Prophylactic Iron Supplementation in Pregnancy: A Controversial Issue

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Biochemistry Insights
Volume 10: 1–8

DOI: 10.1177/1178626417737738

ABSTRACT: In our world today, iron deficiency (ID) is the most frequent nutritional deficiency and it is being considered as an epidemic public health crisis. Women of reproductive age and infants are at particular risk of ID, especially in underdeveloped countries. During pregnancy, iron deficiency anemia is a specific risk factor associated with negative maternal and perinatal outcomes. Many countries have iron supplementation (IS) programs—as recommended by the World Health Organization—during pregnancy; however, IS clinical benefits and risks are unclear. This review aims to discuss the threats and benefits of routine IS on maternal and infant outcomes.

KEYWORDS: Iron supplementation, pregnancy, iron deficiency anemia

RECEIVED: November 25, 2016. **ACCEPTED:** September 25, 2017.

PEER REVIEW: Five peer reviewers contributed to the peer review report. Reviewers' reports totaled 597 words, excluding any confidential comments to the academic editor.

TYPE: Review

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Introduction

Nutritional iron deficiency (ID) is the most widespread nutritional deficiency disorder, afflicting more than 2 billion people worldwide. Although pregnant women and infants from developing countries are at higher risk, it frequently occurs not only in underdevelopment countries but also in developed ones.[1,2]

Although ID is the major cause of anemia in pregnancy and it is the world's most common nutritional deficiency, infection, genetic factors, hypovitaminosis (A, B_{12}, and folate), and other dietary deficiencies are, similarly, frequent causes of anemia in pregnancy.[3]

World Health Organization (WHO) data showed that anemia's global prevalence is at 14%. Iron deficiency anemia (IDA) in pregnant women has a prevalence of 17.4% in industrialized countries, whereas in underdeveloped countries, it goes close to 60%. Most of the anemic pregnant women were already anemic antecedent to conception.[2,3]

Iron deficiency anemia in women brings extensive consequences to the individual's health. Iron deficiency anemia leads to poor pregnancy outcomes, decreased educational performance, and reduced work capacity and productivity and other socioeconomic vulnerabilities. It is well established that the incidence of ID and IDA in infants born to mothers who are anemic is higher.[2,4]

Iron deficiency anemia usually presents with subtle signs and symptoms. It ought to be understood as a chronic and gradually progressing condition that despite several warnings and alerts campaigned by the WHO, it is habitually underestimated and untreated worldwide.[5–13]

Both ID and IDA in pregnant women are associated incremented risks of developing preeclampsia, low birth weight, prematurity, perinatal mortality, delayed fetal maturation, and irreversible compromise to infants' neurocognitive development and motor capacity.[4,14]

Animal model studies consistently evidenced that inadequate iron intake during pregnancy would lead to permanent changes in the offspring's brains (structure and function wise).[14]

This body of evidence initiates the idea that the prevention of IDA in pregnant women would lead to the prevention IDA in infancy and its severe repercussions.[3]

The prevention of ID and IDA in pregnancy in many countries is commonly done with routine iron supplementation (IS), once the iron obtained from diet usually does not reach the recommended daily intake levels.[3]

Most studies on IS focus on the maternal outcomes rather than the iron status of infants, and only a very few trials with long-term follow-up further than birth.[3,4]

Even though routine IS in pregnancy is widely practiced, its effects on both pregnancy and infants are uncertain, and currently, experts worldwide diverge on whether IS should be a routine during pregnancy.[2–4,14]

Iron Homeostasis: Body Distribution, Transport, Metabolism, and Regulation

Iron is a vital element. Highlighting its redox activity, it can be toxic for it catalyzes the formation of reactive oxygen species (ROS) in the organism. Thus, iron intake, transport, distribution, and storage are accurately organized to balance these double characteristics of essentiality and toxicity, and this physiological system is critical for normal body homeostasis.[15,16]

