Lactoferrin Versus Ferrous Sulphate for the Treatment of Iron Deficiency Anemia during Pregnancy (A Randomized Clinical Trial)

Thesis

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List of Abbreviations

Abb.	Full term
APC	*Activated Protein C*
BMI	*Body Mass Index*
BUN	*Blood urea nitrogen*
CBC	*Complete blood count*
CTG	*Cardio topography*
DMT	*Divalent metal transporter 1*
FDP	*Fibrin degradation products*
FG	*Ferric gluconate*
FHR	*Fetal heart rate*
Hb	*Hemoglobin*
IDA	*Iron deficiency anemia*
IS	*Iron sucrose*
IV	*Intravenous*
LMWID	*Low-molecular weight iron dextran*
MCHC	*Mean corpuscular haemaglobin concentration*
MCV	*Mean Cell Volume*
PBF	*Peripheral blood film*
PCV	*Packed cell volume*
RBCs	*Red blood cells*
TAT	*Thrombin–antithrombin complexes*
WBC	*White blood cell*
WHO	*World Health Organization*

INTRODUCTION

Iron deficiency anemia (IDA) is the condition in which there is decrease in the number of red blood cells or the amount of hemoglobin in the blood. It is caused by insufficient dietary intake and absorption of iron, or iron loss from bleeding. Bleeding can be from a range of sources such as the intestinal, uterine or urinary tract. IDA develops when available iron is insufficient to support normal red cell production and is the most common type of anemia ***(Stedman's Medical Dictionary, 2006).***

Anemia has a significant impact on the health of the fetus as well as that of the mother. It impairs the oxygen delivery through the placenta to the fetus and interferes with the normal intrauterine growth, leading to fetal loss and perinatal deaths. Anemia is associated with increased preterm labor (28.2%), preeclampsia (31.2%), and maternal sepsis ***(Sharma, 2008)***.

Iron homeostasis is tightly regulated through iron absorption, storage and transport ***(Bothwell, 2008).***

Iron absorption occurs in the proximal duodenum and includes in the apical site of enterocytes the reduction of ferric ions by a ferrireductase (duodenal cyto- chrome B, DCYTB), the apical uptake and the trans- cellular trafficking via divalent metal transporter 1 (DMT1), the storage into ferritin and finally,

the basolateral efflux by the iron transporter ferroportin ***(De Domenico et al., 2008).***

Ferroportin, the only known cellular iron exporter from tissues into blood, has been found in all cell types involved in iron export, including enterocytes, hepatocytes, placental cells ***(Donovan et al., 2005)*** and macrophages which recycle 20 mg of iron daily from lysed erythrocytes for erythropoiesis ***(Nemeth and Ganz, 2010).***

Recently, in the clinic, significant decreases of total serum iron and serum ferritin combined with increases of serum IL-6 have been observed in pregnant women ***(Paesano et al., 2009, 2010)*** and in haemodialysis patients ***(Provenzano et al., 2009)*** treated with oral ferrous sulfate.

These results strongly support the possibility that iron supplemented via ferrous sulfate is not exported from cells to circulation, but it is accumulated inside host cells resulting in inflammatory conditions ***(Baker and Baker, 2012).***

This evidence has raised serious questions regarding the safety/efficacy of oral ferrous sulfate, resulting in new approaches for treating ID and IDA and avoiding toxicities associated with iron overload ***(Paesano et al., 2009, 2010).***

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, 2008).***

Lactoferrin (formerly known as lacto transferrin) is a glycoprotein, and a member of a transferrin family, thus belonging to those proteins capable of binding and transferring iron ***(Metz-Boutigue et al., 2005).***

Lactoferrin is a protein found in cow milk and human milk. Colostrum, the first milk produced after a baby is born, contains high levels of lactoferrin, about seven times the amount found in milk produced later on ***(Kochhar et al., 2013).***

Lactoferrin is also found in fluids in the eye, nose, respiratory tract, intestine, and elsewhere.

Lactoferrin is used for treating stomach and intestinal ulcers, diarrhea, and hepatitis C. It is also used as an antioxidant and to protect against bacterial and viral infections ***(Donovan et al., 2005).***

Other uses include stimulating the immune system, preventing tissue damage related to aging, promoting healthy intestinal bacteria, preventing cancer, and regulating the way the body processes iron. Some researchers suggest Lactoferrin might play a role in solving global health problems such as iron deficiency and severe diarrhea ***(Paesano et al., 2009).***

It also seems to protect against bacterial infection, possibly by preventing the growth of bacteria by depriving them of essential nutrients or by killing bacteria by destroying their cell walls. The lactoferrin contained in mother's milk is credited with helping to protect breast-fed infants against bacterial infections ***(Sharma and Jain, 2014).***

Lactoferrin also seems to be involved with regulation of bone marrow function (myelopoiesis), and it seems to be able to boost the body's defense (immune) system. Lactoferrin is a multifunctional protein exhibiting both dependent and independent biological activity based upon its iron binding capacity ***(Valenti and Antonini, 2005).***

