



Early Human Iron Equilibrium: A Review

Prameela Kannan Kutty^{1*}

¹*Department of Pediatrics, Faculty of Medicine and Defence Health, National Defence University of Malaysia, Kem Sungai Besi, Kuala Lumpur, Malaysia.*

Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

Article Information

DOI: 10.9734/JAMMR/2021/v33i730868

Editor(s):

(1) Dr. Sinan Ince, Afyon Kocatepe University , Turkey.

Reviewers:

(1) Farcas Anca Corina, University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca, Romania.

(2) Paolo Arosio, University of Brescia, Italy.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/66570>

Review Article

Received 12 January 2021

Accepted 16 March 2021

Published 26 March 2021

ABSTRACT

The biological equilibrium of iron, a potent, multifunctional micronutrient is a decisive factor in the holistic health of the mother and child. Iron dysequilibrium impairs organ function, effects growth and development and predisposes to a spectrum of disease states. This article revisits the homeostasis of body iron in early life as a sequential continuum from prenatal to early post- natal life ,then reviews, compares and attempts to integrate intra and early extra uterine events related to iron metabolism. The “adaptive evolutionary” mechanisms involved in iron homeostasis in early life such as the transfer of iron from the mother to the fetoplacental unit and from the lactating mammary glands into breastmilk are revisited as both organs support life during dynamic developmental stages of growth and differentiation. The checks and balances of iron metabolism in pregnancy also endow some iron to the fetoplacental unit, by actively transporting iron from the mother to the developing fetus. In early postnatal life the mechanisms involved in iron absorption are not yet fully mature, and other sources of iron such as transplacentally transferred iron and the iron stored from hemolysis of the rapidly decreasing red blood cell (RBC) mass contribute to early iron equilibrium. Additionally, although breastmilk is low in iron, the concept of active iron bioavailability in the breastfed infant provides utilizable iron. The lactating mammary glands may adopt unique features of iron metabolism adapted to the individual infant with the iron content in breastmilk largely, but not entirely, independent of maternal iron status. Early physiological iron equilibrium reflects essential homeostatic complexity, highlighting that exogenous iron, when required, must also be weighed for its benefits against its risks, as evident in the cautious homeostasis in our biological systems.

*Corresponding author: E-mail: prameela.kutty@yahoo.com;

Keywords: Iron; homeostasis; lactation; early life.

1. INTRODUCTION

Iron is an essential micronutrient in the body with crucial roles in the transport of oxygen growth, cellular respiration, energy production and other notable iron dependent processes [1]. Iron deficiency anemia is a public health menace of significant magnitude throughout the world and the main nutritional anemia amongst women of reproductive age and children [2]. While the prevalence of anemia among children aged 6–59 months was 42.6% globally, Africa and Southeast Asia were most critically affected [3]. Further highlighting health impact is that iron deficiency contributes to a whopping 86–93% of childhood anemias in some parts of the world [4].

Reviewing iron metabolism from in utero events must embrace fetomaternal transfer and the dynamics of lactational iron in the first six months of natural feeding. Revisiting early iron metabolism permits better public health appreciation of integrated events; those that contribute to anemia in early life such as maternal factors as well as infant feeding mode and duration [5].

The importance of iron in the growing child for physical and cognitive development cannot be overstated [6,7]. Synapses, neurotransmitters and myelination in the developing brain depend on iron containing proteins that impact brain-energy responses and neurocognition [8]. Pregnancy heightens risk for iron deficiency, as iron requirements could easily exceed intake [9], with impaired absorptive capacity or excessive iron losses compounding this. In pregnancy an index of suspicion of asymptomatic iron deficiency is necessary as subtle symptoms such as inadequate weight gain may signal its deficiency [9]. The tight-knit integration of maternal and child health is most evident in iron metabolism, as risk factors such as preterm birth or low birth weight which are important morbidities, are linked to maternal anemia [9].

Normally, daily iron absorption is much less than its requirements. RBCs contain iron in hemoglobin and their lysis provides the main iron pool for early homeostasis. The recycling of iron released by lysis of senescent RBCs provides iron that is taken up by splenic macrophages which then deliver iron into circulation [10]. Modulation of intestinal iron absorption, through maturation and development of iron homeostatic

processes, continue to maintain iron balances [10,11].

In the human body, iron exists convertably in ferrous and ferric oxidation states, and serves electrons in the electron transport chain reactions for metabolic energy [10]. Iron is largely bound to protein because free iron is perilous and is vied by disease-causing microbes. Specific factors in the neonate can further adversely influence iron homeostasis and predispose the infant to bacterial infections [6]. While iron deficiency is of great health impact, excess iron also causes adverse effects through pro-oxidative reactions, nutrient interactions [12] or the negative impact it can have on intestinal microbial pathogens that require iron for survival and proliferation, thus altering useful commensal microflora [10-13]. For instance, iron fortified foods of low bioavailability, when not completely absorbed generate reactive oxygen species whereas foods rich in antioxidants prevent this [12-13]. Free iron can impair physical growth and cognition; it also increases incidence of diarrheal illnesses and interacts with other trace elements such as copper and zinc with negative impact on health [13].

2. METHODOLOGY

Topics reviewed were prenatal, birth and postnatal factors that could influence iron metabolism and search words included headings related to all subtopics. The search word common to all subtopics were iron deficiency and iron deficiency anemia. Data from prenatal and relevant post-natal events was analysed, compared and integrated.

