Iron for Human Brain Development: A Fulfill Strategy in the First 1,000 Days of Life

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Abstract: Every child has the right to live, survive, and optimal growth and development. Iron has a fundamental role in brain development. Iron deficiency (ID) in the first two years of life harms the child's long-term development (possibly irreversible), even though ID has been corrected. For optimal child development, the first two years of life are a crucial period. Iron deficiency during pregnancy can cause adverse pregnancy outcomes, both maternal and newborn, resulting in long-term disruption to the child's growth and development. We must pay special attention to the adequacy of iron needs from conception to two years of age. This article describes the importance of iron for human brain development and what should we do to ensure iron adequacy, especially in the first 1,000 days of life.

1 INTRODUCTION

Every fetus in pregnancy and the baby (after birth) has the right to live, survive, and has optimal growth and development (ILO, 1999). Children are the next generation of a nation and have a strategic role in ensuring the nation's existence and continuity (UU RI 23, 2002). The successful development of children, especially the brain, determines the future fate of the country. The first 1,000 days period, from conception to her child's second birthday, offers a brief critical brain's window of opportunity (as the golden period) (Bellieni, 2016) to shape the development of children. The fulfilment of both macro and micronutrient nutrients is very fundamental for the successful development of a child.

Iron, as an essential micronutrient, has a strategic role in developing the human brain. Iron deficiency/ iron deficiency anaemia (ID/IDA) at the end of the fetal period and early in the infant period can cause decreased cellular respiration in the hippocampus and frontal cortex. It also may lead to abnormal neurotransmitter concentrations, altered fatty acid profiles, and impaired myelination, potentially disrupting infant growth and development (Georgieff, 2007).

Poorly child fares of iron fulfil in this period, potentially causing neurological disorders (Georgieff, 2007), interfering with the child's long-term development (Mattei & Pietrobelli, 2019; Pietrobelli et al., 2017) and might irreversible, across the lifespan (Lozoff, 2006; Halterman, 2009). The success of nutrition management in the first 1,000 lives provides a vast opportunity to improve human resources with transgenerational impacts (Martorell, 2017). It should be a priority not only for the government but also for all community groups and individuals, including academics. This article describes the importance of iron for human brain development and what we should do to ensure iron adequacy, especially in the first 1,000 days of life.

2 THE HUMAN BRAIN DEVELOPMENT

The human brain develops from the prenatal and continues to the postnatal period. The brain structures are designed gradually and begin in the third gestational week with the differentiation of the neural progenitor cells (Thompson & Nelson, 2001); (Stiles & Jernigan, 2010) (See figure 1). Approximately 22 days after conception, the neural plate begins to fold

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inward, forming the neural tube, which eventually becomes the brain and spinal cord (Prado & Dewey, 2014). In the prenatal period, neurulation (i.e., the formation of the neural tube from which eventually evolves the central nervous system) occurred at 18-24 prenatal days, followed by the generation, proliferation, migration, and, finally, differentiation of neurons. Seven weeks after conception, cell division begins within the neural tube, creating nerve cells (neurons) and glial cells (cells that support neurons). After a neuron is made, it migrates to its place in the brain, where it then grows axons and dendrites projecting out from its cell body (Prado & Dewey, 2014).

At the beginning of the last (third) trimester of fetal life, both myelinations (the fatty insulation of neurons) runs up to 5-10 years of age. It is continuing into adult life, and also the synaptogenesis (forming relationships between cells) continues up to the age of 15 -18 years). These events are essential to developing the functional architecture of the brain (Thompson & Nelson, 2001; Stiles & Jernigan, 2010; Mattei & Pietrobelli, 2019).

Especially in the third trimester and the first two years after birth, the brain faces extraordinary growth, increasing its dimension, differentiating gradually in a highly specialized organ, and slowly losing plasticity. It is known that the higher rate of growth in this period, the greater the risk of damage due to insufficient nutrients (Fox et al., 2010; Mattei & Pietrobelli, 2019). The brain has unique developmental trajectories and a set of nutrient requirements, so we must pay more attention to it.

