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LITERATURE REVIEW

The importance of iron to support optimum cognitive development

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Abstract

The fetal brain anatomy development starts during the last trimester of pregnancy and continue in early months of life. This critical process makes it vulnerable to insufficient nutrition, while brain growth continues into adulthood, micronutrient status can affect functioning beyond childhood. Iron is an important nutrient for the production and growth of cells in the immune and neural systems. Iron deficiency (ID) is the most common nutrient deficiency in the world, affecting about half of all pregnant women and their offspring. Iron deficiency anemia has long been believed to affect the central nervous system. Iron deficiency in late trimester and in newborn leads to abnormal cognitive function and emotional control that may continue in adulthood.

In summary, despite some evidence that iron supplementation enhances cognitive performance. Evidence of the role of iron in brain development and the effect of iron deficiency or iron supplementation on early development is uncertain.

Keywords iron, fetal, children, cognitive development

Introduction

CNS and cognitive development

Pregnancy and the first few years of life are critical times for brain development. Human brain formation is continuously processed from the third week of pregnancy through late adolescence, beginning with the differentiation of the neural progenitor cell. In this time span, the brain is evolving rapidly and dynamically. Thus, the golden age of the development of cognitive, motor and socio-emotional skills through childhood into adulthood.[1-4]

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The brain is one of the most active organs in the body, consume for at least 20% of the body's energy intake for its high-rate metabolic energy requirements.[5,6] Sufficient iron supply is needed to provide the energy. The concept of the role of iron in normal brain function has improved over the lately, focusing on elaborate the cellular and molecular signals that direct the transport and metabolism of iron in the brain.[5,7]

The fetus' neural plate folds inward, becomes a neural tube, and develops into brain and spinal cord about the 22nd days following conception. Nutrients such as folic acid, copper and vitamin A affect the growth of neural plates and neural tubes. Therefore, adequate maternal nutrition is a very important starting point. Seven weeks after conception, cell division begins within the neural tube, producing neurons and glial cells (neuron-supporting cells). After the shape of a neuron, it migrates to its position in the brain and from the cell body it develops axons

and dendrites. These branching projections enable connections to other cells, known as synapses, which transmit nerve signals from one cell to another. These processes of neurodevelopment begin during pregnancy and continue in infancy.[1]

Brain growth is affected by experience described as "experience-expecting" and "experience-dependent" systems and the brain depends on distinctive feedback for normal development in the systems. The brain, for example, expects visual feedback from the optic nerve to establish a regular visual cortex or other sensory stimulation. The absence of these anticipated interactions is detrimental to neurodevelopmental processes. On the other hand, mechanisms that rely on experiences refer to the way the brain organizes itself in response to the experience and skills of the individual, which is a life-long mechanism. Although experiential mechanisms relate to environmental characteristics that are universal, experiential mechanisms refer to aspects of the environment that are specific to the individual. These latter processes allow people to adapt and prosper in their unique culture and climate. Adequate nutrition is a component of the environment that the brain normally expects to develop.[1,2,8] In general, the first 1000 days of life is considered as the most important time for brain development. Deficits that arose during this time, including low academic performance, mental well-being, and long-term economic productivity can have long-term consequences.[4]

Cognition is a complex construction and consists of a field of thinking process where individual information is recorded, encoded, selected, retained, transformed, stored and retrieved. This includes visual and somato-sensory perception, thought, memory and learning. Attention is another important aspect, an integrated process through which the person focuses on knowledge, which is vital to his development and growth from childhood onwards. It requires an intact ability to react and to concentrate on one item without distracting stimuli. In the first year of life, the child learns to build minds that rely on expectations and movement of the body. It further develops its focus skills by discovering and reflecting on the novel aspects of its environment and applies it to knowledge testing and organization throughout pre-school years. Action and motor skills are an important part of the development of the attention system through increased environmental response. A lethargic child with delayed engine activities has fewer chances of exploring and concentrating on specific items or events. At that age the operation will be directly related to motor movements. Cognitive growth continues throughout school years as a cycle of concrete operations, learning abilities such as thinking, memory and language. During the phase, several stimuli are simultaneously appreciated and the ability to give attention to become the maximum adult intellect and reasoning during adolescence is enhanced with a greater understanding and memory.[9] The impact of iron supplementation on cognitive development and function measures on babies, teenagers and adolescents was evaluated by Hermoso et al.[10] from 14 RCTs. Eight RCTs in anemic and non-anemic children over 5 years of age showed, despite limitations, that iron supplementation had a positive impact on various cognition tests.