2.1 Publications Characteristics

Original articles, systematic reviews, meta-analyses, narrative reviews, experimental studies, prospective studies, retrospective studies and case reports were included. Excluded were letters to editor and publications in foreign language and unpublished papers. A total of 79 articles including a chapter from a standard paediatric textbook were chosen from the materials perused.

2.2 Topic Characteristics

Inclusion criteria on topics reviewed were prenatal events that influence iron metabolism in

pregnancy, in the fetus and placenta, factors that influence iron at birth and postnatal factors related to iron metabolism. Perusal also included iron, breastmilk and the lactating mammary gland.

One book chapter reviewed prenatal, natal and post-natal causes of iron deficiency and iron deficiency anemia.

Excluded were articles on iron deficiency due to major inherited or acquired maternal medical or surgical illnesses except for those relevant in the initial discussion overview, fetal chromosomal anomalies and inborn errors involving iron metabolism or iron storage.

3. DISCUSSION

3.1 Factors Impacting Iron Metabolism in Early Life

An overview of factors impacting iron metabolism at critical stages of development is essential here. Maternal health and social habits potentially affect fetal iron stores [14-20]. Normally, relative intrauterine hypoxia stimulates fetal erythropoiesis [17], and maternal iron stores are transferred to the fetus in late pregnancy; this results in a high RBC mass and high hemoglobin levels at birth [15-17]. Factors that affect both maternal and fetal health include maternal body mass index, maternal diabetes and birth weight z score [18]. Cumulative risk factors may worsen neonatal iron status [18].

Infants of diabetic mothers (IDM) may develop increased erythropoiesis with a limited iron supply leading to iron deficiency [18,19]. Maternal smoking causes low concentrations of iron markers in umbilical cord blood, with a subclinical fetal iron deficiency [20]. Adverse perinatal outcome of maternal iron deficiency include intrauterine growth restriction, prematurity, and low birth weight [9]; small-for-gestational-age neonates (weight below the 10th percentile for gestation), very-low-birth weight (weight below 1500 grams at birth) and preterm neonates [15-21]. In addition, a study also found that neonates who were large for gestational age (weight above the 90th percentile for gestation) born to women with comorbid obesity and diabetes had the worst iron profile, and this stresses the importance of identifying risk factors [18].

Transplacental haemorrhage which occurs in 5-15% of pregnancies, when severe, may lead to

clinically detectable anemia at birth [19]. Congenital hypoplastic anemias, congenital infections and congenital leukemias cause anemias in newborn infants. Chronic intrauterine blood loss, alpha thalassemia syndromes, immune and nonimmune hemolytic anemias are other predisposing factors. Blood loss due to frequent blood sampling, feto-placental hemorrhage, placental hemorrhage and umbilical cord haemorrhage are causes of anemia in the newborn [19]. Infants born through Caesarian section may have a lower hematocrit, while a two minute delay in clamping of the umbilical cord, can increase body iron stores with effects lasting up to 6 months of age [22].

Postnatally, the mode of feeding influences neonatal and infant iron profiles as breastfeeding, especially if for more than 6 months, without commencing iron rich foods can cause iron deficiency [23]. Male gender, independent of rapid growth or longer breastfeeding duration, also predisposes to iron deficiency [24]. At around 8-12 weeks in term infants and about 6 weeks in preterm infants, there is a physiological decline in the amount of iron in the body with haemoglobin levels at about 11g/dl in term 7-10g/dl in preterm infants [19]. The hemoglobin nadir is lower and occurs earlier in more premature infants [25]. A study reports that biochemical iron deficiency where serum iron and ferritin are low without clinical evidence occurred in 17% of screened neonates at birth and who were at risk of iron deficiency [16]. A significant percentage of between 25% up to 85% of preterm infants could manifest evidence suggestive of iron deficiency in infancy [21,25].

Lower birth weight and serum ferritin concentrations, a marker of body iron stores, are independently associated with iron depletion at 6 weeks of age [26]. As the preterm infant has a high growth velocity, there is greater depletion of tissue iron stores in them and this is most pronounced in the very premature infant linked to a rapid catch up growth [21,25].

A spectrum of social and psychological influences have the potential to cause iron deficiency. Women's education levels, household poverty, food insecurity due to insufficient resources for supplements or iron fortified foods and lack of knowledge about iron deficiency are important factors [27]. Social factors associated with common mental disorders in the antenatal clinic predispose to iron deficiency in mother and child

at every stage impacting prenatal, birth and post-natal outcome [27].

3.1.1 Changes in pregnancy

The physiological changes that occur in pregnancy are considered in context of iron homeostatic processes in the mother. Pregnancy increases basal oxygen consumption with changes in energy utilization by different organs including the fetoplacental unit. The highly vascular placenta with abundant mitochondria can consume up to about 1% of the basal metabolic rate of the pregnant woman [28,29]. Hemodynamic changes in pregnancy alter iron homeostasis through hormonal responses, iron absorptive processes and iron distribution [30-39]. The iron requirements in mid and late pregnancy are high and physiological demand for iron is three times greater during pregnancy, increasing in the second trimester with maximum iron requirement in the third trimester [33]. The plasma volume gradually increases in the first trimester and up to about 30 to 34 weeks [30], with erythropoietin increasing the red cell mass, early in pregnancy until delivery. In tandem with changes that occur in pregnancy, anemia by laboratory testing is reflected in a hemoglobin concentration of less than 110 g/l in the first trimester and 105 g/l in the second and third trimesters and less than 100 g/l in the postpartum period [34].