The brain regions or processes have developmental trajectories that begin and accelerate in fetal life or shortly after birth. Every area of the brain and every process has two crucial moments, (i) the critical period and (ii) the sensitive period. Conceptually, they can be defined as follows: the former is an early life period where irreversible long-term consequences follow insults. The latter represents broader periods when the brain is more susceptible to environmental factors, such as nutrient deficiencies (including iron), but the effect is not inevitably permanent (Mattei & Pietrobelli, 2019). The logical consequences of failure to construct a brain region during its critical period can lead to permanent disorders, such as residual structural defects (Jorgenson et al., 2003), persistent neurochemical and electrophysiological abnormalities, and even altered gene expression (Tyagi, 2015; Barks et al., 2018; Mattei & Pietrobelli, 2019;). Thus, ensuring adequate nutrient, especially iron, is necessary to allow a time-coordinated brain development and create an integrated healthy working brain structure.

In the human biological system, the brain is the most complex organ. It contains 100 billion neurons (information processing cells) and between neuron cells make connections with other neuron cells (through synapses) to create the information processing networks responsible for all of our thoughts, sensations, feelings, and actions. Since each neuron has more than 1,000 other neurons, the adult brain is estimated to have more than 60 trillion neuronal connections (synapses) (Stiles & Jernigan, 2010).

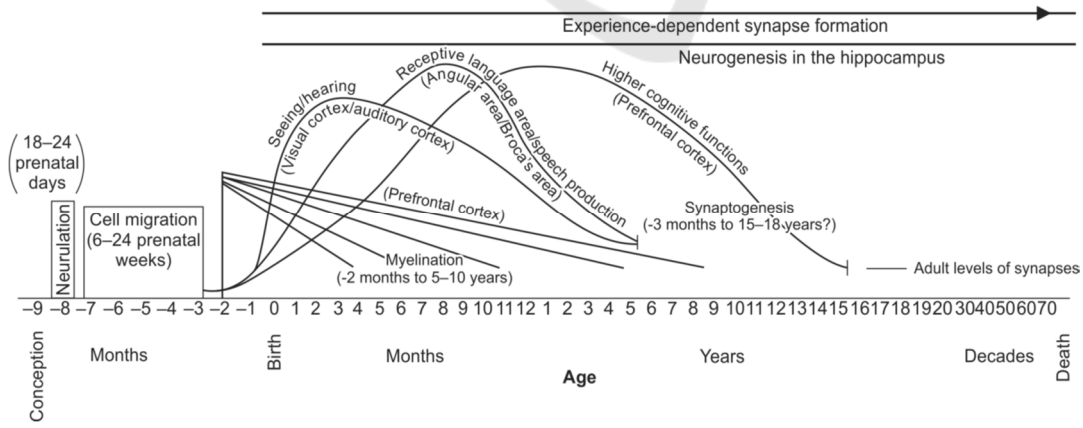

Figure 1. Development course of the human brain (Thompson & Nelson, 2001)

Neuron populations are linked by fibres extending from individual neurons' cell bodies, namely dendrites and axons (see Figure 2). Dendrites are short visible fibres like the branches of a tree, which function to receive electrochemical input signals from other neurons. In contrast, axons are long connecting fibres that extend over great distances and make connections with other neurons (often at the dendrites) to send electrochemical signals to neurons located at distant locations (Stiles & Jernigan, 2010).

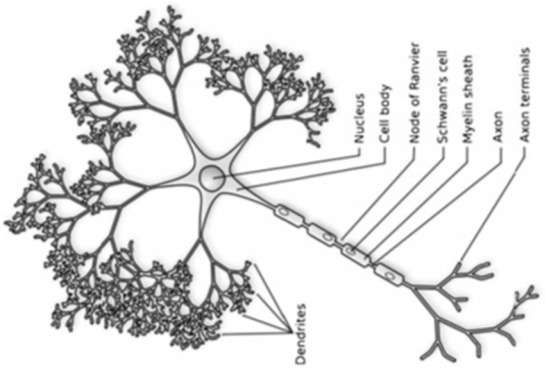

Figure 2. Schematically illustration of a neuron (Stiles & Jernigan, 2010)

Individual axon collections from many different neurons (in one brain region) form fibre channels that extend to and make connections with groups of neurons in the other areas of the brain, developing information-processing networks. The axons are encased in a fatty substance called myelin, like the insolation in telephone wires, making the transmission of electrochemical signals between regions efficient (Stiles & Jernigan, 2010). The efficiency of information transmission in the pathways is greatly enhanced by myelin, which unsheathes the axons. This myelination process needs iron so that ID during the rapid growth period (the first 1,000 days of life) will harm the child's future.

