

## The Etiology, Treatment and Effective Prevention of Iron Deficiency and Iron Deficiency Anemia in Women and Young Children Worldwide: A Review

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### Abstract

The current review identifies the root causes of the problem, assesses the clinical impact of iron deficiency and iron deficiency anemia with a specific focus on the condition in developing countries, and outlines the potential solutions to address the problem. Iron deficiency, the most common micronutrient deficiency in the world, results from an imbalance in the access and use of iron in the body. Although it is found in the developing and developed world, it predominantly affects women and children especially those living in poverty. The clinical effects of iron deficiency are profound: mild deficiency results in the loss of concentration in children – affecting their performance at school, and reduces work capacity in adults – affecting their ability to work a full week of work; more profound effects can seriously and permanently damage cognitive development and pose serious health issues in pregnancy and child birth. Despite substantial international efforts to address iron deficiency, the levels have continued to rise over the last decade. As we have the technology to solve this problem, the Copenhagen Consensus Centre (which meets every four years) has identified iron deficiency as the principal health challenge facing the world: the health and economic burden falling predominantly on women of reproductive age.

**Keywords:** Etiology; Iron deficiency; Women

### Introduction

Iron deficiency is the most common micronutrient deficiency in the world [1-3]. It is the only deficiency that is present in both the developing and the developed world [4-6] and arises when there is an imbalance of iron intake, iron stores and the normal recycling of iron that occurs within the body [7].

Iron comprises 5% of the world's crust and is critically involved in biological processes including:

1. The formation of heme proteins [e.g. hemoglobin which is vital in oxygenation of tissue][8]
2. Mononuclear proteins, such as superoxide dismutase, that are vital in limiting the production of damaging oxygen radicals [9]
3. The formation of diiron-carboxylate proteins such as ribonucleotide reductase and ferritin [10] that are essential for storing and transferring iron around the body; and [4] iron-sulphur proteins such as aconitase that are implicated in preventing metabolic conditions and diseases such as myopathies and exercise intolerance [11], Friedreich's ataxia [12] and some of the side-effects of diabetes [13].

The majority of iron in the body is present as hemoglobin located within erythrocytes [7]. Lack of iron, therefore, leads to a reduction in hemoglobin available for the red blood cells. Hence the most common clinical sign of more severe forms of iron deficiency manifests as iron deficiency anemia.

Despite the abundance of iron in the external environment and, not withstanding significant international effort to supplement dietary iron, iron deficiency remains a critical problem in humans [14,15].

Since 2004, the Copenhagen Consensus Centre has repeatedly called for action against iron deficiency as, not only the most significant health challenge facing the world, but also the micronutrient deficiency with the most profound negative impact on global GDP.

This review sets out to outline the normal homeostasis of iron in body and the factors that perturb this balance, the negative impacts of iron deficiency on women and child health and the effectiveness of potential solutions to alleviate iron deficiency with a particular focus on the challenges of addressing the condition in the developing world.

### Worldwide prevalence of iron deficiency and iron deficiency anemia

The World Health Organization [7] estimates that 30-50% of anemias in children are caused by iron deficiency. The health burden of iron deficiency is not distributed evenly across the world: the majority of cases are seen in the developing world [five-fold increase compared with the developed world] with equatorial and sub-equatorial regions experiencing the highest burden [Table 1]. Although developed countries are less affected, nevertheless significant populations in the developed world are at risk. For example, pregnant women, aboriginal populations, people living in poverty, and people with iron-poor diets [especially vegetarians and vegans] have a higher risk of suffering from iron deficiency and iron deficiency anemia in North America.

Region	Children years] [0-5	Non-pregnant women	Pregnant women
Africa	64.6%	44.4%	55.8%
Asia	47.7%	33.0%	41.6%

Europe	16.7%	15.2%	18.7%
Latin America	39.5%	23.5%	31.1%
North America	3.4%	7.6%	6.1%
Oceania	28.0%	20.2%	30.4%

**Table 1:** Prevalence of anemia in infants and young children [0-5 years of age] and women Adapted from McLean et al., 2009

## Iron metabolism in the body

Iron homeostasis in the body remains relatively stable. The majority of iron is bound in hemoglobin within red blood cells. There are three variables that determine the production of red blood cells. These include: tissue oxygenation; the turnover of red blood cells; and the loss of red blood cells through hemorrhage. Erythrocytes have a limited half-life with approximately 20 mL of senescent red blood cells are cleared daily from the circulation [16]. The iron from these cells [which represents about 20mg] is recycled for the production of new erythrocytes and very little iron is lost unless there is a change in the use or production or loss of the red blood cells.

Iron is the central component of hemoglobin [17]. It is derived, principally, from mono- or diferric transferrin in the plasma. This transferrin, in turn, is derived from three sources:

- [a] Dietary absorption which means that there must be adequate iron in the diet;
- [b] Macrophages that are in the process of recycling iron from senescent erythrocytes; and
- [c] Stores in the liver [ferritin].