Body iron exists in different physiological forms, such as heme iron which is transported by heme carrier protein 1 (HCP1), an intestinal iron transporter, while non-heme iron in the ferric form is initially reduced to ferrous iron. This is done by enzymes such as duodenal cytochrome b (DCYTB) [35,36]. Iron is then transported into the enterocyte of the gastrointestinal tract by divalent metal transporter 1 (DMT1) [36]. Intracellular ferrous iron is transferred across the enterocyte by ferroportin (FPN), and is then oxidized to ferric iron by hephaestin (HEPH), a transmembrane multi-copper ferroxidase (MCF) with iron efflux from cells through the iron transporter, ferroportin 1 (FPN1) [35-38].

Iron absorbed from the gastrointestinal tract and iron released from the lysis of senescent RBCs and its recycling by splenic macrophages, is regulated by hepcidin [37], a key iron regulator hormone which is suppressed in pregnancy [32]. Hepcidin binds and degrades its receptor, ferroportin on the enterocytes and macrophages to exert its important action. The synthesis of

hepcidin is controlled by factors such as iron levels, infections and inflammation, anemia and erythropoietic activity [37], and the lower levels of maternal hepcidin increases supply of iron into the circulation as it enhances absorption of dietary iron and increases release of iron from stores [32].

Storage iron is as ferritin, while ferrous iron is oxidized by ceruloplasmin to ferric iron and incorporated into transferrin found in plasma [38]. Serum ferritin is a marker of body iron stores, but is influenced by inflammatory cytokines and other factors [33]. In pregnancy, serum ferritin concentrations gradually decrease in the third trimester due to the hemodilution and efficient iron mobilization from stores as hepcidin concentrations decrease during pregnancy [32,33]. Iron stores in pregnancy are assessed by serum ferritin and iron deficiency is reflected by a serum ferritin level of less than 30 ng/mL [33]. Due to these physiological changes, all pregnant women must receive adequate advice on iron rich diet, as iron deficiency is the most common cause of anemia in pregnancy and hemoglobin concentrations should be routinely measured [34].

3.1.2 The fetus and placental iron

The mother endows a fraction of her iron to the developing fetus through the placenta which is actively involved in this transfer [32], hence maternal iron transport to the placenta, is possibly modulated by fetal signals, as maternal liver stores of iron during pregnancy decrease significantly [39] and this impacts the fetus, the newborn and the infant [39,40]. As pregnancy progresses, increased placental blood flow, thinning of the syncytiotrophoblast and increased placental transferrin receptors are mechanisms that enhance the transfer of iron to the placenta and the fetus [41,42]. The placenta is rich in mitochondria and this potentially can produce reactive oxygen species (ROS), which increases the release of free iron. Hence the placenta plays an important dual function of mediating iron exchange [29] between the mother and the fetus as well as possessing defense mechanisms against free radical damage. [29,43]

The placenta retains some iron for its own function, and transports much more of it to the fetus in a unidirectional manner from mother to fetus only. Most of the iron transferred to the fetus, is bound to transferrin which is produced in increasing amounts during pregnancy,

especially during the third trimester, coinciding with the lowest maternal hepcidin expression [32,39]. However, maternal iron status does not seem to significantly impact the iron in her breastmilk [44].

The fetus produces erythropoietin the main hormone that stimulates erythropoiesis, in the liver, a function which then occurs in the kidneys [45]. During the third trimester of gestation, fetal red cell production is taken over from hepatic to marrow erythropoiesis [45,46]. However, fetomaternal conditions can impact this; maternal anemia, fetal growth restriction and intrauterine hypoxia can influence fetal erythropoietin production [30]. The fetus is able to modulate its own iron levels but with limited capacity as below a critical iron level, the maternal liver responds to the iron deficiency to attempt to restore its own concentrations of iron [39].

Most of the fetal iron is obtained in the last trimester of pregnancy, explaining why infants born before this time are iron deficient. Fetal capillaries are in close contact to the syncytiotrophoblast, separated only by fetal endothelium [29]. The placenta uptakes transferrin bound iron and non-transferrin bound iron. Placental uptake of transferrin bound iron is by the presence of the transferrin receptor 1. Ferrous iron, through the divalent metal transporter 1 (DMT1), or an alternate method, enters into the cytoplasm of the syncytiotrophoblast [31]. Iron that is not bound to transferrin from the maternal circulation may be transported by zinc and iron related protein 8 (ZIP8) or zinc and iron related protein 14 (ZIP14), expressed on the apical side of the syncytiotrophoblast [31].

Ferroportin transports iron out of the placenta while ceruloplasmin, zyklopen and hephaestin endow the fetal circulation with iron by trans-endothelial transfer [47]. Hpcidin may also be important in fetoplacental iron regulation, as when increased fetal iron transport occurs in the last trimester of pregnancy, the fetus synthesizes hepcidin, influencing placental iron equilibrium [47].

3.2 Iron and the Neonate

Iron transferred to the fetus and the various events that determine iron levels at birth are so important because these predict physical and neurological development for up to 2 years of life [40]. A study identified predictors of serum ferritin

and serum soluble transferrin receptor in healthy newborns and found that both these parameters correlated with important fetomaternal indices. For instance, cord serum ferritin was related to the cessation of smoking and the use of iron supplements during pregnancy (partial $r = -0.12$ and 0.16 ; $P < 0.05$ for both) while cord serum soluble transferrin receptor was linked to body mass index (BMI) in the first trimester, gestational age, and male gender (partial $r = 0.30$, 0.24 , and 0.19 , respectively; $P < 0.01$ for all) [40].