Distribution of Body Iron

A healthy adult human has 45 mg (in women) and 55 mg (in men) per kilogram of ideal body weight, which makes up nearly 3 to 5 g of iron. Nearly 2 g—a bit more than two-thirds—is trapped inside developing erythroid precursors and mature red blood cells (RBCs), combined to their hemoglobin.[16,17] The remaining third of iron in the body is stored inside reticuloendothelial macrophages (approximately 0.6 g) and in hepatocytes (approximately 1 g) combined to the major iron storage protein, ferritin.[15–17]

In lesser quantity, iron is found in myoglobin (approximately 0.3 g) within muscles and in other proteins and enzymes (approximately 8 mg).[15,16]

Iron Absorption and Transport

Dietary iron is absorbed mainly at the small intestine—duodenum and jejunum (specifically its proximal section). Because the body is effectively unable to excrete this element, the role of homeostasis lies with the regulation of the dietary absorption.[15,17–20]

Many phases are implicated, and a normal individual absorbs 1 to 2 mg of dietary iron daily. Iron balance is very close in normal conditions, as about 1 to 2 mg of iron is lost daily by epithelial and mucous cell desquamation.[15,17–20]

There are 2 forms of dietary iron and their absorption occurs underneath different mechanisms: heme iron (HI) and nonheme iron (NHI). Nonheme iron makes up for 90% of all dietary iron, and its absorption implicates the release of iron on its elementary form from digested products and its maintenance in a soluble form. This is acquired partly by the low pH of the stomach acid, which dissolves the inorganic iron and allows its reduction from Fe3+ to Fe2+ by ferric reductases on the apical surface of intestinal absorptive cells at the duodenum.[15,17–20]

Next, Fe2+ is transported by the divalent cation transporter 1 (DCT-1) across the intestinal epithelium in a proton-coupled mechanism. DCT-1 is not an iron-specific protein, and it also transports other divalent elements such as copper, zinc, and cobalt.[15,16,17]

Heme iron, which accounts for 10% of dietary iron, is transferred into the intestinal absorptive cells by a putative heme carrier protein 1 (HCP-1). HCP-1 is a protein found in the membrane of proximal intestine cells—where HI absorption is greater—and its identification has not yet been completed.[17–20]

Once inside in the intestinal absorptive cells, heme oxygenase metabolizes the dietary HI to release Fe2+, which follows the same metabolic pathway of the dietary NHI before leaving the enterocytes.[17]

Ferroportin 1 mediates the basolateral iron transport. After that, hephaestin—a multicopper oxidase enzymatic protein similar to plasma ceruloplasmin—oxidizes iron. Next, a strong iron chelating agent—plasma transferrin—binds to iron in a tight but reversible way to transport it to places where it will be used or stored.[17]

The transferrin-iron complex enters erythroid, immune, and hepatic cells through a process of clathrin-mediated endocytosis. Transferrin-iron complex accounts to in a human adult not more than 3 to 5 mg of iron; nonetheless, it still is considered the most kinetically active pool.[15,17]

Intestinal absorptive cells in senescence undertake phagocytosis by the mononuclear phagocytic system. Heme iron is metabolized by heme oxygenase, and iron is stashed as ferritin.[17]

Iron is released from macrophages and binds to transferrin, which transports it to the bone marrow, according to hematopoiesis requirements. Such "recycling" of this element is crucial for meeting all necessities (30 mg/d) for normal hematopoiesis.[17]

Regulation of Iron Homeostasis

Hepcidin (acronym for hepatic bactericidal protein) is a fundamental hormone that regulates iron and the gene that encodes it is the HAMP. It is produced by the hepatocytes and binds to ferroportin.[15,17–20]

The iron entrance into the circulation is regulated by hepcidin. Once hepcidin binds with ferroportin, it removes iron from the plasma and limits cellular iron absorption from enterocytes and iron release from the reticulum endothelial system.[15,17–20]

In situations that the levels of hepcidin are higher than normal—for instance, in hyperinflammatory situations—serum iron levels decrease. This occurs mainly because macrophages and liver cells trap the iron within them and also due to the decreased stomach iron absorption through cellular internalization of ferroportin. As a consequence of insufficient serum iron levels for erythropoiesis, anemia is developed.[15,17–20] In cases where the hepcidin levels are lower than normal, iron excess takes place because of the increased iron efflux, which is mediated by ferroportin from the mononuclear phagocytic system and increased enterocyte iron absorption, an example of such is hereditary hemochromatosis.[15,17–20]

