Oral Administration of Bovine Lactoferrin Versus Iron Polymaltose for management of Iron Deficiency Anemia during Pregnancy: A Randomized Clinical Trial

Thesis

Submitted for Partial Fulfillment of the Master Degree in Obstetrics and Gynecology

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Dedication

To

My Husband (Gamal Ali Boraqta)

Who Helped Me a Lot and Pushed Me

Forward in Every Step of My Life

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List of Abbreviations

APCs : Antigen presenting cells

BCG : Bacille Calmette-Guerin

bLf : Bovine Lactoferrin

CD4 : Cluster of differentiation 4

CD8 : Cluster of differentiation 8

ConA : Concanavalin A

CYP1A2 : Cytochrome P450 1A2

ELISA : Enzyme-linked immunoassays kit

GMA : Granulocyte and monocyte adsorptive apheresis

HCP1 : Haem carrier protein 1

HCV : Hepatitis C virus

HIV : Human immunodeficiency virus

HS : heparin sulfate

Ht : Hematocrit

IBD : Inflammatory bowel disease

ID : Iron deficiency

IDA : Iron deficiency anemia

IFI : Invasive fungal infections

IPC : Iron(III)-hydroxide poly-maltose complex

IRIDA : Iron-refractory iron deficiency anemia

LC : Langerhan cells

LF : Lactotransferrin

LFA-1 : Leukocyte function associated antigen

LPS : Lipopolysaccharide

LR : Likelihood ratio

MCV : Mean red cell volume

MHC II : Major histocompatibility complex II

MRSA : Methicillin-resistant Staphylococcus aurous

NF-κB : Nuclear factor-kappa B

NK : Natural killer

NO : Nitric oxide

NTBI : Non-transferrin-bound serum iron

PMNs : Polymorph neuclear leukocytes

PRISMA : Preferred Reporting Items for Systematic

RBC : Red blood cell

RCT : Randomized clinical trial

RDW **:** Random distributed width

RMA : Reviews and Meta-Analyses

ROS : Reactive oxygen species

TIBC : Total iron binding capacity

UC : Ulcerative colitis

VLBW : Very low birth weight

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PROTOCOL OF A THESIS FOR PARTIAL FULFILMENT OF MASTER DEGREE IN OBSTETRICS & GYNAECOLOGY

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What is already known on this subject? AND What does this study add?
Iron deficiency anemia (IDA) caused by increased iron requirements during pregnancy, represents a high risk for preterm delivery, fetal growth retardation, and low birth weight. Oral iron poly maltose for IDA in pregnancy often fails to increase hematological parameters, causes adverse effects and increases inflammation. Recently, many researchers are studying safety and efficacy of oral administration of bovine lactoferrin (bLf) in pregnant women suffering from IDA.

1.INTRODUCTION:

Anemia has a significant impact on the health of the fetus as well as that of the mother **(Lee and Okam, 2011)**. It impairs the oxygen delivery through the placenta to the fetus and interferes with the normal intrauterine growth, leading to fetal loss and prenatal deaths. Anemia is associated with increased preterm labor (28.2%), preeclampsia (31.2%), and maternal sepsis (**Rezk et al., 2015**).

Pregnancy anemia is defined as a decrease in the level of plasmatic hemoglobin below 11 g/dL in the first and third trimester 10.5 g/dL in the second trimester **(Breymann et al., 2015)**. Up to 70% of the total body iron is found in hemoglobin, while the remaining 30% is found in ferritin, hemosiderin, and myoglobin or in other iron-binding proteins **(World Health Organization criteria, 2011)**.

Iron deficiency anemia (IDA) is the condition in which there is anemia due to a lack of iron. IDA develops when available iron is insufficient to support normal red cell production and is the most common type of anemia **(Kochhar et al., 2013)**.

