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Ferric polymaltose complex in treatment of iron deficiency and iron-deficiency anaemia with pregnancy

Kompleks polimaltozy z wodorotlenkiem żelaza w leczeniu niedoboru żelaza i niedokrwistości z niedoboru żelaza w okresie ciąży

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Abstract

Introduction. *Iron deficiency (ID), and iron deficiency anaemia (IDA) are consistently associated with reduced maternal cognitive function and increased depressive disorders. In addition, the pre-term delivery, and intra-uterine growth restriction were reported as an adverse neonatal outcome for ID and IDA. This study designed to evaluate the efficacy of ferric hydroxide polymaltose (FPM) in treatment of ID, and IDA during pregnancy.*

Materials and methods. *One hundred and twenty-two women with ID (ferritin < 15 μg/L), and moderate IDA (haemoglobin ≥ 7 and < 10 g/dL) during pregnancy were included in this study. Studied women treated with FPM tablets for ≥ 3 months. The pre-treatment ferritin, haemoglobin, red blood cells (RBCs)-mean corpuscular volume (MCV), and -mean corpuscular haemoglobin (MCH) were compared by post-treatment values.*

Results. *The mean pre-treatment ferritin, and haemoglobin significantly increased from 12.4 ± ± 5.6 μg/L and 7.8 ± 3.3 g/dL; respectively to 116.5 ± 6.9 μg/L and 11.1 ± 2.8 g/dL; respectively, 3-months' after FPM treatment (p = 0.02 and 0.0002; respectively). In addition, the mean pre-treatment RBCs MCV, and MCH significantly increased from 73.5 ± 4.6 fL and 24.2 ± 7.7 pg; respectively to 94.0 ± 3.8 fL and 31.7 ± 6.3 pg; respectively 3-months' after FPM treatment (p = 0.02 and 0.01; respectively).*

Conclusion. *The FPM (Ferose®) is an effective therapeutic option for treatment of ID, and IDA during pregnancy with high safety profile, and low side effects. The superior tolerability of FPM is an important advantage because compliance to oral iron is the main obstacle toward effective treatment of ID, and IDA during pregnancy.*

Key words: ferric polymaltose complex, iron, deficiency, anaemia, pregnancy

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Streszczenie

Wstęp. *Niedobór żelaza (ID) i niedokrwistość z niedoboru żelaza (IDA) wiążą się z pogorszeniem funkcji poznawczych i zwiększonym ryzykiem zaburzeń depresyjnych u matki. Ponadto zgłaszano niekorzystne skutki ID i IDA dla noworodków, poród przedwczesny i wewnątrzmaciczne zahamo-*

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wanie wzrastania płodu. Celem niniejszego badania była ocena skuteczności polimaltozy wodorotlenku żelazowego (FPM) w leczeniu ID i IDA podczas ciąży.

Materiały i metody. *Do badania włączono 122 kobiety z ID (ferrytyna < 15 μg/l) i umiarkowaną IDA (hemoglobina ≥ 7 i < 10 g/dl) w czasie ciąży. Badane kobiety przyjmowały FPM w tabletkach przez co najmniej 3 miesiące. Stężenia ferrytyny i hemoglobiny, średnią objętość (MCV) krwinek czerwonych (RBC) i średnią masę hemoglobiny (MCH) w RBC przed leczeniem porównano z wartościami po leczeniu.*

Wyniki. *Średnie stężenia ferrytyny i hemoglobiny przed leczeniem istotnie wzrosły z 12,4 ± 5,6 μg/l i 7,8 ± 3,3 g/dl, odpowiednio, do 116,5 ± 6,9 μg/l i 11,1 ± 2,8 g/dl, odpowiednio, 3 miesiące po leczeniu FPM (p = 0,02 i 0,0002 odpowiednio). Ponadto średnie RBC MCV i MCH przed leczeniem istotnie się zwiększyły z 73,5 ± 4,6 fl i 24,2 ± 7,7 pg, odpowiednio, do 94,0 ± 3,8 fl i 31,7 ± ± 6,3 pg, odpowiednio, 3 miesiące po leczeniu FPM (p = 0,02 i 0,01 odpowiednio).*