## Clinical signs of iron deficiency

There is a considerable spectrum of signs and symptoms associated with iron deficiency and iron deficiency anemia. Hemoglobin levels are used as the clinical gold standard for defining iron deficiency anemia. There are differences in the reference levels of hemoglobin that vary according to age, race, sex and the source of blood used to determine the hemoglobin levels [18,19]. Portable diagnostic tests, such as the Hemocue™, are 95% accurate within 1-2 g/dL of reference values [20,21] are the most common tests used, particularly the field. There is vast panoply of symptoms of iron deficiency and iron deficiency anemia that are reported. Mild conditions include: poor mental performance and cold intolerance [22], fatigue and exercise intolerance [23-25], exercise-related dyspnea [26], glossitis and dysphagia [27,28] restless leg syndrome that is particularly noticeable in pregnancy [29,30], pica [31], reduced resistance to other diseases [32-36] and retardation of infant brain development [37]. More severe conditions include: severe anemia; low birth-weight infants that may be associated with fetal stunting [38], an increased incidence of pre-term labour [39], and badly affected women may even die in labour [38,40].

## Principal causes of iron deficiency and iron deficiency anemia

### Dietary iron deficiency of iron

Iron homeostasis in adults is dependent on the absorption of ~1mg iron a day. As approximately 10% of iron in the diet is normally

available for absorption, the diet should contain ~10mg of iron a day. Lack of iron in the diet per se may not be the sole cause of iron deficiency and iron deficiency anemia in the developed world [7]. It is nonetheless important as one of the contributing factors to the etiology of the condition. It has even been shown that there is sufficient iron in a strict vegan diet providing there is a sufficiently diverse diet available [41]. But, low or absent dietary iron, combined with other factors such as reproductive demands or concomitant disease may tip the balance of body iron. The lack of dietary iron can be severe. In some parts of South-East Asia, Wallace et al. and Ramsey reported that the 50% of the normal diets consumed by rural Cambodians completely lacked any iron [42,43].

### Pregnancy and lactation

Lee and Okam [44] estimate that ~1200mg iron are required from conception through to delivery to provide sufficient iron for fetal development and compensate for blood loss in delivery. In addition, maternal erythrocytes increase in mass by 180-250 mL during pregnancy, presumably as a response to increased demands to supply tissue oxygen. Failure to provide additional dietary iron at this time is accompanied by a reduced expansion of red blood cells mass [45] and can impact fetal development through a lack of tissue oxygenation. Maternal iron deficiency not only risks maternal health [38] but also has significant deleterious effects on the neonate. Deficits include: fetal anemia; reduced fetal brain maturation; and cognitive impairment [46]. Unless addressed in early neonatal life, these deficits are permanent [7].

Iron is also lost as lactoferrin in breast milk [47]. This loss compounds iron homeostatic challenges experienced by the mother and inadequate transfer of lactoferrin further compromises fetal iron status.

### Neonatal development

Sufficient iron is critical for neonatal development. Starting with inadequate iron stores from the mother augmented by failure to provide sufficient lactoferrin in breast milk or failure to breast-feed only compounds the challenges. Fetal iron stores are directly correlated with maternal iron stores [48]. Demands for total body iron are substantial during fetal growth: it is estimated that total body iron increases by 240 mg [49] during growth in the first year of life with 50% needed for hemoglobin production and 30% to be allocated to sufficient iron stores and demands continue to increase in the first 3000 days [50]. A lack of iron affects physical and cognitive development at a critical time of life leaving permanent impairments unless corrected.

### Blood loss

Acute bleeding, and chronic hemorrhage, from repeated, on-going menstruation and hookworm infestation can result in profound iron loss with a decrease in red blood cell mass and iron available for erythropoiesis [48]. However, excessive intestinal bleeding [51] and even repeated blood donation and nose bleeds can also result in iron loss [7,52].

### Malaria

As malaria is predominantly found in equatorial and sub-equatorial regions, malaria and iron deficiency co-exist. In fact, features of

malaria compound the challenges of iron deficiency: malaria provokes intravascular hemolysis and subsequent loss of hemoglobin in urine [53]; suppresses erythropoietin [54], reduces erythropoiesis [55]; and increases hepcidin expression [56], which restricts iron available for recycling.

### Hookworm

Despite international efforts to treat and prevent hookworm the burden of hookworm infestation remains a significant public health challenge in the developing world [55]. Individuals infected with hookworm experience profound intestinal bleeding [56,57]. In addition, there is a strong correlation between areas that are affected by malaria and those affected by hookworm [58]; together the negative impacts of these two diseases compound the challenges of maintaining adequate iron balance in the body.