A significant fall in hemoglobin during the first 6 weeks of life due to RBC hemolysis [30,32], inkeeping with the oxygen rich extrauterine environment, and a fall in plasma erythropoietin levels occur [48]. In the term infant, hepcidin, the key iron regulator, increases significantly in early life, leading to a short period of hypoferrremia, perhaps as a defense against sepsis by iron utilising microbes, but this is followed by increases in iron and transferrin saturation by the end of the first month [47]. There is a 'physiologic anemia', recognised as normal, at around 3 months of age, in the term infant, when the full-term healthy infant is observed to have a body iron content proportionate to weight [49]. Whereas, premature infants experience a lower nadir of hematocrit with a normocytic, normochromic anemia coincident with low reticulocyte counts and Epo levels [50].

3.2.1 Iron and lactation

3.2.1.1 Milk iron

An average of about 1200mg of iron is required from conception to delivery for fetal development and to make up for delivery blood losses [51]. Some iron is also lost as lactoferrin in milk [52], with human breastmilk having low iron concentrations compared to maternal serum where colostrum iron concentrations are at about $0.8 \mu\text{g/mL}$ which then declines in mature milk to about $0.2\text{--}0.4 \mu\text{g/mL}$ [10, 53]. Unlike the iron transferred to the unborn fetus, iron concentrations in breast milk do not seem to be significantly dependent on maternal iron status or iron intake. A study shows that iron concentration at 9 months postpartum was not related to maternal mineral status which included iron [54] suggesting an active transport mechanism in the mammary gland [44,55]. However, others indicate that the quantity of iron during lactation may be influenced by maternal iron status during pregnancy [56].

Breastmilk contains abundant cell types [57] and milk epithelial cells may be an important source of milk iron [53,58]. Comparable to placental transport of iron, gene profiles suggest iron transport pathways in the lactating human epithelial cell [58], such as dimetal transporter 1 (DMT1), and ferroportin 1 (FPN1) [58,59], which, like concentrations of iron itself, decrease during lactation. Transport mechanisms may contribute to dynamic iron equilibrium in breastmilk from colostrum to mature milk, with peak iron levels in transitional milk followed by a steady decline [5], a scenario that cannot be emulated in formula milk. Transport mechanisms also support the notion that breastmilk iron is independent of maternal iron status and may explain why maternal iron supplementation does not increase breastmilk iron [54].

3.2.2 Breastmilk lactoferrin and iron

A multifunctional iron transport whey protein in breastmilk, lactoferrin, is produced and secreted by glandular epithelial cells in the mammary gland which depend on maternal weight during late pregnancy and maternal iron status [44]. Lactoferrin has efficient, dynamic antimicrobial potential [60]. Iron transport proteins are modulated by genes, responsible for the uptake and fate of iron, shielding the mammary gland and the breast fed infant against iron deficiencies and excesses [59]. Other receptors such as the transferrin receptors, as found in the placenta, may also play a role in iron uptake and release into milk [61].

Upon intracellular transport of milk iron, ferrous iron may be stored as ferritin or may be bound to iron-transport proteins. Iron bound lactoferrin, is incorporated into iron-containing enzymes, such as xanthine oxidase and secreted with the milk fat globule [44]. Levels of breastmilk iron and lactoferrin vary during a feed, influenced by the time of feeding, with foremilk and hindmilk differing in iron content [44,60], with milk iron decreasing as lactation progresses [52].

Breastmilk iron and lactoferrin were not found to be associated with maternal iron status. This is deduced as a fall in hemoglobin and serum ferritin in infants occurred regardless of whether the mother was anemic or not, correlating with reductions in breast milk iron and lactoferrin concentrations [52]. High colostrum lactoferrin levels at about 8 mg/mL, with lower levels in mature milk at levels of 3.5-4 mg/mL [60], reflect iron carrier mechanisms that enhance early

innate protection, possibly also contributing to protection for breastfed infants even in the context of the current pandemic [60].

The trend of breastmilk iron content follows that of breastmilk lactoferrin, although the amounts of iron in milk is much less than that of lactoferrin. Noteworthy is that the iron content of breast milk from mothers who had preterm babies is higher when compared to mothers who had term babies [62]. The stimulus for dynamic milk iron levels during lactation is not completely clear, but many factors including hormonal changes contribute to these levels with seeming purpose [63-68]. Early milk volumes maybe reduced until the mother establishes milk feeds, but high colostrum iron concentrations offers critical, timely protection [44,60]. The mammary gland itself also utilizes iron for energy utilized in the processes involved in lactation [67]. Rodent experiments suggest that breastmilk contains enteral erythropoietin (Epo), and the administration of Epo in conjunction with iron, may increase hemoglobin and hematocrit levels [68].

3.2.3 Iron transport in the infant gut

There are differences in the absorption and utilization of iron in the nursing infant compared to the formula fed infant with varying intestinal iron binding mechanisms and iron binding proteins. Additionally, the premature infant may have different iron absorptive mechanisms and risk factors compared to the term infant [44,69-75].