Wniosek. *Polimaltoza wodorotlenku żelazowego (Ferose®) jest skuteczną opcją terapeutyczną w leczeniu ID i IDA u kobiet w ciąży, ponieważ lek ten cechują wysoki profil bezpieczeństwa i niewielkie działania niepożądane. Doskonała tolerancja FPM jest ważną zaletą, ponieważ nieprzestrzeganie zaleceń terapeutycznych dotyczących stosowania doustnych soli żelaza jest główną przeszkodą w skutecznym leczeniu ID i IDA w okresie ciąży.*

Słowa kluczowe: kompleks polimaltozy żelazowej, żelazo, niedobór, anemia, ciąża

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Introduction

Iron deficiency anaemia (IDA) is the commonest type of nutritional deficiencies affecting 30% of women in high-resource countries and > 50% of women in low-resource countries [1, 2]. The iron requirements increase during the second and third trimesters of pregnancy [3].

Iron metabolism in healthy women reflects iron intake, iron loss, and current demand. The iron intake depends on the nutritional iron intake and gastrointestinal tract (GIT) iron absorption ability [4]. The presence of GIT pathology (such as chronic inflammatory condition) reduces the iron absorption in the GIT. The human body regulates iron absorption in response to iron status via intestinal and hepatic proteins [4]. The placental transfer of iron from maternal plasma to the foetus during pregnancy is controlled by foetal hepcidin [4].

The daily requirement of iron for non-pregnant women is about 1–8 mg daily [5]. However, more external iron is required in pregnancy [5]. This significant increase in iron demand in pregnancy is required for foetal and placental development and increased mother's blood volume. The daily recommended amount of iron for pregnant women is about 27 mg [5]. In addition, the blood loss during deliveries increases maternal anaemia [6, 7] and maternal anaemia is a leading cause of adverse perinatal outcome [8–11]. Froessler et al reported that iron deficiency (ID) and IDA were associated with reduced maternal cognitive function and increased depressive disorders [12]. Froessler et al. [12] also reported the preterm delivery (PTD) and intrauterine growth restriction (IUGR) as an adverse neonatal outcome for ID and IDA.

Peripartum anaemia increases the need for packed red blood cells (RBCs) transfusion [13, 14] and the RBCs transfusion corrects only the haemoglobin, not the underlying cause [15]. Iron supplementation is crucial during pregnancy to reduce the adverse outcome related to ID and IDA [16]. The conventional iron salts (ferrous salts) are associated with gastric discomfort (colicky pain), vomiting, and constipation in about 50% of women, and those side effects adversely affect compliance [17, 18].

Ferrous salt is characterized by variable absorption rates, and its absorption decreased by intake of antacids and/or proton pump blockers [5]. The new oral heme-iron forms are effective in treatment of IDA, they improve compliance and ensure continuous iron intake, but are still expensive, and not affordable by all patients [19].

In the past, intravenous (i.v.) iron preparations (iron dextran) were associated with undesirable and serious side effects [5]. However, in recent years, new forms of i.v. iron introduced with better tolerability and recommended in various guidelines including i.v. iron sucrose and ferric carboxy-

maltose (FCM) [5]. However, a meta-analysis found the i.v. iron sucrose safe alternative to address the ID problem in women require rapid replacement of iron stores [20] and a randomized controlled trial (RCT) concluded that i.v. iron sucrose is beneficial for pregnant women presented with anaemia at later gestation when rapid replacement of iron stores is required [21].

The ferric hydroxide polymaltose (Ferose®) tablets contain tolerable, chocolate flavour, non-ionic iron in form of ferric hydroxide-polymaltose (FPM) complex which improves compliance and ensures continuous iron intake [22]. In addition, the adverse GIT troubles were less frequently reported with FPM compared to conventional iron salts [23, 24].

The tolerability and side effects of iron preparation are the major challenges in treatment of ID and IDA during pregnancy. Therefore, this study was designed to evaluate the efficacy of the FPM (Ferose®) tablets in treatment of ID and IDA during pregnancy.

