Efficacy of Weekly versus Daily Antenatal Oral Iron Supplementation in Preventing Anemia during Pregnancy

Thesis

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Submitted by

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List of Abbreviations

Abb.	Full term
APC	*Activated protein C*
CRH	*Corticotropin releasing hormone*
dL	*Deciliter*
FDPs	*Fibrin degradation products*
Fe	*Iron*
fL	*Femtoliters (**fL**, or 10^{-15}L)*
Hb	*Hemoglobin*
Hct	*Hematocrit*
HIV	*Human immunodeficiency virus*
ID	*Iron deficiency*
IDA	*Iron deficiency anemia*
IUGR	*Intrauterine growth retardation*
MCV	*Mean corpuscular volume*
PGE2	*Prostaglandin E2*
RBC	*Red Blood Cells*
SF	*Serum ferritin*
SGA	*Small for gestational age neonates*
STfR	*Transferrin receptor*
TAT	*Thrombin–antithrombin complexes*
TSAT	*Transferrin saturation*

INTRODUCTION

Anemia is the most frequent physiologic problem in the world throughout the life of women. It is defined as the reduction in absolute number of circulating red blood cells (RBCs), indirectly measured by a reduction in hemoglobin (Hb) concentration, hematocrit (Hct) or RBC count. It is serious condition in poor resources countries. The most common causes of anemia are iron deficiencies which accounts for 75% of all kinds of anemia in pregnancy. Other causes include poor nutrition, micronutrients deficiencies including folic acid, vitamin A and vitamin B12.

Diseases like malaria, hookworm infestation, schistosomiasis, infection by HIV (human immunodeficiency virus) and genetically inherited hemoglobinopathies like thalassemia are all among the causes of anemia ***(Di Renzo et al., 2015).***

During pregnancy iron deficiency anemia is relatively common due to increased demands of iron and many women start pregnancy with decreased poor stores. Depending on the severity and duration of anemia and the stage of gestation, there could be different adverse effects including low birth weight and preterm delivery. Also it can be one of the major causes of the postpartum blood loss so it affects the women's health even after delivery. In consequent pregnancies it can lead to serious outcomes.

Beyond iron deficiency, a lack of other micronutrients can occur during pregnancy, influencing fetal–maternal outcome. For instance, folic acid depletion can increase risk of neural tube defects and calcium deficiency is associated with pre-eclampsia and growth restriction. Roughly 20–30% of women show a vitamin deficiency ***(Hovdenak and Haram 2012)***

Guarding against anemia during pregnancy improves the woman's condition and prevents more severe forms, which are strongly associated with increased risk of fetal and maternal mortality and morbidity. Iron and Folic acid supplementation is considered the standard prophylaxis against anemia in pregnancy. The frequency of intake is usually daily. Studies have suggested that weekly intake of Iron and folic acid supplementation can give the same results with better patient compliance and decreased coast ***(Muslimatun et al., 2001; Ridwan et al., 1996)***.

In the current study we are comparing the daily Iron and Folate intake to the weekly regimen as a prophylaxis of anemia during pregnancy.

It is thought that an intestinal epithelial cell becomes saturated with a single oral dose of iron, resulting in reduced iron absorption. Therefore, as intestinal cell turnover occurs every five to six days, if oral supplements are administered weekly, new intestinal epithelial cells would be exposed to each

subsequent dose, resulting in improved iron absorption. Weekly supplements have been shown to produce similar maternal and infant outcomes as daily supplements. Furthermore it is known to reduce the risk of the undesirable high levels of iron in mid and late pregnancy.

Intermittent oral iron supplementation may also reduce peroxidase and free radical mediated oxidative stress that damages the intestinal mucosa resulting in the unpleasant gastrointestinal side effects associated with daily oral iron supplements.

Therefore, weekly regimens may be more acceptable to women and increase their compliance ***(Goonewardene and Senadheera, 2018).***

Iron consumption for pregnant women is undesirable, because of the side effects. The probable cause is the effect of oxidative stress of high doses of Iron, which leads to gastrointestinal intolerance.

