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CORRELATION OF ANEMIA IN PREGNANT WOMEN WITH STUNTING INCIDENCE: A REVIEW

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ABSTRACT

The prevalence of stunting is still one of the biggest nutritional problems in the world. Around 150.8 million children under five years old were stunted in 2017, or 22.2% of the population. In 2017, more than half (55%) of children under the age of five who had stunting were from Asia, and more than a third were from Africa (39%). North Asia has the biggest percentage (58.7%) of Asia's 83.6 million children under the age of five. From 2005 to 2017, there was a 36.4% annual increase in the prevalence of stunting in toddlers in Indonesia. One of the factors that cause stunting and low birth weight babies (LBW) is pregnant women who experience anemia. Anemia is a condition of decreasing blood hemoglobin concentration due to micronutrient deficiencies, especially iron, which often occurs in the world affecting more than half of the global population. The most susceptible demographics to anemia are children and women at childbearing age. This research uses the study literature review method. The study was conducted using the results of research from 2016 – 2022 regarding the correlation of anemia in pregnant women and stunting. It is known that macronutrients and micronutrients are correlated with the occurrence of stunting and anemia. It is certainly necessary to make efforts to improve health in both pregnant women and children to prevent the occurance of anemia.

INTRODUCTION

Z-score for height according to age that is less than -2 standard deviations (SD) based on growth standards might indicates stunting, a persistent nutritional issue during the time of development and growth. Stunting in toddlers can inhibit development and growth with negative impacts in the form of decreased intellectuality, susceptibility to non-communicable diseases (de Onis & Branca, 2016). Stunting is linked to an increase of child morbidity, and mortality, as well as decreased levels of cognitive and academic success in children (WHO, 2014). In addition, there is strong evidence that stunting risk factors are fetal growth limitations, insufficiently born months (premature), and environmental exposure such as poor sanitation. Stunting occurs within the first 1000 days of life, and its impacts are probably irreversible after this time (Nachvak et al., 2020).

The proportion of short toddlers in Indonesia tends to be static. According to the Baseline Health Research survey from 2007, there were 36.8% children in Indonesia who were stunted. The percentage dropped slightly to 35.6% in 2010. However, in 2013 the proportion of short toddlers increased again to 37.2%. According to the survey conducted in 2018 revealed that 30.8% of adolescents and 29.9% of toddlers under the age of two had stunting. In addition, stunting was a problem for 27.67% of children in 2019 (Kemenkes RI, 2019). One of the biggest nutritional issues in the world is still the prevalence of stunting. Around 150.8 million children under the age of five, or 22.2%, were stunted in 2017. In 2017, more than half (55%) of young children with stunting

lived in Asia, while more than a third (39%) did so in Africa. North Asia has the biggest percentage of Asia's 83.6 million under-fives (58.7%). Between 2005 and 2017, Indonesia had an average frequency of 36.4% stunted toddlers (Laksono & Kusrini, 2020).

One of the factors that cause stunting and low birth weight babies (LBW) is pregnant women who experience anemia. Anemia is a condition of decreasing blood hemoglobin concentration due to micronutrient deficiencies, especially iron, which affects more than half of the world's population and is widespread over the globe (McKee et al., 2017). Anemia occurs due to non-existent iron deposits as well as signs of impaired iron supply to tissues (Gosdin et al., 2018). Children and women of childbearing age are the most vulnerable groups to anemia (Iqbal et al., 2019).

In addition, the incidence of anemia during pregnancy is one of the factors that can affect the weight of the baby at birth. Severe anemia during pregnancy increases the likelihood of a low birth weight baby, stunting, to bleeding before and during childbirth and even the death of mothers and babies (WHO, 2014). Pregnant women who experience anemia will experience impaired distribution of oxygen and food substances from the mother to the placenta and fetus, so it will affect the function of the placenta. Decreased placental function results in impaired fetal growth and development (Karaşahin et al., 2007). Pregnant women who suffer from anemia have the potential to be 4 times greater to cause children to be stunted compared to mothers who do not suffer from anemia during pregnancy (Widyaningrum and Romadhoni, 2018). Based on this, the researcher evaluated previous studies on the correlation of stunting with anemia in pregnant women.