Material and methods

Study design

The current study conducted over 6 months during the year 2019; after ethical committee approval, patients' consent in accordance with the Declaration of Helsinki, and trial registration (trial ACTRN12619000230156) [25]. One hundred and twenty-two women with ID (ferritin < 15 μg/L) and moderate IDA with pregnancy (haemoglobin ≥ 7 and < 10 g/dL) were included in this study. The diagnosis of ID was based on serum ferritin (μg/L), normal serum ferritin (15–150 μg/L), and the diagnosis of IDA was based on serum ferritin (μg/L), haemoglobin concentration (g/dL), RBCs-mean corpuscular volume (MCV), and -mean corpuscular haemoglobin (MCH) [26–29]. IDA classified according to the world health organization (WHO) definition into severe anaemia when haemoglobin < 7 g/dL, moderate anaemia when haemoglobin between 7–10 g/dL, and mild anaemia when haemoglobin is > 10 g/dL [2, 16]. Studied pregnant women were treated for correction of ID and IDA with FPM tablets for ≥ 3 months. Inclusion criteria include pregnant women ≥ 20 years old, 14-26 weeks' gestation with serum ferritin < 15 μg/L, and haemoglobin ≥ 7 and < 10 g/dL (moderate IDA). Pregnant women with intolerance or hypersensitivity to oral iron and/or anaemia other than IDA, and women received blood transfusion during their current pregnancy were excluded from this study. The studied pregnant women received FPM (Ferose®) tablets three times daily for correction of ID and IDA (27 mg of iron required daily during pregnancy) for ≥ 3 months. The ferric iron of the FPM (Ferose®) tablets (Ferose®, Spimaco Addwaeh, Saudi Arabia) is absorbed in the duodenum and jejunum via an active-controlled mechanism and reaches the blood bound to transferrin (no unbound iron reaches the blood) then stored in the liver as ferritin which will be available for the hemopoiesis process [22]. The maximum iron absorption capacity from FPM (Ferose®) tablets reached 30 minutes after the oral intake, and continuously increased over 24 hours [30]. About 10–15% of the ferric iron is absorbed from the FPM (Ferose®) tablets after oral intake (10-15 mg is absorbed from each 100 mg FPM (Ferose®) tablet) [22]. Studied women received oral folic acid with FPM (Ferose®) tablets to avoid folate deficiency. Participants were asked during each antenatal care visit about their compliance to oral FPM (Ferose®) tablets and the side effects related to FPM (Ferose®) tablets as metallic taste, GIT intolerance and/or constipation. The pre-treatment ferritin, haemoglobin, RBCs-mean corpuscular volume (MCV), and -mean corpuscular haemoglobin (MCH) were compared by the 3 months' post-treatment values to detect the efficacy of FPM in treatment of ID and IDA during pregnancy [31, 32].

The primary outcome measures the efficacy of FPM (Ferose®) tablets in treatment of ID and IDA with pregnancy. The secondary outcome measures the tolerability and side effects related to the FPM (Ferose®) tablets.

Sample size

The required sample size was calculated using G-Power software version 3.17 for sample size calculation, setting α — error probability at 0.05, power (1 — β error probability) at 0.95%, and effective sample size (w) at 0.5. An effective sample includes ≥ 110 women needed to produce a statistically acceptable figure.

Statistical analysis

Collected data were statistically analysed using Statistical Package for Social Sciences (SPSS) version 20 (Chicago, IL, USA). The mean and standard deviation (± SD) were used to present numerical values, while the number (N) and percentage (%) were used to present categorical values. Student *t*-test was used to compare the pre-treatment ferritin, haemoglobin, RBCs-MCV, and MCH by the 3 months' post-treatment values. P-value < 0.05 was considered significant.

