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- Iron deficiency in Indonesia: known facts
- The role of iron adequacy for maternal and fetal health
- The role of iron for supporting children's growth and development
- The importance of iron to support optimum cognitive development
- Optimizing iron adequacy and absorption to prevent iron deficiency anemia: The role of combination of fortified iron and vitamin C
- Anemia status and its related factors among Indonesian workers: Hemoglobin surveys in three different workplaces

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Supplementary Paper

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LITERATURE REVIEW

Iron deficiency in Indonesia: known facts

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Abstract

More than half cases of anemia are due to iron deficiency. Anemia is a major and global public health problem that affects maternal and child mortality, child cognitive development and eventually productivity. Infancy, adolescence, and pregnancy are particularly at risk. Indonesia is a low middle country with the prevalence of anemia as high as 48.9% in pregnant women and 38.5% in children under 5 years old. It is even higher among adolescents aged 12-18 years, especially in rural areas. Low income and level of education seem to also contribute to iron deficiency. Indonesia government aims to prevent anemia in young and pregnant women by providing iron pills. Still, the etiology of anemia in Indonesia is various and many elements are preventing Indonesia women to consume pills and/or iron-rich foods. We aim to review the prevalence, risk factors associated with iron deficiency especially among women of reproductive age in Indonesia, including the socio-determinant influence on iron deficiency. We will also discuss the management of iron deficiency in Indonesia in comparison with international guideline to identify the potential gaps.

Keywords iron deficiency, anemia, Indonesia

Introduction

Prevalence of iron deficiency in Indonesia

Iron deficiency (ID) is a common micronutrient deficiency found in low-middle income countries.[1,2] This is the commonest type of nutritional status that have significant impact on health of different age groups in different stage of life especially in children, maternal woman and woman in reproductive age. A recent study in seven Southeast Asian countries found iron deficiency in more than half of the female reproductive age population.[1] In Indonesia, the overall prevalence of anemia regardless gender and age group is 23.7%. Whereas in pregnant woman and children under 5 years old, shown 48.9%, 38.5%, respectively.[2] In iron deficiency cases, the prevalence of children in adolescent age group ranged from 14.1% to 18.4% ; the prevalence of iron-deficient anemia was 5.8%.[3] The high prevalence of anemia among adolescent aged 12-18 years living in rural areas outside Java Island in Indonesia was 57.9%.[4] The prevalence of iron-deficiency anemia (IDA) among adolescent girls aged 12-15 years of low socioeconomic status family in urban areas of Java Island is 15.8%.[5]

Chronic manifestation of iron deficiency is clinically seen in anemic condition and it is known as iron-deficiency anemia (IDA) or nutritional anemia. Iron deficiency can disrupt optimal functioning of the endocrine and immune systems

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and be associated with increased absorption of environmental metal toxins. The iron deficiency has impaired cognitive function in children that will affect a child's future quality of life.[3,6–8]

Risk factors of iron deficiency

Studies have been trying to determine the risk factors for ID, however due to the significant manifestation is ID-anemia related, hence data that makes the risk factors for IDA to be more accessible. Some risk factors have been identified in this article, and author is trying to update data from Indonesian analysis. There are three physiological risk factors that encourage IDA, i.e. infancy, adolescence in girls, and pregnancy. Blood loss, malabsorption, chronic diseases (e.g., chronic kidney diseases, cancer), and genetic abnormalities are the medical conditions that contribute to IDA.[7] Serum ferritin is the standard laboratory indicator of non-inflammatory ID, while serum ferritin and hemoglobin levels are taken into account in IDA.[7]

Age

Children in younger age groups are vulnerable to moderate/severe anaemia, i.e. children aged 6-11 months are 4.71 times more likely to have anaemia than children older than 60 months of age. [9] This age group may have inadequate consumption of iron nutrient which may have resulted in iron deficiency anaemia. There is an increased risk of IDA due to the menstrual cycle in teenage girls.[7]

One Indonesian study found that the incidence of anemia in pregnant women age 21 – 35 years was lower than other age groups. [10] Myanmar and Indian women indicate that different age classes are at higher risk, i.e. women >40 years of age are more likely to be anemic.[11,12] One study in Tanzania found that rising age was associated with an increased risk of anemia.[13] In rural China, women aged 45-49 are more likely to have anemia compared to younger people.[14] The different results suggested a higher prevalence of anemia among adult women than among young women, as contraception protects younger women from bleeding and abortion and the number of live births increases the risk of anemia.[15]

Parity, Number of Live Births and Miscarriages'

Multiparity is related to the number of pregnancy and childbirth, leading to blood loss. Iron deficiency anemia will increase the bleeding episode during labour. Thus, multiparity women were at risk of having more than one bleeding episodes in childbirth. One study found that women with more than two children were not significantly associated with anemia.[12] However, women with more than three children appear to be anemic, as revealed in one study in Ethiopia and Myanmar.[11,16] Studies in India found that anemia was more general among women of high parity due to recurrent pregnancy and insufficient spacing between pregnancies.[17] There was no association between parity and anemia in an observational study conducted in East Java.[18] However, analysis from large sample studies in Indonesia have shown that multiparity increase the risk of anaemia by 58%.[10]

Bleeding by miscarriage can cause anemia. One rural research in China found that women with a history of miscarriage were more likely to have anemia than to adapt to other independent variables. [14] In the study, women had a history of miscarriage and also a history of intrauterine device (IUD) use. The risk of anemia will decrease compared to women with a history of miscarriage but not to women with a history of IUD use.[14] Bleeding has two pathways to induce anemia; the first is through direct blood loss, and the second is through prolonged blood loss. The most common cause of miscarriage is direct blood loss, including loss of hemoglobin-containing red blood cells. Decreased amounts of hemoglobin also lead to anemia. Women suffering miscarriage, in general, can also suffer blood loss. Disorder can be aggravated by extreme bleeding in women. The number of miscarriages in this study will be further explored in order to determine its relationship with anemia.[19]

Body mass index (BMI)

The body mass index (BMI) is measured at the individual level as the height and weight are female-derived measurements. BMI can describe the history of the intake of anemia-induced nutrients. Women with BMI <18.5 kg/m^2 (underweight) were significantly more likely to be anemic than women

with normal weight. BMI was related to malnutrition, which included a dietary deficiency of iron, so women seemed to have anemia. In addition, overweight status was clarified as a protective effect.[20] Increasing BMI was correlated with the risk of recovery from anemia, which indicates that underweight individuals tended to have anemia.[21] However, current research indicated that obesity was more likely to have a duplicitous relationship with ID and it was considered as a nontraditional risk factor of ID.[22,23] Two Indonesian studies back up this janus-faced clinical condition of obesity in pre-marital reproductive-aged women and female adolescent.[24,25] In a premarital reproductive-aged women (age 18 to 22 years) with obesity, their iron status were slightly lower than those who are not obese.[24] Different result shown from another study involving female adolescent (age 10 to 18 years), there was no difference in the iron status of obese adolescent female with normal BMI.[25] The regulation of iron metabolism in the obese occurs, is still on debate. There was an indication that it was through a hepcidin regulation. While there are links between obesity and ID, decreased dietary iron absorption, and increased serum hepcidin, it is still unclear how weight gain affects iron status mechanistically.[23] However, a current study found that hepcidin levels did not contribute to the development of IDA in obese children.[26]

Pregnancy

Pregnancy is the individual state of women because of inner processes. Pregnancy is one factor that may affect anemia because the mother supplies nutrients to her fetus. Pregnancy greatly raises the risk of anemia. Individual level variables revealed anemia-related pregnancy. [27] Pregnant women not only face anemia due to inadequate intake of micronutrients, but also a shortage of iron pills. Pregnant women must eat at least 90 iron pills during pregnancy. Increased needs of iron during pregnancy is one cause of anemia worldwide.[28] Pregnant women provide iron to the fetus so they need more iron for themselves and the fetus.[18]

Level of education and literacy status

Training is a vital aspect of living that has been repeatedly investigated. Training has a long-term role to play in terms of work opportunities, health knowledge, and income that can affect health. One study in Bali confirmed these findings, explaining how education influences the awareness of disease.[29] Ethiopian women without formal education were more anemic than educated women,[30] and uneducated women seemed to have anemia more than educated women in Mali.[20] Education is related to anemia and increased education decreases the risk of anemia in North Sumatra Province.[31] Women in rural China who have completed only or below primary school, were more likely to have anemia than those in higher education.[14] Training influences the knowledge of fitness, socio-economic status and profession, such that women with higher education tend to have knowledge of the prevention of anemia. They had a higher socio-economic status and work that could meet their normal nutritional needs.[29] In addition, low levels of education have been related to unemployment and low socio-economtyle to ease contact. Literacy is defined as the ability to read and write.[32]

Literacy is directly linked to lifesage properly and is related to knowledge to prevent anemia. Illiteracy was significantly associated with high prevalence of anemia during pregnancy.[17] Women's level of literacy was associated with anemia based on a study in Tamil Nadu, India.[33] Women's educational status is important and has led to greater understanding of the value of iron-rich diet, personal hygiene and environmental sanitation.[33]

Frequency of micronutrient intake

The intake of micronutrients is an important eating behavior. Iron-containing micronutrients can increase hemoglobin levels. Fish and meat produce high iron relative to eggs, milk and vegetables. One study in China showed that insufficient riboflavin (B_2) intake was associated with anemia.[34] In low-income countries, riboflavin deficiency was one of the most common vitamin deficiency, particularly in a community where rice was the main food with insufficient milk and meat intake.[35] In support of previous research, pernicious anemia was the most

common risk due to vitamin B_{12} deficiency, a nutrient found in meat, fish, eggs and milk. [36] Intake of micronutrients such as energy, fat, total protein iron, nonheme iron, heme iron, vitamin C, riboflavin and fiber has been significantly associated with anemia in China.[34] Dietary considerations included significant risk factors for iron anemia deficiency due to lower intake of iron from meat.[18] However, a micronutrient rich supplement drink increase haemoglobin level in school-aged children in Indonesia.[37]

Region/Province

Region is one element that defines living environments, such as living in risky areas, which may impact access to food. An analysis of anemia determinants in Myanmar has shown that the geographical region, especially the coastal region, was more likely to have anemia than the delta, central plain and hilly areas.[11] Coastal and delta lands have been vulnerable to natural disasters, including cyclones, floods and landslides that threaten to cause food shortages, increasing food prices and reduced salaries.[38] Study in rural areas has shown that women living in the northwest are more likely to have anemia than other areas.[14] In Indonesian scope, each province had its own geographical characteristics which could constitute a risk factor for anemia.

Birth attendants

The involvement of childbirth attendants is related to accessibility of health facilities. The role of birth attendants includes the management of bleeding and the use of health services to prevent anemia. Traditional birth attendants have played an important role in preventing disease and promoting healthy childbirth in difficult-to-access areas where antenatal clinics have rarely been held.[39] However, unskilled childbirth attendants could not handle bleeding episodes during delivery if there was a shortage of childbirth medical equipment and decreases hemoglobin levels were stabilized.