Prevalence of iron deficiency

A significant problem for mothers and children worldwide is a micronutrient deficiency. It is estimated that 25% of the world's population suffers from anemia of iron deficiency.[1] The iron deficiency of pregnancies, infants and young children is particularly prevalent in times of rapid development due to high requirements of iron. Iron deficiency in young children significantly increases the risk of delays in development and behavioral disorders. The cause of iron deficiency (IDA) anemia is also known.[11-12]

The World Health Organization has described iron deficiency anemia as the highest stage of iron deficiency, which occurs worldwide. Generally speaking, the mean blood concentration of hemoglobin was 111 g/L (95% credit interval [CI]: 110–113) in children, 126 g/L (90% CI: 124—128) and 114 g/L (95% CI: 112—116) in pregnancies; all population groups were above moderate anemia threshold on average (110 g/L for children and women in pregnancy and 120 g/L for non-pregnant women). In 2011, the highest prevalence was among infants (42.6%, 95% CI: 37-47), and in non-pregnant women, the lowest prevalence was (29.0%, 95% CI: 23.9-34.8). In addition, the global anemia

prevalence for all women of reproductive age was 38.2% (95% CI: 33.5—42.6), and 29.4% (95% CI: 24.5% — 35.0%). In this study, iron-deficiency allocation to anemia prevalence was measured as a unanemic population if iron supplements had been provided. To the benefit of iron in the body, the iron requirement of untroubled homeostasis and organ growth in the body must be met.[13]

Risk factor for iron deficiency in early childhood

Iron deficiency is the world's most prevalent micronutrient deficiency and is particularly prevalent in pregnant women, children, and toddlers due to high demands of iron during periods of rapid development. [4,14] Iron deficiency progresses in stages, generally due to insufficient intake of food, decreased absorption, or excessive intake of milk and blood loss from parasite infection.[4,15] When iron supply is low, iron reserves are used more rapidly than can be resupplied, which contributes to iron loss. The situation is defined as a decrease of ferritin levels while measurements of iron in the blood flow (serum iron, soluble transferrin receptor (STfR) and red blood cell measures (medium bone volume (MBI), mean cell hemoglobin (MCH), zinc protoporphyrin (ZPP), and free erythrocytic protoporphyrin (FEP)) in normal limits. This situation is defined as a decrease in the ferritin concentrations. Un-intervened iron depletion progresses into an iron deficiency (ID) in which the body lacks iron to fulfill its current normal function requirements. This is indicated biochemically by a reduction in serum iron and TSAT and an increase of sTfR. Iron control is changed to improve absorption and some activity dependent on iron is regulated because iron is ideally used for the synthesis of red blood cells. If iron deficit continues, the ID increases to iron deficiency anemia (IDA), whereby the red blood cell synthesis is affected, as well as the decreasing concentration of hemoglobin (Hb) and further changes according to the above-described ID biomarkers.[4,16]

During pregnancy, fetal development depends on maternal placental support for fetal oxygen. Adequate concentration of maternal hemoglobin should therefore be assisted. Iron in cytochromes catalyzes the generation of ATP at a time when the rate of consumption of fetal oxygen is very high, driven largely by the structural development of fetal organs, particularly the brain, which consumes more than 60 % of fetal consumption, this high need for oxygen is needed for structural neurodevelopment and glia.[20] Anemic or iron-deficient mothers may be less likely to provide their babies with adequate stimulation.[17]

Pregnancy raises maternal iron demand to satisfy rising red cell volume, growing fetuses and placenta plus any expected or unanticipated blood loss at delivery.[18-19] Maternal plasma and blood levels during pregnancy are increased, and the fetus needs iron to provide itself with metabolism and oxygen and to load its rather large endogenous reserves of iron that are used during the first six months of its life.[20]

