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Efficacy of Amino Acid Chelated Iron versus Iron Polymaltose Complex in Treatment of Iron Deficiency Anemia in Pregnancy:

A Randomized Controlled Trial

Thesis

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By

Hazem Yousry Abdulaleem Hussein Ammar
M.B.B.Ch., Ain Shams University (2012)
Resident Physician Mataria Teaching Hospital

Under Supervision of

Prof. Hatem Hussein El-Gamal
Professor of Obstetrics and Gynecology
Faculty of Medicine – Ain Shams University

Dr. Mohamed Abdellatif Abdelhaleem
Lecturer in Obstetrics and Gynecology
Faculty of Medicine – Ain Shams University

Faculty of Medicine
Ain Shams University
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Hazem Yousry Abdulaleem Hussein Ammar

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List of Abbreviations

Abb.	Full term

AOAC ..... *Association of analytical chemists*

AUC ..... *Area under curve*

BMP ..... *Bone morphogenic protein*

Dcytb ..... *Duodenal cytochrome-b*

DMTI ..... *Diovalent metal transporter-1*

EPI ..... *Expanded program of immunization*

Fe II ..... *Iron in ferrous form*

Fe III ..... *Iron in ferric form*

Fe ..... *Iron*

Fe-s ..... *Iron sulphur*

FPNI ..... *Ferro protein-1*

Hb ..... *Haemoglobin*

HCP1 ..... *Haem carrier protein-1*

Hct ..... *Haematocrite value*

HJV ..... *Hemojuvelin*

HO1 ..... *Haemoxygenase-1*

HP ..... *Hephaestin*

ID ..... *Iron defiency*

IDA ..... *Iron deficiency anaemia*

IRP ..... *Iron regulatory protein*

Lf ..... *Lacto ferrin*

LIP ..... *Labile iron pool*

MCHC ..... *Mean corpuscular haemoglobin concentration*

List of Abbreviations cont...

Abb.	Full term
MCV	*Mean corpuscular volume*
MTf	*Melano transferring*
PHD	*Prolyl hydroxylase domain enzymes*
PIX	*Protoporphyrin IX*
Rc	*Reticulocytic count*
RDA	*Recommended daily allowance*
sHJV	*Soluble Hemojuvelin*
SMAD4	*Signaling mothers against decapentaplegic homolog4*
STAT3	*Signal transducer and activator of transcription 3*
Tf	*Transferrin*
TfR	*Transferrin receptors*
TfRI	*Transferrin receptors 1*

INTRODUCTION

The World Health Organization (WHO) describes anemia in a pregnant woman as a hemoglobin (Hb) concentration of < 11 g/dl. Iron deficiency anemia (IDA) is the most prevalent type of anemia in pregnancy. Normally, the body's iron content is maintained constant by controlling the quantity absorbed to balance the quantity lost ***(WHO, 2011)***.

Many observational studies have explored the association between adverse maternal and infant health outcomes (such as postpartum hemorrhage, preterm birth, low birthweight, and perinatal death) and iron deficiency or iron deficiency anemia in pregnancy ***(Cantor et al., 2015)***.

The WHO estimates that 46% of pregnant women in African region, 38% in Eastern Mediterranean region, 25% in European region and 24% in the region of the Americas are anemic mainly because of iron deficiency ***(WHO, 2011)***. The prevalence of anemia among pregnant women in Egypt is 22.6%, according to the Global Health Observatory Data Repository ***(WHO, 2016)***.

It’s wise to consider any patient at the start of pregnancy with a Hemoglobin level that is less than 11gm/dL to be treated as anemic. As, blood dilution is a normal physiology and starts at the eighth week and progresses till the 34th week of pregnancy ***(Chowdhury et al., 2014)***.