Socio-determinant influence on iron deficiency

Income level

The level of income is included in the lifestyle domain, as income is derived from work activities. The amount of income is one factor that reflects the economic status and its relationship to access to food. Poor families are more likely to be anemic because of access to healthy food.[40] Family income was correlated with anemia, with household incomes below GDP (Gross Domestic Product) appearing to have anemic family members.[18] Women in Bangladesh's reproductive age were more likely to have anemia. This could be demonstrated by the activities of rural communities and agricultural sectors.[41] The low socio-economic status of pregnant women in rural India was a risk factor for anemia.[17] The socio-economic status was closely linked to anemia due to lack of nutrition and poor health care. In addition, one study in the Indian tribal community showed that women with low economic status were more likely to be anemic.[12] They were unable to access their own income or wealth due to lower rates of extra household employment and reduced economic influence within the household.[40] Lower income households tended to have anemia that could be related to the family dependency ratio. Large low-income families could only meet their basic needs and nutritional needs, but lack access to iron sources and other nutritious food sources.[18] Women with low income levels would have low purchasing power for healthy food.[42]

Increased income, particularly in low to middle income countries, is very important in deciding how to safeguard basic needs such as food. Women with higher incomes will meet various nutritional and food requirements. Lower consumption of nutrients is related to anemia. The income level was also included in this analysis in order to better understand its relationship with anemia.

Social and community networks

Social and community networks generally describe how people interact and engage with their peers. Women's involvement in group activities can reflect social and community networks. Women who

contribute to and engage in group events will affect their health literacy and empowerment. In health care, iron pills are usually given, health support is provided, and other activities are implemented by community services, including women's groups, religious groups and other community organizations.[43] In addition, women's activities were mostly related to health and mostly organized through the Community Health Centre, making it easier to share health information. The Semarang, Central Java study found that peer groups of fertile elderly women in a community such as PKK RT (*Pemberdayaan Kesejahteraan Keluarga Rukun Tetangga*; Family Empowerment and Welfare Organization Neighborhood Association) were significantly associated with anemia prevention knowledge, attitudes and skills.[44] The role of peer group education has changed behavior and improved health promotion and prevention practices. The quasi-experimental research has shown varying levels of understanding, skills and attitudes between intervention and control groups.[45]

Occupation

Occupation is linked to working conditions that can affect women's health. The study stated that women, working as agriculturalists, engaged in risky activities, e.g. working barefoot, so that hookworms could cause infection. Parasitic infection is likely to destroy red blood cells. Similar to farmers, gardeners also had a high risk of anemia because exposure to a pesticide may lead to aplastic anemia. Women working in the industrial sector were also at risk of anemia due to toxic pollutant effects, including cadmium and mercury corresponding to hemolytic anemia.[46] However, one study in Nigeria found that occupation was significantly associated with anemia in which housewives were more likely to have anemia compared to civil servants and traders.[32] According to this report, housewives do not have their own income to select food.

Household food security

Depending on living conditions, household food insecurity is related to food access. A household with food stock can prepare healthy food and is related to prevention of anemia. Food insecurity is characterized as a state of insufficient access to enough food for growth and development processes. Studies have shown a conflicting correlation between food security and iron deficiency. While there is no clear connection between food insecurity and anemia, the widespread assumption of food insecurity is related to household capacity to prepare safe food stock. For families with low economic status or low-income status.[47-49]

Migration is another factor causing food insecurity in the family. Migration is an aspect that defines human movements from the place of origin to the final destination in terms of living conditions. Migrants adapting to a new location may have trouble of getting food. Women from low-income countries were more likely to be anemic since they were an ethnic group that had migrated. They have experienced a lack of access to food.[50] The major cause of migration is economic factors. The key causes of migration were economic factors. Migration can influence diet spending and on improving health outcomes. One analysis in China found that the rates of anemia in migrant households were slightly higher because they were unable to adapt economically well.[51]

Management of iron deficiency in Indonesia (government programs, available guidelines, and policies) in comparison with international guideline: potential gaps

The management of iron deficiency in Indonesia is focusing on the supplementation of iron pills. These tablets, also known as a blood replacement pills, are administered to both pregnant women and women of reproductive age. This act aims to prevent menstrual and iron-deficiency anemia. According to the Ministry of Health regulations, women in reproductive age may take iron pill once weekly and once during menstruation. Pregnant women should take iron pills daily, with a minimum intake of 90 pills. The pill should at least contain 60 mg elemental iron and 400 μg folic acid.[52]

Iron pills intake is linked to the practice and discipline of taking medicine. Distribution of iron pills for the prevention anemia is part of community health care. The evidence based on finding that women who did not regularly take iron pills were more likely to be anemic than women with daily iron

pills.[29] Adequate iron pill intake was associated with anemia based on a thesis from Deli Serdang District, North Sumatra, Indonesia.[31] The qualitative study found that women in Southeast Sulawesi perceived that iron tablets could enlarge the fetus, making difficult to deliver.[53] In addition, avoiding these types of food was thought to have an effect on anemia.[53] Another barrier that prevents female adolescents from taking iron tablets is their perceived benefit from doing so. A study done in an urban city of East Java found that, they are skeptical of the benefits of iron supplements.[54] Still, more research are needed to support that findings.

There is no regulation or guidance in Indonesia to provide initial nor regular screening/assessment of iron status among high risk population. The World Health Organization (WHO) guideline for IDA comprises of assessment, prevention, and control. Before iron supplementation as prevention, assessment of iron deficiency anemia should be done to determine the magnitude, severity, and distribution of iron deficiency and anemia, and preferably its main causes. WHO recommended that assessment of iron status is done by examining the hemoglobin and hematocrit values—a relatively simple and inexpensive measurement. In resource-poor settings where routine laboratory testing of haemoglobin or haematocrit is not feasible, clinical signs should be regularly used to screen individual women and children. The purpose of this screening should be to identify high-risk subjects before the onset of life-threatening complications.

WHO advised to prevent IDA firstly by food-based approaches through dietary improvement. The government should ensure the access to these iron-rich foods. Iron supplementation is the most common strategy currently used to control iron deficiency in developing countries, including Indonesia. This may remain as the only approach until significant improvements are made in the diets of entire populations.

In populations with a severe prevalence of anemia (>40%), iron supplementation should start during pregnancy and continue during lactation for at least three months post-partum, at dosage of 60 mg iron and 400 µg folic acid daily. Similarly, in areas where the prevalence of anemia among women of childbearing age and pubertal girl is severe (> 40%), preventive iron supplementation of 60 mg/day iron with 400 µg folic acid for 3 months should be considered. Supplementation dosage and duration for adolescent girl and boy is the same in that area.

Iron supplementation programmes should be carefully assessed, and their efficiency and effectiveness monitored, to improve critical aspects of the system. Governement should establish a surveillance system to ensure appropriate monitoring of iron status and of programme implementation.[48]

Obviously, there is a big gap between programme set by Indonesia government to prevent IDA and what is guided by WHO. Increased advocacy, exchange of information, development of human resources, and action-oriented research may be the solution for accelerating the achievement of the goals for reducing iron deficiency.

Summary

National socioeconomic development, as well as personal health and productivity, are impaired by iron deficiency. Iron deficiency affects a significant part, and often a majority, of the population in nearly every country in the world.

Pregnancy and women of child-bearing age poses a higher risk for women to develop iron deficiency anemia due to physiological and socio-economic reasons. Programmes for the prevention of iron deficiency, particularly iron supplementation for pregnant women are essential. However, it has also become increasingly evident that the main target group for supplementation to prevent iron deficiency should be all women of childbearing age (in addition to infants older than 6 months, preschool children, and adolescent girls). This target group should not be limited to pregnant women, who are often accessible only through the health system and late in pregnancy.

If women enter pregnancy with adequate iron reserves, iron supplements provided during pregnancy will be more efficient at improving the iron status of the mother and of the fetus. As a result, the risk of maternal anemia at delivery and of anemia in early infancy will be reduced.

The government should mobilize the effective participation of community groups, the private sector, and nongovernmental organizations in

programmes promoting sustainable primary health care, maternal and child health, and prevention of iron and other micronutrient deficiencies.

Finally, iron supplementation programmes should be carefully assessed, and their efficiency and effectiveness monitored, to improve critical aspects of the system. To get here, the Governement should establish a surveillance system to ensure appropriate monitoring of iron status and of programme implementation.

Conflict of Interest

The authors declared no conflict of interest regarding this article.

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LITERATURE REVIEW

The role of iron adequacy for maternal and fetal health

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Abstract

Nearly half of pregnant women in the world are reported to suffer anemia. And most of them are caused by iron deficiency, while the others by folate, vitamin B_{12} or vitamin A deficiency, chronic inflammation, parasite infections and hereditary disorders. Anemia in pregnant women is characterized when <11 g/dL or any time during pregnancy. And when followed by low iron, it's called iron deficiency anemia.

Iron plays an important role in many metabolic processes by transporting oxygen and allowing cells to generate energy. Low iron levels during pregnancy leading to anemia, related to an heightened risk of mother and fetus disease. Iron deficiency anemia can affect fetal development and persist long-term, while mild and serious pregnancy anemia can lead to premature birth, maternal and child mortality, bleeding, and infectious disease. The iron requirement during pregnancy exceeds 1000 mg for red cell expansion, 300 mg – 350 mg for developing fetus and placenta, and 250 mg for variable blood loss at delivery. Iron adequacy during pregnancy can be assured by proper nutrition, iron supplementation and fortification, and intravenous iron or blood transfusion. Iron supplementation is only enough to cover the prenatal iron requirements.

Summary: Iron deficiency leading to anemia, rising risk of negative pregnancy outcomes. To meet increasing iron requirements during pregnancy including iron supplementation, fortification of staple iron foods, and intravenous iron or blood transfusion if required.

Keywords iron, maternal, fetal, health

Introduction

Macro-elements and micro-elements are important for the proper functioning of living organisms. Iron, which is mostly inorganic, is an essential micronutrient and plays a major part in many of the human body's metabolic processes, including oxygen transport, oxidative metabolism, and cell growth.[1-3]

Approximately 3-5 g iron is present in the adult human body (44-55 mg per kg body weight in adult men & women), with hemoglobin incorporating more than 2/3, a four-unit molecule, one heme group and one protein chain that can be fully oxidized into the lungs and can be carried out by the lungs via the arteries to all cells across the body.[2,4,5] The erythrocytes contain many of the iron in the body, such as hemoglobin, whilst ferritine and hemosiderin contain many enzymes in the liver, spleen, bone marrow and myoglobin, including catalase, peroxidase and cytochrome.[3,5]

The intake of iron is present in both iron to heme (10%) and those without heme (90%). Heme iron includes any type of iron from animal products in which the iron is chemically bonded within the porphyrin ring structure as shown in both myoglobin

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and hemoglobin. Iron that is not heme iron is called non-heme iron.[3,5,6]

Iron absorption occurs in the small intestine specifically in the duodenum and the upper portion of the jejunum.[1,6,7] Heme irons are soluble and are easily absorbed by a less unknown process of heme oxygenase 1 (HO-1) through the brush boundary of the enterocyte. Non-heme iron occurs in the intestinal lumen as an oxidized form of $Fe3^{+}$ (ferric) and transformed to Fe^{2+} (ferrous) form either via a brush boundary membrane ferric reductase, probably a duodenal cytochrome b (Dcytb), or by a dietary reducing agent before it can be transported via the intestinal epithelium by a transporter called the divalent metal transporter 1 (DMT1) together with zinc, copper.[1]

It is important to ensure the balance of iron homeostasis in the body as iron plays an integral role in several metabolic processes. Iron homeostasis is also required to prevent iron toxicity, non-protein bound iron (NPBI) reacts with oxygen and produces reactive oxygen species (ROS) with the ability to damage DNA, proteins, lipids, other cellular molecules and stem cells.[1,7,8] Iron homeostasis is controlled by a hepatocyte-producing hormone receptor and binds to ferroprotein named hepcidin (hepatic bactericidal protein) by control of intestinal and tissue release of iron. When iron storage and availability are limited, the amount of hepcidin is limited so that any excess absorbed in the gut or deposited in tissues is released. The contrary is true when storage and bioavailability are high. Then, the amount of hepcidin increases and controls the release of iron from the body through the plasma.[4,7-11]