In hepatocyte, a variety of systemic signals—body iron stores, erythropoiesis, hypoxia, and inflammation—modulate the expression of hepcidin.[15,21,22]

Recently, other pathways involved in hepcidin expression in this study are bone morphogenetic proteins/suppressor of mothers against decapentaplegic (BMP/SMAD), bone marrow–derived erythroferrone, and steroid hormone signaling through PGRMC1 (progesterone receptor membrane component 1).[15,21,22]

The synthesis of hepcidin in the liver increases in situations when levels of iron in the body are high. When hepcidin binds to the external segment of ferroportin, it triggers the upregulation of Janus kinase 2. Stimulation of Janus kinase 2 leads to a process that internalizes, ubiquitinates, and degrades the ferroportin, which decreases iron transference to the intravascular space.[23–25]

Erythroferrone is a protein hormone produced by erythroblasts that suppresses hepcidin expression, therefore, promoting iron transfer into circulation and increasing the amount of iron available for hemoglobin synthesis.[15]

Matriptase-2 and the SMAD signaling pathway are very important in hepcidin suppression by erythropoiesis, and it is possible that erythroferrone exerts its effects via this pathway as well.[15]

Iron-dependent regulation of hepcidin is mediated by the BMP/SMAD signaling pathway, with multiple studies indicating that BMP6 is the key BMP involved,[15,21] but recent studies in animal models have demonstrated that it is possible to stimulate the hepcidin expression even in the absence of BMP6. It has been suggested that other BMPs generate this regulation via an alternative pathway involving HFE (hemochromatosis protein) and TFR2 (transferrin receptor 2). These exciting findings must be confirmed in further studies.[15,22]

Hypoferremia, characteristic of infection and inflammation, is a process wherein proinflammatory cytokines stimulates the synthesis of hepcidin.[15,26]

Conversely, a recent mice model study showed that ferroportin can be reduced in response to inflammation even in the lack of hepcidin. The mycoplasma-derived molecule FSL1 decreased ferroportin messenger RNA and protein levels through a mechanism involving the TLR2/TLR6 heterodimer, with TLR6 seeming to be critical for this regulation. This direct action of microbe-derived molecules on ferroportin expression will possibly characterize an alternative route of protection for the body in response to infection, even though the real effect of this signaling pathway in vivo has yet to be studied in depth.[15,27]

The study describes a new pathway for the regulation of ferroportin which is independent of hepcidin. This, and other studies, shows that although hepcidin has a key part in regulating traffic and homeostasis of iron, other pathways also exist.

Metabolism of Iron in the Mitochondria

Once iron is delivered into cytoplasm, it can be either used in cellular processes or stored by a protein called poly r(C)-binding protein 1 (PCBP1) which transfers iron from the endosome to ferritin.[24,28]

Iron can also enter the mitochondria, as other molecules. They cross the mitochondrial outer membrane protein called *porin*, which is a large diameter voltage-dependent anion channel.[24,29]

Once iron is inside the mitochondria, it can be stored or used in biochemical processes. Two examples of important reactions that occur in the mitochondria and that iron is directly related are biogenesis of heme and iron-sulfur clusters. Iron-sulfur clusters are known to play an important role in various protein functions. Found in the mitochondria, cytosol, endoplasmic reticulum, and nucleus, they are fundamental to several cellular processes, such as the transportation of electrons, citric acid cycle, genetic regulation, and reduction-oxidation reaction of molecules.[24,30]

To get nontoxic iron levels inside the mitochondria, a strict control of the element influx, and its maintenance in bound form is necessary because it is in its ferrous (Fe^{2+}) form.[24] Inside the mitochondria, the iron storage is made through 2 proteins: *frataxin*—which is a bifunctional protein such as iron-responsive element-binding proteins—and *mitochondrial ferritin*.[24,30,31]

