**Heme-bound iron (Optifer®) versus intravenous iron (Ferosac®) in treatment of pregnancy associated iron deficiency anemia**

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**Running Head:** Heme versus intravenous iron in pregnancy associated IDA.

**Study Design:** Comparative study.

**Place of the study:** Ahmadi hospital.

**Protocol of the study:** Ahmadi Hospital, Kuwait Oil Company (KOC).

**Heme-bound iron (Optifer®) versus intravenous iron (Ferosac®) in treatment of pregnancy associated iron deficiency anemia**

**Background:** The World Health Organization defined hemoglobin <11 gm/ dl as anemia. The iron requirements during pregnancy are high and it increase furthermore during the second and third trimesters. Maternal anemia is a leading cause of perinatal morbidity and adverse outcome.

**Objectives:** This study designed to compare the efficacy and tolerability of the heme-bound iron (HIO) Optifer® versus iron saccharate complex (Ferosac®) in treatment of pregnancy associated iron deficiency anemia (IDA).

**Introduction**

The World Health Organization (WHO) defined hemoglobin <11 gm/ dl as anemia [1]. Iron deficiency is the most common cause of anemia among other nutritional deficiencies (B12 and folic acid) [2].

The iron requirements during pregnancy are high and it increase furthermore during the second and third trimesters [3].

In addition; blood loss of ≥1 Liter occurs in 7% of vaginal deliveries and 23% of the cesarean deliveries associated with 1000-1500 ml blood loss [4-5].

Maternal anemia is a leading cause of perinatal morbidity and adverse outcome [6-9]. Recently; *Froessler at al,* reported that the iron deficiency and its related anemia associated with adverse outcome as reduced maternal cognitive activities and increased maternal depressive disorders. While, they reported the preterm labor (PTL), IUGR (intra-uterine growth retardation), IUFD (intra-uterine fetal death) and neonatal infection as adverse neonatal outcome [10].

Peri-partum 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 perinatal morbidity related to iron deficiency anemia [14].

Oral iron therapy is safe, cost-effective treatment for iron deficiency anemia (IDA) during pregnancy. The conventional non-heme iron preparations given on empty stomach and associated with gastric discomfort, constipation, which adversely affect the compliance and the treatment outcome [15-16].

The heme-iron is well tolerable, effective oral iron preparation, improves the compliance and ensures continuous iron intake during pregnancy [15-17].

*Nissenson et al, concluded* that theuse of hem-iron for 6 months in hemodialysis patients was effective in treatment of IDA and replaced the intravenous iron preparations [18].

*Abdelazim et al,* concluded that the heme iron is safe, effective, well tolerable oral iron preparation as well as intravenous iron for treatment of IDA during pregnancy [17,19].

In addition; *Hoppe at el,* concluded that the dietary-based treatment containing heme-iron has few side effects and can be used efficiently to improve the iron status of women of reproductive age [20].

Optifer® is a new genuine heme-bound iron supplement made under HACCP (hazards analysis and critical control points) standards in Sweden. This comparative study designed to compare the efficacy and tolerability of the heme-bound iron (HIO) Optifer® versus iron saccharate complex (Ferosac®) in treatment of pregnancy associated IDA.

**Patients and methods**

This comparative study will be conducted in Ahmadi hospital, Kuwait Oil Company (KOC), Kuwait over 6 months from June 2019 till December 2019; after approval of the study by the Obstetrics and Gynecology department ethical committee.

Pregnant women with pregnancy associated IDA and hemoglobin ≤10 gm/dl (8-10 gm/dl) will included in this study after informed consent.

Studied women will receive either HIO (Optifer®) tablets (PO group) or intravenous iron saccharate (Ferosac®), (IV group) for correction of pregnancy associated IDA.

Inclusion criteria includes; pregnant women ≥ 20 years old, 14-26 weeks` gestation, with hemoglobin ≤ 10 gm/dl (8-10 gm/dl). Pregnant women with anemia other than IDA and/or received blood transfusion during current pregnancy will excluded from this study.

IDA will be diagnosed by the following parameters; hemoglobin concentration (gm/dl), serum ferritin (ug/l), mean Corpuscular Volume (MCV) and mean corpuscular hemoglobin (MCH) [7-9].

The HIO (Optifer®) tablets (L`Avenir Med., MediTec FerroCare., Sweden) contain 18 mg heme-bound iron. The heme iron content of the Optifer® tablets has a unique carrier intestinal receptors Heme Carrier Protein-1 (HCP-1). After oral intake of HIO (Optifer®) tablets, the iron content of the tablets will be absorbed by the HCP-1 receptors of the small intestine and the serum peak of iron reached within 2-4 hours. Each tablet of HIO (Optifer®) increases the serum iron by 3.15 mg [9].

Women in the PO group will receive HIO (Optifer®) tablets twice daily (1 tablet morning and 1 tablet evening) not related to meals for ≥3 months till hemoglobin level of 11-12 gm/dl then one tablet daily as maintenance dose (according to manufacturer instructions) [18].

Women in the IV group will receive the calculated intravenous iron dose according to the formula; total iron needed in mg = 2.4 × pre-pregnancy weight in kg × (target hemoglobin concentration - actual hemoglobin concentration) gm/dl + 500 mg [17]. Twelve (12) gm/dl is the target hemoglobin concentration and 2.4 is a correction factor, while the 500 is the amount of stored iron in adult pregnant women [17]. The calculated total intravenous iron dose will be given over 6-8 sessions, in each session 200 mg of iron saccharate complex (Ferosac®, Spimaco, Al-Qassim Pharma, Saudi Arabia) will be diluted in normal saline and given by intravenous infusion over one hour every other day and the studied women will be monitored during the first 15 minutes for signs of intolerance, hypotension, tackycardia or anaphylaxis [17].

Iron sucrose (iron saccharate complex) is stable, cleared from serum within 5-6 hours and used immediately for erythropoiesis.

Studied women will receive oral folic acid with HIO (Optifer®) or intravenous iron (Ferosac®) to avoid folic deficiency and participants will asked during each ante-natal care visit for any side effects related to HIO (Optifer®) or intravenous iron (Ferosac®) as gastrointestinal upset, metallic taste, constipation and/or intolerance.

The HIO (Optifer®) and intravenous iron (Ferosac®) efficacy will checked by comparing the pre-treatment hemoglobin, ferritin, MCV and MCH by the 3 months` post-treatment values [21,22].

Primary outcome measures; the efficacy of the heme-bound iron (HIO) Optifer® compared to intravenous iron (Ferosac®) in treatment of pregnancy associated IDA. While the secondary outcome measures; the tolerability and the side effects related to the HIO (Optifer®) and intravenous iron (Ferosac®).

**Sample size calculation**

The required sample size calculated using data from previous studies [18,19] and G Power software version 3.17 for sample size calculation (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 will statistically analyzed to evaluate the efficacy of the heme-bound iron (HIO) Optifer® compared to intravenous iron (Ferosac®)in treatment of pregnancy associated IDA.

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