Pregnant women are prone to hematological disorders, such as hereditary anemias, immunological thrombocytopenia, and malignancies. Iron-deficiency and megaloblastic anemias may occur during pregnancy due to pregnancy-induced demands. Pregnancy may also unmask underlying hematological disorders such as compensated hemolytic anemias caused by hemoglobinopathies or red cell membrane defects ***(Williams Obstetrics 2014).***

Microcytosis generally signifies a reduced hemoglobin content within the red blood cell and is usually linked to a simultaneous decrease in mean corpuscular hemoglobin, resulting in hypochromic pattern on blood smear. The most common causes of microcytosis are iron deficiency, thalassemia, and anemia of chronic inflammation. Iron deficiency and thalassemia are both characterized by decreased hemoglobin production, due to insufficient availability of heme or globin, respectively ***(Schrier et al., 2018).***

Almost all cases of iron deficiency anemia respond readily to treatment with iron supplementation, patients do not always respond adequately to oral iron therapy because of noncompliance due to side effects. Gastrointestinal disorders namely, constipation, diarrhea, colicky pain, nausea, vomiting, and gastric distress may happen in pregnant women taking iron preparations ***(Kambar et al., 2013)***.

Daily oral iron of with 30 mg to 60 mg of elemental iron and folic acid supplementation of 400 µg of folic acid is recommended for pregnant women to prevent maternal anaemia, puerperal sepsis, low birth weight ***(WHO, 2016)***.

Two main drugs are commonly used for oral iron supplementation, i.e., ferrous sulfate and ferrous fumarate. The advantages of these drugs are their availability, low cost, and safety ***(Peyrin-Biroulet et al., 2015)***.

Ferrous sulphate is known to produce intestinal side effects (nausea, vomiting, constipation, bloating) in many users. Ferrous fumarate has less gastrointestinal side effects and is readily absorbed than ferrous sulfate ***(Cancelo-Hedalgo et al., 2013)***.

Tolerability is an important factor that determines the choice of iron form. Since, if the preparation is not well tolerated, abandoning of this treatment will lead to persistence of anemia (***Abdel Moety et al., 2017)***.

Moreover, ferrous salts are characterized by low and variable absorption rates. Its absorption can be resctricted by the ingestion of certain foods as well as mucosal luminal damage ***(Saber et al., 2019)***.

Oral iron polymaltose complex increases hemoglobin and serum ferritin levels more than oral ferrous sulfate and

produces less adverse effects than ferrous sulfate ***(Elsenity et al., 2018).***

Low-dose ferrous bisglycinate (Amino Acid Chelated Iron) appears to be as effective as ferrous sulfate, most likely due to the higher bioavailability of bisglycinate iron. Ferrous bisglycinate supplementation also tends to exhibit a lower frequency of black stools, indicating a lower fecal excretion of non-absorbed iron ***(Milman et al., 2014).***

The structural and absorption characteristics of amino acid chelated Iron and iron polymaltose complex may contribute to the differences in their bioavailability and efficacy relative to other compounds ***(Name et al., 2018).***

AIM OF THE WORK

This study aimed to compare between the efficacy of amino acid chelated iron and iron polymaltose complex in treatment of iron deficiency anemia during pregnancy.

Chapter One
IRON AND PREGNANCY

Iron Metabolism

Iron (Fe) is a mineral found in every human cell. It is essential for nucleic acid synthesis, respiration and biologically important reactions. The amount of iron within the cell is strictly monitored, as accumulating iron is presumed to cause oxidative stress, understood as an increase in the steady state concentration of oxygen radical intermediates ***(Bresgen et al., 2015).***

In contrary to other minerals, iron levels in the human body are controlled only by absorption. The mechanism of iron excretion is an unregulated process depending on loss in sweat, menstruation, shedding of hair and skin cells, and through rapid turnover and excretion of enterocytes. In the human body, iron exists mainly in erythrocytes as the heme compound hemoglobin ***(Yiannikourides et al., 2015).***

The comprehension of iron digestion is based upon its ingestion in the duodenum then by its conveyance to tissues through the plasma iron transport protein transferrin (Tf). Transferrin ties to transferrin receptor-l (TfRl) on the plasma membrane and is engulfed by receptor-mediated endocytosis. Iron is then utilized for cell functions, and excess iron is stored in the protein ferritin. Intracytoplasmic iron level is post-