Iron Deficiency Anemia and Pregnancy

A normal human's dietary requirement of iron remains between 1 and 8 mg daily. However, increased iron intake is required to equilibrate the increased demand for this element (especially during growth, pregnancy, and lactation due to increased physiological necessity in these situations).[2,3]

Under normal conditions, maternal iron requirements during pregnancy include 300 to 350 mg for the development of the embryo and placentation, 500 mg for the increase in the mother's RBCs, and 250 mg for the blood loss during the child birth. After that, the iron necessity increments from 800 µg/d in the first trimester to 7500 µg/d in the last trimester of pregnancy.[32,33]

Consequently, the demand for iron regarding all stages of gestation and lactation is nearly 1 g. Hence, the iron intake from diet in gestation should be at least 27 mg and in lactation is 10 mg, instead of 1 to 8 mg in the general adult population.[2,3,34–36]

The average circadian dietary iron intake in occidental societies is at best one-fifth of the necessary. Consequently, pregnant women must use the iron stored within them, enhancing the chance of developing IDA.[33]

Nevertheless, mobilization of iron deposits and increased iron absorption occur during pregnancy, specifically when the woman begins pregnancy with an ID risk (serum ferritin <20 µg/L).[2]

This substantial improved need for iron is required to develop the fetus and also for maintaining the mother's blood volume. Furthermore, pregnant women are susceptible to iron loss during and after delivery.[2]

Therefore, it is essential that women initiate gestation with an appropriate iron status to avoid the risks produced by ID and IDA.

The Centers for Disease Control and Prevention (CDC) recommends that all pregnant women begin a 30 mg/d IS at the first prenatal visit, whereas the WHO suggests 60 mg/d for all pregnant women. However, British guidelines do not recommend IS routinely in normal gestation.[33,37–39]

In Brazil, we follow the recommendations for intermittent iron and folic acid supplementation in nonanemic pregnant women according to WHO guidelines.[40]

Diagnosing ID during Pregnancy

Because variations in normal maternal physiology may affect the endogenous markers for ID, diagnosing it may be problematic in the course of gestation.[33]

Hemoglobin and hematocrit levels

The WHO defines gestational anemia as a hematocrit of <33% and/or a hemoglobin of <11 g/dL or at any time during the pregnancy.[1,33,37]

As for the CDC, the parameters are delimited as a hematocrit less than 32% and/or a hemoglobin less than 10.5 g/dL during the second trimester of pregnancy and a hematocrit less than 33% and/or a hemoglobin less than 11 g/dL during the first and third trimesters.[2,33,41]

Maternal hemoglobin decreases during pregnancy because of hemodilution. Such phenomenon is called *physiologic anemia of pregnancy*. The plasma volume increases nearly 50% relative to the increase in RBC mass of 25%. If ID erythropoiesis is found, a more prominent physiologic anemia of pregnancy may occur, especially during the second and third trimesters of pregnancy.

In line for the considerable variation in hemoglobin level, it cannot be used as a single parameter to estimate iron status.[33,42]

Mean corpuscular volume

Mean corpuscular volume (MCV) is considered a good screening tool for IDA during pregnancy. A low MCV (MCV < 80 fL) has a high sensitivity, although it lacks specificity for IDA.[33] With an exception to places of the world where hemoglobinopathies are prevalent and may be associated with microcytosis (such as the β thalassemia trait). Iron tests—in particular, ferritin level—remain the surrogate marker for IDA.[2,43]

There is a physiologic increase in MCV due to increase in erythropoiesis during pregnancy which makes up for the decrease in MCV of ID. Thus, MCV as a ID marker alone is unreliable in gestation.[33,44]

Ferritin

In the absence of any active disease, ferritin reflects a trustworthy total iron in the body. Iron deficiency is marked with very low levels of such protein and is a very specific sign.[33]

Ferritin gradually decreases during gestation and its nadir occurs during the end of the third trimester, with an increase at 4 weeks prior birth. The lowest levels are close to 15 ng/mL in the absence of IS and 20 ng/mL with IS.[33,45]

Studies that correlate stainable marrow iron with serum ferritin indicate that the 12 ng/mL limit of ferritin levels has a sensitivity of 25% for identifying ID.[46] Contrastingly, a threshold of <30 ng/mL is 92% sensitive and 98% specific for detecting ID.[46] Compared with serum iron, transferrin saturation, and erythrocyte protoporphyrin values, ferritin has a higher sensitivity and specificity for ID[47] and is the best marker for ID in gestation when decreased.