Iron will reach the human body under two conditions, from the placenta during pregnancy to the wall of duodenum, and from the dietary intake to the upper part of the jejunum.[20-22] The supply of iron during early postnatal life is minimal and relies on maternal iron during the final weeks of pregnancy.[12,22] Breast milk can be the baby's only dietary source in the first 6 months, so the baby relies on the iron stored in the fetal life to help hemoglobin production and organ growth over that time. Moreover, the fetus requires iron for its own metabolic and oxygen delivery needs as well as loading its relatively broad endogenous iron storage. [20,23] The need for iron increases dramatically 4-6 months after birth and is about 0.7-0.9 mg/day for the remaining first year.[23]

Postnatal iron deficiency was thought to be due to a combination of low dietary iron intake and blood loss (due to intestinal infections) in the recent research. However, a recent major randomized trial of pregnant women in a Chinese population with a moderate iron deficiency incidence found that postnatal iron deficiency in the offspring was primarily due to the neonate iron status and was therefore a result of fetal iron loading.[20]

Physiological anemia occurs during the postnatal period, with iron reserves adequate to cause erythropoiesis without significant blood loss during the first six months of the lifetime. The most common causes for IDA in children include poor intake and rapid development, low birth weight and gastrointestinal loss due to excessive consumption of cow's milk. The absorption of iron in cow's milk

is much lower than in breast milk, children are fed iron-poor food after the sixth month when almost all of their iron supplies are depleted, and iron deficiency developed easily.[24]

Blood loss as a basic cause should be considered in older children if there can be an insufficient intake or a lack of response to oral iron therapy. Chronic iron deficiency anemia with occult bleeding in children is seen at a relatively lower rate and may occur due to gastrointestinal disease including peptic ulcer, Meckel diverticulum, polyp, hemangioma, or inflammatory bowel disease. Unsensitive blood loss rarely occurs in developing countries with Celiac disease, chronic diarrhea, or pulmonary siderosis, or parasitosis.[24]

Neonatal iron deficiency is often characterized by low serum cord ferritin concentration, suggesting lack of fetal iron reserves. Reduced ferritin concentrations occur in children born to iron-deficient mothers with serum ferritin < 13.4 mg/L. Mother-born children may be more likely to be iron-deficient and anemic early in life. This can irreversibly affect children's physical growth and cognitive development. [20] Iron sufficient mothers with hypertension during pregnancy, mothers who smoke cigarettes and mothers with glucose intolerance / diabetes mellitus during pregnancy. Delayed cord clamping tends to be beneficial to neonates by increasing maternal blood flow and loading iron accumulation in infants. It therefore has enough iron to sustain a sufficient supply of iron to supply the developing tissues and to increase the red cell mass for up to 4 to 6 months.[20,25]

The importance of iron in brain development

Iron is an essential micronutrient that plays an important role in many of the human body's metabolic processes, including oxygen transport, oxidative metabolism, and cell growth.[26-28] Abbaspour et al. suggested that the synthesis of the protein from iron oxygen transport is also necessary for the synthesis and formation of heme enzymes and other iron containing enzymes involved in the transfer and oxidation of electron, in particular hemoglobin and myoglobin, deoxyribonucleic acid (DNA) synthesis.[23] Iron is one of the most important micronutrients and it can have a positive effect on children's cognitive development.[29]

In some cases, iron requirements have increased, such as pregnancy, menstrual bleeding and infancy. As fast growth with high iron demands, infants and young children are especially vulnerable to iron deficiency anemia (IDA), in particular those aged between 6 to 24 months.[10] Early postnatal and fetal life is a time of fast brain growth and development. Iron is the essential nutrient for rapid tissue proliferation or differentiation. As a result, the fast developing fetal neonatal brain is more vulnerable than the slow growing brain of later childhood and infancy to high iron demands. Indeed, the severity of adverse effects on brain development will depend primarily on how timely, dose and duration any nutrient deficiency exists, and will depend on the coincidence of two factors: the time of accelerated growth, development and development in a nutrient-dependent area and the probability of nutrient deficiency in this age. [30-31] Since it is an essential method, nutrients are required for optimal brain maturation, and brain development is especially susceptible to metabolic homeostasis disruption.[31]