The role of iron in maternal and fetal health

Iron has been discovered to be necessary for vital physiological body functions, e.g. oxygen transport, hemoglobin and myoglobin synthesis, and cell growth and differentiation.[1]

The average adult body contains around 3–5 g of iron (45–55 mg/kg adult men's body weight).[2] Iron requirements increase dramatically during pregnancy to support an increasing volume of red cells, growing fetuses and placenta plus any expected or unforeseen blood loss at delivery, particularly with caesarean delivery.[5,12] The need for iron for pregnancy is more than 1000 mg, 500 for red cell enlargement, 300-350 for fetal and placental development, and 250 for variable blood loss when delivered.[7,13]

Iron is vital for the production of hemoglobin and is required during pregnancy for the development of the fetal brain. Throughout pregnancy., it is necessary to maintain an adequate maternal diet only enough to provide the critical nutrient for fetal development and birth outcomes. The disparity in maternal nutrition contributes to a rise in the risk of chronic post-life disease.[14]

Maternal health related to iron

The iron requirement increases during pregnancy, the maternal hematological system undergoes physiological changes to accommodate the growth of the fetus and placenta throughout pregnancy. Plasma volume increases and the red cell mas duplicates to ensure proper circulation and oxygen supply to the maternal organs including to the placenta for fetal development and to promote the impact of blood loss during supply.[12,14-16]

Iron deficiency is a major micronutrient deficiency in the world. The prevalence of iron deficiency between expectant mothers, babies and young children may be due to high iron requirements during periods of rapid development.[8,14,17] Pregnancy anemia is the result of nutritional deficiency due to the lack of iron and folate in the diet, but other factors can additionally cause anemia including decreased absorption, chronic blood loss, increased demand, concomitant medical disorder, and malaria.[18] That describes gestational anemia as a hematocrit <33 % and/or hemoglobin < 11 g/dL or at any time during pregnancy. The Centers for Disease Control and Prevention (CDC) describes anemia as hemoglobin < 11 g/dL and/or hematocrit less than 32 % in the first and third quarters and hemoglobin < 10.5 g/dL and/or hematocrit less than 32 % in the second.[7,13,19]

Women who are pregnant are identified to have adverse maternal and newborn health effects and make a greater threat of death during pregnancy and during the post-natal period. The potential negative health consequences for the mother include fatigue, weakened immune function, reduced tolerance to blood loss during delivery, an increased risk of infection, and a shortened lifespan due to heart

failure. Postpartum depression and behavioral problems exist in some cases of childbirth. Anemia during pregnancy is linked to several health risks including preterm birth or low birth weight. Preterm and Low Birth Weight are still the leading causes of neonatal death in some of the countries, often associated with an increased risk of intrauterine death, a low APGAR score of 5 minutes, and an intrauterine growth restriction.[10,19-23] The A study confirms a connection between low hemoglobin levels in women during pregnancy and possible increased risk for postpartum hemorrhage and includes evidence of a connection between extreme anemia and uterine atony requiring emergency hysterectomy.[18]

Fetal health related to iron

Restricting fetal growth is significant for determining a child's health in the immediate future. Infants who do not grow to their maximum size are at higher risk of dying in their first year and of developing chronic diseases later in life, including coronary heart disease and type 2 diabetes. The infant is dependent on certain nutrients passed from mother to child. However, maternal nutrition plays a vital role in fetal development, and it is during the first trimester when fetal growth is most vulnerable. Iron deficiency is by far the greatest micronutrient deficiency. Data indicates that early pregnancy iron deficiency has an adverse effect on fetal development. Maternal anemia frequently exhibits a risk of low birth weight, either due to premature birth or reduced fetal growth linked to IDA, or due to delayed neurocognitive development.[10,14,24] Iron is essential for enzymes involved in specific cerebral functions including serotonin and dopamine, a precursor to epinephrine and norepinephrine, myelination and production of neurotransmitters.[14]

There is evidence that iron deficiency during pregnancy and/or anemia later in pregnancy affects learning, motor and emotional development, and children who experience perinatal iron deficiency are at greater risk of failing to meet educational goals. In addition, children who also undergo iron deficiency are more likely to bear as adults. As a result, a shortage of iron in one generation will lead to a shortage of iron in the next. Given the possible neurological effects, such as stunted motor development, lower IQ, learning disabilities, and memory deficits.[25,26]

An alteration in the gut microbiome through an increase in intestinal iron results in the growth of potentially pathogenic bacteria. By at least one week of life, elevated intraluminal iron is most likely to occur in elevated dietary iron intake, inflammation, or both. Both are states characterized by low iron absorption as well as high levels of non-absorbed iron that remain intraluminal. Whether changing the microbiome increases the incidence of infectious diseases is a significant issue. These findings will likely affect future policy decisions.[8] The main nutritional function of iron is to promote post-birth erythropoiesis, with insufficient preterm infant iron stores unable to support post-natal erythropoiesis and post-birth development.[13]

Risk factors for iron deficiency in maternal, infancy, and toddlerhood

Iron is typically in low amounts in diets. If iron is not being absorbed from the diet the person may have a nutritional iron deficiency.[1] Iron deficiency anemia is the highly typical form of anemia that occurs in adolescents and has several risk factors ranging from low iron intake, menstrual status and pattern, obesity, socio-economic and malnutrition as risk factors for IDA, especially in developing countries.[27] Maternal pregnancy smoking and pregestational or gestational diabetes mellitus are major risk factors for low fetal iron status.[14] Iron deficiency in pregnancy is one of the most commonly diagnosed causes of pregnant women's health issues and the poor health of newborns. The factors of primary food shortages, parasites, and parasitic disease during pregnancy are major causes of anemia.[28]

Iron accretion occurs during the third quarter of pregnancy. Infants have enough iron at birth to cover their iron needs during the first four to six months. Iron transfer from mothers to children in conditions like diabetes is reduced, but in children less than 5 years of age, iron is not impaired by maternal anemia or factors leading to decreased iron transport during pregnancy.[29]

Management of iron deficiency during pregnancy and lactation

Iron and anemia are important health indicators in mothers and in children. Iron deficiency is a significant health issue for pregnant women before, during, and after pregnancy and this deficiency directly associates with negative pregnancy outcomes. Effective management is crucial to minimize the need for red cell transfusion, and especially the need for transfusions for a pregnant woman. The purpose of encouraging iron fortification during pregnancy is to reduce maternal morbidity, to provide sustenance for the fetus, and to prepare a newborn for early postnatal life. The growing evidence supports the notion that prenatal iron status affects iron status in the children.[8]

During pregnancy, a mother takes in an average of 1,000 mg of iron. The baby's dosage rose from 6 mg/day in the first trimester to 19 mg/day in the second trimester to 22 mg/day in the third. Unlike the recommendation for non-pregnant, non-lactating women, the recommendation for lactating women is based on only the presumption of lactation-induced amenorrhea and does not take into account that some women enter or end iron insufficiency or deficiency during pregnancy.[7,13,30]

UK guidelines recommend that pregnant women be advised of iron-rich food sources and any factors that may inhibit or promote iron absorption, as well as why fulfilling iron requirements during pregnancy is beneficial. The recommended daily intake of iron as a function of age is approximately 27 mg in the UK and 30-60 mg in most other countries.[7,16,31,32] The estimated population requirement or average population requirement (AR) ranges from 7 mg/day to 22 mg/day and the recommended daily dietary allowance (RDA) or population nutrient intake (PNI) or recommended dietary intake (RNI) ranges from 11.5 mg/day to 27 mg/day for 97.5 mg/day in the population.[9]

During pregnancy, iron absorption triples, with the woman's iron requirement rising from 1-2 mg to 6 mg per day. The foods with the highest levels of dietary heme iron are red meat, poultry, and fish. Heme or non-heme iron absorb 2-3 times faster. The food as a whole has many other organic compounds. that enhance the bioavailability of non-heme iron in other sources. Vitamin C (ascorbic acid) aids in the absorption of iron by non-heme foods, thus increasing vitamin C in the meal. Fermentation and germination increase the bioavailability of non-heme iron by reducing the phytate content, an inhibitor for iron absorption. Coffee and tea tannins hinder the absorption of iron in the body. If a woman becomes iron-deficient in pregnancy, she must be supplemented through diet or by taking oral formulas. The minimum daily dosage of iron for iron deficiency is 100-200 mg. High doses of these nutrients should be avoided, as high doses cause increased oxidative stress and an increased risk of infection.[33,34] For better purposes, it is advised to take iron supplements on an empty stomach because it is absorbed less efficiently when taken on a full stomach.[30,31] The increase in hemoglobin levels in the blood indicates a positive response to the treatment and supports the diagnosis. The maximum rate of iron absorption is 20 to 25 % among individuals who are iron deficient when taking oral iron supplements. The effectiveness of oral iron supplementation is reduced when intestinal absorption is compromised (e.g., in celiac disease, autoimmune gastritis, ACD, or post-gastric or duodenal resection,) or the iron loss is significant and/or persistent. Adherence to oral iron therapy can be an obstacle to treatment since a patient may experience GI adverse reactions such as nausea, epigastric pain, diarrhea and constipation.[35,36]

Intake of intravenous iron helps treat the symptoms of iron-deficiency anemia. Parenteral therapy can be used in patients unable to consume or tolerate oral therapy, such as those who have undergone gastrointestinal surgery or pregnant women who have experienced inadequate oral therapy. In patients with confirmed iron deficiency anaemia and Hb <100 g/L after 34-week gestation, IV iron should be considered. Blood transfusion is recommended for pregnant women with hemoglobin levels less than 8 g/dL unless reassuring fetal cardiac tracing and normal amniotic fluid volume is present.[35,37] Two units of packed red blood cells should be administered if transfusion is performed, and the condition of the patient should be re-evaluated to guide future care.[35] Transfusion is simply a short-term solution for a problem, and proper care must include the diagnosis and treatment of the underlying condition. In addition, intravenous iron (as well as erythropoiesis-stimulating agents, if

necessary) tends to maintain Hb levels and iron stores, and avoids transfusions in the future.[36]

Conclusion

Iron deficiency during pregnancy provides women and their babies with better outcomes. The usefulness of iron supplementation more than counterbalances any dangers to pregnant women that lack iron. During pregnancy, the mother's body requires an increased amount of iron to support the growth of red blood cells, fetus, and placenta and blood loss at delivery. During pregnancy, meeting the iron requirement is vital to preventing adverse health outcomes for the mother, child, and fetus. The most prevalent nutrient deficiency worldwide is iron deficiency, and it is most prevalent in pregnant women because the additional iron critical for fetal development is not readily received by the mother's body. WHO recommends universal oral iron supplements for pregnant women. The recommendation to take iron or iron-folic acid supplements to reduce the risk of adverse pregnancy outcomes and increase offspring iron stores. Provision of low doses of iron and folic acid when stores are nearly depleted is the most effective and safest way to achieve iron status.

Conflict of Interest

The authors declared no conflict of interest regarding this article.