3 HOW DOES IRON DEFICIENCY INTERFERE WITH BRAIN DEVELOPMENT?

Iron deficiency is the most prevalent nutritional deficiencies in the world (Bastian, 2020). Iron is an essential micronutrient for normal cellular function in roles as varied as oxygen transportation, energy metabolism/energy production, cellular respiration, cell signalling, gene expression/ DNA synthesis and the regulation of cell growth and differentiation, and more (Musallam & Taher, 2019; Ferreira et al., 2019).

Heme is an iron complex with protoporphyrin IX, which is essential for all aerobic cells' function. Cells need heme as a prosthetic part for key hemoprotein, including haemoglobin, cytochromes, and myoglobin. Another ones are catalase, peroxidases, and nonheme-containing enzymes involved multiple metabolic activities. The dominance function of iron as the cofactor for intracellular processes is due to the chemistry and redox properties of iron, which enable it to bind oxygen, transfer electrons and catalyze various reactions (Aisen, 2001; Musallam & Taher, 2019; Ferreira et al., 2019). In case the brain, as a metabolically active organ, is susceptible to iron homeostasis changes, there is still much uncertainty (Ferreira et al., 2019).

Cells in the brain do not directly access nutrients, including iron, in the systemic circulation because the blood-brain barrier and the blood–cerebrospinal fluid barrier separate the CNS from the systemic circulation (Ferreira et, 2019). The iron can cross the blood-brain border by binding to transferrin. The transferrin-iron complex will attach to the transferrin receptor on the capillary endothelium. It results in further internalization by forming endocytic vesicles. The iron is then pumped out via the expression divalent metal transporter 1 (DMT1) in the "ferrous" form. In the cytosol, ceruloplasmin oxidase Ferro to ferric form. It releases to the extracellular space by ferroportin (Rouault, 2013).

Disruption of iron homeostasis in the brain significantly impairs oxidative metabolism of neural cells, with dramatic consequences for synaptic plasticity, myelination, and synthesis of neurotransmitters (Beard & Connor, 2003; Nnah & Wessling-Resnick, 2018). Iron is a double-edged sword, "deficiency" and "overload" of iron lead to detrimental consequences. It means that both deficiency and iron overload are associated with

disruption of neurophysiological mechanisms previously associated with impaired cognition, altered social behaviour, and other brain functions (Ferreira et al., 2019). Iron deficiency further threatens the body's physiological processes during the fast-growing life period.

During pregnancy and the early phases of human life (first 1,000 days of life), the needs for macro and micronutrients (including iron), energy, and other resources increase. The effects of ID are profound on cells with the highest metabolic rates, possibly because ID disrupts mitochondrial and cellular energy (Beard & Connor, 2003). Mitochondrial function can be severely impaired because iron is a cofactor for both heme and nonheme-containing enzymes in the mitochondrial electron transport chain (Georgieff et al., 2019). The consequences of ID are more significant during development when the oxygen consumption rates of cells are highest, driven by the energy demands of growth and differentiation (Kuzawa, 1998; Georgieff et al., 2019), such as during the late stages of pregnancy and early life.

As an illustration, the total-body oxygen consumption of a neonate is three to four times greater than that of an adult. The infant's brain is estimated to consume 50–60% of the total metabolic expenditure. The neonatal human brain alone utilizes 60% oxygen consumption, compared with 20% in the adult brain (Kuzawa, 1998; Georgieff et al., 2019). As a result, because of the high use of iron in rapid brain development, the early life period is the most susceptible to ID.