In the first year of development, the brain is undergoing an incredible transformation into a complex organ. During this time major neurodevelopmental processes include synaptogenesis, the organization of neurotransmitter systems, and the onset of myelination, especially in the hippocampus, which is central processing area of declarative learning and memory, the visual system, and the auditory system.[29,30] Regions of faster growth of cortical thickness after birth include speech and language regions [Heschel's gyrus, Rolandic operculum], the insula and cingulate cortex as well as some higher association areas. [2] Environmental influences may change gene expression during those time periods through epigenetic mechanisms. Studies by both animals and humans have shown that nutrition is one of the key environmental factors and that nutrition, including iron, can affect gene expression directly. Evidence suggests that the development of brain morphology and neurochemistry and neurophysiology can be affected considerably by nutrition deficiency timing. Environmental influences may change gene expression during those time periods through epigenetic mechanisms. Studies by both animals and humans have shown that nutrition is one of the key

environmental factors and that nutrition, including iron, can affect gene expression directly. Evidence suggests that the development of brain morphology and neurochemistry and neurophysiology can be affected considerably by nutrition deficiency timing. [28]

In the latest study, the inhibition control, settling shifts, the planning and the memory recognition of participants with good iron status were difficult to test young adults with chronic severe iron deficiency. The previous study showed that global cognitive, affective and engine performance measurements in children and at age 5, cognition and effects at age 11-14, and the overall cognitive functioning at age 19, impaired participants. The pattern of results reflects the altered function of frontostria and hippocampuses and suggests that neurodevelopmental changes may have a long-term effect on management functioning and memory recognition during the first 2 years of life.[37] Iron affects these production processes at different stages. Iron is a crucial nutrient which contributes to the growth of the fetal and neonatal brain in important cellular processes in an immature brain, including neural cell energy status, myelination and homeostasis monoamine neurotransmitters.[29,32] Recent studies have shown a linkage between ID/IDA and low neuronal/cognitive effects in newborns that last longer than ID and could affect motor growth, memory sensors, social-emotional activity and CNS maturation.[29,33-34]

Iron deficiency suggested to affect motor function, cognition and social behavior.[5] In particular, anemia and developmental delays such as poor motor skills, visual engine integration, acquisition of languages and total IQ affect the psycho-physiological and latter-school development of younger children.[1,4, 33] Scientists who observed a cohort in Chile have shown the problems with the inhibitory control and reaction time at 10 years of age in comparison to a non-IDA group when infants who were identified as iron deficient of anemia (IDA) in infancy and were subsequently iron supplemented for at least 6 months.[35]

Iron deficiency and deficit in cognitive development

Nutrient disorder impaired brain growth and function were projected to adversely alter the planet's IQ capacity by at least 10 points. Iron deficiency is the most common of these nutrient deficiencies. While the clinical syndrome of iron deficiency is most evident, neurobehavioral effects are of major concern as they continue long after the treatment of iron and anemia.[30] Iron deficiency without anemia can cause cognitive disturbance, whereas iron deficiency anemia is associated with emotional and behavioral attention, intelligence, and sensory perception.[36] In order to support a decent brain process, it is necessary for brain development, iron deficiency is believed to compromise the development of the fetal and neonatal brains in the immature brain, in conjunction with critical cellular processes, such as the maintenance of neural cell energy, myelination and monoamine neurotransmitter homeostasis.[29]

In a 10-year study of the effects of childhood IDA on management, those who have anemia have slower reaction times, less accuracy, higher N2 lateness and lower P300 wave amplitude (correlated to work memory) in the electroencephalogram (EEG).[36] Other studies have shown that iron deficiency adverse behavioral effects include learning and memory, and affective and social behaviour. Iron deficiencies occurring in early life (late gestation to age 2-3) lead to learning and memories deductions that continue beyond ID duration despite prompt iron therapy, while Larson et cetera found evidence of the benefit of iron therapy in anemic primary school children, younger children and particularly children under 2 years of age to cognitive performance.[17 30,37]