METHOD

This research uses the *study literature review* method. The study was conducted using the results of research from 2016 – 2022 regarding the correlation of anemia in pregnant women and stunting using PRISMA method. There are 5 steps in this method, namely determining the topic of literature, finding sources, selecting relevant sources, grouping and analyzing, and summarizing. Researchers search through several search engines, namely Google scholar, SAGE journal and PubMed. The article criteria used in this study are based on inclusion criteria made by researchers, namely Indonesian and English articles from various countries, quantitative research, research articles with primary data, full text articles that are available free and accessible, articles published in the 2016-2022 range and articles have conformity with the objectives of the research carried out. The keywords used in article searches on Google Scholar, SAGE journal and PubMed are "Anemia", "Deficiency", "Macronutrients", "Micronutrients", "Pregnancy", "Pregnant Women", and "Stunting".

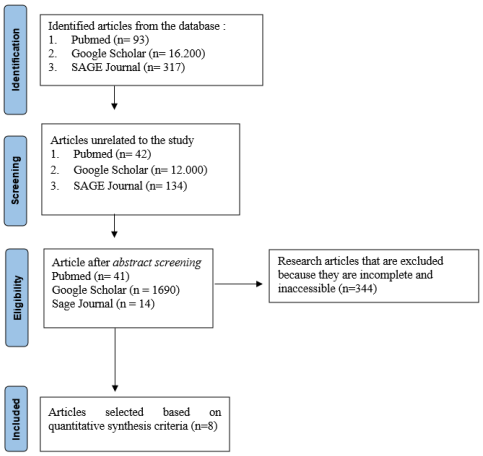

Figure 1. Literature Review Article Search Process (Processed by the Author (2022))

RESULT AND DISCUSSION

Table 1. Reviewed Articles

Researchers	Titles	Designs	Results
Meikawati W, Rahayu D, Purwanti I (2021)	Low Birth Weight and Maternal Anemia as a Predictor of Stunting in Children Aged 12-24 Months in the Genuk Health Center Area, Semarang City (*Berat badan lahir rendah dan anemia ibu sebagai prediktor stunting pada anak usia 12–24 bulan di Wilayah Puskesmas Genuk Kota Semarang*)	Cross sectional	History of BBLR (p=0.004) and anemic status of mothers during pregnancy (p=0.001) are most at risk of stunting
Novriani Tarigan, Lora Sitompul, Siti Zahra (2021)	Intake of energy, protein, iron, folic acid and anemia status of pregnant women in the working area of the Petumbukan Health	Cross sectional	There is a significant association with the intake of energy, protein, iron and folic acid to the status of anemia in pregnant women.

Researchers	Titles	Designs	Results
	Center (*Asupan Energi, Protein, Zat Besi, Asam Folat Dan Status Anemia Ibu Hamil Di Wilayah Kerja Puskesmas Petumbukan*)		
Fikawati S, Syafiq A, Ririyanti RK, Gemily SC. (2021)	Energy and protein intakes are associated with stunting among preschool children in Central Jakarta, Indonesia: a case-control study	Case-control	Stunting was more likely to occur in children with inadequate energy and protein diets than in those with adequate intakes. For the purpose of preventing stunting, macronutrient intakes are crucial and should be met daily.
Mousa, Aya, Amreen Naqash, and Siew Lim. (2019)	Macronutrient and Micronutrient Intake during Pregnancy: An Overview of Recent Evidence	Narrative Literature-Review	It is advised to consume a balanced amount of protein and energy while also taking into account each individual's gestational weight growth targets and pre-pregnancy BMI. Iron and folic acid supplements are crucial for preventing anaemia and neural tube abnormalities, respectively. In order to maintain appropriate maternal reserves, support foetal growth and bone development, and prevent hypertensive diseases, supplements of vitamin D and calcium are also advised during pregnancy, especially in cases when the mother is at a high risk of deficiency or inadequate dietary consumption, while vitamin A intake should be restricted to prevent teratogenicity. PUFAs, zinc, vitamins C and E, B-complex

