.5%, respectively versus 3.3% and 2.5%, respectively), (*p*=0.01 and *p*=0.0001, respectively).

CONCLUSION: Heme-iron OptiFer® is an effective therapeutic option for the treatment of iron deficiency anemia during pregnancy with low side effects. heme-iron OptiFer® can be used in women who have low compliance, and/or gastrointestinal intolerance to conventional iron salts.

Keywords: Heme-iron OptiFer®, Iron deficiency anemia, Pregnancy

Gynecol Obstet Reprod Med 2022;28(1):1-6

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Submitted for Publication: 29.08.2020 Revised for: Publication:19.09.2020
Accepted for Publication: 27.10.2020 Online Puplished: 31.12.2020
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Quick Response Code:	Access this article online
	Website: www.gorm.com.tr e- mail: info@gorm.com.tr
	DOI:10.21613/GORM.2020.1147

Introduction

Anemia affects 1.5 billion worldwide (1). Iron deficiency (ID) is the commonest nutritional deficiency compared to others (B12 and folic acid) (1-2).

The iron requirement increases during the second and third trimesters of pregnancy (3). Froessler et al reported that the ID and iron deficiency anemia (IDA) were associated with adverse maternal outcomes as reduced cognitive activities and increased depressive disorders (4). In addition, they reported the preterm delivery, intrauterine growth retardation, intrauterine fetal death, and neonatal infection as adverse neonatal outcomes related to ID and IDA (4).

Maternal anemia increases the peripartum red blood cells (RBCs) transfusion (5-6). The RBCs transfusion corrects the hemoglobin temporarily, and not the underlying cause (7).

How to cite this article: *Abdelazim IA, Abu-Faza M. Al-Ajmi SM. Amer OO. Shikanova S. Karimova B. Heme-Iron OptiFer® in the Treatment of Iron Deficiency Anemia During Pregnancy. Gynecol Obstet Reprod Med. 2022;28 (1):1-6*

Iron supplementation during pregnancy reduces the adverse outcome and IDA related morbidity (8). The conventional oral iron salts are associated with gastric discomfort/upset, constipation, and intolerability, which adversely affect the compliance, and treatment outcome (9-10).

The heme-iron is an effective, tolerable oral iron preparation, improves compliance, and ensures continuous iron intake during pregnancy (9-11).

Nissenson et al found the hem-iron an effective treatment option for IDA in hemodialysis patients and replaced intravenous iron preparations (12). Abdelazim et al found the heme iron, safe, effective, well tolerable oral iron preparation for the treatment of IDA with pregnancy (13). In addition, Hoppe et al concluded that the dietary-based treatment containing heme-iron can be used to improve the iron status for reproductive-age women (14). Therefore, this study designed to compare the effcacy and tolerability of heme-iron OptiFer® (HIO) to ferrous fumarate (FF) in the treatment of iron deficiency anemia (IDA) during pregnancy.

Material and Method

This prospective comparative study was conducted during the years 2019 and 2020, after approval by the ethical committees of the Obstetrics and Gynecology departments of Ahmadi hospital, Kuwait, and West Kazakhstan Marat Ospanov Medical University, Kazakhstan (Approval number OB_1707_18, date of approval 17 July 2018). Two hundred and thirty-four (234) pregnant women with moderate IDA during pregnancy (hemoglobin >7 and <10 gm/dL) were included in this study after informed consent in accordance with the Declaration of Helsinki. The trial was registered under the trial number ACTRN12618001482257 (15).

The moderate IDA diagnosed when serum ferritin <15 ug/l (normal 15-150 ug/l), hemoglobin (>7 and <10 gm/dl), RBCs-mean corpuscular volume (MCV) <80 fl (normal 80-100 fl), and RBCs-mean corpuscular hemoglobin (MCH) <28 pg (normal 28-32 pg) (16-19).

Studied pregnant women received either, HIO tablets twice daily (HIO group) or Trihmeic 350 mg oral FF tablets once daily (FF group) for ≥3 months for correction of their IDA.

Inclusion criteria include, pregnant women ≥20 years old, 14-26 weeks` gestation, with serum ferritin <15 ug/l, hemoglobin >7 and <10 gm/dL, MCV <80 fl, and MCH <28 pg.

Women with intolerance or hypersensitivity to oral iron, anemia other than IDA, hemoglobin <7 gm/dL, received a blood transfusion during current pregnancy were excluded from this study.