A substantial proportion (33%) of breastmilk iron is in milk fat, specifically in the outer fat globule membrane contained in xanthine oxidase, which has receptors for iron binding, and much less in the inner fat globule membrane and triglyceride core. The whey component has 58% of iron and 9% of breastmilk iron is in casein [44]. Iron is bound to lactoferrin in milk whey which is not significantly found in some infant formula [64]; lactoferrin and other iron binding proteins in breastmilk could contribute to high iron bioavailability despite relatively low breastmilk iron levels.

It is suggested that iron redistribution may occur in the gastrointestinal tract such that most iron is incorporated into lactoferrin [44], unique iron absorption by a specific receptor in the small intestine of newborn infants is proposed [66,70]. A recent study found that urinary hepcidin levels in infants fed breastmilk compared to formula

were lower, suggesting that the lower infant hepcidin levels contribute to milk iron bioavailability [71].

Factors such as milk ferric reductase activity and others are linked to ferric iron solubilization and enhanced absorption and citric acid solubilizes the ferric iron, reduced by other heat labile components leading to increased uptake in intestinal cells [44,72,73].

The constituents in gold standard infant nutrition when compared to milk formula promote iron absorption. Breastmilk lactose, its ideal protein content, phosphate and calcium levels as well as its hormone profile such as epidermal growth factor-like substances all augment iron absorption contributing to superior bioavailability [44].

Infants may have age related differences in iron homeostasis. No difference was found between iron-supplemented and unsupplemented infants at 6 months of age, unsupplemented infants had higher iron absorption at 9 months of age, suggesting that homeostatic regulation of iron absorption although absent in young infants, matures by 9 months of age [10,74]. Changes in the regulation of iron absorption between 6 and 9 months enhance the infant's ability to adapt to a low-iron diet and may help to avoid iron deficiency despite low iron intakes at this age. In addition to absorption, the utilization of iron by the breastfed infant, was significantly greater than in formula-fed infants over time [75].

3.3 Breastfed Infants and Iron Status

Dorrea (2000) found that there is no support for the need of extra iron (or copper, of which metabolism is interrelated to that of iron), besides amounts provided by milk in the full-term breastfed infant, at least during the first 6 months [76]. Indirect support that the low quantities of breastmilk iron is sufficient for most infants can be deduced from studies of iron content in infant formula; where reducing iron content in formula from 8 to 2 mg/L did not increase risk for iron deficiency at 4 or 6 months of age [77]. Maternal conditions such as infections, undernutrition, adolescent motherhood, environmental variables, iron reserves, together with maternal diet and smoking and the use of hormonal contraceptives before and during lactation do not seem to reliably affect milk mineral concentrations including iron [54,76].

However, if exclusive breastfeeding is for more than 6 months in developing countries there is predisposition to anemia, especially among mothers with a poor iron status, where maternal anemia was independently ($P = 0.03$) associated with a 3-fold increased risk of infant anemia [5]. A lower infant Hb at 9 months was linked to increased duration of expressed breastmilk in mothers with a history of anemia ($\beta = -0.07$, $P = 0.003$), but not among mothers without such history [5]. However, extreme conditions such as severe maternal anemia can still have some impact on breastmilk iron [78].

Most healthy term infants require iron rich weaning foods after 4-6 months of age and additional supplemented iron may be considered if such foods are not easily available or accessible [75]. Unlike full term infants, who may develop iron deficiency in the second half of infancy, if predisposed by prolonged breastfeeding without the addition of proper weaning foods or by any other risk factor, preterm infants are believed to be at risk for developing iron deficiency much earlier [21]; in these cases the benefits of iron supplementation must be carefully weighed against potential risks of iron excesses [79].

4. CONCLUSION

The healthy body thrives on optimal iron balances as both iron deficiency and iron excess effect immediate and long term health. The dynamic homeostasis of iron carefully develops through prenatal and pregnancy-related events, followed by birthing and postnatal scenarios, and also embrace unique homeostatic methods in the lactating mammary glands and in the nursing infant's gut.

Natural checks and balances involving the homeostasis of iron, and possible differences in homeostatic mechanisms at various stages in early life, highlight complex pathways used in the physiological maintenance of body iron levels. The placenta, an organ enabling the viability of the feto-maternal unit, has capacity for a dual role in supporting iron transfer from mother to fetus and at the same time, protecting against free radical damage due to excess iron.

A woman's iron status during pregnancy also impacts the iron status of her fetus and the newborn child, and for some time thereafter. The iron transferred to the fetus in the last trimester and the iron stores from RBC hemolysis provide for much iron in the young infant. Additionally,

holistic maternal health and the will to sustain exclusive breastfeeding for 6 months also provide some differences in iron bioavailability in the breastfed compared to the formula fed infant. Check and balances of iron absorption and its regulatory control take time to mature in the newborn. A healthy, exclusively breastfed full term infant whose mother was iron replete prior to and during pregnancy does not require additional iron in the first six months of life. Risk factors in the mother or infant necessitate individualized evaluation for iron supplementation.

The complex early mechanisms involved in maintaining iron equilibrium reflect a carefully selected evolution in the homeostasis of this important mineral. Likewise, it is important that every clinical scenario that may consider iron therapy warrants deliberation on benefits of adequate iron weighed against the dangers of excess iron. A thoughtful, thorough evaluation of the individual clinical setting with reflection on the biological methods of early iron equilibrium is educational.

CONSENT

It's not applicable.