Researchers	Titles	Designs	Results
			vitamins, and other minerals all play important roles.
Ayuningtyas, Demsa Simbolon, Ahmad Rizal (2018)	Intake of Macro and Micronutrients to the Incidence of Stunting in Toddlers (*Asupan zat gizi makro dan mikro terhadap kejadian stunting pada balita*)	Cross sectional	The incidence of *stunting* is mostly caused by lack of energy intake, macronutrients, and zinc. The results showed a significant relationship between energy intake, macronutrients, and zinc with the incidence of *stunting* in toddlers.
Patel, A., Prakash, A. A., Das, P. K., Gupta, S., Pusdekar, Y. V., & Hibberd, P. L. (2018)	Maternal anemia and underweight as determinants of pregnancy outcomes: cohort study in eastern rural Maharashtra, India	Prospective observational cohort study	Anaemia in the mother is linked to an increased incidence of stillbirth, neonatal mortality, and LBW. If anaemia and underweight were both present, the risks increased
Kristiana Tri Warsini, Hamam Hadi, Detty Siti Nurdiati (2016)	A history of CED and anemia in pregnant women is not related to the incidence of stunting in children aged 6-23 months in Sedayu District, Bantul, Yogyakarta (*Riwayat KEK dan anemia pada ibu hamil tidak berhubungan dengan kejadian stunting pada anak usia 6-23 bulan di Kecamatan Sedayu, Bantul, Yogyakarta*)	Case-control	Factors that influence the incidence of stunting in children aged 6-23 month were pregnant mother with anemia, history of low birth weight, food insecurity, and stunted mother. Stunted mother was associated with the incidence of stunting.
Nair et al. (2016)	Association between maternal anaemia and pregnancy outcomes : a cohort study in Assam, India	Retrospective cohort study	Iron deficiency anemia is a serious public health problem in Assam. Maternal anemia was linked to higher risk for PPH, low birthweight, small-for

Researchers	Titles	Designs	Results
			gestational-age babies, and perinatal mortality.

Stunting

Children 0-59 months old may experience stunting, a growth and development issue. Stunting is experienced by children who experience malnutrition, recurrent infections, and lack of psychosocial stimulation. Children are said to be stunted when high based on their age of more than two standard deviations below the median standard of child growth issued by the World Health Organization (WHO, 2014). The short-term effects of stunting are correlated with a reduction in a child's cognitive and physical development, while adult productivity and working ability are negatively impacted by stunting's long-term impacts, which also raise the risk of degenerative diseases in old age (Leroy & Frongillo, 2019).

Infection status and food intake are factors that directly influence stunting. Macronutrient and micronutrient intake in babies plays a significant role in growth and the prevention of growth problems (Savarino et al., 2021). Low protein, carbohydrate, and energy intake is significantly associated with an increase in global DNA methylation of high levels in stunted two- to three-year-olds in Bangladesh (Iqbal et al., 2019).

Additional research has connected children's fat consumption to stunting. The hormone leptin, which affects bone growth, is one of the numerous hormones that depend heavily on fat for their production. Additional research has revealed that leptin affects bone growth by stimulating fibroblast growth factor 23 (FGF-23) (Tsuji et al., 2010). Leptin also affects and regulates osteocalcin which in turn regulates insulin sensitivity and energy expenditure (Ferron & Lacombe, 2014).

Low protein consumption has been linked to stunting, according to studies. The growth of a child's length or height is strongly correlated with protein intake (Arsenault & Brown, 2017). Chronic protein deficiency in children under five years of age hinders their growth. Stunting is 1.4 times more likely to occur in children who do not consume protein (Krasevec et al., 2017). Anemia, immunodeficiency, and protein and energy deprivation will induce inflammation and boost cytokine production (Bianchi, 2016). Since macronutrient deficiencies such as wasting and low weight have become public health problems in Indonesia, protein and energy malnutrition affect physiological functions. The lack of nutrients causes growth failure because micronutrients cannot provide maximum benefits based on their function in linear growth (Dewi & Mahmudiono, 2021).