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LITERATURE REVIEW

The role of iron for supporting children's growth and development

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Abstract

According to the World Health Organization (WHO), Iron Deficiency (ID) affects around 2 billion people worldwide. Early childhood ID has been associated with permanent cognitive deficits associated with CNS structural, metabolic impairment, growth retardation, impaired immune response, psychological abnormalities, and behavioral delays. This literature review will focus on the important role of iron in child growth and development.

Iron is necessary for various cellular processes in the growing brain especially when it comes to memory and learning. Children with early ID show cognitive deficits that persist; however, prompt iron treatment soothes the problem. A chronic ID group reported substantially lower scores of vocabularies, ambient sound perception, and motor measurements in a recent study relative to infants with normal nutritional iron status at 6 months and 14-18 months. Children's iron requirement differentiates based on individual age. The daily iron requirement for one- to three-year-old children is 7 mg. Some risk factors of infants and toddlers in developing ID are insufficient food intake, poor bioavailability, reduced absorption, increase demand, increase losses, cow's milk enteropathy hookworm infection, and maternal gestation.

Iron plays an important role in promoting children's growth and development. Physical health and nutrition are important in the first two years of life. Children who are unable to achieve iron adequacy will possibly show permanent cognitive deficit and impaired motor growth. Thus, iron supplementation may only be successful in early prescription after diagnosing iron deficiency.

Keywords iron, children, growth and development

Introduction

Every child has the right to gain optimum cognitive, social and emotional behavioral development. Children who have yet to meet their developmental and growth potential are likely to experience problems in school and lower their lifetime income, resulting in greater socioeconomic inequality and leading to more generational poverty.[1,2] It is widely accepted that health and nutrition are important in the first two years of life. This period is the window of opportunity that may also be ideal for mental growth, because the brain's intellectual potential reaches its greatest extent before the age of three years.[1, 3]

Nutritional deficits which affect brain growth and cognitive function have been shown to reduce global IQ by at least 10 points. Iron deficiency affects more than 2 billion people around the world. In preschool children, the prevalence rate is highest among 4- to 23-month-old (47.4 %). Iron is essential for the growth and the differentiation of different tissues. The neurons and brain tissue in the developing fetus and newborn are more sensitive to the lack of nutrition than the brain in later childhood and adulthood.[4]

Early childhood ID has been linked to many consequences, some of which have been potentially

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permanent cognitive deficits associated with structural and metabolic impairment of the CNS. Neuropsychiatric symptoms are of utmost concern even though they take place after treatment with iron and anemia.[4,5] A few medical sequences are linked to ID. These include impaired immune response, poor temperature control and compromised growth. In general, emotional regulations and affective responses are present in the literature as mental and physiological abnormalities or delays which follow ID; impaired motor growth and fine motor control; general and unique cognitive delays.[6]

The review of relevant literature will address the role of iron in children's growth and development, its effects on ID, and who are at risk of it. We also present a range of recommendations for iron consumption, how to fulfil the iron requirement in children, and recent research on the role of iron in children.

The role of iron for supporting growth and development in children

Iron is required to produce energy and cellular metabolism. For many mitochondrial enzymes, iron is an important mineral integrated for the development of oxidative phosphorylation and ATP, including cytochromes, NADPH and flavoproteins. Iron encourages cells to proliferate and grow through ways such as improving oxygenation and hemoglobin levels, and growth factors such as growth factor-1 (IGF-1). Iron deficiency anemia (IDA) induces a hypoxic condition in the body which consequently inhibits liver growth hormone, insulin-like IGF-1, and IGFBP-1. Stunting suggests both a sequential failure in development and a low total childhood iron status. The cause of stunting is diversified, but most include under optimal impact of infant and young child feeding (IYCF), infections and inadequate healthcare practices.[4,7]

Not only for physical growth, but iron is also required to sustain neuronal production and synaptic activity. At birth, the brain is made up of 50 % of the resting metabolic capacity. More than half of the energy used in the brain comes from what is required to maintain the Na^+, K^+, and Ca^{2+} gradients necessary for synaptic transmission. When creating and sustaining complex neuronal structures, a lot of energy is needed. A large amount of iron is required for multiple biological processes in the developing brain by incorporating iron into heme-containing proteins and non-heme iron-based proteins (e.g. hydroxylases, iron regulatory proteins, and enzymes involved in the metabolism of nucleic acids).[4]

Several studies have shown the negative effect of ID on learning and memory, behavior, affective and social behavior. In humans, late gestation through 2-3 years of age is associated with maternal iron deficiency which causes learning and memory deficits which persist beyond the time of maternal iron treatment. There are two types of memory: explicit and non-explicit (or implicit). Declarative memory is information and events that a person can consciously remember. Non-declarative memory refers to memory for tasks or skills that don't need to be consciously remembered. Neural structures responsible for long-term and short-term memory are intricate with multiple connected areas. Many factors can influence the proper growth and development of the brain such as growth factors, synaptic activity, and climate. As the hippocampal memory growth accelerates, it becomes most vulnerable to develop early IDs during gestation through age 2-3 years. During the developmental period when humans are most vulnerable to memory impairments, hippocampal function is at its peak. The hippocampus is responsible for memory formation and processing. Studies have shown that the hippocampus is especially vulnerable to early ID damage. The fragility is largely due to rapid maturation during the late fetal-neonatal phase in human and animal trials, which are iron-deficient. Early-life ID's impair brain function due to defects in iron-containing proteins.[4]

Observational research found relationships in children with low cognitive growth, poor school performance, and behavioral problems. Several possible pathways connect iron deficiency anemia (IDA) to cognition. Children with IDA tend to not move about or explore their world, which contributes to developmental delay. In children with IDA the neural transmission of auditory and optic nerve impulses occurs at a slower rate. A study demonstrated an association between changes in nerve myelination and deficiencies in iron status.[8] Behavioral issues are hypothesized by decreasing Da-Dd2 (dopamine Dd2) receptor functional activity. One of the main consequences of iron

deficiency was the reversal of circadian pain threshold cycles, stereotyping, motor function, and thermoregulation. Beaton study from iron in the infant diet book concluded that circadian cycles of hemoglobin, hematocrit, serum iron, and transferrin saturation in male and female rats are consistent. The blood index levels are also age dependent. In normal populations, these levels at 0-13 years of age are higher than 14-20 years of age, and they rise later in life. Some researches have found that anemic infants were less sensitive to the examiner, their mother, and other people. In general, they were unhappier, less goal-driven, less attention spans, less verbal, and less moving.[9]

Impact of iron deficiency in children

Disruption of the supply and demand of fetal iron early in life results in total body and/or tissue-specific ID. There is a compelling evidence that infants (6-24 months) with intellectual developmental disorder are at risk of poorer short- and long-term development. Children with early ID show cognitive deficits that persist; however, prompt iron treatment soothes the problem. [4, 10] Changes in the mesolimbic pathway, where dopamine plays a critical role in behavior, can help explain altered socio-emotional activity in iron-deficient infants.[10]

A chronic ID group exhibited significantly lower scores on vocabulary, ambient sound perception and motor measurements in comparison to infants with regular dietary iron status at 6 and 14-18 months. Results from this study found that cognitive and motor functions were significantly reduced due to prenatal exposure to ID. Iron deficiency anemia slows down cognition in infants while limiting brain lesions. Children and teens who smoke often have impaired fine-motor skills and have weak gesture apraxia.[9]

For instance, 9- and 12-month-old children with IDA who have a short-term impact show a degraded memory processing. Iron-deficient diabetic mothers' new-born babies show diminished auditory memory of the mother's voice. Long-term effects of iron deficiency in children is that the deficiency of 3.5 years of age has impaired memory recall during imitation activities, and the degree of memory and learning dysfunction is directly associated with the degree of ID at birth. Low iron stores in 5-year-old children can affect how the children develop in terms of cognitive skills, fine motor skills, and problem solving. Children with IDA have lower psychomotor development scores, increased frequency of school grade repetition, reduced visual memory output, and increased anxiety, social issues, and attention problems as young as 11-14 years. These brain function defects persist despite the normalization of iron status in early childhood.On the other hand, 3.5-year-old children who have been iron-deficient at birth showed poorer memory performance during incited impersonation activities, and their degree of learning and memory deficiency was directly associated with the level of birth ID. At five years of age, children born with insufficient dietary iron showed a decline in language development, fine motor skills and handling ability which was not observed in children born with sufficient iron stores. As early as 11-14 years of age, children suffering from IDA had lower psychomotor development scores, increased frequency of grade repetition, reduced visual memory output, and increased problems with anxiety and attention, compared to those who were iron-deficient as babies. These cognitive defects persist into adulthood despite iron levels normalizing in early childhood.[4]

Recent studies on iron role for supporting growth and development in children

Jáuregui-Lobera's studies demonstrate that harmful effects occur with ID, including cognitive deficit, actions and motor skills impairment. External variables such as socioeconomic status can confuse the causal relation between ID and the negative results. Iron deficiency, iron deficiency anemia, and non-iron deficiency anemia lead to certain cognitive deficits although it remains unclear if these deficits are the same. These cognitive deficits can happen at any time. Hemoglobin levels appear to indicate cognitive efficiency, but at the same time iron supplementation can enhance cognitive function regardless of hemoglobin levels. The ID hypothesis is linked to the brain damages such as changes to the hippocampus, mitochondrial damage, brain dopamine metabolism, and myelination. Supplements should be used only based on

established indications, as not to abuse regular use. Using multi-supplements does not seem to add value compared to using individual supplements. Supplementation progress could be dependent on early prescription after diagnosing iron deficiency. Whether this supplementation is effective or not remains controversial, depending on therapy timing (e.g. critical periods).[10]

Iron deficiency (ID) may alter basal ganglia function, resulting in changes in dopaminergic activity causing reduced motor cortex myelination and related areas. Some of the processes underlying the processes arise late in pregnancy and early in infancy. Samantha McCann et al. found early childhood iron supplementation to be beneficial in promoting motor growth, but this effect may be minimized during later childhood. Their findings support the timing hypothesis and indicate that infant iron nutrition may be particularly relevant for motor development.[11]

Ana Ferreira *et al*.[12] revealed that iron deficiency and impairment correlated with motor and cognitive disability and changed social functioning. Studies showed that iron interventions could only effectively correct altered iron levels but failed to reverse cognitive or behavioral changes. The shortcomings of intervention studies was illustrated by claiming that iron dysregulation cannot be reversed by intervention. Cognitive stimulation and social interventions must be coupled with iron levels, a recommendation that is in accordance with findings from psychologists and sociologists.

David Mattei *et al*.[13] have proposed that early life environments, especially the fetal and early post-natal environment, affect health outcomes and risk of disease in multiple organ systems later on. Nutrition plays a central role in all environmental factors. The basis for lifespan functions is formed from conception to approximately 3 years. Well-nourished children are more likely to have positive social repercussions in their cognitive, motor, and socio-emotional capacity. Early exposure to these skills is essential for future neuropsychological disorders, mental diseases, poor school performance, early school dropout, low-skilled jobs, and poor care of future children. Epigenetics is the leading theory for the long-term effects of early environment, especially early childhood.