Table 1. Demographic data* of the studied pregnant women with iron deficiency (ID) and iron deficiency anaemia (IDA)

Tabela 1. Dane demograficzne badanej grupy kobiet ciężarnych z niedoborem żelaza (ID) i niedokrwistością z niedoboru żelaza (IDA)

Variable	Studied pregnant women with ID and IDA (N = 114)
Maternal age (years)	27.6 ± 3.2
Parity	4 (1–5)
Maternal weight [kg]	81.5 ± 4.3
Maternal BMI [kg/m^2]	27.4 ± 6.4
Gestational age at inclusion (weeks')	18.3 ± 5.1
Pre-treatment ferritin [μg/L]	12.4 ± 5.6
Pre-treatment haemoglobin [g/dL]	7.8 ± 3.3

*Data presented as mean ± standard deviation and median (range); BMI — body mass index

Results

Demographic data of the studied pregnant women

One hundred and twenty-two women with pregnancy-associated ID (ferritin < 15 μg/L) and moderate IDA (haemoglobin ≥ 7 and < 10 g/dL) were included in this prospective study and treated with FPM (Ferose®) tablets for ≥ 3 months. Eight women were excluded from the final statistical analysis due to preterm delivery (2 women), travelling (3 women), and lost follow-up data (3 women). The study completed with a final analysis of data from 114 pregnant women with ID and IDA. Table 1 shows the demographic data of the studied pregnant women with ID and IDA.

The pre-treatment ferritin, haemoglobin, MCV and MCH compared to the post-treatment values

The mean pre-treatment ferritin and haemoglobin significantly increased from 12.4 ± 5.6 μg/L and 7.8 ± 3.3 g/dL respectively to 116.5 ± 6.9 μg/L and 11.1 ± 2.8 g/dL; respectively 3-months' after FPM treatment (p = 0.02 and 0.0002; respectively). In addition, the mean pre-treatment RBCs MCV, and MCH significantly increased from 73.5 ± 4.6 fL and 24.2 ± 7.7 pg; respectively to 94.0 ± 3.8 fL and 31.7 ± 6.3 pg; respectively 3-months' after FPM treatment (p = 0.02 and 0.01; respectively).

The reported compliance, GIT side effects

The reported poor compliance, GIT intolerance, and constipation rates with FPM in this study were 6.1% (7/114), 2.6% (3/114), and 4.4% (5/114), respectively.

Discussion

IDA affects 30% of women in high-resource countries and > 50% of women in low-resource countries [1, 2]. The iron requirements increase during the second and third trimesters of pregnancy [3]. The daily requirement of iron for non-pregnant women is about 1–8 mg daily [5]. However, more external iron is required in pregnancy and the daily recommended amount of iron for pregnant women is about 27 mg [5]. Maternal anaemia is a leading cause of adverse perinatal outcome [8–11]. ID and IDA were associated with reduced maternal cognitive function and increased depressive disorders [12]. The PTD and IUGR were also reported as adverse neonatal outcomes for ID and IDA [12]. Peripartum anaemia increases the need for packed RBCs transfusion [13, 14]. Iron supplementation is crucial during pregnancy to reduce the adverse outcome related to ID and IDA [16]. The conventional iron salts (ferrous salts) are associated with gastric discomfort and constipation which adversely affect compliance [17, 18]. A daily dose of 150–200 mg of elemental iron is usually needed to treat ID and IDA using iron salts (ferrous sulphate) in adults, which means 3 tablets of ferrous sulphate/day (each tablet contains 60 mg

Table 2. The pre-treatment ferritin, haemoglobin, red blood cells (RBCs)-mean corpuscular volume (MCV), and -mean corpuscular haemoglobin (MCH) compared to the post-treatment values

Tabela 2. Porównanie wartości stężeń ferrytyny I hemoglobiny, średniej objętości (MCV) krwinek czerwonych (RBC) i średniej masę hemoglobiny (MCH) przed leczeniem i po leczeniu

Variable	Pre-treatment values	3-months' post-treatment values	P-value (95% CI) significance
Ferritin level [μg/L]	12.4 ± 5.6	116.5 ± 6.9	0.02* (–116, –114.1, –112.1)
Haemoglobin [g/dL]	7.8 ± 3.3	11.1 ± 2.8	0.0002* (–4.2, –3.3, –2.4)
RBCs MCV [fL]	73.5 ± 4.6	94.7 ± 3.8	0.02* (–22.3, –21.2, –20.09)
RBCs MCH [pg]	24.2 ± 7.7	31.7 ± 6.3	0.01* (8.7, 10.5, 12.3)