ETHICAL APPROVAL

It's not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Winter WE, Bazydlo LAL, Harris NS The molecular biology of human iron metabolism 2014;45(2):92-102.
2. Available: <https://www.who.int/news/item/20-04-2020-who-guidance-helps-detect-iron-deficiency-and-protect-brain-development> Accessed on 12.1.2021
3. Ntenda PAM, Nkoka O, Bass P, Senghore T Maternal anemia is a potential risk factor for anemia in children aged 6-59 months in southern Africa: a multilevel analysis. BMC Public Health. 2018;18(1):650.
4. Houghton LA, Trilok-Kumar G, McIntosh D, Haszard JJ, Harper MJ, Reid M, et al.

- Multiple micronutrient status and predictors of anemia in young children aged 12-23 months living in New Delhi, India. PLoS One. 2019;14(2):e0209564
5. Derr MJK, Guerrero ML, Altaye M, Gallegos HO, Palacios GMR, MorrowAL Risk of infant anemia is associated with exclusive breast-feeding and maternal anemia in a Mexican cohort J Nutr 2006;136(2):452-8.
 6. Collard KJ Iron homeostasis in the neonate. Pediatrics. 2009;123(4):1208-16.
 7. Lozoff B, Beard J, Connor J, Barbara F, Georgieff M, Schallert T Review Long-lasting neural and behavioral effects of iron deficiency in infancy. Nutr Rev. 2006;64(5Pt 2):S34-43.
 8. Bastian TW, Rao R, Tran PV, Georgieff MK. The Effects of Early-Life Iron Deficiency on Brain Energy Metabolism Neurosci Insights. 2020;29:15:2633105520935104.
 9. Abu-Ouf NM, Jan MM. The impact of maternal iron deficiency and iron deficiency anemia on child's health. Saudi Med J. 2015;36(2):146–149.
 10. Lönnerdal B, Georgieff MK, Hernell O Developmental physiology of iron absorption, homeostasis and metabolism in the healthy term infant J Pediatr. 2015;167(40):S8–S14.
 11. Kortman GA, Raffatellu M, Swinkels DW, Tjalsma H Nutritional iron turned inside out: intestinal stress from a gut microbial perspective. FEMS Microbiol Rev. 2014;38(6):1202-34.
 12. Romeu M, Aranda N, Giralt M, Ribot B, Nogues MR, Arija V, et al. Diet, iron biomarkers and oxidative stress in a representative sample of Mediterranean population. Nutr J. 2013;12: 102.
 13. Lonnerdal B Excess iron intake as a factor in growth, infections, and development of infants and young children Am. J. Clin. Nutr 2017;106(Suppl 6):ajcn156042.
 14. Cappellini MD, Musallam KM, Taher AT Iron deficiency anaemia revisited J Intern Med 2020;287(2):153-170.
 15. Rao R, Georgieff MK Iron in fetal and neonatal nutrition Semin Fetal Neonatal Med. 2007;12(1):54–63.
 16. MacQueen BC, Christensen RD, Ward DM, Bennett ST, O'Brien EA, Sheffield MJ, et al. The iron status at birth of neonates with risk factors for developing