Required daily iron intake for children by stage

In the 1950s, studies of body iron in the human body found that the very first body iron is around 75 milligrams per kilogram at birth. In normal birth weights babies, there is most of the body's iron in the blood hemoglobin, but some is also contained in the body's stable term infant, normal birth weight equivalent to approximately 25 % of the body's iron. [14] When iron is recirculated from senescent cells by erythrocytes, it is moved from hemoglobin to iron stores. For the next few months, as the baby develops and increases blood volumes, iron is carried into the blood cell from stores, making the baby self-reliant with iron until the baby doubles its birth weight at around 4-6 months. Even though exclusive breastfeeding may be deficient in iron of a low concentration, it is meeting the requirements of infant iron.[15]

From age 6 to 24 months, the infant is dependent on additional iron intake and the requirement for iron per kg of body weight is high as compared to any other lifespan due to rapid growth. According to previous studies, the total volumes of a person's total body iron must be double from 300 to 600 mg, assuming an average body weight of 7.5 kg at 6 months (or 70 mL/kg), and a 7 mg/kg (or 10 mg/kg) at 24 months. The theoretical requirement for iron is 0.076 mg/kg/day, but only 0.76 mg/kg/day is absorbed, which is less than half the required intake. After puberty, iron requirements are lower because an individual's body reaches a more mature stage of development. Various authorities recommended various daily intakes of iron, which are 6-12 months of 0.9-1.3 mg/kg, 5.8-9 mg at age 1-3, 6.1 to 10 mg at age 4-8 and between 9-13 years of age 8 and 11 mg/day.[15]

For children between 1 and 3 years of age the average RDAs in Europe are around 10 mg. Recommended iron for infant between 6 and 36 months of age is 7 to 8 mg per day in many European countries, including France, Germany, Italy, Spain, the Netherlands and the United Kingdom. Using the current analysis the estimated average (EAR) requirements for 6-12 months and 12-36 months are 6 mg/day and 5.3 mg/day and the intake of iron deficiencies for the 6-12 months at 7.8 mg/day and for 12-36 months at 6.9 mg/day in the United

Kingdom RDA.[16] The iron RDA in Indonesia is approximately 7 mg/day for 6-11 months, 8 mg/day for 1-3 years, and 9 mg/day for 4-6 years of age.[17]

Risk factors of inadequacy of iron intake

Infants and toddlers are at risk of developing ID. Here are some explanations about the risk factors of ID in children.

1. *Dietary inadequacy and low bioavailability.* Insufficient consumption in the developed world is the most common cause of malnutrition in infants. Iron is absorbed more effectively in infants fed breast milk than in infants fed formula milk. Therefore, the needed intake of breastfeeding infants is correspondingly lower. The iron found in cow's milk is less bioavailable. For adequate absorption of iron, one needs a diet containing a combination of meat, egg, fruit and vegetables.[14]
2. *Impaired absorption.* Malnourishment of proteins and energy may impede mucosal absorption, protein synthesis, exacerbation and deficiency caused in such children almost inevitably. Other disorders which are rare in infants include bowel disorders including celiac disease, inflammatory bowel disease, blind loop syndrome and gastric disease.[14]
3. *Increased demand.* Children have a high need for iron during their first year of existence and during rapid growth periods. Enough iron is available during a baby's early development to promote healthy development up to age 6. Children who are born prematurely will likely not have fully developed iron stores and may require additional iron. It is already well known that iron in milk alone is inadequate to sustain the continued rapid development of this child. Further dietary iron is necessary to avoid iron deficiency. Iron requirements are particularly high during a teenager's adolescent growth period.[14]
4. *Increased losses*. Iron deficiency results from blood loss. Chronic gastrointestinal failure in older children can also occur due to inflammatory bowel disease, which may be "silent" before anemia is progressed due to adaptation.[14]
5. *Cows' milk enteropathy.* Colitis in infants can occur in those fed on cow's milk, or in those fed on cow's milk-derived formula. The occult blood loss has a major impact on the iron reserves of younger babies. Studies show that the amount of occult blood decreases at a steady pace until it is essentially gone by age one. For one reason, it is recommended that children should not be fed whole cow's milk until after the first year. The only two good substitutes are iron-fortified formula or breast milk.[14]
6. *Hookworm infection*. Hookworm infection is caused by *Ascaris lumbricoides or Ancylostoma duodenale*, which affects 1 billion people worldwide. Eggs released through the digestive tract hatch into larvae that can survive for three weeks before humans come into contact with them when walking through polluted soil. The larvae enter the lungs via the respiratory vasculature, climb into the bronchi, and enter the larynx via the epiglottis. The larvae develop into the adults in the small intestine where they attach and feed off from the hosts. Adults worms are capable of living for 2 years or so. With a chronic lack of blood, an iron deficiency is observed. The prevalence of hookworm infection increases as one approaches adulthood, reaching a plateau in late adolescence.[14]
7. *Maternal gestational complications.* Neonates may also have impaired iron status due to extreme maternal ID, uncontrolled diabetes mellitus, high blood pressure, smoking, infection, placental insufficiency, premature birth, and rapid fetal development.[4]

How to meet iron intake adequacy

There is a responsibility to ensure adequate access to food that is rich in iron. Iron enrichment of agricultural crops (rice, maize, flour, cornmeal) is also practiced in some countries, including Asia, Africa and Latin America, and is suggested by the World Health Organization. For infants 6 to 23 months, the WHO recommends that the supplement to prevent ID/IDA should be 10-12.5 mg of iron per day (drops, viscous recipes or tablets), and children between 5 and 12 years of age should receive 30-60 mg of iron per day (tablet or capsule) for three months per year.[18] WHO recommends that all children between the ages of 6 and 23 months living in areas where the prevalence of anemia exceeds 20% should be given fortified complementary foods.

Minimal Nutrient Platforms (MNPs) are single-dose containers of liquid-coated iron paired with other micronutrients that can be blended into food to provide micronutrient intake. MNPs are emerging as the preferred community-based solution to address iron deficiency in children; Over 16 million children were treated with MNPs in 2017.[19]

Iron levels are low in human milk, but absorption is high. Exclusive nursing delivers high levels of iron during the first few months of life. After the second half of the first year, human milk cannot meet the increased iron needs; rather, iron-fortified formulas must be used. Using infant formula can also help mitigate this type of issue. In developing countries, there are numerous additional foods that can be added to the infant diet for about 6 months. However, they are usually low in iron and do not replace the iron that is depleted in breast milk.[6] Currently, about 45% of children under 5 years old have ID with anemia while the number is less than 7% in developed countries. From two years ago until the present day, an estimated 2 % to 6 % of European children are affected. The introduction of enriched food and supplements led to this reduction.[10]

Premature babies (less than 37 weeks in gestation.) who are exclusively breastfed should receive 2 mg of elemental iron supplementation each day from birth until at least 12 months of age, except for those who have received multiple blood transfusions. In full-term safe babies, hematologic components are enough to manage the first six months of life. The American Academy of Pediatrics (AAP) suggests that the first four months of a baby's life is the optimal time to supplement with iron. **Table 1** lists the daily iron supplements recommended for children. **Table 2** demonstrates different oral iron formulations and suggests which product is best suited for treatment of anemia. *Ikatan Dokter Anak Indonesia* (IDAI) or Indonesian Pediatric Society recommends iron supplements for all infants and children below two years of age who live in areas where there is a high prevalence of iron deficiency, or those who are not receiving fortified foods. Infants who were breastfed exclusively and didn’t take in enough iron from their diet are recommended to take a supplemental iron supplement of 1 mg/kg per day **Table 4**.[21]

Adults at risk for iron deficiency anemia are suggested to take iron supplements without screening if the prevalence of iron deficiency is over 40%. Iron supplementation given as 2 mg/kg/day equivalent for 3 months can be effective. For young children, iron supplementation is generally recommended at a dosage of 60 mg per day. By feeding infants formula which has enough iron in it, formula-fed infants rarely need additional iron. For children aged one to three, the approximate 7 mg daily iron requirement is met by eating iron-rich foods. Inadequate intake of iron can lead to iron deficiency. Greater improvement in hemoglobin concentration can be achieved through iron supplementation, but healthy children are more likely to tolerate iron-fortified foods. **Table 3** lists various infant foods and their iron content in milligrams. If iron supplementation is difficult, supplement given intermittently would still increase hemoglobin concentration and reduce the risk of iron deficiency.[20,21]

Summary

Exposure to iron plays an important role in the health of children. Cell metabolism and proliferation are required to produce energy. As well as, iron supports neuronal activity and the growth of the brain. Physical and nutritional health is critical for the child's health in the first 24 months of life, as this is when the brain is most malleable. It affects cognitive function, motor functions, socio-emotional development, and neurophysiological development. The iron requirement differs between individuals, depending on age. Children who do not receive sufficient iron will often develop permanent cognitive deficits and motor deficits. Iron supplementation is only effective when prescribed early on after the patient is diagnosed as being iron deficient. In the end, it is best to meet the iron needs according to children's age to avoid irreversible effects, and for further research to be conducted so that iron supplementation can repair those negative effects.

Table 1. Elemental iron supplementation or requirement in children[20]

Age	Iron supplementation or requirement
Preterm (<37 weeks' gestation) infants: 1 to 12 months	2 mg per kg per day supplementation provided exclusively during breastfeeding. A suggested 1 mg per kg per day ingestion for iron-fortified formula.
Term infants: 4 to 6 months to 12 months	One milligram per kilogram per day supplementation for exclusively breastfed children. It's unnecessary to take supplements if using iron-fortified formula.
Toddlers 1 to 3 years	Take 7 mg daily; modify your diet and/or supplement if anemic.
Children 4 to 8 years	Require 10 mg daily; Modify diet and/or supplement if anemic.

Table 2. Oral iron formulations and doses[20]

Formulation	Doses (element iron)
Ferrous fumarate	Tablet: 90 (29.5) mg, 324 (106) mg, 325 (106) mg, 456 (150) mg
Ferrous gluconate	Tablet: 240 (27) mg, 256 (28) mg, 325 (36) mg
Ferrous sulfate	Drops and solution: 75 (15) mg per mL Elixir and liquid: 220 (44) mg per 5 mL Syrup: 300 (60) mg per 5 mL Tablet: 300 (60) mg, 324 (65) mg, 325 (65) mg Extended-release tablets: 140 (45) mg, 160 (50) mg, 325 (65) mg
Polysaccharide-iron complex and ferrous bisglycinate chelate	Capsule: elemental iron (150 mg, 150 mg with or without 50 mg vitamin C) Elixir: elemental iron (100 mg per 5 mL)

Table 3. Iron content in common foods[20]

Food (serving size)	Amount of elemental iron (mg)
Soybean: cooked (1/2 cup)	4.4
Lentils: cooked (1/2 cup)	3.3
Spinach: cooked/ boiled, drained (1/2)	3.2
Beef, cooked (3 oz)	2.5
Beans (lima, navy, kidney, pinto): cooked (1/2 cup)	1.8 to 2.2
Baby food brown rice cereal: dry (1 tbsp)	1.8
Baby food green beans (6 oz)	1.8
Baby food oatmeal cereal: dry (1 tbsp)	1.6
Turkey and chicken: dark meat (3 oz)	1.1 to 2.0
Baby food lamb or chicken (2.5 oz)	1.0 to 1.2
Baby food peas (3.4 oz)	0.9

Table 4. Elemental iron supplementation dosage and duration of supplementation[21]

Age	Iron supplementation dosage or requirement	Duration of supplementation
Baby*:LBW (Low Birth Weight)	3 mg/kg/day	Age 1 month – 2 years old
Term infants	2 mg/kg/day	Age 4 months – 2 years old
Toddlers 2 – 5 years	1 mg/kg/day	Twice a week for 3 months per year
Children 5 – 12 years	1 mg/kg/day	Twice a week for 3 months per year
Adolescents 12 – 18 years	60 mg/day#	Twice a week for 3 months per year

Notes: * Maximum dose for a baby: 15 mg/day, a single dose
Add 400 μg folic acid for girls

Conflict of Interest

The authors declared no conflict of interest regarding this article.

