The effect of orally administered iron-saturated lactoferrin on systemic iron homeostasis in pregnant women suffering from iron deficiency and iron deficiency Anaemia

Thesis

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Abstract

Background: Anemia is a common medical disorder affecting a lot of women in pregnancy in the developing countries. Anemia is the second indirect obstetric cause of death after cardiac causes. **Aims:** To compare the safety, tolerability, efficacy and hematological response of lactoferrin in treatment of iron deficiency anemia during pregnancy versus ferrous sulfate capsules. **Methodology**: Hematological Response to lactoferrin versus ferrous sulfate in Treatment of Anemia with Pregnancy". Study site: Ain Shams University hospital. Study design: A double blind clinical trial. Study population: The study was included Two-hundred pregnant females with iron deficiency anemia attending the outpatient clinics of Ain shams university maternity hospital for routine antenatal care. For each pregnant woman, age, parity and gestational history were taken before treatment. All pregnant women took their allocated treatment regularly for eight weeks after diagnosis of iron deficiency anemia with hemoglobin level and serum ferritin level and followed up after four and eight weeks. Also, epigastric pain, diarrhea, constipation, nausea, vomiting or gastric distress reported to assess tolerability of the drugs. **Results:** The study included 188 pregnant women in a double blind study: Group I (lactoferrin): 95 cases were received 100mg of bovine lactoferrin (Pravotin sachets, Hygint, Egypt) twice a day. Group II (ferrous sulfate): 93 cases were received 150mg of dried ferrous sulphate + folic acid (vitamin B9) 0.50mg (Ferrofol, E.I.P.I.C.O, Egypt) three capsules per day. **Conclusion:** lactoferrin is more tolerable than ferrous sulphate. It has lesser GIT side effects and seems to icrease both hemoglobin and serum ferritin more than iron salts. **Recommendations:** Lactoferrin is recommended for patients with iron deficiency anemia.

Keywords: Hematological Response, lactoferrin, ferrous sulphate. Iron deficiency Anemia with Pregnancy.

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Khaled Balsha

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List of Abbreviation

CBC	**:**	Complete blood count
CDC	**:**	Center for disease control and prevention
CRP	**:**	C-reactive protein
DRI	**:**	Dietary references intakes
ED	**:**	Emergency department
FDA	**:**	Food and drug administration
Fe	**:**	Iron
Fp	**:**	Ferroprotein
Gm/dL	**:**	Gram per decileter
Hb	**:**	Hemoglobin
HCT	**:**	Hematocrite
HIP	**:**	Heme iron polypeptide
IDA	**:**	Iron deficiency anemia
IL-6	**:**	Interlukin-6
IM	**:**	Intramuscular
IPC	**:**	Iron polymaltose complex
IV	**:**	Intravenous
K	**:**	Kilogram
MCH	**:**	Mean corpuscular hemoglobin
MCHC	**:**	Mean corpuscular hemoglobin concentration
MCV	**:**	Mean corpuscular volume
PV	**:**	Plasma volume
RBCs	**:**	Red blood cells
RDW	**:**	Red cell distribution width
RES	**:**	Reticuloendothelial system
TF	**:**	Transferrin
TFR	**:**	Transferrin receptor
TIBC	**:**	Total iron binding capacity
WHO	**:**	World health organization

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INTRODUCTION

Iron deficiency (ID) and iron deficiency anemia (IDA) are the most common iron disorders throughout the world. ID and IDA, particularly caused by increased iron requirements during pregnancy, represent a high risk for preterm delivery, fetal growth retardation, low birth weight, and inferior neonatal health. These pregnancy complications are thought to occur as a consequence of an increased iron requirement, related to enhanced blood volume and development of the fetoplacental unit ***(Paesano et al., 2010).***

ID and IDA are still a major health problem in pregnant women. To cure ID and IDA, iron supplements are routinely prescribed. The preferred treatment of ID/IDA, consisting of oral administration of iron as ferrous sulphate, often fails to exert significant effects on hypoferremia and may also cause adverse effects ***(Paesano et al., 2010).***

The World Health Organization (WHO) defines anemia in pregnancy as a hemoglobin (Hb) concentration of < 11 g/dl. Iron deficiency anemia (IDA) is the most common type of anemia in pregnancy. The iron content of the body is normally kept constant by regulating the amount absorbed to balance the amount lost ***(WHO, 2011)***.

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)***.

Anemia is a common medical disorder affecting a lot of women in pregnancy in the developing countries ***(Sunitha et al., 2010)***.

Anemia is the second indirect obstetric cause of death after cardiac causes ***(Hamza, 2005)***.

Iron deficiency anemia is 1.8% in the 1st trimester, 8.2% in the 2nd trimester ***(Scholl, 2005)***, and 27.4% in the 3rd trimester. Hb levels of < 10g/dL are observed in up to 30% of women, with more sever anemia (Hb <8g/dL) seen in 10% ***(Mumtaz and Farooq, 2011)***.