The destruction of iron homeostasis significantly impairs the oxidative metabolism of the neuronal cells in the human brains, with drastic consequences on synaptic plasticity, myelination and neurotransmitter synthesis. This indicates that the disruption of neurophysiological processes that were previously associated with impaired memory and modified social behavior involve both iron deficiency and excess.[5,38] With regard to mechanisms linking iron status dislocation to neurophysiological and cognitive impairments and

changes in social behavior, iron-induced disruption of major dopamine pathways was previously suggested.[5,39] Particularly, studies of dopamine-dependent pathways have shown that the altered frontal-striatal dopamine circuits in children and young adults with persistent, extreme iron deficiencies with or without childhood anemia have proved to involve management, sustained focus, memory, and motivation.. The authors have demonstrated particularly that early serious iron deficiency is most likely to lead to decreased motor and neurocognitive function and social behavior changes in the childhood at 5 and 11–14 years of age.[5,40]

Iron supplementation to support optimum cognitive development

Iron deficiency is considered to be the main cause of anemia as the mineral required to bring oxygen to hemoglobin. Iron deficiency can result from poor intake or absorption of dietary iron, an increase in need during developmental periods, increased menstrual losses in adolescent girls, or intestinal helminth infection such as schistosomiasis or infection of hookworms in areas endemic to these parasites. During pregnancy, the risk of anemia in children begins. Anemia in the baby's mother is associated with increased risk of low birth weight and mortality among mothers and children. Children born to mothers with anemia can be more anemic and deficient in iron early in life. This can have an irreversible impact on children's physical growth and cognitive development. [15] Iron deficiency in infancy tends to cause lasting and irreparable damage to the neural tissue and activity of the neurotransmitter. Iron deficiency was associated with concurrent delays in memory and attention growth at 9 months.[35,41]

Key concepts for iron deficiency anemia treatment include diagnosis, disease investigation that causes iron deficiency and iron deficiency removal, deficiency replacement, diet improvement, and patient and family education. Iron has two dietary forms: non-heme iron and heme iron. Non-heme iron is present in non-meat foods and meat products contain heme iron. Heme iron absorption is much higher, but only 10% of the diet iron is heme iron. While heme iron absorption is influenced by very low environmental factors, non-heme iron is influenced by other food substances and environmental pH. Therefore, increased intake of meat and meat products is necessary to prevent and treat iron deficiency.[24]

Several iron supplementation benefits, independent of increasing hemoglobin, were identified, including those related to immune function, physical health, thermoregulation, cognition, and restless leg syndrome. Considering cognitive functions, it is important to know if iron supplementation will enhance them. Supplementation, fortification, or therapy should be viewed without distinction to examine cognitive development in ID and IDA.[36]

Daily iron supplementation is advised in babies aged 6-23 months living in high-prevalence anemia as a public health measure to avoid iron deficiency and anemia. The recommendation consists of 10–12.5 mg elemental iron per drop or syrup preparation daily over three consecutive months of the year. (Strong recommendation, moderate quality of evidence) Regular iron supplementation in pre-school infants aged 24–59 months, living with high-prevalence anemia, increasing levels of hemoglobin, and enhancing iron conditions is recommended as public health measures. There was a mistake (strong recommendation, very low-quality evidence). Preparation for 3 consecutive months per year of 30 mg of elementary iron per day in drops/sirup/tablets. Regular iron supplementation as public health in children aged 60 months and older who live in highly prevalent areas of anemia, is recommended to avoid iron deficiency and anemia (strong recommendation, high quality of evidence). Preparation for each 3 consecutive months of 30–60 mg elemental iron in tablets or capsules daily. Regular supplementation of oral iron is a preventive population technique. If infant anemia is detected, national anemia guidelines should be followed.[15]

Therefore, prevention is key to the addition of risky mothers, to the delay in clamping umbilical cord and to supplement risky babies from birth. However, it should be remembered that it is not advisable to supplement full-bodied individuals or children living in areas where malaria is of concern. [35] In addition to sufficient complementary feeding, interventions to promote exclusive breast-feeding for the first 6 months of life and continuation of

breast-feeding will not increase cognitive growth despite additional efficacy evidence.[1]

Summary

For subsequent lifelong function, optimal maternal and child nutrition during the time of accelerated brain growth is essential to the stability of neural substrate. Iron is a major nutrient in metabolic processes of the human body, including oxygen transport, oxidative metabolism, and cell growth. Fulfilling the iron requirement will likely have a positive effect on children's cognitive growth. As early pregnancy begins with fetal development, adequate maternal nutrition is an important starting point. Iron-deficient mothers may be less able to provide enough hemoglobin to facilitate fetal oxygen supply. Some methods are used to prevent iron deficiency, such as supplementing at-risk mothers, delayed umbilical cord clamping, exclusive breastfeeding, and baby fortification or supplementation.