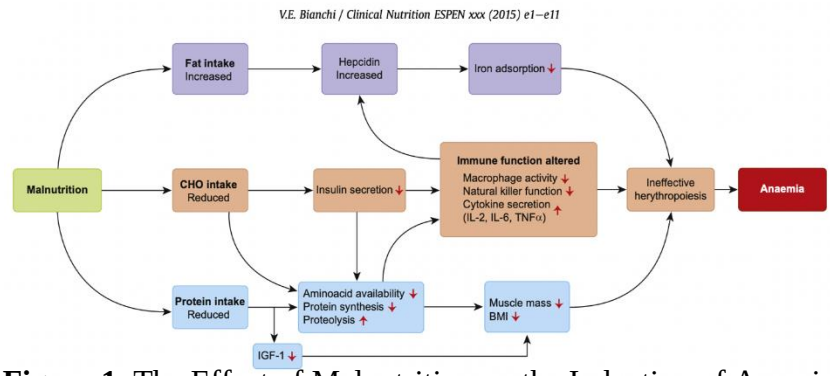

Figure 1. The Effect of Malnutrition on the Induction of Anemia

A decrease in protein intake leads to proteolysis due to a decrease in amino acid availability and a decrease in IGF-1 levels. Reduced carbohydrate intake will boosts the secretion of proinflammatory cytokines while decreasing insulin secretion. Both of these substances impair immunological response and macrophage activity. Fats from food encorage the release of hepsidines, which prevent iron absorbtion. Such mechanisms work together to disrupt the production of herithropoiesis and heritropoietin (Bianchi, 2016).

Anemia caused due to malnutrition of proteins and energy causes the ineffectiveness of erythropoiesis in addition to an increase in the number of erythropoetin. Hemoglobin and hematocrit decreased slightly but significantly after 8 days in a protein diet. As a result, malnutrition is a clinical condition that alters many aspects of the immune response, including decrease in cell migration, stimulation of phagocytosis, bactericidal response, changes in the production of reactive oxygen and nitrogen species, as well as the production of pro-inflammatory cytokines (Bianchi, 2016).

Although the prevalence of stunting globally is high, the pathogenesis underlying the failure of linear growth is less known. Interventions to promote healthy growth remains unclear and no scientific studies have ever normalized linear growth among children in developing countries. From epidemiological studies, it seems that breast milk is less than optimal and the practice of complementary feeding of breast milk, recurrence of infections and micronutrient deficiencies are important determinants in stunting (Dewey & Mayers, 2011).

Anemia

Anemia is a group of diseases characterized by a decrease in either hemoglobin or the volume of red blood cells, thus causing a decrease in the capacity of oxygen carriers to the blood. Anemia in children usually occurs due to primary hematological abnormalities. The risk of iron deficiency anemia increases due to the encouragement of rapid growth and deficiency in food intake (DiPiro

et al., 2017). Anemia is a continuation of macronutrient deficiencies such as carbohydrates, proteins, fats, and micronutrient deficiencies such as vitamins and minerals. Anemia affects the growth and development of children under five years of age. Based on studies conducted in Nigeria, children with crescent anemia have lower IQ, memory, and memory processing speed than healthy children (Oluwole et al., 2016).

Iron deficiency anemia is the type of anemia that most often contributes to global disease (McKee et al., 2017). Iron is needed to form hemoglobin which is an important chemical substance in the process of binding oxygen. Thus, when iron levels decrease, organs and tissues do not get enough oxygen and cause fatigue, decreased performance, and immunity. Untreated iron deficiency will cause serious problems such as delays in growth and development processes (McKee et al., 2017). Iron deficiency anemia in children also have detrimental effects on brain function, metabolism and immune system (Melku et al., 2018).

