STOP THE PRESSES

Summary on Adverse Effects of Excess Iron

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Introduction

India has made rapid economic progress, however most of this growth has been an inequitable progress leading to less than appreciable to minuscule changes on several health and nutritional status indicators, particularly anemia. prevalence of anemia among young women, pregnant women and children has seen little improvement in the last decade, with a rather small decline between 2005-06 to 2015-16(nfhs-3, nfhs-4). The etiology of anemia is multifactorial and often when high prevalence of anemia is seen, the most likely causal factor is nutritional deficiency of iron. Iron-deficiency anemia is a serious public-health concern not only in India but across most developing countries. It results in increased maternal mortality, morbidity and decreased child survival and is estimated to cause 591,000 perinatal deaths and 115,000 maternal deaths globally (1).

This huge burden affects not just the individual suffering from anemia but large populations and the country as a whole, therefore prevention and control of iron deficiency anemia among various vulnerable groups is of paramount importance. The World Health Organization (WHO) has also called on the governments to initiate programs for the development of assessment, advocacy, prevention, and control initiatives, in most countries, to reduce this global burden.

In countries where the burden of anemia is high apart from diversification of food, fortification and supplementation are other strategies to combat anemia. Caution also needs to be exercised while rolling out such programs as excess intakes of iron could have adverse effects.

Oral iron supplementation with FeSO4 and folic acid is a primary approach for the treatment of iron deficiency anemia (IDA) in places with high prevalence of IDA (2). In India, the National Iron+ Initiative (NIPI) is currently operational and is a lifelong iron supplementation approach from the age of 6 months onwards in all vulnerable target groups (6-59 months: Bi-weekly 20 mg elemental iron and 100 microgram (mcg) folic acid, 6 - 10 years: Weekly supplementation of 45 mg elemental iron and 400 mcg folic acid per child per day for children from 1st to 5th grade in Government & Government Aided schools, and at anganwadi centers for out of school children, 10-19 years: Weekly dose of 100 mg elemental iron and 500 mcg folic acid with biannual de-worming, 19> :Weekly dose of 100 mg elemental iron and 500 mcg of folic acid, Pregnant and lactating women: 100mg daily for 100 days, starting after the first trimester and repeated for 100 days post-partum).

NIPI is a country wide program and for it to be effective and successful, the compliance to the supplementation needs to be good. However, several studies on the earlier supplementation programs have all shown poor compliance among pregnant women at 64.7%, (3) and school children at 52.8%.

Adverse effects of excess iron on the gut

A major reason for poor compliance is adverse effects such as gastric irritation, nausea, epigastric discomfort and constipation(4).Studies have shown that the absorption of iron from iron supplements range from 2 to 13% and 5 to 28% in subjects with low iron stores (5) when consumed with and without food, respectively. In resource poor settings often unsafe water, sanitation and hygiene (WASH) promote the transmission of enteric pathogens causing WASH-related enteric infections ofdiarrheal diseases and may contribute to chronic inflammation (6)(7),a state of environmental enteric dysfunction (EED) occurs (8). These conditions are known to reduce the absorption of nutrients(9)(10) and may further blunt the absorption of iron causing even more supplemental iron to remain unabsorbed. In these contexts its largely unknown if the interplay of excess iron in the gut along with the poor environment further exacerbate the associated adverse outcomes.

Iron is one most reactive elements and the unabsorbed iron can turn to be toxic via the formation of reactive oxygen species (ROS), generated through the Fenton and Haber–Weiss reaction(11)(12). Of the ROS, one of the most reactive species known is the highly reactive hydroxyl ion OH−that reacts with any molecule within the immediate environment, resulting in a cascade of reactions in which lipids, proteins, and DNA may get damaged. Iron-induced oxidative damage in the intestine after oral ingestion of iron supplements may in part be responsible for these adverse gastrointestinal side effects. Supplementation of 100 mg Fe/d to mildly anaemic women resulted in an increase in oxidative stress(13)(14) and a 40% increase in free radical production in the faeces of human healthy volunteers who consumed iron supplements were seen(15).Invivo double lumen perfusion experiments show that even a single dose of oral ferrous sulfate (80 mg) induces oxidative damage in the small intestine in healthy volunteers(lipid peroxidation increases from 0.07 µM to 3.35 µM)(16) and alters gut permeabilitywhich inturn favors pathogenic bacteria to cross the intestinal barrier(17).

Studies done in rats and mice have shown that supplemental iron with ferrous sulfate resulted in iron-mediated oxidative stress in the small intestine causing a decrease in cell turnover, shortening of microvillus height, and partial or complete erosion of the microvilli in the duodenum (18). Epidemiological and animal studies have shown iron supplementation to promote colon tumorigenesis (19)(20)(21)(22) and increased inflammatory processes in rats with colitis (23)(24)(12).