The Student's *t*-test was used for statistical analysis. Data presented as mean and ± standard deviation (SD). *Significant difference; CI — confidence interval

of elemental iron). Since 10% of elemental iron is absorbed in the GIT, the haemoglobin concentration may be fully corrected after 4 weeks in women with moderate IDA. Also, another 4 weeks of iron salts treatment are needed to replenish iron stores [33]. Unfortunately, about 20% of women experience some GIT troubles/discomfort while taking 180 mg of elemental iron/day using this regimen of treatment, and 30% of them will self--discontinue the medication [33]. The new oral heme iron forms are effective in the treatment of IDA, they improve compliance and ensure continuous iron intake, but are still expensive, and not affordable by all patients [19]. The iron sucrose (IS) was approved in the States and Europe in November 2000. The incidence of serious life--threatening anaphylaxis with IS is 0.002%, and the hypersensitivity reactions have not been reported with IS [5]. The required IV iron sucrose dose for correction of ID and IDA are calculated according to the following formula: required IV iron dose = body weight/kg × target Hb (120 g/dL) – actual Hb in g/dL × constant factor (0.24) + 500 mg to replace the iron stores. IS showed a high safety profile during pregnancy in the largest published trial [5]. The main disadvantage of iron sucrose is the need for multiple infusions as the maximum weekly dose should not exceed 600 mg (200 mg i.v. in each session every other day, and 3 sessions/ /week) [28, 29]. The new i.v. iron form FCM is under phase II and III of clinical trials from the authorised organizations in Europe and the States and can be potentially used in non-pregnant women for correction of postpartum IDA and IDA anaemia following uterine bleeding according to the regional health authority approval [5]. However, a meta-analysis found the i.v. iron sucrose safe alternative to address the problem of ID in women require rapid replacement of iron stores [20] and a randomized controlled trial (RCT) concluded that i.v. iron sucrose is beneficial for pregnant women presented with anaemia at later gestation when rapid replacement of iron stores is required [21]. The ferric hydroxide polymaltose (Ferose®) tablets contain tolerable, non-ionic iron in form of FPM, which improves compliance and ensures continuous iron intake [22]. In addition, the adverse GIT troubles were less frequently reported with FPM compared to conventional iron salts [23, 24]. The tolerability and side effects of iron preparation are the major challenges in the treatment of ID and IDA during pregnancy. Therefore, this study was designed to evaluate the efficacy of the FPM (Ferose®) tablets in treatment of ID and IDA during pregnancy. One hundred and twenty-two women with pregnancy-associated ID (ferritin < 15 μg/L) and moderate IDA (haemoglobin ≥ 7 and < 10 g/dL) were included in this study and treated with FPM (Ferose®) tablets for ≥ ≥ 3 months. Eight women excluded from the final statistical analysis, and the study completed with final analysis of data from 114 pregnant women with ID and IDA. The mean pre-treatment ferritin and haemoglobin significantly increased from 12.4 ± 5.6 μg/L and 7.8 ± 3.3 g/dL; respectively to 116.5 ± 6.9 and 11.1 ± 2.8; respectively 3-months' after FPM treatment (p = 0.02 and 0.0002; respectively). In addition, the mean pre-treatment RBCs MCV, and MCH significantly increased from 73.5 ± 4.6 fL and 24.2 ± 7.7 pg; respectively to 94.0 ± 3.8 fL and 31.7 ± 6.3 pg; respectively 3-months' after FCM treatment (p = 0.02 and 0.01; respectively). Although the gastric side-effects are common with conventional oral iron salts, the reported poor compliance, GIT intolerance, and constipation rates with FPM (Ferose®) tablets in this study were low and insignificant [6.1% (7/114), 2.6% (3/114) and 4.4% (5/114); respectively]. Yasmeen et al. found significant difference in haemoglobin, RBCS MCV, MCH, and serum ferritin after 12 weeks of FPM treatment for IDA with pregnancy, and concluded that the FPM is a safe and cost-effective therapeutic option for IDA with pregnancy [34]. Geisser [23] found the FPM tablets are an effective treatment option in IDA due to their kinetic properties and higher iron dose compared to ferrous iron. Also, Geisser [23] reported lower rates of treatment interruption and GIT side effects with FPM compared to ferrous salts. Saha et al. [35] randomized double-blind study concluded that the FPM is useful for the treatment of IDA during pregnancy for those who cannot tolerate other iron preparations (ferrous salts). In addition, they found the overall adverse effects were more common in ferrous sulphate group compared to FPM group (78% vs. 31%, p < 0.001). The compliance rate was significantly higher for FPM (91%) compared to ferrous sulphate (87%), (p < 0.05) [35]. Although al-Momen et al. [36] reported a poor compliance rate (30%) and gastric symptoms (30%) with the traditional oral iron salts, the reported poor compliance and GIT intolerance with FPM (Ferose®) in this study were low and insignificant [6.1% (7/114) and 2.6% (3/114) respectively]. Ortiz et al. [24] found that the adverse events were significantly less common with FPM [29.3% (12/41)] compared to ferrous sulphate [56.4% (22/39)], (p = 0.015). Ortiz et al. [24] concluded