In pregnancy, iron deficiency (ID) and iron deficiency anemia (IDA) represent factors that increase maternal, fetal and neonatal mortality and morbidity **(Horowitz et al., 2013).**Early diagnosis and correct treatment are mandatory in order to reduce both maternal, as well as fetal risks **(Paesano et al., 2010)**.

Lactoferrin (lactotransferrin) LF is a non-haem iron-binding protein, and a member of a transferrin family, which includes serum transferrin, ovotransferrin, melanotransferrin and the inhibitor of carbonic anhydrase (**Paesano et al., 2006)**, it is belonging to the proteins that are capable of binding and transferring Fe 3+ ions. In humans, lactoferrin gene is located on the third chromosome in the locus 3q21-q23 **(Rodriguez et al., 2005)**.

LF was first isolated by Sorensen and Sorensen from bovine milk in 1939. In 1960 it was determined to be the main iron binding protein in human milk. The molecular structure and amino acid sequence of human lactoferrin were discovered in 1984. Lactoferrin was then classified as a member of the transferrin family, due to its 60% sequence identity with serum transferrin **(Adlerova et al., 2008)**.

LF is produced by mucosal epithelial cells in various mammalian species, including human. Subsequent research identified lactoferrin in secretions from exocrine glands and in specific granules of neutrophils. Neutrophils after degranulation were observed to be the main source of

lactoferrin in blood plasma, lactoferrin has an extensive variety of biological functions, many of which do not appear to be connected with its iron binding ability **(Brock, 2002).**

The oral route is the first choice to replace iron stores as this allows the normal mechanism of absorption to be used, in addition to being an inexpensive and effective treatment **(Sharma et al., 2004).** Side effects of oral iron therapy are a common problem in the treatment of patients with iron deficiency **(Ragip et al., 2005)**. Gastrointestinal disturbances such as nausea, heartburn, pain, constipation, and diarrhea are the most commonly reported side effects, irrespective of the type of iron preparation. Gastrointestinal adverse effects and poor compliance with oral iron was up to 30% in previous studies (**Rezk et al., 2015**).
This study was conducted to evaluate the efficacy, safety and acceptability of lactoferrin in comparison to iron poly maltose for management of IDA during pregnancy.

2.AIM :

This study aim to assess the efficacy of oral lactoferrin, in management of iron deficiency anemia compared to iron poly maltose during pregnancy.

Research hypothesis:

In pregnant women with IDA, lactoferrin may be effective as iron poly maltose in management of this iron deficiency anemia.

Research question:

In pregnant women with IDA does lactoferrin, effective or treat this anemia as iron poly maltose?

3.METHODOLOGY:

Patients and Methods

Study design: A Randomized clinical trial.

Study Setting: Ain Shams university Maternity Hospital.

Study Population: 96 pregnant women in mid-trimester attending the antenatal clinic and suffering from iron deficiency anemia.

Sample Size: A previous study reported that the mean ± SD total increase in hemoglobin was 2.28 ± 0.56 g/dl versus 1.16 ± 0.442 g/dl in women receiving lactoferrin or iron poly maltose, respectively. The incidence of side effects necessitating drug withdrawal was 6% versus 27% in either group, respectively ***(Rezk et al, 2015).***So, it is estimated that a sample size of 48 patients in either study group (total 96 patients) achieves a power of 80% (type 2 error, .20) to detect a statistically significant difference of 21% between the 2 groups as regards the incidence of side effects necessitating drug withdrawal using a two-sided chi-squared test with a confidence level of 95% (type 1 error, .05). This sample size would have a power exceeding 99.9% (type 2 error < .01) to detect a statistically significant difference of 1.12 g/dl as regards the total increase in hemoglobin using a two-sided unpaired t test with a confidence level exceeding 99% (type I error <.01) **(Levesque, 2007)** .

All patient will be distributed in 2groups:

Group A: 48 pregnant women with iron deficiency anemia will received oral lactoferrin 100mg sachets (Pravotin, HYGINT, Egypt)before meals since15minutes twice daily for 8weeks.