Anemia may antedate conception, is often aggravated by pregnancy, and the accidents of labor may perpetuate it ***(Thirunavukkarasu and Bhandary, 2009)***.

Iron deficiency (ID) and iron deficiency anemia (IDA) are the most common iron disorders throughout the world. When iron requirement is higher than that absorbed, a negative iron balance occurs and iron store decrease. In ID without anemia, total serum iron concentration decrease,

while Hb levels remain normal. In IDA, the deficit of iron is so sever that iron stores are absent or unavailable resulting in abnormally low Hb and RBC. ID and IDA, particularly caused by increased iron requirements during pregnancy, represent a high risk for preterm delivery, fetal growth retardation, low birth weight, and inferior neonatal health ***(Scholl, 2005)***.

Anemia during pregnancy and its management remain an important issue in prenatal medicine. Correct diagnosis and treatment leads to effective management of fetal and maternal risk and improved prenatal outcome ***(Lynch, 2000; Christian, 2002)***.

Diet alone can't supply the 30-40 mg iron that is required for absorption of 4-6mg iron per day needed during the later stage of pregnancy so iron supplementation is strongly recommended for all females in developing countries ***(Jai, 2004)***.

Traditional therapeutic options of iron deficiency anemia during pregnancy were administration of oral iron shows lack of compliance and side effects and often limited intestinal absorption and bioavailability ***(Sefakis and Pharmakids, 1999)***.

The most commonly used treatment for ID and IDA currently consists of oral administration of iron as ferrous sulphate. However, ferrous sulphate administration often fails to exert any significant effects on these pregnancy-associated pathologies, and frequently causes several adverse effects (gastrointestinal discomfort, nausea, vomiting, diarrhoea, constipation). This is likely due to the poor bio-availability of inorganic iron requiring the administration of large quantity of ferrous sulphate. ***(Schumann et al., 2007).***

Lactoferrin is a multifunctional protein of the transferrin family. Lactoferrin is a globular glycoprotein with a molecular mass of about 80 kDa that is widely represented in various secretory fluids, such as milk, saliva, tears, and nasal secretions. Lactoferrin is also present in secondary granules of PMN and is secreted by some acinar cells. Lactoferrin can be purified from milk or produced recombinantly. Human colostrum (*"first milk"*) has the highest concentration, followed by human milk, then cow milk (150 mg/L). ***(Sánchez et al., 1992)***

It has been suggested that lactoferrin, a major protein in human milk, has multiple biological roles: an antimicrobial protein; an inhibitor of bacteria, viruses, and

yeasts; an immunostimulatory compound; a mitogenic protein; an anticancer agent; and an enhancer of iron absorption ***(Lönnerdal et al., 1995).***

AIM OF THE WORK

To compare the safety, tolerability, efficacy and hematological response of lactoferrin in treatment of iron deficiency anemia during pregnancy versus ferrous sulphate capsules.

Chapter (1):

ANEMIA

Definition of Anemia:

Anemia is a common medical disorder affecting a lot of women in pregnancy in the developing countries ***(Sunitha et al., 2010)***.

The definition of anemia varies by sex and age. The most common used definitions of anemia come from the centers for disease control and prevention (CDC) and the world health organization (WHO) ***(Killip et al., 2007)***.

C.D.C. defines anemia as hemoglobin (Hgb) or hematocrite (Hct) values less than the fifth percentile of the distribution of Hgb or Hct in a healthy reference population based on the stage of pregnancy. Classification derived from an iron supplemented population lists the following levels as anemia: Hgb (g/dL) and Hct (percentage) levels below 11g/dL and 33%, respectively, in the first trimester, 10.5g/dL and 32% respectively in the second trimester and 11g/dL and 33% respectively in the third trimester ***(Marhatta, 2007; Killip et al., 2007)***.

For assessment of the severity and magnitude of anemia the following categories were proposed:

- Mild anemia: (hemoglobin 9.0-10.9 g/dL)
- Moderate anemia: (Hemoglobin 7.0-8.9 g/dL).
- Sever anemia (Hemoglobin <7.0 g/dL)

(Broek et al., 2000; Adam, 2005)

Types of anemia with pregnancy:

1- Iron deficiency anemia:

Iron deficiency is thought to be the most common nutrient deficiency among pregnant women. Iron deficiency involves an insufficient supply of iron to the cells following depletion of the body's reserves ***(Juan et al., 2015).***

2- Anemia of chronic disease in pregnancy:

In over all population anemia of chronic disease is second in frequency to iron deficiency as a cause of anemia. Because of the tendency of patients with sever-systemic disease to prevent or delay pregnancy, anemia of chronic disease is relatively uncommon but not rare, among obstetric patients ***(Gardner et al., 2008)***.