Potential mechanisms contributing to this disorder include deficits in brain energy metabolism, nerve transmission, and myelination. A comprehensive review shows the brain's reduced energetic capacity as a mechanical driver of impaired neurobehavioral development due to fetal-neonatal ID. Permanent metabolic reprogramming, which occurs during the ID period, results in chronic disruption of neuronal energy and mitochondrial capacity in adulthood, limiting neuroplasticity and neuro-behaviour in adults (Bastian et al., 2020). Unfortunately, ID in the late fetal and early life period can cause abnormal cognitive performance and emotional regulation, which can persist into adulthood despite iron repletion.

4 STRATEGY FULFILL IRON NEED 1,000 DAYS OF LIFE

The strategy to fulfil the iron need in the first 1,000 days of life is a meaningful way to prevent the adverse effects of ID that harms the child's long-term development, even though ID has been corrected. So, clear that prevention is the best solution.

General ID Prevention Strategies Approaches

In principle, ID prevention must involve various sectors, both government and non-government organizations. Individual preventive approaches will not have an impact on the broader community.

General strategies approach of ID prevention is including food-based procedures, infection disease control program, and iron supplementation (WHO, 2001).

1. Food-based approaches

a. Dietary improvement

Add substances that enhance iron absorption and remove inhibitors of iron absorption substances in the diet menu (WHO, 2001). Iron absorption enhancers (such as ascorbic acid, Muscle tissue) (Seriki et al., 2017; Cappellini et al., 2020) or inhibitors (such as calcium, phytates [cereals], polyphenols [black tea], tannins [tea and coffee], proteins [milk proteins, egg proteins]) should also be aware of when supplying iron-rich food menus (WHO, 2001; Seriki et al., 2017; Cappellini et al., 2020).

b. Provide a diet menu that is heme iron-rich food sources

Low dietary intake of bioavailable iron is an essential factor in the development of ID. Increased access to and consumption of iron-rich foods should always be a priority (WHO, 2018a; Cappellini et al., 2020). Complementary foods should not forget to provide animal food sources rich in heme iron which is easily absorbed.

c. Food fortification

The food fortification (or enrichment of food) is adding micronutrients (including iron) to food. It is usually considered the deliberate addition of one or more micronutrients to particular foods to increase these micronutrient (s) intake to prevent or correct a demonstrated deficiency (WHO & FAO, 2006). For

example, enrichment of food (rice, maize flour, cornmeal) with iron. Food manufacturers can carry it out (or by governments as a public health policy) to reduce the number of people with a low iron diet and risk of ID within a population (WHO & FAO, 2006).

2. Infection disease control program

In particular, this effort to hookworm, schistosomiasis, and malaria control, can enhance IDA control program effectiveness in a population with moderate to severe levels of infection (WHO, 2001).

3. Iron supplementation

Supplementation is the most common strategy currently and often used to treat existing IDA (WHO, 2001). Iron supplementation program has successfully reduced the prevalence of ID/ However, we must realize that iron is a "double-edged sword," deficiency and iron overload lead to detrimental consequences (Georgieff, 2007).

The WHO (2016) recommends iron supplementation (without screening) to prevent DI / IDA in a population where the prevalence of anaemia is 40% or higher (: children 6–23 months (10–12.5 mg elemental iron daily), three consecutive months in a year), 24–59 months (30 mg elemental iron daily), three straight months in a year), 5–12 years (30–60 mg essential iron daily), three consecutive months in a year) (WHO, 2016).

Recommendation from WHO, pregnant women are given a daily oral iron and folic acid supplementation with 30 - 60 mg of elemental iron and 400 g (0.4 mg) of folic acid to prevent maternal anaemia, puerperal sepsis, low birth weight, and preterm birth (WHO, 2018c).

When daily iron is not acceptable due to side-effects, and in populations with anaemia prevalence among pregnant women of less than 20%, intermittent oral iron and folic acid supplementation with 120 mg of elemental iron and 2800 μg (2.8 mg) of folic acid once weekly (WHO, 2018b).