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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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LITERATURE REVIEW

Optimizing iron adequacy and absorption to prevent iron deficiency anemia: The role of combination of fortified iron and vitamin C

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Abstract

Iron is a vital nutrient to promote the availability of tissue oxygen, cell growth and control of differentiation, and energy metabolism. Preventing Iron Deficiency Anemia (IDA) is necessary because iron is vital to central nervous system growth and development especially in the first years of life. Iron-rich complementary foods are recommended in infants around 6 months of age because iron store is depleted. Better understanding of iron absorption process and factors affecting its absorption and bioavailability is necessary to prevent iron deficiency and can be a dietary strategy to mitigate iron deficiency. Meat and iron-fortified food are the main sources of iron in the diet, and it is essential to introduce supplementary food to improve iron absorption. Additional foods such as cereals, cow milk and soybeans such as phytate, polyphenol and calcium are inhibitors which require care to prevent IDA. Ascorbic acid is an effective iron-absorbing enhancer, which is useful to reduce the effects of any known nonheme iron inhibitor. In iron-fortified foods, combination use of vitamin C (ascorbic acid) is recommended in molar ratio of 2:1 (with cow's milk and low-phytate cereal foods) and higher molar ratio of 4:1 (with higher phytate such as soybeans).

Keywords iron, iron absorption, vitamin C, iron deficiency anemia

Introduction

Iron is a precondition for all human cells and is part of almost all the living cells. Iron is required to promote tissue oxygen, cell growth and the regulation of differentiation and energy metabolism. Body iron levels are mainly managed by controlling iron absorption in small intestine, enabling accurate absorption to match unregulated losses. Depending on physiological demand, mechanisms regulating iron absorption often allow appropriate increases or decreases. Iron bioavailability is also limited, which explains why people vary in iron and iron stores. Various abnormalities and diseases can also influence regulation of iron absorption rate and iron storage. Therefore, dietary iron absorption by the proximal intestine is regulated precisely by cellular and systemic factors to ensure adequate body iron levels.[1]

Body iron present at birth is necessary in the first six months of life for the physiological requirements of infants with an adequate birth weight. The infant relies quickly on readily absorbed iron. The body iron content could increase around 70% in between 4 and 12 months. The average dietary daily requirement for iron in 7–12 months age was at 0.69 mg. The requirements reduced after 12 months, an

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average 0.63 mg/day for a child aged 18 months. Breast-fed babies with adequate weight rarely experience iron deficiency by 6 months. However there is a rapid rise in risk for those who remain breastfed for the next three months when there is no rich supply of iron in other dietary products.[2]

The World Health Organization estimates that an iron deficiency anemia (IDA) is an estimated 25 % of the world population. Most of this anemia due to lack of iron diet, but iron absorption and available iron can also be reduced due to infectious diseases and other chronic inflammation. Micronutrient deficiency is found worldwide, and iron deficiency (ID) is the most common. Young children have higher risk since they need high iron requirements to grow. Some risk factors include higher IDA prevalence, underweight baby birth, excess cow's milk, small intake of iron-rich complementary foodstuffs, low socioeconomic status, and immigrants.[3]

IDA prevention is needed, since iron is important for the growth of the central nervous system mainly throughout the first year old. *In vivo* experiments have demonstrated that iron is important for several brain development aspects, eq. Myelination, activity of the neurotransmitter, neuronal and glial energy metabolism and dendritogenesis of the hippocampus.[4] Some studies show strong correlation between infancy IDA and long-term low cognitive and behavioral performance. Children with IDA also have long term behavior issues such as discomfort, reluctance, and outsourcing and internalizing problems. ID without anemia was suggested to be correlated with poor cognitive/behavioral results, but this needed further research. There is still a lack of research connecting dose-by-dose indicators with later cognitive outcomes.[3,5]

ID and IDA risk factors in infants include birth weight underweight, early cord clamping, male, low socio-economic status, low intake of iron ingestion and iron fortified foods and excess consumption of milk from cows. [3] In Indonesia, several problems with hygiene and chronic infection worsen. Suggested ID prevention interventions are supplementation during pregnancy and infants, delayed umbilical cord clamping, meat products, cow's milk avoidance formula with fortification and/or complementary food, also iron-fortified milk use. A meta-analysis shows that iron supplementation has a modest positive effect on mental development and motor development.[3,6]

To prevent IDA, it is important to uunderstand the sufficiency of iron and how to improve it. High iron intakes can adversely affect iron adequate infants, so it is crucial to diagnose iron status in young children and understand intervention strategies such as enhancer or iron absorption inhibitors to achieve optimum iron adequacy.

The importance of iron adequacy and its challenges

During early infancy, the small iron in human milk meets iron requirements. Iron is found mostly in hemoglobin in the neonate, but a healthy infant has iron stores that depict 25% of total body iron. At birth, newborn goes to transition from hypoxic environment in the uterus to rich oxygen environment. This transition stopped hemoglobin synthesis and reduced hemoglobin to 120 g/dL in 6 weeks infants. Recirculating iron in erythrocytes is transferred to iron storage augmenting it size. After 6 weeks, iron is transferred back from the storage to blood as the infant continue to grow and expand their blood volume. This regulation maintains infant iron levels by themselves when they most needed it to grow at around 4 to 6 months of age. Exclusive breastfeeding during this period are adequate to fulfill iron requirements eventhough breast milk have low iron concentrations.[3]

Between age of 1 and 6 years old, the body iron content is again doubled. Between the age of 6 and 24 months, infants rely on complementary dietary iron and, due to higher requirements in growth than during any other lifespan. Iron levels between 6 and 24 months needs to be doubled from 300 mg.[3] Growth spurt in adolescents are also the time in need of more iron. Girls usually spurt before menarche, but boys shows increased hemoglobin concentration during puberty which marked rise of iron requirements.[7]

The iron role in brain development has been revealed by over 50 human studies, including observational studies, supplementation and iron therapy studies. The development of normal fetal brain anatomy, myelination, and dopamine, serotonin, and norepinephrine systems is important

with iron. The sooner the brain is prevented from being inferior to iron the better for instance, in prenatal and early infancy. Various findings have indicated that mothers who had iron supplementation during pregnancy, their children achieved better in multiple intellectual, executive, and motor tests than placebo. Moreover, mistimed or excessive iron can lead to worse neurodevelopmental outcomes, as shown in a decade follow-up study in a Chilean iron baby supplement. In the study, children aged 6 months receiving iron-enforced formulas with high haemoglobin performed in a series of neurodevelopmental tasks much poorer 10 years later and children receiving iron-enforced medicines with low-hemoglobin performed much better. These results emphasize that the nutrient benefits differ at one dose and can be toxic at another.[8]

The role of iron in neural transmitter synthesis makes it antenatally and postnatally important for brain development. Iron also alters brain epigenetic landscape. Iron deficiency could result in reduced myelin development, decreased synaptogenesis and decreased basal ganglia performance, adverse development of psychomotors and mental capacity.[5] Some research suggests that anemia is correlated with poor cognitive functions such as concentration, intelligence, memory and learning skills. A research by Hurtado et al. (1999) showed that the risk of moderately mentally delayed children below the age of a decade with IDA was increased. It was not based on maternity, gender, nationality, birth weight, social class, age and education. Children with hemoglobin below 100 g/dL with an IDA have a low score for international primary school development rates. These results show how important childhood anemia is to be monitored.[9]

Emotional and psychological behavior are also affected by iron deficiency. This linked to persistent changes in dopamine metabolism, GABA, function and structure of the hippocampus, and myelinization. Studies also shown that early iron deficiency can significantly impact cognitive and behavior also irreversible disturbance in motoric. Other consequences of iron deficiency anemia is extensive such as poor growth and development which also school accomplishment.[10] It is therefore important that the iron deficiency is monitored and detected as soon as possible.

It is critical to meet the daily intake of iron as the impact of iron deficiency on brain development may be irreversible. Recommended daily intakes of iron are as follow: 11 mg for 6 to 11 months, 7.0 mg for 1 to 3 years, 10 mg for 4 to 6 months, and 10 mg/day for 7 to 9 years.[11] This recommended daily intake (RDA) for children is directed towards children after 6 months as many authorities recommend exclusive breast feeding, but exclusive breast feeding after 6 months is strongly related to IDA. The iron-rich complementary food is recommended to avoid iron depletion after six months of age. This comprises meat, iron-enforced follow-up formulas and other iron-enforced products, such as cereals. There is some evidence that enhanced formulas reduce the risk of anemia in comparison with pure cow's milk (unmodified). Pure cow's milk should be avoided in infants under 12 months of age.[3]

In order to prevention ID and IDA in children, the early introduction of these iron rich additional foods such as meat and iron-fortified foods is likely to be important. Several analyses have assessed the effects of complementary iron-fortified foods on iron conditions in children. Iron-fortified complementary foods (6.2 g/L higher than controls) significantly affected hemoglobin. It is shown to reduced risk of anemia (defined as Hb<105 or 110 g/L), by 50% (95% CI 0.33–0.75) with complementary, iron-fortified food. High-meat supplementary foods are shown to improve hemoglobin. One study shows that a substantial meat intake affects the status of iron like iron-fortified cereals, even though the cereal group's daily intake is about five times higher. This is compatible with previous studies which show that the absorption of iron from meat is multiple times higher than cereals.[12] Supported by evidence, the European Society for Hepatological and Nutritional Paediatric Gastroenterology (ESPGHAN) recommends that all infants 6 months and older should be given supplementary food rich in iron (meat products and/or iron-enforced foods).[3]

Since the focus of ESPGHAN recommendation is on nutrition, the family availability of meat products, a low socioeconomic status, especially in Indonesia, is more sensitive to unmet iron adequacy. Indonesia is a low-to-middle-income country; in 2017, 10.6% of its population remained poor.