Except in hyperinflammatory situations, ferritin levels >100 ng/mL show sufficient iron storage and a low chance of IDA.[33,48–50]

In summary, ID can be categorized in pregnancy according to the serum ferritin levels: severe ID if ferritin is less than 30 ng/mL and mild-moderate ID if ferritin is less than 100 ng/mL and more than 30 ng/mL.[2,43]

Iron, transferrin, and transferrin saturation

The seric levels of iron comprise both the recycled iron from macrophages and the ingested dietary iron. It varies within the day, being higher in the morning and lower at night. Also, the ingestion of food influences the iron seric levels. Hence, it is impossible to determine a specific value as diagnostic of ID.[33,51]

The levels of seric iron are more exact if measured after an overnight fasting. Total iron-binding capacity (TIBC) and transferrin levels are higher in ID. Inflammatory states, chronic infections, malignant neoplasia, hepatopathy, nephrotic syndrome, and malnutrition can decrease TIBC levels, whereas gestation can increase its levels if ID is absent.[33,44]

Plasma transferrin saturation is the ratio of plasma iron to transferrin. A saturation of <15% implies an insufficient amount of iron due to a decreased quantity of iron in the body (ID) or because of anemia or inflammation, which traps the iron inside macrophages.[33,52]

Soluble transferrin receptor

The soluble transferrin receptor (sTfR) is a section of the transferrin membrane receptor. In ID, the formation of transferrin receptors and sTfR is increased.[33,53] Unlike TIBC and ferritin, the concentration of sTfR is not altered by inflammatory states.[24] A meta-analysis of 10 studies regarding sTfR determined that the test was 86% sensitive and 75% specific.

Still, the test is not yet standardized and cannot be used as a tool in routine diagnosis of IDA.[33,54,55]

Hepcidin

The iron bioavailability is regulated by hepcidin. It is considered the master regulatory protein. Its levels lower as gestation evolves, reaching the nadir in the last trimester.[33,5]

Pregnant women with undetectable serum hepcidin transfer more maternally ingested iron to their fetus than women with detectable hepcidin, indicating that maternal hepcidin in part determines the iron bioavailability to the fetus.[33,56]

Hepcidin is currently being evaluated as a biomarker in pregnancy.[33,57]

In summary, hemoglobin, percent of transferrin saturation, and plasma ferritin are acceptable for assessing iron status in most of the pregnant women, and the association of anemia and ferritin <15 to 30 µg/L is diagnostic of IDA.[33,37]

IS in Pregnancy

In many developed countries, the routine is that during pregnancy, women are advised to take iron supplements of 30 to 60 mg/d. In some countries, such as Australia and the United Kingdom, the protocol is to screen and supplement only those with IDA.[14]

A Cochrane systematic review and an analysis made by the US Preventive Services Task Force (USPSTF) established that even though IS in gestation enhances the iron status of the

mother, there are still not enough data to determine how clinically advantageous this practice is. Particularly, the USPSTF highlighted the necessity to determine the long-term effects of IS on child development as an important area for research.[5,14]

Highlighting the outcomes of ID and IDA worldwide, especially to pregnant women, the WHO suggested weekly supplement of iron-folic acid to avoid ID and IDA and its negative outcomes for the pregnant women and the child as gestation advances.[5,58]

The WHO recommends this weekly supplement that in sites where over one-fifth of women at reproductive age are anemic, and fortification programs of foods with iron and folic acid are improbable to be implemented within the next 2 years.[5–13]

Although the evidence show benefits of early IS in women with low iron storages, it is still contradictory whether IS should be started during pregnancy in those who do not have ID.[59,60] Some authors have observed that IS in that group has positive outcomes for the offspring. However, some studies showed that IS could lead to an iron overload (IOL), which increases ROS and induces hemoconcentration, and outcomes that have a negative influence on pregnant women and their offspring.[5,59–61]