The HIO (OptiFer®) tablets (L`Avenir Med., Sweden) contain 18 mg heme-iron. The heme-iron of the OptiFer® has a unique intestinal receptor called Heme Carrier Protein-1 (HCP-1). After oral intake of HIO (OptiFer®) tablets, the iron content of the tablets is absorbed by the HCP-1 receptors, and the serum peak of iron increased within 2-4 hours. Each tablet of HIO increases the serum iron by 3.15 mg (13).

Women in the HIO group received OptiFer® tablets twice daily (one tablet every 12 hours) for ≥3 months (hemoglobin level of 11-12 gm/dL) than one daily as the maintenance dose (according to manufacturer instructions) (13). Women in the FF group received 350 mg oral FF (TriHemic® 600 tablets, Wyeth pharmaceutical, Karachi, Sindh, Pakistan), once-daily 1-hour after meal for ≥3 months (according to manufacturer instructions).

Studied pregnant women in both groups received oral folic acid with oral iron tablets (OptiFer® or TriHemic®) to avoid folate deficiency. Participants were asked during each antenatal care visit about their compliance to iron tablets, and the side effects related to oral iron as metallic taste, gastrointestinal (GIT) intolerance/upset, and/or constipation. The pre-treatment ferritin, hemoglobin, RBCs-MCV, and RBCs-MCH were compared by the post-treatment values in the two studied groups to detect the effcacy of HIO compared to FF in treatment of IDA during pregnancy as a primary outcome (16-19).

Sample size calculation

The required sample size calculated using data from previous studies (12,13), and G Power software version 3.17 (Heinrich Heine Universität; Düsseldorf; Germany), setting α-error probability at 0.05, power (1-β error probability) at 0.95%, and effective sample size (w) at 0.3. The effective sample includes ≥220 women in two groups needed to produce a statistically acceptable figure.

Statistical analysis

Collected data analyzed using Statistical Package for Social Sciences (SPSS) version 20 (Chicago, IL, The USA). The mean and standard deviation (±SD) were used to present the numerical values, while the number (n), and percentage (%) were used to present the categorical values. Chi-square (X^2) test was used for the analysis of qualitative data. Student (t) test was used to compare the pre-treatment ferritin, hemoglobin, RBCs-MCV, and RBCs MCH by the post-treatment values in the two studied groups. *P*-value <0.05 considered significant.

Results

Two hundred and thirty-four (234) women with moderate IDA during pregnancy (hemoglobin >7 and <10 gm/dL) were included in this study; 121 women in the HIO group, and 113 women in the FF group, to compare the effcacy and tolerability of HIO to FF in the treatment of IDA during pregnancy.

There demographic data of the studied groups (age, body

mass index, and parity) are presented in Table I. The two studied groups were matched, with no difference between the HIO group, and FF group regarding, the gestational age at diagnosis of IDA (24.1±4.3 weeks` versus 25.5±4.9, respectively; *p*=0.9), pre-treatment hemoglobin (7.6±2.7 gm/dL versus 7.8± 2.4, respectively; *p*=0.1), pre-treatment ferritin (14.6±4.6 ug/l versus 12.9±5.7, respectively; *p*=0.9), pre-treatment RBCs-MCV (76.2±7.7 fl versus 78.9±8.2, respectively; *p*=0.7), and pre-treatment RBCs-MCH (27.2±7.8 pg versus 25.5±9.1, respectively; *p*=0.9) (Table I).

The mean post-treatment hemoglobin and ferritin were significantly high in the HIO group (11.2±7.1 gm/dL and 112.8±54.8 ug/l, respectively) compared to the FF group (10.9 ±5.1 and 89.9±43.3, respectively; *p*=0.0002 and *p*=0.006, respectively). The mean post-treatment RBCs-MCV and RBCs-MCH were significantly high in the HIO group (92.0±4.1 fl and 31.9±6.2 pg, respectively) compared to the FF group (87.7 ±2.9 and 28.5±4.7, respectively; *p*=0.0001 and *p*=0.001; respectively) (Table II).

The rates of poor compliance (>50% compliance)/treatment interruption, and GIT intolerance/upset were significantly high in the FF group compared to the HIO group (12.4% and 19.5%, respectively versus 3.3% and 2.5%, respectively), (*p*=0.01 and *p*=0.0001; respectively). No other side effects were recorded in the HIO group, while the metallic taste reported in 13.3% and constipation reported in 20.4% of the studied women in the FF group (Table III).