For the first four to six months after birth, babies who have enough iron deposits to meet their needs must receive iron through food (Gosdin et al., 2018; Rao & Georgieff, 2007). At this time between the ages of one and two years shows the highest risk of anemia. However, in girls, the risk of anemia increases when entering the *menarche* period (Alvarez-Uria et al., 2014). In infants and children, severe chronic anemia causes growth inhibition and long-term effects on neurodevelopment and behavior, mediated by changes in the neurotransmitter myelin, monoamine metabolism in the striatum, which functions on the hypocampus and energy metabolism (Soliman et al., 2014).

Chronic anemia has a negative effect on linear growth during all stages of growth (infancy, childhood and adolescence). Infants with chronic deficiency anemia will experience cognitive, motor, and developmental delays that may last a long time, mechanisms of growth defects in iron deficiency anemia include defects in the secretion of IGF-I. Correction of anemia is associated with improved growth and a significant increase in IGF-I secretion. Although the use of iron supplementation offers an easy method in the primary prevention of iron deficiency anemia, evidence suggest that iron supplementation is only beneficial in the regions where iron deficiency anemia is common, including those region where endemic to malaria. It may also indicate some risk in people with normal Hemoglobin levels (Soliman et al., 2014).

	Chronic hemolytic anemia on repeated RBC transfusion	Iron deficiency anemia
Early brain growth and metabolism	No effect	In-utero and early life leads to altered neurotransmission and monoamine oxidase and other enzyme metabolism
Psychomotor development	No effect	Defective psychomotor development that may persist later
In-utero and early infantile postnatal linear growth	No effect	Defective intrauterine and early postnatal growth
Childhood linear growth	Marked effect	Marked effect
Pubertal growth spurt	Marked effect because of delayed and/or failure of puberty and defective GH-IGF-I axis	Less significant effect
GH secretion	Significant decrease in variable number of patients (pituitary iron overload)	No effect
IGF-I secretion	Marked decrease of IGF-I secretion Hepatic siderosis)	Decreases IGF-I secretion
Effect on appetite and weight gain	Decreases appetite and many have low BMI (correction of nutrition increases IGF-I and weight gain)	Decreases appetite and is associated with underweight in many children and adolescents
Effect on other endocrine glands	Hypothyroidism Hypogonadotropic hypogonadism and diabetes mellitus (iron overload) are common complications	No effect (in adults thyroid dysfunction may occur)
Effect on liver	Liver fibrosis, cirrhosis and failure may occur secondary to iron overload (siderosis)	No effect on hepatic function
Effect on heart	Arrhythmia and heart failure still occur secondary to iron overload and hypoxia	Heart failure is rare and occurs in severe prolonged cases
Effect of treatment of anemia	Adequate blood transfusion and iron chelation improves IGF-I secretion, weight gain and linear growth but short stature is still common complication	Fe therapy; 1 increases IGF-I, weight gain and linear growth (complete catch-up growth)

GH: Growth hormone, RBC: Red blood cell, IGF-I: Insulin-like growth factor I

Table 1. Thalassemia, Growth, and Endocrine Glands: Effects of Iron Deficiency Anemia VS Chronic Hemolytic Anemia (Soliman et al., 2014)

Both anemia and stunting pose significant challenges to the health system and the survival of children, co-occurrence of anemia and stunting will be more detrimental (Mohammed et al., 2019). Based on research conducted by Gosdin et al. (2018) related to the incidence of *co-occurrence* of anemia and stunting, it is proven that anemia and stunting must be managed as separate conditions. Targeting one condition will not identify or address another simultaneously, so there is a need for a multistrategic approach to target the anemia and stunting determinants that are most significant because focusing only on one condition will not reveal or address another.

Anemia is determined based on hemoglobin levels, which might change from day to day (Gosdin et al., 2018). On the other hand, stunting is measured using linear growth and changes very slowly (Gosdin et al., 2018). Anemia is characterized by a decrease in hemoglobin levels. The prosthetic group of hemoglobin, known as heme, gives it its distinctive deep red color. Hemoglobin is a conjugated protein. The cytochromes, which are substances that serve as electron carriers and enzymes like catalase and peroxidase, are also found among the heme proteins. (Blanco & Blanco, 2017). Low hemoglobin concentrations are commonly used as an indicator of public health against impaired iron status, although anemia, similar to stunting, is a multifactor problem (Raiten and Bremer, 2020).