A study was conducted in Adelaide, Australia, to examine the iron status of children between 6 months and 4 years of age whose mothers were randomly allocated to receive 20 mg of iron daily in the second half of the pregnancy or to be in the control group. The conclusion of this study was that the iron status of the subjects did not differ.[4]

In some places, such as the United States and France, pregnant women are advised to take IS of 30 to 60 mg/d routinely. However, in Australia and the United Kingdom, protocol is to screen and then treat those with IDA.[46]

Ten trials addressed the adverse events of routine IS during pregnancy.[46–49, 53,59,60,62–65] These studies had populations of 45 to 1164 subjects with an IS posology of 20 to 200 mg/d. They observed adverse effects, which were mild or moderate and impermanent, such as nausea, constipation, and diarrhea. Generally, no significant difference was observed when comparing IS and control groups. The rates of nausea ranged from close to 30% to a bit over 60% in both groups, and the vomiting rates were both a little over 10% to 41%. The similarity was also found in the rates of constipation (which was defined as 3 or less evacuations per week); it was 4% to 29% in IS and 1.6% to 28% in control groups. The evidence of IS and hypertension was inconsistent, ranging from 1.4% to 7.5% in IS and 0% to 9% in control groups. In summary, the USPSTF concluded with sufficient evidence that the adverse effects of supplementation are virtually inexistent (at worse, little).[46]

After screening 5209 titles, Imdad and Bhutta selected 30 studies for a review. They concluded that daily IS reduced in almost 70% the incidence of anemia and little over 65% reduction in IDA at the time of birth when compared with the control. The quality grade for these outcomes was that of a "moderate" level. Daily IS during pregnancy significantly reduced the incidence of low birth weight in the intervention group by 20% when compared with the control group. Iron supplementation during pregnancy is significantly beneficial in decreasing the incidence of anemia in pregnant women and low birth weight in the offspring.[66]

Based on these studies (probably in developing countries where the screening for IDA in pregnancy is very difficult), IS for all pregnant women could be considered a good strategy because it leads to a significant reduction in anemia incidences during pregnancy and, thus, plays a vital role in reducing maternal morbidity and mortality. A Cochrane review by Pena Rosas and Viteri also showed a significant reduction in incidences of IDA in pregnancy with IS.[66,67]

One of the threats of IS in pregnancy is the development of IOL in iron-replete women and in patients with diseases that lead to IOL, such as some hemoglobinopathies and hereditary hemochromatosis.[68]

Iron overload contributes to the exacerbation of normal apoptosis rates, largely due to its participation in the Fenton reaction and production of ROS. Mitochondria constitute the major intracellular source of ROS and the main target of attack by free radicals.[69]

Iron accumulation in the heart, liver, pancreas, and brain results in dysfunction of these organs. Free radical production due to IOL causes serious complicated side effects such as mental retardation, early neurological diseases (Alzheimer, multiple sclerosis, Huntington), delays in sexual maturity, impotence and infertility, cardiac dysfunction (arrhythmia, cardiomyopathy, hemosiderosis), liver cirrhosis, liver cancer and hepatitis, and metabolic dysfunction (diabetes, hypogonadism, thyroid disorders, parathyroid, and low level of adrenal glands). Others include arthritis, chronic fatigue, depression, hair loss, changes of skin color, abdominal pain, splenomegaly, venous thrombosis, and osteoporosis.[70]

In a case-controlled prospective longitudinal study on the maternal iron status during early to mid-pregnancy and subsequent gestational diabetes mellitus (GDM), 107 women with GDM and 214 controls were investigated using a comprehensive panel of conventional and novel iron biomarkers. In this study, hepcidin concentrations and serum ferritin levels were positively associated with GDM risk, suggesting that elevated iron stores may be involved in the development of GDM from as early as the first trimester. This finding raises potential concerns for the recommendation of routine IS among iron-replete pregnant women.[68]

More relevant studies are required to explore IOL, iron toxicity, and ROS impact in pregnancy, infant, and childhood development.