Controversy Iron Supplementation of Pregnant Women and Children

Although iron supplementation programs have successfully reduced ID prevalence, blindly iron supplementation without detecting iron status is still controversial. Iron has a narrower adequacy range, so iron supplementation might even cause health problems regardless of iron status. Iron supplementation to iron-sufficient individuals is likely unnecessary or has a little additional benefit and may carry health risks for iron-sufficient individuals and potentially some iron-deficient populations (Georgieff, 2007; Georgieff et al., 2019).

However, emerging and preliminary evidence shows a U-shaped risk at both deficiency and iron status overload for birth and infant adverse health outcomes (Dewey & Oaks, 2017). This fact raises questions about the effects of high iron intakes through supplementation or food fortification during pregnancy and infancy, particularly in iron-replete individuals (Brannon & Taylor, 2017). However, the inability to reliably distinguish total-body iron status from three iron-replete states of haemoglobin in nonanemic women (namely: nonanemic ID, optimal iron status, and iron overload) raises a significant problem in determining the "benefit-risk analysis" since the effects of iron supplementation on these three states likely differ (Georgieff et al., 2019). During pregnancy, high iron status is associated with increased risk for maternal and fetal adverse outcomes, related to preterm birth, low birth weight and small for gestational babies (Brannon & Taylor, 2017; Breymann, 2015). There is preliminary evidence that supplementation or high iron status is associated with gestational diabetes mellitus (Zhang & Rawal, 2017). Iron supplementation on iron-replete children increased the risk of vomiting and fever (Pasricha et al., 2013), impaired linear growth (Lönnerdal, 2017), and disturbing microbiome profiles (Brannon & Taylor, 2017; Paganini & Zimmermann, 2017). Iron supplementation without screening is allowed by WHO in populations wit a high prevalence of ID / IDA. The implications of this risk of iron supplementation deserve serious discussion relative to screening and supplementation in these "vulnerable" populations (which are likely iron-replete) (Brannon & Taylor, 2017), not only population in developed countries but also every iron-replete individuals.

The Phase of Human Life, Associated With a Vicious Cycle of Iron Deficiency

Neonates women born to iron deficient mothers will potentially grow up to be children, adolescents, and women of childbearing age with ID and subsequently become pregnant women with ID, thus giving birth to babies with ID. Continuity of care is not only necessary throughout the lifecycle (adolescence, pregnancy, childbirth, the postnatal period, and childhood) but also between places of caregiving (including households and communities, outpatient and outreach services, and clinical-care settings)

(Kerber et al., 2007). It is like a vicious cycle, so to prevent the ID / IDA must cut it at every phase of human life and need an effective continuum of care. See figure 3.

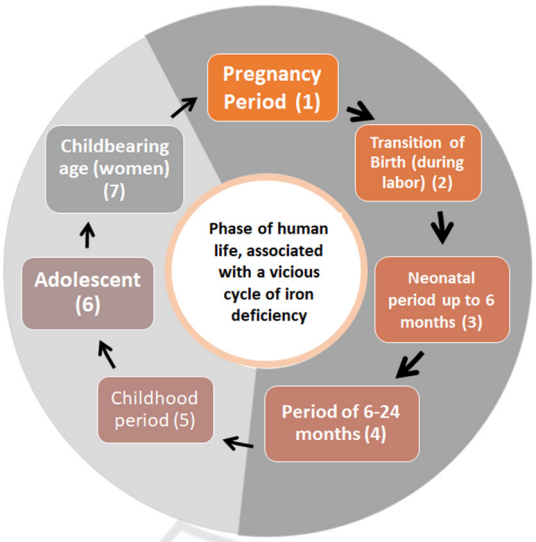

Figure 3. The phase of human life, associated with a vicious cycle of ID

All life periods need to get attention to fulfil human iron needs for brain growth and development in the golden period, the first 1,000 days of life. Throughout the journey of life, infancy, childhood, adolescence, and women of childbearing age, especially during pregnancy, they are the ID risk period due to their high iron requirements. Children (women) who grow up to be anaemic adolescents will become anaemic pregnant women someday. For the success of optimal children's brain development, all ID problems, including chronic inflammation problems, must be cut off and overcome in all human stage life cycles. We must break this vicious cycle of ID.