Poverty is the main cause of most undernutrition, such as iron deficiency. Children and adolescents with poor socioeconomic status are more vulnerable to iron deficiency due to low intake of iron, mainly eating plant-based diets (predominantly non-Heme iron sources) and low-level iron diets (mostly tofu or tempeh eating, which may inhibit iron intake), which are further compounded by chronic blood loss due to parasite and malaria infections. Other factors like chronic menstrual loss of blood and gastrointestinal iron malabsorption can cause IDA in older children and teenagers.[6]

The main goal of adequate iron intake is to prevent childhood delays and cognitive impairment. Iron is well absorbed in human milk but not enough to satisfy the needs of infants for 6 months old. Additional foods besides human milk must be developed to accommodate the needs of the child without replacing human milk. As additional foods are intake limited especially when the iron requirements are highest, it is crucial to provide the iron in a highly bioavailable form. Iron rich supplementary foodstuffs (meat products and iron-fortified foodstuffs) are recommended in infants after 6 months, but in the low socioeconomic status families this challenge is obvious.[3]

Iron absorption to achieve iron adequacy and how to obtain it

Most iron absorption takes place in the small intestines through polarized intestinal epithelial cells or enterocytes. Iron absorption is performed via divalent metal conveyor 1 (DMT1), member of the transported membrane protein solution carrier group. It is then transferred into the blood through the duodenum mucosa to produce red blood cells (RBC) in the cells or in the bone marrow. Feedback mechanisms are in place to improve the absorption of iron in iron-deficient individuals. Hepcidin is one pathway of reducing iron absorption in people overloaded with iron. Ferroprotein is also known to control iron absorption from the mucosal cell into the plasma.[7]

The iron state in the duodenum influences greatly its absorption. The iron ferrous (Fe^{+2}) is quickly oxidized to the ferrous insoluble (Fe^{+3}) at the pH of physiology. Gastric acid lowers the proximal duodenum pH.[13] This improves the solubility and absorption of iron ferric. When the production of gastric acid is impaired, the absorption of iron decreases considerably. Dietary heme can also be transported by unknown mechanisms via the apical membrane and subsequently metabolized by heme oxygenase 1 (HO-1) in enterocytes to release Fe^{+2}. This process is more efficient than inorganic absorption of iron and is pH-independent.[14]

Two forms of dietary iron are heme and nonheme. Hemoglobin and myoglobin from animal meat (cow, chicken and fish) are the primary sources of heme iron, while nonheme iron is made from cereals, legumes, fruit and vegetables. In contrast to heme iron with high bioavailability (15-35%) and unrelated nutritional conditions, non-heme is easily altered by other food elements and less bioavailable (2-20 %). This magnifies the problem as the amount of non-heme iron is plentiful in most meals. Iron nutrition is more influenced to non-heme iron intake than heme-iron despite the low bioavailability of nonheme iron.[15]

Animal meat contains well absorbed heme and promotes further absorption of iron from the diet. Vegetables, however are rich in factors which inhibit non-heme iron absorption. If the gastric juice can pass through a meal containing nonheme iron, it goes into a common pool. The interaction of iron in that pool is more absorbed than the others by iron inhibitors or enhancements in other food components. Vegetable foods, especially in developing countries, have inhibitory factors. Phytates in cereal grains, peanuts, and polyphenols in tea, coffee, cocoa, and certain vegetables and grains are the most important. The absorption of nonheme iron is reduced by calcium ,vegetable proteins and animal protein other than its flesh.[7]

Increasing iron needs after 6 months of age can be replaced by complementary food, but promoting breastfeeding remains the main nutritional intake during infancy and early childhood. It is important to make sure that supplemental with additional foods do not replace human milk. Iron source that used in fortification must be readily available because the quantity of complementary meals are small.[2] The incorporation of meat or fish products should be encouraged where possible due to their heme iron's high bioavailability. 25-50 % of the iron provided as heme is expected to be absorbed in children because

they don't have any significant iron storage.[15] Methods to enhance non-heme iron bioavailability are therefore important, particularly for complementary foods used in cereals. The balance between different dietary factors in weaning foods that influences iron bioavailability must be examined in order to identify ways to improve iron balance during the weaning period. Recent studies showed that increased meat intake in the weaning period is associated with better iron nutrition. Infants are unable to chew properly thus providing infant with meat and in a form that can accommodate this problem is tricky. Fine ground form of meat in weaning foods are expected to have a favorable effect in maintaining iron balance. Generally, prolonged breastfeeding during weaning can provide a small bit of iron but has other benefits.[12]

Some dietary factors that increase iron absorption, such as fructose, copper, vitamin A and β-carotene, major enhancer of the absorption of all ascorbic acid, are also noted for further strategies to enhance iron bioavailability.[1] Contrary to the striking effect of ascorbic acid on iron absorption, it was debatable to improve iron condition in extended vitamin C supplementation.[16]

Vitamin C and its Role in iron absorption

Ascorbic acid is the most effective iron absorption enhancer. Moore and Dubach (1951) first demonstrated ascorbic acid's enhancing properties. They reported dose-related enhancing properties and dependent on ascorbic acid in the upper gastrointestinal tract lumen. Ascorbic acid acts as a common nonheme pool ligand, increasing the absorption in gastric fluid of both innate food iron and iron fortified food. It works only when it is eaten with food. In a report, 500 mg ascorbic acid taken with the test meal was absorbed six times, compared to a low absorption in 4 and 8 hours before meal with the same quantity.[2]

The effect of all identified inhibitors of nonheme iron absorption including phytates, polyphenols, calcium, vegetable and certain animal proteins is useful in reducing ascorbic acid. Cereal grains, cow's milk and peanuts (especially soybeans) are generally used as supplementary foods in developing countries. Food sources and additional food can be combined.[12] Phytate is the major inhibitor of iron absorption in cereal foods and is expected to be the main inhibitor of these foods. Ascorbic acid reverses the inhibitory effects of phytate. Interaction among phytate, ascorbic acid and iron interest researchers in order to develop effective early childhood fortification strategies with specific recommendations for phytate removal and ascorbic acid addition to the cereal complementarity foods.[17]

Cook et al.[18] more rigorously evaluated ascorbic acid efficacy to improve iron absorption from several different cereal grains. From a practical perspective there is a need to measure how much iron is absorbed from complementary food such as cereal under optimal conditions. This measurement predict how much ascorbic acid are adequate to even lowest phytate level. Full-term infants averaging 32 weeks absorbed iron 8.5% of low-phytate meal from wheat flour and grain enhanced with 2.7 mg iron sulfate and ascorbic acid (ascorbic acid molar ratio to iron, 2:1). The food included 25 g of cereal. Lynch [2] stated that in food containing phytate (70-140 mg/d in additional products designed to supply enough of iron to meet the average calculated breast-feeding requirements) the molar ratio between ascorbic acid and iron should be between 2:1 and 4:1.

Human milk is better absorbed than cow's milk. The reason is that the milk of cows is higher in calcium and the milk protein prevents the consumption of iron. The addition of ascorbic acid is shown to improve iron in the cow's milk or cow's milk-based formula significantly. The addition of ascorbic acid to cow milk containing sulphate ferrous in a concentration of 100 mg/L (ascorbic acid-iron molar ratio, 2:1) increased absorption approximately double. Soybean protein is different for complementary foods or for milk with lower iron absorption. Studies show that more ascorbic acid is needed to ensure adequately bioavailable iron in complementary soy foods than in cow's milk or cereal-based foods. The molar ratio of 4:1 ascorbic acid to iron should be used when weaning high amounts of soy bean protein products in high phytate cereals, cerenic foods containing polyphenols or complimentary foods.[2] Iron level in human milk is very small and so it is important to have iron fortified foods with high bioavailability. The Estimated average requirement (EAR) and

Recommended Dietary Allowance (RDA) iron requirements for infants aged 7 to 12 months are 6.9 mg and 11.0 mg for selecting the iron fortification content in supplementary foods of all children. Noted that complementary foods used in developing countries are less bioavailable. The fortification iron is required at 170 μg/g for meeting the EAR and 275 μg/g for meeting the RDA for infants aged 7-12 months (daily consumption, 40 g). For children aged 13-24 months (daily use, 60 g) 115 and 183 μg/g are required, respectively.[19]

We can conclude that enough iron fortified in additional food should be added to ensure the infant's diet. Ascorbic acid is useful in reducing the effect of nonheme absorption inhibitors in cereals, soya, polyphenols and calcium in cow's milk, for example. Experimental studies have shown that absorption levels of approximately 10% for cow's milk and low-phytate or dephytinized grain foods can be anticipated if the iron molar ratio of 2:1 in ascorbic acid is increased by ascorbic acid and ferrous sulphate, while a molar ratio of higher 4:1 is required if inhibitors foods such as soya are used.

Conclusion

Iron belongs to nearly all living cells and is a necessity for all human cells. IDA prevention is important because iron is critical to the growth and development of the central nervous system, especially during the first 12 months of age. In infants around 6 months of age, iron rich supplementary food is recommended because iron shops are depleted. Meat and iron-fortified foods are the main iron sources of dietary use and it is essential to introduce complementary foods early to improve iron absorption. Ascorbic acid is a good iron absorption promoter and is useful to reduce the impact of all known non-hemic iron inhibitors that can help prevent IDs. Foods like cereal, cow's milk and soya contain iron inhibitors such as phytate, polyphenol and calcium. It is recommended that the molar ratio of ascorbic acid 2:1 (for cow's milk and cereal products) and the higher molar ratio 4:1 be added to the ratio (for higher phytate, such as soybeans).

Conflict of Interest

The authors declared no conflict of interest regarding this article.

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ORIGINAL ARTICLE

Anemia status and its related factors among Indonesian workers: Hemoglobin surveys in three different workplaces

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Abstract

This study aims to explore risk factors of low hemoglobin status (anemia) among workers in three different workplaces in Indonesia. Cross-sectional study design was applied to screen hemoglobin value by using a multiwave pulse total-hemoglobinometer Masimo® and obtain socio-demographic characteristics using a questionnaire. Three workplaces were purposively selected to have total population eligible for this study. Health safety protocol was applied both for the subjects and researchers as COVID19 prevention. Statistical analyses were used accordingly to find potential risk factor(s) of anemia among workers. A total of 2386 eligible subjects with mean age of 36.8 ± 9.2 years participated in this study consisted of mainly male workers (85.3%), mostly married (79.0%), never smoke (55.8%) and working in shift (68.7%). Mean of hemoglobin value was 14.2 ± 1.2 mg/dL with anemia prevalence of 9.9%. Risk factor of anemia among workers were female-gender, non-marriage status, never smoking and no-work shift. However, the potential determinant for anemia among workers was female-gender, in which the prevalence of anemia was 24.6% as compared to 7.4% in male-gender. Keep providing free meal in the workplace canteen is a must, but there is a need to provide iron and vitamin C-fortified food and/or iron and vitamin C supplement especially for female workers.

Keywords anemia, iron intake, Masimo®, workers

Introduction

Anemia, especially iron deficiency anemia, is a worldwide public health problem for its alarmingly high prevalence, including in Indonesia. Besides pregnant women and children, there are also significant deleterious consequences of iron deficiency with or without anemia (i.e. as the most severe form of iron deficiency) among workers in relation to their physical working capacity.[1] It is well-known that iron plays an essential role in oxidative energy production, in which it will affect aerobic capacity, endurance capacity, energy efficiency, muscle and brain activities, and finally economic productivity.

As one of developing countries, Indonesia must compete globally in industrial production. This will result in the numbers of worker population increase to more than 100 million. These populations consist of approximately 64.6% and 35.4% male and female workers, consecutively. Several factors are recognized as the risk factors of anemia among workers. These include inadequacy of dietary iron

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intake and the existence of absorption hindering compounds in foods. Others are socio-economic and lifestyle factors such as education, smoking and drinking habit.[2]

As reported by the MoH, the prevalence of anemia that predominantly caused by iron deficiency among Indonesian adults in 2013 was 18.4–20.1%.[1] Among female workers in timber factory and among workers in shoe factory, the prevalence of anemia were 77.7% and 56.0%, respectively. While in industrial workplace, the prevalence of anemia was 14.1%, consisted of 5.6% in male and 32.1% in female workers.[2] There is no specific report on iron deficiency anemia among workers. This study aims to screen hemoglobin value among workers in Indonesia using rapid and safe assessment during the COVID19 pandemic.

Methods

This study used cross-sectional design, done from December 2020 to January 2021. The subjects were all workers in three different working locations who were eligible to participate in this study, i.e. apparently healthy male and female workers, aged 19 to 64 years old. Pregnant women were excluded.

Data collection were done after receiving ethical clearance from the Ethical Committee Faculty of Medicine Universitas Indonesia (No: KET-1407/UN2.F1/ETIK/PPM.00.02/2020).

Data collected consisted of hemoglobin value assessment using *Masimo® Rad-67 Pulse CO-Oximeter (Masimo SET® Measure-through Motion and Low Perfusion Pulse Oximetry and Non-invasive Total Hemoglobin (SpHb®) Spot-check Monitoring)* and subjects' characteristic data, such as age, gender, marital status (single, married or widowed), working shift (yes or no), and smoking habit (never, currently active or had history of smoking).