Conflict of Interest

The authors declared no conflict of interest regarding this article.

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References

1 Prado EL, Dewey KG. Nutrition and brain development in early life. Nutr Rev. 2014;72(4):267–84.
2. Gilmore, J., Knickmeyer, R. & Gao, W. Imaging structural and functional brain development in early childhood. Nat Rev Neurosci 19, 123–137 (2018).
3. Stiles J, Jernigan TL. The basics of brain development. Neuropsychol Rev. 2010;20(4):327–48.
4. McCann S, Amadó MP, Moore SE. The role of iron in brain development: A systematic review. Nutrients. 2020;12(7):1–23.
5. Ferreira A, Neves P, Gozzelino R. Multilevel impacts of iron in the brain: The cross talk between neurophysiological mechanisms, cognition, and social behavior. Pharmaceuticals. 2019;12(3):1–26.
6. Magistretti PJ, Allaman I. A Cellular Perspective on Brain Energy Metabolism and Functional Imaging. Neuron. 2015;86(4):883–901.
7. Falkowska A, Gutowska I, Goschorska M, Nowacki P, Chlubek D, Baranowska-Bosiacka I. Energy metabolism of the brain, including the cooperation between astrocytes and neurons, especially in the context of glycogen metabolism. Int J Mol Sci. 2015;16(11):25959–81.
8. Couperus JW, Nelson CA. Early brain development and plasticity. In: McCartney K, Phillips D, eds. The Blackwell Handbook of Early Childhood Development. Malden, MA: Blackwell Publsihing; 2006:85–105
9. Mamun MA Al, Ghani RBA. The role of iron and zinc in cognitive development of children. Asian J Med Biol Res. 2017;3(2):145–51.
10. Hermoso M, Vucic V, Vollhardt C, Arsic A, Roman-Viñas B, Iglesia-Altaba I, et al. The effect of iron on cognitive development and function in infants, children and adolescents: A systematic review. Ann Nutr Metab. 2011;59(2–4):154–65.
11. Gupta PM, Perrine CG, Mei Z, Scanlon KS. Iron, anemia, and Iron deficiency anemia among young children in the United States. Nutrients. 2016;8(6):10–3.
12. Uijterschout L, Vloemans J, Rövekamp-Abels L, Feitsma H, Van Goudoever JB, Brus F. The influences of factors associated with decreased iron supply to the fetus during pregnancy on iron status in healthy children aged 0.5 to 3 years. J Perinatol. 2014;34(3):229–33.
13. WHO. The global prevalence of anaemia in 2011. Geneva: World Health Organization. 2015.
14. Stevens GA, Finucane MM, De-Regil LM, Paciorek CJ, Flaxman SR, Branca F, et al. Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995-2011: A systematic analysis of population-representative data. Lancet Glob Heal. 2013;1(1):16–25.
15. WHO. Guideline Daily Iron supplimentation in infants and Children. Geneva: World Health Organization. 2016.
16. Barragán-Iba˜nez, G.A. Santoyo-Sánchez COR-P. Iron deficiency anaemia. Rev Med Hosp Gen Méx. 2016;79(2):88–979.
17. Larson LM, Phiri KS, Pasricha SR. Iron and Cognitive Development: What Is the Evidence? Ann Nutr Metab. 2017;71(3):25–38.
18. Grzeszczak K, Kwiatkowski S, Kosik-Bogacka D. The role of fe, zn, and cu in pregnancy. Biomolecules. 2020;10(8):1–33.
19. Juul SE, Derman RJ, Auerbach M. Perinatal Iron Deficiency: Implications for Mothers and Infants.