- iron deficiency: A pilot study *Perinatol.* 2017;37(4):436–440.
17. Kuruvilla DJ, Widness JA , Nalbant D, Schmidt RL, Mock DM, Veng PA. Method to Evaluate Fetal Erythropoiesis from Postnatal Survival of Fetal RBCs *AAPS J.* 2015;17(5):1246–1254.
 18. McLimore HM, Phillips AK, Blohowiak S, Daphne Q, Coe C L, Beth A, Fischer BA, et al. Impact of Multiple Prenatal Risk Factors on Newborn Iron Status at Delivery *J Pediatr Hematol Oncol.* 2013;35(6):473–477.
 19. Maheshwari A, Carlo WA Anemia in the newborn infant *Nelson Textbook of Pediatrics.* ed: Elsevier, Inc. 2016;103:(1)881.
 20. Chelchowska M, Lewandowski L, Ambroszkiewicz J, Swiatek E, Gajewska J, Mariusz O et al The effect of tobacco smoking during pregnancy on concentration of pro-hepcidin and some parameters of iron metabolism in matched-maternal cord pairs *Przegl Lek* 2008;65(10):474-8.
 21. Rao R, Georgieff MK Iron Therapy for Preterm Infants *Clin Perinatol.* 2009;36(1):27–42.
 22. Chaparro CM Timing of umbilical cord clamping: effect on iron endowment of the newborn and later iron status *Nutr Rev* 2011;69:S1:S30.
 23. Chen CM, Mu SC, Shih CK , Chen YL, Tsai LY, Kuo YT et al Iron Status of Infants in the First Year of Life in Northern Taiwan *Nutrient.* 2020;12(1): 139.
 24. Antunes H, Santos C, Carvalho S, Gonçalves S, Pereira AC Male gender is an important clinical risk factor for iron deficiency in healthy infants *Clin Nutr Espen.* 2012;7:6:E219-22.
 25. Halliday HL, Lappin TR, McClure Iron status of the preterm infant during the first year of life. *G Biol Neonate.* 1984;45(5):228-35.
 26. Akkermans MD, Uijterschout L, Abbink M, Vos P, Rovekamp-Abels L, Boersma B, et al Predictive factors of iron depletion in late preterm infants at the postnatal age of 6 weeks. *Eur. J. Clin. Nutr.* 2016;70:941–946.
 27. Tran TD, Biggs BA, Tran T, Casey GJ, Hanieh S, Simpson JA, et al Psychological and Social Factors Associated with Late Pregnancy Iron Deficiency Anaemia in Rural Viet Nam: A Population-Based Prospective Study *PLoS One.* 2013;8(10):e78162.
 28. Sies, H. *Oxidative stress II. Oxidants and antioxidants.* Academic Press, London; 1991.
 29. Casanueva E, Viteri FE Oxidants and antioxidants *J. Nutr.* 2003;133:1700S–1708S.
 30. Pillay PS, Catherine NP , Tolppanen H, Mebazaa A, Tolppanen H , Mebazaa A Physiological changes in pregnancy *Cardiovasc J Afr.* 2016;27(2):89–94.
 31. Cao C, Fleming MD. The placenta: the forgotten essential organ of iron transport *Nutr Rev.* 2016;74(7):421–431.
 32. Fisher AL, Nemeth EA Iron homeostasis during pregnancy. *J Clin Nutr.* 2017;106(Suppl 6):1567S–1574S.
 33. Frayne J , Pinchon D Anaemia in pregnancy *AJGP* 2019;48:3.
 34. Pavord S, Daru J, Prasannan N, Robinson S, Stanworth S, Girling J. BSH Committee UK guidelines on the management of iron deficiency in pregnancy *Br J Haematol.* 2020 ;188(6):819-830
 35. Yiannikourides A, Dada GAL A Short Review of Iron Metabolism and Pathophysiology of Iron Disorders *Review Medicines (Basel);* 2019;6(3):85..
 36. Latunde-Dada GO, Van der Westhuizen J, Vulpe CD, Anderson GJ, Simpson RJ, McKie AT. Molecular and functional roles of duodenal cytochrome B (Dcytb) in iron metabolism. *Blood Cells Mol Dis.* 2002;29:356–60.
 37. Sharp P, Srai SK. Molecular mechanisms involved in intestinal iron absorption. *World J Gastroenterol.* 2007;13:4716–2429.
 38. Vashchenko G, MacGillivray RTA Multi-Copper Oxidases and Human Iron Metabolism *Nutrients* 2013;5(7):2289–2313.
 39. Gambling L, Lang C, McArdle HJ Fetal regulation of iron transport during pregnancy *Am. J. Clin. Nutr.* 2011;94:suppl_6.
 40. Hay G, Refsum H, Whitelaw A, Melbye EL, Haug E, Borch-Johnsen B. Predictors of serum ferritin and serum soluble transferrin receptor in newborns and their associations with iron status during the first 2 y of life. *Am J Clin Nutr.* 2007;86(1):64-73.)
 41. Parkkila S, Waheed A, Britton RS, Bacon BR, Zhou XY, Tomatsu S, et al Association of the transferrin receptor in human placenta with HFE the protein defective in

- hereditary hemochromatosis. Proc. Natl. Acad. Sci. USA. 1997;94:13198–13202.
42. King BF Comparative studies of structure and function in mammalian placentas with special reference to maternal-fetal transfer of iron. Am. Zool. 1992;32:331–342.
 43. Qanungo S, Mukherjea M Ontogenic profile of some antioxidants and lipid peroxidation in human placental and fetal tissues. Mol. Cell. Biochem. 2000;215:11–19.
 44. Lonnerdal B. Iron and Breast Milk Iron Nutrition in Infancy and Childhood, Nestle, Vevey/Raven Press, New York © 1984.
 45. Teramo KA, Widness JA Increased Fetal Plasma and Amniotic Fluid Erythropoietin Concentrations: Markers of Intrauterine Hypoxia Neonatology. 2009;95(2):105–116.
 46. Finne PH, Halvorsen S Regulation of erythropoiesis in the fetus and newborn. Arch Dis Child. 1972;47(255):683-7.1
 47. Cross JH, Prentice AM, Cerami C. Hepcidin, Serum Iron and Transferrin Saturation in Full-Term and Premature Infants during the First Month of Life: A State-of-the-Art Review of Existing Evidence in Humans Curr Dev Nutr. 2020; 4:8.
 48. Halvorsen S Plasma Erythropoietin levels in cord blood and in blood during the first weeks of life Acta Paediatr. 1963;52:425-35
 49. Siddappa AM, Rao R, Long JD, Widness JA, Georgieff MK. The assessment of newborn iron stores at birth: a review of the literature and standards for ferritin concentrations. Neonatology. 2007;92(2):73-82.17.
 50. Kohorn IV, Ehrenkranz RA Anemia in the preterm infant: Erythropoietin versus erythrocyte transfusion — It's not that simple Clin Perinatol. 2009;36(1):111–123
 51. Lee AI, Okam MM Anemia in pregnancy. Hematol Oncol Clin North Am. 2011;25:241–259.
 52. Raj S, Faridi MMA, Rusia U, Singh O. A prospective study of iron status in exclusively breastfed term infants up to six months of age. Int. Breastfeed. J. 2008;3:3
 53. Friel J, Qasem W, Cai C Iron and the Breastfed Infant Antioxidants (Basel). 2018;7(4):54.
 54. Domellöf M, Lonnerdal B, Dewey KG, Cohen R Iron, zinc, and copper concentrations in breast milk are independent of maternal mineral status Am. J. Clin. Nutr. 2004;79(1):111-5.
 55. Leong WI, Lönnerdal B Iron transporters in rat mammary gland: effects of different stages of lactation and maternal iron status Am. J. Clin. Nutr. 2005;81 (2):45–453.
 56. Hampel D, Shahab-Ferdows S, Gertz E, Flax VL, Adair LS, Bentley ME, et al The effects of a lipid-based nutrient supplement and antiretroviral therapy in a randomized controlled trial on iron, copper, and zinc in milk from HIV-infected Malawian mothers and associations with maternal and infant biomarkers. Matern Child Nutr. 2018;14(2):e12503.
 57. Witkowska-Zimny M, El-Hassan EK Cells of human breast milk Cell Mol Biol Lett. 2017; 22:11.
 58. Cai C, Eck P, Friel JKJ Gene Expression Profiles Suggest Iron Transport Pathway in the Lactating Human Epithelial Cell. Pediatr Gastroenterol Nutr. 2017;64(3):460-464.
 59. Lönnerdal B Trace Element Transport in the Mammary Gland Annu. Rev. Nutr. 2007, 27:165-177.
 60. Peroni DG, Fanos V Lactoferrin is an important factor when breastfeeding and COVID-19 are considered Acta Paediatr. 2020;109:10:2139-2140.
 61. Sigman M, Lönnerdal B. Characterization of transferrin receptors on plasma membranes of lactating rat mammary tissue. J Nutr Biochem 1990;1:239–45.
 62. Ejezie F, Nwagha U, Ikekpeazu E, Ozoemena O, Onwusi E Assessment of iron content of breast milk in preterm and term mothers in Enugu urban Ann Med Health Sci Res. 2011;1(1):85-90.
 63. Davidsson L, Kastenmayer P, Wen M, Lönnerdal B, Hurrell RF Influence of Lactoferrin on Iron Absorption from Human Milk in Infants Pediatr Res 1994;35(1):117-24
 64. Lönnerdal B, Erdmann P, Thakkar SK, Sauser J, Destailats F Longitudinal evolution of true protein, amino acids and bioactive proteins in breast milk: A developmental perspective J. Nutr. Biochem. 2016;41:1–11.
 65. Domellöf M Review Iron requirements, absorption and metabolism in infancy and childhood Curr Opin Clin Nutr Metab Care. 2007;10(3):329-35.
 66. Dewey KG, Chaparro CM Review Session 4: Mineral metabolism and body