Protein deficiency or malnutrition is related to higher rates of morbidity and mortality. Individual assessments of malnutrition include the identification of inflammations such as increased concentrations of C-reactive plasma proteins to determine diagnosis based on etiology, accompanied with proof of decreased food consumption, weight loss, decreased subcutaneous fat, and decreased muscle tone, accumulation of localized fluid or generalizations, and decreased physical status function (White et al., 2012). A decrease in access to food in the long term leads to marasmus, which is also called wasting. Individuals with marasmus appearance are very thin with depletion of muscle mass and adipose tissue. The bones look protruding and the skin is sagging. Malnutrition or protein deficiency indicates insufficient protein intake but sufficient energy consumption. Due to an inadequate amount of protein in the blood and cells from a lack of protein

intake from diet, causes water to diffuse out of the blood and out of the cells towards the intercellular, resulting in edema. Edema typically first manifests in the legs, but it can also be found in the face or more commonly throughout the body (Gropper & Smith, 2012).

Myoglobin, a molecule that transports and stores oxygen in the muscles, while hemoglobin is in charge of carrying oxygen throughout the blood. The globin protein, which is abundant in the amino acids lysine, arginine, and histidine, is what creates both *myoglobin* and *hemoglobin* (Blanco, 2017). Low protein intake will lead to limited hemoglobin production. Limited protein intake is not capable of producing the normal amount of globin (Hahn & Whipple, 1939).

Myoglobin and hemoglobin, which are involved in metabolism and the transfer of oxygen in the body, require iron as a necessary component. Additionally, iron is necessary for the formation of lymphocytes and Natural Killer (NK) cells to prevent infection, organic compound excretion and energy metabolism. Immunity is weakened when iron levels are low. Heme and non-heme iron can be found in food. Meat, seafood, and poultry meat are contain heme iron, which is best absorbed through the digestive system. Conversely, when consuming a small amount of meat with foods containing non heme iron, non-heme iron can be absorbed or its absorption will increase. Consumption of foods high in vitamin C can also improved iron absorption (Barrett, 2020).

The Role of Amino Acids and Proteins in Metabolism

Blood Components

Protein is a component of blood transport. For example, hemoglobin in red blood cells is in charge of carrying oxygen. Each hemoglobin subunit contains gugud heme with iron atoms that can bind to oxygen. Other important transport proteins include plasma proteins. Plasma proteins are mostly synthesized and secreted by the liver. Plasma proteins contain simple molecules and also conjugated proteins such as glycoproteins and lipoproteins. Albumin is a transporter of compounds such as fatty acids, bile acids in the portal circulation, and other compounds including some minerals. Other protein transports found in the blood include transferrin, ceruloplasmin, and vitamin D binding protein (DBP), protein containing lipoprotein is a major transporter of fat and fat-soluble compounds (fat-soluble vitamins) (Wildman, 2018).

Blood Clotting

Blood clotting factors are synthesized in the liver and released in the form of zimogen includes factors V, VII (proconvertin), VIII (antihemolytic), IX (natal factor), X (Stuart factor), XI (Thromboplastin plasma, XII (Hageman factor), and XIII (transaminases); fibrinogen, and prothrombin. The freezing mechanism is simultaneous at each stage. The final reaction of the *cascade* results in the activation of fibrinogen into fibrin which forms a *cross-link* structure, which is the basic structure of freezing. The liver also secretes plasminogen which when activated into plasmin works to destroy clots (Wildman, 2018).