Neonatology. 2019;115(3):269–74.
20. Georgieff MK. Iron deficiency in pregnancy. Am J Obstet Gynecol. 2020;223(4):516–24.
21. Friedrisch JR, Friedrisch BK. Prophylactic Iron Supplementation in Pregnancy: A Controversial Issue. Biochem Insights. 2017.
22. Fuqua BK, Vulpe CD, Anderson GJ. Intestinal iron absorption. J Trace Elem Med Biol. 2012;26(2–3):115–9.
23. Abbaspour, N.; Hurrell, R.; Kelishadi, R. Review on iron and its importance for human health. J. Res. Med. Sci. 2014; 19: 164–174
24. Özdemir N. Iron deficiency anemia from diagnosis to treatment in children. Turk Pediatr Ars. 2015;50(1):11–9.
25. Ashish KC, Målqvist M, Rana N, Ranneberg LJ, Andersson O. Effect of timing of umbilical cord clamping on anaemia at 8 and 12 months and later neurodevelopment in late pre-term and term infants; a facility-based, randomized-controlled trial in Nepal. BMC Pediatr. 2016;16(1):1–6.
26. Gupta DCP. Role of Iron (Fe) in Body. IOSR J Appl Chem. 2014;7(11):38–46.
27. Abu-Ouf, NM, Jan, MM. The impact of maternal iron deficiency and iron deficiency anemia on child's health. Saudi Med J.2015;2:146–149
28. Alwan N, Hamamy H. Maternal Iron Status in Pregnancy and Long-Term Health Outcomes in the Offspring. J Pediatr Genet. 2015;04(02):111–23.
29. Wang Y, Wu Y, Li T, Wang X, Zhu C. Iron metabolism and brain development in premature infants. Front Physiol. 2019;10
30. Fretham SJB, Carlson ES, Georgieff MK. The role of iron in learning and memory. Adv Nutr. 2011;2(2):112–21.
31. Bastian TW, Rao R, Tran P V, Georgieff MK. The Effects of Early-Life Iron Deficiency on Brain Energy Metabolism. Neurosci Insights. 2020;15.
32. Cheli VT, Santiago González DA, Marziali LN, Zamora NN, Guitart ME, Spreuer V, et al. The divalent metal transporter 1 (DMT1) is required for iron uptake and normal development of oligodendrocyte progenitor cells. J Neurosci. 2018;38(43):9142–59.
33. Otero GA, Fernández T, Pliego-Rivero FB, Mendieta GG. Iron therapy substantially restores qEEG maturational lag among iron-deficient anemic infants. Nutr Neurosci. 2019;22(5):363–72.
34. Deoni S, Dean D, Joelson S, O'Regan J, Schneider N. Early nutrition influences developmental myelination and cognition in infants and young children. Neuroimage. 2018;178:649–59.
35. Cheatham CL. Nutritional Factors in Fetal and Infant Brain Development. Ann Nutr Metab. 2020;75(l1):20–32.
36. Jáuregui-Lobera I. Iron deficiency and cognitive functions. Neuropsychiatr Dis Treat. 2014;10:2087–95.
37. Lukowski AF, Koss M, Burden MJ, Jonides J, Nelson CA, Kaciroti N, et al. Iron deficiency in infancy and neurocognitive functioning at 19 years: Evidence of long-term deficits in executive function and recognition memory. Nutr Neurosci. 2010;13(2):54–70.
38. Nnah IC, Wessling-Resnick M. Brain Iron homeostasis: A focus on microglial Iron. Pharmaceuticals. 2018;11(4).
39. Lozoff B. Early iron deficiency has brain and behavior effects consistent with dopaminergic dysfunction1-3. J Nutr. 2011;141(4).
40. Algarín C, Nelson CA, Peirano P, Westerlund A, Reyes S, Lozoff B. Iron-deficiency anemia in infancy and poorer cognitive inhibitory control at age 10 years. Dev. Med. Child Neurol. 2013;55:53–458.
41. Carter RC, Jacobson JL, Burden MJ, Armony-Sivan R, Dodge NC, Angelilli ML, et al. Iron deficiency anemia and cognitive function in infancy. Pediatrics. 2010;126(2).