Entry of iron into the body is highly regulated and since no mechanisms exist for the excretion of iron, homeostasis is only maintained by regulating iron absorption, and is upregulated in iron deficient state and downregulated when iron replete (25). Hepcidin is the key regulator of systemic iron balance in mammals (26) and iron supplementation has shown to acutely increase the circulating plasma hepcidin levels (27)(28)(29). A stable isotope study evaluated hepcidin response to varying doses of iron supplementation and time of administration, this study showed that daily dosing can reduce fractional iron absorption by as much as 35-45%, providing lower dosages of 40-80 mg Fe and an alternate day supplementation regimen favors better iron absorption (30). The dosage of iron supplementation in India is among the highest in the world and the policy directs pregnant and lactating women to consume 100mg daily for 90 days, although data is lacking on the appropriate dose and duration of administration among pregnant women, it is reasonable to expect hepcidin mediated reduction in iron absorption when iron is administered daily, leading to significant proportion of the supplemental iron to remain unabsorbed in the lumen of the intestine. The unabsorbed iron interacts with the gut bacteria adversely, altering the gut microbiome. In iron supplemented states a decrease in the abundances of beneficial barrier commensal gut bacteria (e.g., bifidobacteria and lactobacilli) and increase in the abundance of enterobacteria including enteropathogenic Escherichia coli is seen (31)(32). These changes also induce varying levels of gut inflammation mediated through the generation of ROS and host immune response to the presence of harmful pathogenic bacteria. These effects in part explain increased incidence of diarrhea in infants and children given iron supplements (33). Studies have also shown the gut microbiome changes that are caused due to iron supplementation especially during pregnancy can be transferred to the neonate during the birthing process (34) and thereby the effects of excess iron in the gut can lead to intergenerational effects that are yet to be well understood. Evidence to the plausible

intergenerational effects can be seen with the use of antibiotics in pregnancy that alters the maternal microbiome which in turn increase the risk of childhood obesity (35) and asthma (36) in the offspring. Disrupting the normative mother-to-newborn transfer of the microbiome due to iron supplementation and its effects in later life warrants detailed studies.

ROS that is generated by excess tissue iron loading may provoke changes in redox metabolism that has the potential to alter the pattern of DNA methylation and during pregnancy is also associated with pre-eclampsia and an elevated risk of premature rupture of membranes (37), as well as an elevated risk of metabolic syndrome in later life (38). Thus oxidative stress may contribute to the developmental origins of many forms of adult chronic disease in later life(39).

Adverse effects of excess iron on growth, fetal development and infection

Emerging evidence from human studies (infants and children) indicates that iron supplementation has a negative effect on linear growth and weight gain especially in iron replete states (0.14kg/month vs 0.25mgkg/month, iron therapy vs placebo group; p<0.001)(40)(41)(42). Similar adverse effects were seen when non anemic pregnant women were given iron supplements in the second trimester, a higher number of babies born (15.7%)were small for gestational age as compared to the control group (10.3%) and a higher incidence of hypertensive disorders in the mother was seen (43).Another study showed that pregnant women who consumed the recommended dose of supplemental iron during pregnancy had a higher risk of delivering low-birth-weight baby(44).Although the exact causal factors and mechanisms of alterations in growth outcomes has not been clearly understood, scientific evidence does support the fact that iron supplementation in iron replete states may adversely impact optimal height and weight gains.

Fetal hematopoiesis starts at about 2–3 weeks after fertilization and, initially, takes place in the yolk-sac. During fetal life, hematopoiesis gradually moves to the liver, and then after the development of the bones, at about 5–6 weeks takes place in the bone marrow (45).

Iron supplementation during pregnancy and resulting high maternal serum ferritin concentration is associated with reduced numbers of hematopoietic stem cells (HSCs) in cord blood (46). The differentiation of HSCs to erythropoietic progenitors is vital for fetal hemoglobin synthesis and iron uptake from transferrin is critical and at this very early stage, any form of oxidative stress leads to ineffective erythropoiesis (47). These findings along with data from in vitro studies show that high iron levels blocks early progenitor development and erythroblast differentiation primarily through ROS (48) suggesting that exposures to high iron during early life hematopoiesis might induce anemia. Similar negative effects due to ROS are seen on Mesenchymal stem/progenitor cell (MSPC) proliferation and differentiation (39). It has been shown that the iron loading of MSPCs in vitro increases cell proliferation but blocks their differentiation to osteogenic stem cells (49)(50). In contrast, ROSs appear to increase adipogenesis (51).

Iron influx into the brain is high during the postnatal period and studies done in rats have shown that exposure to high levels of iron postnatally result in functional deficits in spontaneous motor activity and habituation (52). Mouse pups given daily iron supplements at a level similar to that provided to human infants fed iron-fortified formula showed increased nigrostriatal iron, and displayed progressive mid-brain neurodegeneration (53). Similar adverse effects were seen in developmental outcomes in 10-y-old children who were given an iron-fortified formula postnatally (54).

The role of iron supplementation on infectious disease morbidity and mortality is unclear, data from two studies with adequate power to examine this relationship has been inconclusive. Studies done in Nepal show no benefits or adverse effects on iron and folic acid supplements in children (55), while a large study done in Zanzibar show iron and folic acid supplementation in malaria endemic regions with limited access to health care to have serious adverse events including 15% of the death attributed to routine iron supplementation(56). Insufficient data is available on iron supplementation in relation to HIV or tuberculosis outcomes for conclusions to be drawn about possible benefits or risks.

Conclusion

Available scientific evidence does show untargeted iron supplementation to have unfavorable consequences, that is yet to be fully understood. In the backdrop of these findings, untargeted iron supplementation runs the risk of doing more harm

than good and therefore targeted iron supplementation as a public health strategy may be more appropriate. Development of Low Dose Highly Bioavailable Iron formulations in a cost-effective format for use in supplementation programs is urgently needed. Well planned research in this direction is required to evaluate in diverse settings clinical and functional outcomes to low dose highly bioavailable iron supplementation to better understand efficacy and adverse effects if any in the both short and long term.

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