As gut mucosal turnover rates is about three days, administering iron during these days may lead to lower iron absorption. Periodic iron supplementation may let the mucosa to heal and gets better iron absorption, previous studies reported, continuous administration of oral iron impairs the absorption of a subsequent iron dose, however, intermittent supplementation programs have been shown to increase the risk

of mild anemia at term, especially in communities where the prevalence of anemia and iron deficiency is relatively high like most of developing countries ***(Bouzari, 2011)***.

The reduction of gastrointestinal side effects per se may not improve compliance, and other strategies may be required to improve compliance in addition to the effectiveness of antenatal oral iron supplementation programs.

As Overtreatment should be avoided as it may increase risks (preterm delivery, gestational diabetes mellitus, IUGR) when maternal iron stores are normal or overloaded, so we must keep balance of iron during pregnancy to avoid undesirable effects of both iron deficiency anemia and iron overload as both can cause hazardous outcomes on pregnant mothers and fetuses ***(Hovdenak and Haram, 2012)***.

Aim of the Work

The study aims to compare the effectiveness of daily versus weekly supplementation of Iron and folic acid in prophylaxis of anemia in non-anemic pregnant women.

Study hypothesis:

In non-anemic pregnant women weekly antenatal oral iron and folate supplementation may be similar to daily regimens in preventing iron deficiency anemia during third trimester

Study Question:

Does weekly antenatal oral iron and folate supplementation has similar effect in preventing iron deficiency anemia as daily regimen in third trimester in non-anemic pregnant women?

Chapter 1

PHYSIOLOGICAL CHANGES IN HEMATOLOGICAL PARAMETERS DURING PREGNANCY

In pregnancy many physiological hematological changes are happening, which may appear to be pathological in non-pregnant state. this review highlights most of these changes along with the scientific basis trying to explain why these changes are important during pregnancy, with a special reference to the red blood cells, white blood cells, platelets and hemostatic profile.

Red Blood Cells:

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. Around one liter of blood of this 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. Plasma renin activity tends to increase during pregnancy and atrial natriuretic peptide levels tend to reduce, so in pregnant state, the elevation in plasma volume is in response to an under filled 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). 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 MCV (due to a higher proportion of young RBCs which are larger in size). However, MCV does not change significantly during pregnancy and a hemoglobin concentration less than 9.5 g/dL in association with a mean corpuscular volume less than 84 fl probably indicates co-existent iron deficiency or some other pathology. Post pregnancy, plasma volume decreases as a

result of diuresis, and the blood volume returns to non-pregnant values. Hemoglobin and hematocrit increase consequently. Plasma volume increases again two to five days later, possibly because of a rise in aldosterone secretion. So it takes at least 4–6 months post pregnancy, to restore the physiological dip in hemoglobin to the non-pregnant value ***(Levy et al., 2005)***.

White blood cells:

White blood cell count is increased in pregnancy with the lower limit of the reference range being typically 6,000/mm^3. Leukocytosis, occurring during pregnancy is due to the physiologic stress induced by the hormones of pregnancy. Neutrophils are the major type of leucocytes on differential counts. Immature forms as myelocytes and metamyelocytes may be found in the peripheral blood film of healthy women during pregnancy and do not have any pathological significance. They simply indicate adequate bone marrow response to an increased drive for erythropoesis occurring during pregnancy. Lymphocyte count decreases during pregnancy through the first and second trimesters and increases during the third trimester. There is an absolute monocytosis during pregnancy, especially in the first trimester, but decreases as gestation advances. Monocytes help in preventing fetal allograft rejection by infiltrating the decidual tissue (7th– 20th week of gestation) possibly, through PGE2 mediated immunosuppression. The monocyte to lymphocyte ratio is markedly increased in pregnancy. Eosinophil and basophil