The non-invasive multi-wave pulse total-hemoglobinometer Masimo® was purposively chosen because it is a valid device to monitor hemoglobin value and can be used to screen low hemoglobin value in a clinical setting, i.e. during surgery. To have a minimal contact then the device is suitable to be used in a non-clinical setting to screen for low hemoglobin value among apparently healthy population.[7]

During the COVID19 pandemic situation, all enumerators were required to conduct safety protocol for data collection, i.e. wearing protective suit, surgical masks, face shields, applying physical distancing and frequent hand washing with minimal contact with the subjects. The subjects were required to wear masks properly. All enumerators were also required to do PCR-swab test to confirm their safety at before and during the data collection.

The workplaces provided once daily free meal. Daily menu lists for a month were collected from the canteen catering providers and analyzed with Nutrisurvey 2007 for Windows to obtain the energy and nutrient values.

Descriptive analysis was done to obtain subjects' characteristics. Chi-square test was used to analyse risk factors of anemia, and logistic regression analysis was performed to find the determinant factor of anemia among subjects. Data were analysed using the Statistical Package for Social Science (SPSS) program version 20.0.

Results

As shown in **Table 1**, 2386 eligible subjects were included, with mean of age of 36.8 ± 9.2 years old, in which mostly were under 50 years of age (90.2%). By gender, as expected, there were more male than female subjects, i.e. 85.3% versus 14.7%. The subjects were mostly married (79.0%), never smoke (55.8%), and working in shift (68.7%).

Table 2 shows hemoglobin value of the subjects with the mean of 14.2 ± 1.2 g/dL. The anemia status among the subjects was 9.9%. **Table 3** shows that anemia status among female workers was higher, i.e. 24.6% compared to 7.4% in male workers. As also shown in **Table 3,** significant risk factors of anemia among workers were gender (female higher than male), marital status (not married is higher than those who are still married), smoking status (never smoking was higher than those who had history or currently active smoking) and working in shift (non-shift was higher than shift workers). **Table 2** also shows the oxygen saturation data presented by the Masimo® device, in which it has a weak negative association with hemoglobin, that need further explanation.

Data on nutritional facts provided from several menu collected and analyzed to be associated to the

Indonesian RDA for energy, iron and vitamin C intake that should have correction for the intensity working level, was shown in **Table 4**. The menu was provided once from the workplace canteen, in which assumed to contribute approximately 30–40% from total daily energy and nutrients intake. We assumed that the energy intake for one meal at the workplace, based on Indonesian RDA, was 40% x 2000 kcal or 800 kcal for those working in the sedentary working level, in which it was well provided in this study. However, we should add 400 kcal for working level adjustment for those working in a moderate working level.[3] Then the total energy intake of 1200 kcal should be provided within one meal in the workplace. While for iron and vitamin C intake, **Table 4** shows that the inadequacy intake, i.e. less than 80% to fulfill 30-40% of the RDA requirements, even before adjustment correction for the working intensity level.

Discussion

This study included workers aged 19–64 years old at which their intake adequacy was classified based on their age classification in the RDA guidelines for Indonesian.[4] For age category, most of the subjects were at early and middle adulthood period in which they are very productive to have working experience, raising family (i.e. almost 80% were married), and economic earning. By gender, approximately 85% of the subjects were male in which higher as compared to national data of 64.6%. In this study, the higher proportion of male workers in this study might also be related to type of workplaces selected, i.e. more in the factories than offices.

This is also related to the findings that mostly the subjects working in shift, because the factories usually run for 24 hours. In addition, this is also the reason related to the finding that smoking status was still reaching to more than 40%. Marginalization in the labor market is believed to be associated with likelihood of being smoker as well as a heavy smoker. In addition, other factors such as unstable job position, unstable life and less favorable working conditions in precarious work (i.e. low salaries, limited access to welfare benefits and less job control) may prevent workers from quitting smoking. This might be due to the lack of coping resources to manage their stress, However, again, this is also beyond of the scope of this study to explore more.[5]

The assessment of hemoglobin value in this study used a non-invasive multi-wave pulse total-hemoglobinometer Masimo®. The device was used because it is non-invasive, practical and having minimal systematic bias if the subjects were apparently healthy by means having normal perfusion index or predicted hemoglobin value were between 8 and 11 mg/dL and the oxygen saturation is more than 97%.[6] Thus, the Masimo® is suitable to screen hemoglobin value in a non-clinical setting but should be taken into caution as decision-making tool for transfusion.

The mean hemoglobin value found in this study was still in a normal range, i.e. 14.2 ± 1.2 mg/dL. Based on the cut-off point for low hemoglobin value or anemia status, for male of less than 13 mg/dL and for female less than 12 mg/dL,[7] it is revealed that 9.9% of the subjects in this study were categorized as anemic. Based on the World Health Organization (WHO) classifications for public health severity of anemia [8], the proportion between 5.0–19.9% is categorized mild public health problem of anemia.

However, if we stratified by gender, it is revealed that the proportion of anemia among female workers was 24.6% or categorized as moderate public health problem (i.e. between 20.0–39.9%). Female gender is the determinant of anemia found in this study. A study on anemia and its associated factors among women at reproductive age shows that the prevalence of anemia was ranging from 19.23% to 53.98% in eastern Africa. Furthermore, the study also found that using modern contraceptive methods, have a history of terminated pregnancy, and having high parity were associated with a higher prevalence of anemia.[9] It is then recommended by the World Health Assembly, especially for women at reproductive age to reduce the proportion of anemia by 50% by the year 2025. Improvements of nutritional and non-nutritional modifiable factors may be required to reduce anemia among female workers.

For nutritional factors of anemia, food-based intervention is still mostly prioritized for workers by provision of one meal serving during working hours in the workplace canteens or caterings. A study on the effectiveness of workplace nutrition program on

anemia status among non-pregnant female workers in Bangladesh, revealed that provision of lunch meal at the workplace were satisfying, because the lunch was good in quality, quantity, taste and satisfied their hunger. Furthermore, as the most important outcome, the mean hemoglobin was significantly improved.[10] Besides the adequacy of dietary energy intake, dietary iron intake should also be prioritized, while those subjects with non-lunch at workplace mostly consumed only rice with vegetables at home. Along with and/or without the food-based and/or iron-folate supplementation provided at the workplace, they are provided with behavior change communication program. This study shows that by providing a combination of intervention (i.e. a freshly prepared, nutritionally enhanced lunch with fortified rice, increased diversity, and combined with a weekly iron-folate tablet) over a significant period of at least 10 months could reduce anemia significantly.

Based on the findings of this study in several workplaces in Indonesia, it is suggested that meal planning should be re-visited to accommodate dietary iron and vitamin C intake, as the enhancing of iron absorption. It is well-known that iron absorption is regulated by dietary and systemic factors. Dietary iron is predominantly non-heme iron, and its absorption is significantly affected by other components of the diet. Among others, ascorbic acid or vitamin C is the most effective enhancer of non-heme iron absorption, thus should be provided along within the meals rich in iron content.[11] If necessary, additional portion of iron and vitamin C fortified food can help increase the hemoglobin level,[12] before last decision for provision of iron[13] and/or micronutrient supplement is given to those workers with low hemoglobin status.

In this study, we found that there is a weak inversed correlation between hemoglobin value and oxygen saturation. There are several important determinants regarding the delivery of oxygen by arterial blood to the body tissues, i.e. blood oxygen concentration, saturation and partial pressure, hemoglobin concentration and cardiac output. Although assessing arterial oxygen saturation can be done using pulse oximetry, however there are some limitations. Therefore, blood gas analysis or arterial blood sampling remains the gold-standard method of assessing ventilation and oxygenation.[14] Thus, the results of oxygen saturation in this study is needed only to show the prerequisite to assess hemoglobin value of the subjects.

There are several limitations of this study. We did not assess iron status, i.e. individual dietary iron intake and ferritin level. Factors of hindrance and enhancer of iron absorption were also not examined. However, by using nutritional facts of the several meals provided, it is obvious that there is a need to improve the dietary iron and vitamin C intake among workers, especially female worker, aiming to reduce the proportion of anemia.

Table 1. Subjects' characteristics (n = 2386)

Subjects' characteristics	
Age, years	36.8 ± 9.2
Age category, n(%)	
<50 years old	2152 (90.2)
50 years old and over	234 (9.8)
Gender, n (%)	
Male	2036 (85.3)
Female	350 (14.7)
Marriage status, n (%)	
Single or widowed	500 (21.0)
Married	1886 (79.0)
Smoking status, n (%)	
Never	1332 (55.8)
Currently active or had history of smoking	1054 (44.2)
Working in shifts, n (%)	
No	748 (31.3)
Yes	1638 (68.7)

Table 2. Hemoglobin concentration, anemia status and oxygen saturation of the subjects (n = 2386)

Subjects' clinical data	
Hemoglobin, g/dL	14.2 ± 1.2
Anemia, n (%)	237 (9.9)
Oxygen saturation, %	98.4 ± 2.1

Pearson's correlation analysis found a weakly negative significant association between hemoglobin concentration and oxygen saturation (P<0.001 and r = -0.101)

Table 3. Associations between anemia status and subjects' characteristics (n = 2386)

	Anemia	**Non-anemia**	**P-value**	**OR**
Age category, n(%)				
<50 y	221 (10.3)	1931 (89.7)	0.096	0.64
50 y and over	16 (6.8)	218 (93.2)		(0.379–1.086)
Gender, n(%)				
Male	151 (7.4)	1885 (92.6)	<0.001	4.067
Female	86 (24.6)	264 (75.4)		(3.029–5.459)
Marital status, n(%)				
No	76 (15.2)	424 (84.8)	<0.001	1.920
Yes	161 (8.5)	1725 (91.5)		(1.433–2.574)
Smoking status, n(%)				
No	147 (11.0)	1185 (89.0)	0.043	0.753
Yes	90 (8.5)	964 (91.5)		(0.571–0.992)
Work shift, n(%)				
No	105 (14.0)	643 (86.0)	<0.001	0.537
Yes	132 (8.1)	1506 (91.9)		(0.409–0.705)

Logistic regression analysis reveals that only gender was a potential contribution to anemia status (P <0.001, and OR = 4.353)

Table 4. Nutritional facts and its adequacy from meals provided at the three different workplaces

Nutrients content	Workplace-1	Workplace-2	Workplace-3
Energy, kcal	873.8 ± 85.7	717.9 ± 56.0	882.6 ± 53.8
Carbohydrate, g	126.0 ± 10.7	111.5 ± 11.7	118.0 ± 9.2
Fats, g	25.3 ± 6.8	18.3 ± 3.5	33.7 ± 3.8
Iron, mg	5.6 ± 2.5	6.4 ± 2.3	4.6 ± 1.2
Iron (%RDA)			
For men	62.0 ± 27.6	71.3 ± 26.0	51.8 ± 13.7
For women	31.0 ± 13.8	35.7 ± 13.0	25.9 ± 6.8
Vitamin C, mg	46.6 ± 26.6	33.3 ± 17.8	54.9 ± 31.3
Vitamin C (%RDA)			
For men	51.7 ± 29.6	37.0 ± 19.7	61.0 ± 34.8
For women	62.1 ± 35.5	44.4 ± 23.7	73.2 ± 41.7

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Conflict of Interest

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