Table I: *Demographic data, pre-treatment hemoglobin, ferritin and red blood cells - mean corpuscular volume and mean corpuscular hemoglobin, mean corpuscular volume, in the two studied groups*

Variables	HIO group n=121	FF group n=113	*p* (95% CI)
Age (years)	27.4±5.4	29.6±4.9	0.1 (-3.5, -2.2, -0.88)
BMI (Kg/m^2)	26.9±6.1	27.3±5.5	0.1 (-1.9, -0.4, 1.1)
Parity	3.6±2.7	4.1±3.2	0.9 (-1.3, 0.5, 0.27)
Gestational age at the diagnosis of IDA (Weeks`)	24.1±4.3	25.5±4.9	0.9 (-2.6, -1.4, -0.21)
Pre-treatment hemoglobin (gm/dL)	7.6±2.7	7.8±2.4	0.1 (-0.86, -0.2, 0.46)
Pre-treatment ferritin (ug/l)	14.6±4.6	12.9±5.7	0.9 (0.36,1.7, 3.043)
Pre-treatment MCV (fl)	76.2±7.7	78.9±8.2	0.7 (-4.75, -2.7, -0.65)
Pre-treatment MCH (pg)	27.2±7.8	25.5±9.1	0.9 (-0.49, 1.7, 3.89)

HIO: Heme-iron OptiFer®, FF: Ferrous fumarate, BMI: Body mass index, CI: Confidence interval, IDA: Iron deficiency anemia, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, Data presented as mean ± SD (Standard deviation)

Table II: *The post-treatment hemoglobin, ferritin, red blood cells-mean corpuscular volume and mean corpuscular hemoglobin in the two studied groups*

Variables	HIO group n=121	FF group n=113	*p* (95% CI)
Hemoglobin (gm/dL)	11.2±7.1	10.9±5.1	0.0002* (-1.3, 0.3, 1.88)
Ferritin level (ug/L)	112.8±54.8	89.9±43.3	0.006* (10.2, 22.9, 35.6)
RBCs-MCV (fl)	92.0±4.1	87.7±2.9	0.0001* (3.39, 4.3, 5.2)
RBCs-MCH (pg)	31.9±6.2	28.5±4.7	0.001* (1.99, 3.4, 4.8)

**: significant difference, HIO: Heme-iron OptiFer®, FF: Ferrous fumarate, CI: Confidence interval, RBCS: Red blood cells. MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin. Data presented as mean and ± SD. The student's t-test was used for statistical analysis.*

Table III: *The compliance, treatment interruption, and side effects recorded in the two studied groups*

Variables	HIO group Number 121	FF group Number 113	*p*
Poor compliance (>50% compliance) and treatment interruption	3.3% (4/121)	12.4% (14/113)	0.01*
Metallic taste	-	13.3% (15/113)	-
GIT intolerance/upset	2.5% (3/121)	19.5% (22/113)	0.0001*
Constipation	-	20.4 (23/113)	-

**: Significant difference, HIO: Heme-iron OptiFer®, FF: Ferrous fumarate, GIT: Gastrointestinal, Chi-square (X^2) test for analysis, Data presented as number and percentage (%)*

Discussion

The traditional oral iron salts used in the treatment of IDA are associated with treatment interruption and poor compliance which adversely affect the treatment outcome (1).

The authors previously reported that the heme-iron is an effective, tolerable oral iron preparation, improves compliance, and ensures continuous iron intake during pregnancy (11-13). Therefore, two hundred and thirty-four (234) women with moderate IDA during pregnancy (hemoglobin >7 and <10 gm/dL) were included in this study (121 women in the HIO group and 113 women in the FF group), to compare the effcacy and tolerability of HIO to FF in the treatment of IDA during pregnancy.

The two studied groups were matched with no significant difference regarding, the gestational age at diagnosis of IDA (p=0.9), pre-treatment hemoglobin (p=0.1), pre-treatment ferritin (p=0.9), pre-treatment RBCs-MCV (p=0.7), and pre-treatment RBCs-MCH (p=0.9).

Women in the HIO group received OptiFer® tablets twice daily not related to meals for ≥3 months (hemoglobin level of 11-12 gm/dL) then one daily as a maintenance dose (13). Women in the FF group received 350 mg oral FF (TriHemic®, 600 tablets), once-daily 1-hour after meal for ≥3 months.