Lactoferrin (Lf) is a 78-80 kDa single chain iron binding glycoprotein, belonging to the transferrin family, found in high concentrations in human and other mammals milk, in most exocrine secretions and in secondary granules of polimorphonucleates (PMN), able to reversibly chelate two Fe(III) ions per molecule with two times higher affinity than serum transferrin. This innate iron-binding protein possesses antibacterial, antiviral, antimycotic, antiparasitic, antineoplastic, anti-inflamatory and immunomodulatory activities, regulates the intestinal absorption of iron, promotes the growth of the intestinal cells and regulates myelopoiesis ***(Steele et al., 2005).***

Its actions are mediated by specific receptors, by direct effect on the cellular membrane wall, competition for the iron

ions or through its enzymatic function, only to mention few mechanisms through which it realizes all these activities. Its proprieties are facilitated by its capacity of maintaining the iron bound in low pH environment, as well as the ability to bind to other substances, such as lipopolysaccharides, heparin, glycosaminoglycans, DNA, oxalates, carboxylates, or other metallic ions (Al3+, Ga3+, Mn3+, Co3+, Cu2+, Zn2+) ***(Sharma and Shankar, 2014).***

A previous study was published in April 2010, about (Lactoferrin efficacy versus ferrous sulfate in curing iron deficiency and iron deficiency anemia in pregnant women) and found that lactoferrin represent an extremely valid natural drug which, without any adverse effects, prevents and cures ID and IDA more effectively than ferrous sulfate.

Aim of the Work

The study aims to compare the efficacy and the safety of Lactoferrin versus ferrous sulphate for the treatment of iron deficiency anemia during pregnancy.

Chapter One

PHYSIOLOGICAL CHANGES IN HEMATOLOGICAL PARAMETERS DURING PREGNANCY

Pregnancy is a state characterized by many physiological hematological changes, which may appear to be pathological in the non-pregnant state. The review highlights most of these changes along with the scientific basis for the same, as per the current knowledge, with a special reference to the red blood and white blood cells, platelets and hemostatic profile.

Red blood cell

During pregnancy, the total blood volume increases by about 1.5 liters, mainly to supply the demands of the new vascular bed and to compensate for blood loss occurring at delivery. Of this, around one liter of blood is contained within the uterus and maternal blood spaces of the placenta. Increase in blood volume is, therefore, more marked in multiple pregnancies and in iron deficient states. Expansion of plasma volume occurs by 10–15 % at 6–12 weeks of gestation. During pregnancy, plasma renin activity tends to increase and atrial natriuretic peptide levels tend to reduce, though slightly. This suggests that, in pregnant state, the elevation in plasma volume is in response to an underfilled vascular system resulting from systemic vasodilatation and increase in vascular capacitance, rather than actual blood volume expansion, which would produce the opposite hormonal profile instead (i.e., low plasma renin and elevated atrial natriuretic peptide levels) ***(Ramsay, 2010).***

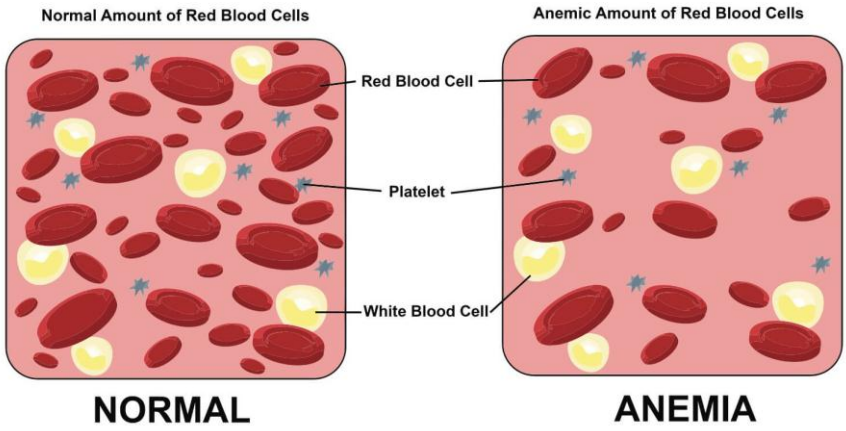

Figure (1): Red blood cells.

Red cell mass (driven by an increase in maternal erythropoietin production) also increases, but relatively less, compared with the increase in plasma volume, the net result being a dip in hemoglobin concentration. Thus, there is dilutional anemia. The drop in hemoglobin is typically by 1–2 g/dL by the late second trimester and stabilizes thereafter in the third trimester, when there is a reduction in maternal plasma volume (owing to an increase in levels of atrial natriuretic peptide). Women who take iron supplements have less pronounced changes in hemoglobin, as they increase their red cell mass in a more proportionate manner than those not on hematinic supplements. The red blood cell indices change little in pregnancy. However, there is a small increase in mean corpuscular volume (MCV), of an average of 4 fl in an iron-replete woman, which reaches a maximum at 30–35 weeks gestation and does not suggest any deficiency of vitamins B12 and folate. Increased production of RBCs to meet the demands of pregnancy, reasonably explains why there is an increased