- composition iron status of breast-fed infants Proc Nutr Soc. 2007;66(3):412-22.
67. Montalbetti N, Dalghi MG, Albrecht C, Hediger MA Nutrient Transport in the Mammary Gland: Calcium, Trace Minerals and Water Soluble Vitamins J. Mammary Gland Biol. Neoplasia. 2016;19:3–90.
 68. Kling PJ, Willeitner A, Dvorak B, Blohowiak SE. Enteral erythropoietin and iron stimulate erythropoiesis in suckling rats. JPGN. 2008;46:202–207.
 69. Etcheverry P, Miller DD, Glahn RP A Low-Molecular-Weight Factor in Human Milk Whey Promotes Iron Uptake by Caco-2 Cells J Nutr 2004;134(1):93–98.
 70. Suzuki YA, Shin K, Lönnerdal B Molecular cloning and functional expression of a human intestinal lactoferrin receptor Biochemistry 2001;40(51):15771-9.
 71. Verhaeghe R, George K, Westerman M, Olbina G, McCann D, Parrow N, et al Hepcidin Status at 2 Months in Infants Fed Breast Milk Compared with Formula Neonatology. 2020;117:474–479.
 72. Pullakhandam R, Nair MK, Kasula S, Kilari S, Thippande TG Ferric reductase activity of low molecular weight human milk fraction is associated with enhanced iron solubility and uptake in Caco-2 cells Biochem Biophys Res Commun 2008;374(2):369-72.
 73. Palika R, Mashurabad PC, Kilari S, Kasula S, Nair KM, Raghu P Citric Acid Mediates the Iron Absorption from Low Molecular Weight Human Milk Fractions J. Agric. Food Chem. 2013;61(46):11151–57.
 74. Domellöf M, Lönnerdal B, Abrams SA, Hernell O Iron absorption in breast-fed infants: effects of age, iron status, iron supplements, and complementary foods Am J Clin Nutr. 2002;76(1):198-204.
 75. Hernell O, Fewtrell MS, Georgieff MK, Krebs NF, Bo Lönnerdal B. Summary of Current Recommendations on Iron Provision and Monitoring of Iron Status for Breastfed and Formula-Fed Infants in Resource-Rich and Resource-Constrained Countries J Pediat. 2015;167(4 Suppl):S40-7.
 76. Dorea JG. Iron and copper in human milk. Nutrition. 2000;16: 209–20.
 77. Björmsjö M, Hernell O, Lönnerdal B, Berglund SK. Reducing Iron Content in Infant Formula from 8 to 2 mg/L Does Not Increase the Risk of Iron Deficiency at 4 or 6 Months of Age: A Randomized Controlled Trial Nutrients 2021;13: 3.
 78. Kumar A, Rai AK, Basu S, Dash D, Singh JS Cord blood and breast milk iron status in maternal anemia Pediatrics 2008;121(3):e673-7.
 79. Iannotti LL, Tielsch JM, Black MM, Black RE. Iron supplementation in early childhood: health benefits and risks Am J Clin Nutr. 2006 ;84(6):1261–1276.

© 2021 Kutty; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:

The peer review history for this paper can be accessed here:
<http://www.sdiarticle4.com/review-history/66570>