The mean post-treatment hemoglobin and ferritin were significantly high in the HIO group compared to the FF group (p=0.0002 and p=0.006, respectively). In addition, the mean post-treatment RBCs-MCV and RBCs-MCH were significantly high in the HIO group compared to the FF group (p=0.0001 and p=0.001, respectively).

Nissenson et al found the hem-iron an effective treatment option for IDA in hemodialysis patients and replaced intravenous iron preparations (12). Abdelazim et al found the heme iron, safe, effective, and well tolerable oral iron preparation during the treatment of IDA with pregnancy (13).

In addition, Hoppe et al concluded that the dietary-based treatment containing heme-iron can be used to improve the iron status for reproductive-age women (14).

Nagaraju et al, randomized controlled trial found the heme-iron polypeptide (HIP) was similar in effcacy to intravenous (IV) iron sucrose in maintaining hemoglobin in non-dialysis chronic kidney patients (20).

Abdelazim et al, in another study, concluded that the HIP is a well tolerable oral iron with similar effcacy to IV iron in the treatment of IDA during pregnancy (11).

Moreover, when an intrinsically labeled 58Fe-heme and non-heme 57Fe (ferrous sulfate) were given in the third trimester and cord blood samples collected during labor to assess the 58Fe and 57Fe levels. The maternally absorbed 58Fe tracer present in the neonates was significantly high compared to 57Fe tracer (2.7±1.3 versus 2.2±1.4; respectively). This suggests that the heme-iron has favorable transport through the placenta to the fetus (21).

The rates of poor compliance (>50% compliance)/treatment interruption and GIT intolerance/upset were significantly high in the FF group compared to the HIO group (p=0.01 and p=0.0001, respectively). No other adverse effects were reported in the HIO group, while the metallic taste and constipation were reported in the FF group (13.3% and 20.4%, respectively).

Similarly, al-Momen et al reported high rates of poor compliance (30%) and GIT symptoms (30%) with conventional oral iron salts (22).

The higher poor compliance, treatment interruption, and side effects with the FF can be explained by the absorbed amount of iron from the oral iron salts (only 1-8%). The oral iron absorption increases with increasing oral iron doses only up to 160 mg/day. Accordingly, the recommended dose of elemental iron for treating IDA in pregnancy is 100-200 mg/day. Increasing iron dose beyond the recommended dose leads to increased GIT side effects without improving the effcacy (23).

The rates of poor compliance/treatment interruption (3.3%) and GIT intolerance/upset (2.5%) were significantly low in the HIP group compared to the FF group.

Abdelazim et al reported GIT intolerance/gastric upset in 1.7% (2/117) with HIP during the treatment of IDA with pregnancy (13). Pal et al, reported a 4% poor compliance rate (<50% compliance) in the heme-iron treated group compared to 12% in the non-heme iron treated group (21).

Habib et al studied the hemoglobin outcome in pregnant women with IDA in relation to their compliance to iron, and they concluded that the hemoglobin significantly improved only among strictly compliant women (24). Anemia was significantly high in non-compliant women (p<0.0001) (24).

In this study, the HIO is an effective therapeutic option for the treatment of IDA during pregnancy with low side effects. HIO can be used in women who have low compliance, and/or gastrointestinal intolerance to conventional iron salts. The tolerability of the HIO is an important advantage because compliance with oral iron supplements is the main obstacle to the effective treatment of IDA during pregnancy.

This study was the first registered multicentered prospective comparative study conducted to compare HIO to FF in the treatment of IDA during pregnancy. Incomplete patients` records because of preterm delivery and traveling was the only limitation faced during this study. The effcacy of HIO should be confirmed and compared to other heme-iron or intravenous iron preparations in future comparative studies.

Conclusion

Heme-iron OptiFer® is an effective therapeutic option for the treatment of IDA during pregnancy with low side effects. HIO can be used in women who have low compliance, and/or gastrointestinal intolerance to conventional iron salts.

Acknowledgment: Authors are grateful to women who agreed and gave consent to participate in this study.
Funding: None
Authors` contribution: IAA: Is responsible for the study design, data collection, registration of the trial, final revision before publication, and submission for publication. MAF: Is responsible for data collection, Microsoft editing, and final revision before publication. SMA: Is responsible for ethical approval, intellectual content, and final revision before publication. OOA: Is responsible for Microsoft editing and final revision before publication. SS: And Bakyt Karimova (BK) are responsible for the collection of data, Microsoft editing, intellectual content, references update, and final revision before publication.
Conflict of interest: Authors declare no conflict of interest in relation to this study.

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