that the oral FPM had superior safety profile compared to ferrous sulphate during treatment of IDA with pregnancy. In addition, Toblli et al. [37] found the FPM had negligible colonic tissue erosion and/ /or systemic oxidative stress or inflammation effects, even at high therapeutic doses. Toblli et al. [37] concluded that FPM is an effective oral treatment for ID in inflammatory bowel disease. Toblli and Brignoli meta-analysis [22] found the adverse drug reactions were less frequent with FPM (14.9%) compared to ferrous sulphate (34.1%), particularly upper digestive troubles and diarrhoea. Toblli and Brignoli [22] concluded that the tolerance of FPM in adults was significantly better than that of ferrous sulphate which reflects a better risk/benefit ratio of FPM in adults. This study found the mean pretreatment ferritin, haemoglobin, RBCs MCV, and MCH significantly increased 3-months` after FPM treatment for ID and IDA with pregnancy. The reported poor compliance, GIT intolerance, and constipation rates with FPM in this study were low and insignificant [6.1% (7/114), 2.6% (3/114) and 4.4% (5/114); respectively]. This study concluded that FPM is an effective therapeutic option for treatment of ID and IDA during pregnancy with high safety profile and low side effects. The superior tolerability of FPM (Ferose®) tablets is an important advantage because compliance to oral iron salts is the main obstacle toward effective treatment of ID and IDA during pregnancy. The current study was the first registered study conducted to evaluate the efficacy of FPM in treatment of ID and IDA during pregnancy. Incomplete follow-up and lost medical records because of PTD and travelling were the limitations faced during this study. The efficacy of FPM in treatment of ID and IDA during pregnancy should be evaluated, and compared to the new available heme-iron preparations in future comparative studies.

Conclusion

The FPM (Ferose®) is an effective therapeutic option in treatment of ID and IDA during pregnancy with high safety profile, and low side effects. The superior tolerability of FPM is an important advantage because compliance to oral iron is the main obstacle toward effective treatment of ID and IDA during pregnancy.

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Ethical considerations

The study was approved by the Obstetrics and Gynaecology departments ethical committee (OB_10_12_18) and registered under the trial number ACTRN12619000230156.

Conflict of interest

The authors declare no conflict of interests in relation to this study.

Financial disclosure

None.

Authors contribution

Ibrahim A. Abdelazim (IAA) is responsible for study concept, study design, data collection, statistical analysis, data interpretation, final revision before publication and submission for publication.

Mohamed Farghali (MF) is responsible for study concept, study design, data collection, statistical analysis, data interpretation, final revision before publication.

Osama O. Amer (OOA) is responsible for statistical analysis, manuscript preparation, and literature search.

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