Iron and Protein Metabolism

Numerous proteins have been shown to be involved in iron metabolism. The main blood iron transporters are proteins like ferritin or Tf, while peptides like iron regulatory proteins (IRP), hepsidine, and matriptase (Mt2) are crucial regulators of iron at various physiological levels. Iron is transported through cellular membranes by a variety of proteins, primarily divalent-1 metal transporters (DMT1), ferroportin (FPN1), and transferin receptors (Tfrs), which are all ferroxidases. These proteins include duodenal cytochrome B, ceruloplamin (Cp), and heme transport proteins (HCP1). Since they require iron to work, other proteins such as myoglobin, Hb, and several enzymes are the results of iron metabolism (Waldvogel-Abramowski et al., 2014).

It is impossible to discuss iron metabolism without mentioning the role of hepsidine. Hepcidine is a hormone of 25 amino acid peptides, commonly produced by hepatocytes. Hepcidine production is controlled by a variety of methods. The liver often produces peptides in response to a variety of causes. Inflammation causes more intracellular and extracellular iron to be stored, which raises the level of hepcidine in the blood. Conversely, when the need for iron is high, as in the increase in erythropoesis, hepsidin levels become low. Hepsidin recoups iron production from hepatocytes, macrophages from FPN1 (Waldvogel-Abramowski et al., 2014).

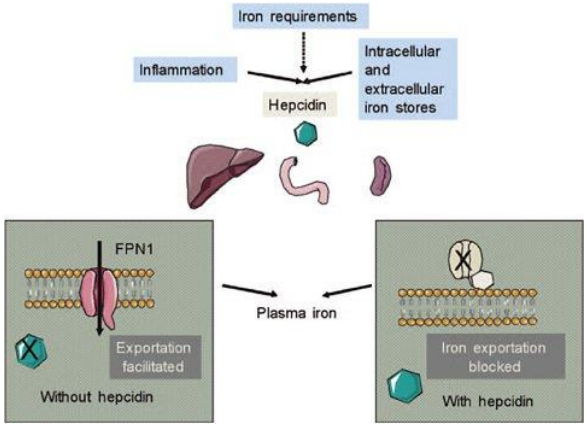

Figure 2. The Mechanism of Regulation of Hephidin Synthesis

Peptides are produced by the liver. Hepsidin closes the entry of iron from hepatocytes, macrophages of enterocytes, by binding to ferroportin (FPN1) (Waldvogel-Abramowski et al., 2014). In anemic states, hepsidin mRNA is suppressed, but the effect is likely to be indirect, depending on the production of erythropoetin. At least three other proteins also participate in the interaction between BMP and BMP receptors. Hemojuvelin (HJV) is the initial protein, Mt2 controls the amounts of HJV-bound membranes, and neogenin is a transmembrane protein that is ubiquitously produced and has a variety of functions (Enns et al., 2012). Many polymorphisms of Mt2 gene affect iron metabolism characteristics, especially in patients with iron deficiency anemia (Waldvogel-Abramowski et al., 2014).

Hepcidine is found in the blood in both mature and pro-hormone forms (Prohepsidin). Due to the discovery that prohepsidin selectively binds to STAT3 in HAMP gene promoters, it is presumed that prohepsidin influences the expression of its own genes, indicating an autoregulation loop of the hepsidine gene (Pandur et al., 2013).

Iron Regulation Proteins

Different cell types contain different types of iron, which serves a specific purposes as an iron source or a storage for iron. Enterocytes, which accept iron from digested food, macrophages, and hepatocytes are examples of iron export cells. Both of these cells recycle iron as needed. Iron then transported into the fetal circulation by placental cells. IRP1 and IRP2 maintain cellular iron homeostasis, iRP binds to IRE residing in untranslatable areas and mRNA proteins participating in iron retrieval, utilization storage, and export (Waldvogel-Abramowski et al., 2014).

CONCLUSION

Considering the outcomes of the literature review on the correlation of anemia in pregnant women with stunting incidence, it is known that both macronutrients and micronutrients are correlated with the occurrence of stunting and anemia. It is known that nutrient in infants, both macronutrient and micronutrient have a large role in growth and prevention of growth disorders. It is certainly necessary to make efforts to improve health in both pregnant women and children to prevent anemia, both through cross-program and across sectors.

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