### Alleviating iron deficiency

Prevention and control of iron deficiency is achieved by boosting iron levels in the diet. There are two forms of dietary iron:

1. Heme iron, derived from hemoglobin in blood, which is found in red meat, poultry and fish and;
2. Non-heme iron, which is found in plant foods such as lentils and beans. Although the body more readily absorbs heme iron, non-heme iron is usually used to supplement diets because it is more easily available and less expensive.

Four types of iron supplementation have been used to alleviate the condition. These include:

1. Iron fortification of food staples like flour, rice, and pasta [6,61]
2. Iron supplementation using oral tablets, often complemented with folic acid and other micronutrients that boost absorption of iron [62]
3. Adventitious sources of iron - providing iron from other sources. For example, cooking food in iron pots [63,64] so that iron leaches from the pots and is absorbed in the cooked food or adding an iron ingot to the cooking pot [65-68] and
4. Fortified iron powders [for example, "*Sprinkles*"] which are sprinkled onto daily breakfast food [6, 69].

Although all four supplementation options can be successful, access to these may be limited and, in the case of pills or powders there is a risk of toxicity if they are not used properly [70]. To be effective, the supplementation options must be consistently available but in many parts of the developing world, this is not possible. Either the supplementation options are not available, may not be available on a reliable and continuing basis, may be too expensive, or are culturally unacceptable so compliance levels are low. For example, fortified staples are not produced and distributed widely in many parts of the developing world, especially in rural areas. Iron pills or powders, and iron cooking pots are too expensive for people living below the United Nations definition of abject poverty [less than \$1.25 US per day]: both iron pills and powders cost approximately \$2.50 to \$4.00 per person per month. Even where pills and powders are provided by government or aid-agency programs, the compliance levels are low. Cooking in iron pots are too heavy and expensive, simply not practical and iron pots may not be available in many rural communities in the developing world. Recently, however Charles and colleagues published the results of using an alternate source of adventitious iron - an iron ingot that can be added to the cooking pot when preparing food or

sterilizing drinking water [66]. Unlike the heavy and expensive cast iron pots, the iron ingot is lightweight and not expensive: the ingot retails at \$5 and it lasts for at least five years and serves the whole family [GR Armstrong, personal observation] which is considerably less expensive than iron pills or powders. But the most important feature of the iron ingot is that it is cast in the shape of a fish that is culturally known as the shape of "luck" in Cambodian culture. The shape of the fish encouraged women to use the fish regularly and when they felt better, they reported that it was the "luck of the fish" - hence the name "Lucky Iron Fish". Used on a regular basis the *Lucky Iron Fish*<sup>™</sup> results in an increase in circulating and stored iron and halves the incidence of anemia in the villages where the fish has been tested [65-68]. Contrary to other treatments and preventives for iron deficiency and iron deficiency anemia, the compliance rate and the continued use of the fish after 12 months suggest that the *Lucky Iron Fish*<sup>™</sup> might offer an effective way of breaking the cycle of iron deficiency worldwide.

In addition, clinical interventions can also substantially affect iron status. For example, in 1954, Colozzi published a report showing that delayed clamping of the umbilical cord reduced fetal mortality [71]. Although not originally recognized, it is now known that a 5 minute delay in clamping results in the transfer of an additional ~150 mL of blood from the placental circulation [72]. Furthermore, it has been shown that placing the neonate on the mother's abdomen immediately after vaginal delivery and delaying clamping the cord until it stops pulsating significantly increases blood transfusion into the newborn [73]. Daniel and Weerakkody recommend that in any event where delayed clamping is precluded [for example, in cesarean section], simply clamping as close as possible to the placenta improved mortality and morbidity. In the same year, Piscane showed that the positive effects of the changes in clinical practice were to boost the newborn's iron levels in the first six months of pregnancy [74]. These observations have been confirmed in a number of other studies [75-77]. But simple changes in behaviour can also affect iron status. For example, in Cambodia it is not uncommon for women in the rural villages to cease eating meat altogether during pregnancy and in the perinatal period [42]: changing behaviours that increase access to bioavailable iron should also be part of any strategy to ensure adequate intake of iron especially among women of reproductive age.

### Conclusion

The ubiquitous and persistent nature of iron deficiency and iron deficiency anemia and its impacts on health and on economies worldwide make this condition a critical public health challenge. The fact that women, particularly those of reproductive age and children are the most exposed to this condition only compounds the importance of finding an adequate solution to the problem. Moreover, the condition is circular: women who are iron deficient give birth to and rear children who will be iron deficient and this cycle keeps people in poverty. Major strides have been made with fortification programs that have shown that they can be effective in communities able and willing to use fortified products. In addition, supplementation programs focused on at risk populations i.e., pregnant women, make a difference in regions where taking tablets is culturally understood and acceptable. Despite these efforts, iron deficiency rates continue to rise and it is important to find alternative solutions to enrich diets with bioavailable iron, especially in populations where access to a diverse diet is not possible for a variety of reasons.

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