As stated before, even though the USPSTF found sufficient evidence that the negative effects of IS are little to none, it failed to find adequate data to support those IS benefits.

Reported benefits of IS were limited to intermediate outcomes (maternal hematologic indexes), and evidence of the benefits of IS on maternal and infant health outcomes was inadequate because of inconsistent results and underpowered studies. Given the inconsistency of the data and the lack of adequate studies on the effect of IS on the outcomes for the mother and the child, the USPSTF could not establish the balance of benefits and harms of IS.[46]

The Relationship between Iron Deficiency and Malaria

Malaria represents a serious risk to the fetuses' and pregnant women's health, and its prevention reduces maternal and neonatal mortality.[33,71,72–78]

Annually, 23 million pregnant women are exposed to malaria in endemic zones in Africa, especially to the form caused by the *Plasmodium falciparum*.[33,73]

Malaria's prevalence is higher among pregnant when compared with nonpregnant women. When contracted at gestation, it increases the mother's risk of developing anemia. Fetal infection and congenital malaria are associated with low birth weight and increased infant mortality.[33,79]

The WHO suggests treating malaria intermittently and preventively during gestation, with 3 or more doses of sulfadoxinepyrimethamine during the second and third trimesters, along with the usage of mosquito nets treated with insecticide for pregnant women in areas with medium and high malaria prevalence.[33,72]

Coincidentally, severe anemia is seen in places with very high malarial prevalence being commonly observed in young children and pregnant women.[33,73] In some endemic areas of Africa, malarial anemia afflicts 60% to 80% of all pregnant women.[33,74]

The malarial anemia's pathogenesis comprises the hemolysis of erythrocytes (with or without the parasite), sequestration of erythrocytes at the spleen and liver, direct myelosuppression, and ineffective erythropoiesis.[33,80]

The correlation concerning ID and malaria is an area of intense study because the 2 often co-exist. Studies in vitro demonstrated that *Plasmodium falciparum* infects erythrocytes from ID individuals fewer than erythrocytes from normal iron status humans. This result was supported by some clinical studies.[33,75,76,81]

In a research with nearly 450 Tanzanian pregnant women, it was found that the risk of placental malaria was lower in those with ID. In a research in Malawi, ID had a lower incidence among women with placental malaria than those without.[33,76,81] In a Cochrane systematic review with 35 randomized controlled trials, it was found that IS did not increase the cases of clinical malaria of children under IS living in areas with hyperendemic or holoendemic malaria transmission.[33,77] Unfortunately, pregnant women were not included in this review. There is controversy regarding the establishment of IS during pregnancy in malaria-endemic sites because there are worries that IS may exacerbate malaria and other infectious diseases. It has been shown that oral IS promotes the growth of bacteria ex vivo,[33,78] although 2 studies with pregnant women in malaria endemic countries showed that there is no significant difference in placental malaria and parasitemia between IS and control group.[33,76,81]

Conclusions

In conclusion, the present state of knowledge on IS for pregnant women is a debatable topic, which does have many arguments regarding the maternal and infant positive outcomes.

There is no doubt that to choose a side requires not only a deep understanding of how iron is metabolized but also both maternal and infant iron needs at different stages of pregnancy.

More randomized controlled trials are needed to clarify the real impact of prophylactic IS during pregnancy, especially in developing countries, taking into account culture, geography, social and economic status, lifestyle, nutritional status, and all issues that determine health conditions in pregnancy and infancy.

Therefore, consideration of ID and IDA in pregnancy must include the possible convergence of several causative factors.

For pregnant women in developing countries in situations where screening of IDA is not adequate and possible, we strongly recommend IS during pregnancy.

Authors Contributions

JRF and BKF conceived of and designed the experiments, analyzed the data, wrote the first draft of the manuscript, contributed to the writing of the manuscript, agree with manuscript results and conclusions, jointly developed the structure and arguments for the paper, made critical revisions and approved final version.

Disclosures and Ethics

As a requirement of publication, the authors have provided the publisher with a signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality, and (where applicable) protection of human and animal research subjects. The author has read and confirmed his agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that he has permission from rights holders to reproduce any copyrighted material.

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