5 PLACENTAL TRANSFUSION: IMPORTANT BUT OVERLOOKED IN ID PREVENTION

The general prevention strategies of ID (including iron supplementation) can be practised from infants aged six months until pregnant women. However, in infants under six months is quite complicated, and there is still a controversy regarding supplementation in exclusive breastfeeding infants. Then, what is the ID/ IDA preventive solution for children aged 0-6 months?

An inexpensive and easy preventive ID/ IDA solution for infants 0-6 months has been provided by delaying cord clamping at birth. In the first few minutes after the baby is born, there is still circulation from the newborn's placenta. Blood flow from the neonate to the placenta (through the umbilical artery) only occurs during the first 20-25 seconds after the baby is born. Otherwise, the closure of blood flow in the umbilical vein (from the placenta to neonate) can last up to the first 3 minutes, and after that, the blood flow is minimal and meaningless (Dewey & Chaparro, 2007).

The debate about umbilical cord clamping time has occurred for more than two centuries (Philip & Saigal, 2004). The Pan American Health Organization believes that the optimal timing of umbilical cord clamping for all babies (regardless of gestational age or weight) is when the cord circulation stops, usually about 3 minutes or more after the baby is born (Chaparro et al., 2007). The American College of Obstetricians and Gynecologists (ACOG) argues that delayed clamping for the mother does not affect postpartum haemorrhage incidence. In contrast, for term infants, there is not enough evidence of benefit for them, and the risk of hyperbilirubinemia should be considered (Committee on Obstetric Practice ACOG, 2012).

WHO recommend clamping the umbilical cord at 1-3 minutes after birth for all deliveries in 2012 (WHO, 2012a). They did not suggest an early clamping (<1 minute) unless the neonate is

asphyxiated and requires immediate resuscitation (WHO 2012a; WHO, 2012b). Delayed umbilical cord clamping (1-3 minutes) is recommended for improved maternal and infant health and nutrition outcomes (WHO, 2014). The care protocol for expected delivery in Indonesia, *Jaringan Nasional Pelatihan Klinik-Kesehatan Reproduksi* (JNPK-KR, 2017), recommends clamping of the umbilical cord 2-3 minutes after birth if there is no need for resuscitation of the baby (JNPK-KR, 2017). Due to the importance of delayed cord clamping, WHO gives remarks that for basic neonatal resuscitation, if the baby rescue team in the delivery process has experience providing adequate positive-pressure ventilation without cutting the umbilical cord, actually ventilation can be initiated before cutting the cord (WHO, 2014).

Delaying to clamp the umbilical cord for 2–3 min, or until cord pulsations cease, facilitates a physiological blood transfer of placental blood to the infant (called "placental transfusion"), the majority of which occurs within 3 min. The placental transfusion provides sufficient iron reserves for the growth and development of the baby's brain in the first 6–8 months of human life and prevents or delays the development of ID until other interventions – such as the use of iron-fortified foods– can be implemented after exclusive breastfeeding period (WHO, 2016).

6 SUMMARY

This article describes brain development and the crucial role played by iron. As an essential micronutrient in human brain development, fulfil iron needs in the first 1,000 days of life is a fundamental step to achieve optimal child development in the future. However, both deficiency and iron overload harm maternal and neonatal outcomes. Iron deficiency in the first two years of life impairs the child's long-term development (possibly irreversible), even though ID has been corrected. ID prevention is essential—general ID prevention strategies approach, including food-based approaches, infection disease control program, and iron supplementation. Complementary foods should provide animal food sources that are rich in heme-iron, which is easily absorbed. Children (girl) who grow up to be anaemic adolescents will become anaemic pregnant women someday, so all ID problems must be cut off and overcome in all human life cycles. We must break this vicious cycle of ID. Especially for exclusively breastfed babies in the 0-6 month period, the delay of umbilical cord clamping (about 2-3 minutes) after birth provides sufficient iron reserves for the baby's life for 6-8 months.

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