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Correlation between Zinc and Folic Acid Intake with Hemoglobin Levels in Pregnancy

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ABSTRACT (9 PT, Book Antiqua, Ful English)

The deficiency of micronutrients and anemia are nutritional problems in pregnancy. WHO in 2019 and Riskesdas in 2018 reported that anemic pregnant women in Indonesia were 44.2% and 48.9%. Public Health Service also reported there was an increased prevalence of this problem in West Sumatra and Padang City in 2019 which was 18.1% and 11.2%. Micronutrient deficiency affected the hemoglobin (Hb) level, which is one of the indicators marking anemia in pregnancy. The objective was to determine the correlation between zinc and folic acid with hemoglobin levels in the third trimester of pregnancy. This analytical cross-sectional research was held in the Health Center and laboratory of Lubuk Kilangan on May-July 2022. The population and samples were 64 third-trimester pregnant women with total sampling. Intake data were collected through interviews using the Food Frequency Questionnaire (FFQ). Hemoglobin levels were examined by a hematology analyzer. Pearson correlation was used to identify the correlation of the variables ($P< 0.05$) . The mean levels of zinc and folic acid intake and hemoglobin levels were 7.35 mg, 215.56 mcg, and 11.08 g/dL. There was a positive correlation between zinc (p=0,015) and folic acid (p=0.004) with hemoglobin levels in the third trimester of pregnancy.

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INTRODUCTION

Anemia is one of the nutritional problems in pregnancy worldwide (Cortés-Albornoz et al., 2021). World Health Organization (WHO) 2019 published data about the prevalence of anemia in pregnancy in Indonesia, which was 44,2% (WHO, 2021). The Basic Health Research Report of Indonesia also reported that there was an increasing prevalence of anemic pregnant women, which was 37.1 in 2013 was % to 48.9% in 2018 (Kemenkes RI, 2018). This problem also happened in West Sumatra, the percentage of anemic pregnant women increased from 15.92% in 2015 to 18.1% in

2017. This problem also happened in Padang City, in 2017 was 7.10% to 11.2% in 2019 and at the Lubuk Kilangan Health Center in 2018 was 6.5% to 25.7% in 2019 (Dinkes Kota Padang, 2020).

Causes of anemia during pregnancy include an increased need for nutrients and low and poor intake (Gibore et al., 2021). The development of pregnancy requires increased nutritional needs (Darnton-Hill and Mkparu, 2015) and increased nutritional needs tend to be higher in the third trimester of pregnancy (Grzeszczak et al., 2020). Changes in the hematology of pregnant women, namely hypervolemia, also occur in the third trimester of pregnancy (Cunningham et al., 2018). The blood volume of pregnant women will increase by ±40-45%. The blood volume of pregnant women will increase by ±40-45%. These changes occur gradually from the 6-8th week to the 32-34th week of pregnancy. At the same time, renal erythropoietin will increase the number of erythrocytes by 20-30%, but this increase is not proportional to the increase in plasma volume resulting in hemodilution and a decrease in hemoglobin levels (Prawirohardjo, 2013).

Micronutrients are needed by the body to ensure body functions work properly (Farias et al., 2020). Micronutrient deficiencies during pregnancy contribute to cases of iron deficiency and anemia (Avantika Gupta, 2018), (Lipoeto et al., 2020). The most common micronutrient deficiencies during pregnancy are deficiencies of iron, zinc, folic acid, vitamins A, B, and C (Balarajan et al., 2011). Zinc is the second essential micronutrient that the body needs the most (Kambe et al., 2015). Zinc acts as part of the essential carbonic anhydrase enzyme in erythrocytes and is required in the activity of the superoxide dismutase enzyme to protect the surface of the erythrocytes from damage (Linder, 2006).

Erythroblasts also require folate for proliferation during their differentiation. A deficiency of folate inhibits purine and thymidylate syntheses impair DNA synthesis, and causes erythroblast apoptosis, resulting in anemia (Koury & Ponka, 2004). Anemia during pregnancy can be measured by an indicator called hemoglobin levels. A pregnant woman has been diagnosed with anemia with hemoglobin levels <11 g/dL (WHO, 2020a) (WHO, 2020b).This research aimed to determine the correlation between zinc and folic acid intake with hemoglobin levels in the third trimester of pregnancy.

RESEARCH METHOD

This research was an analytical cross-sectional. The research was held at the Lubuk Kilangan Health Center and the Laboratory of Lubuk Kilangan Health Center on May- July 2022. The population were 64-trimester pregnant women in seven sub-districts of the Lubuk Kilangan Health Center and the sampling used total sampling based on some inclusion and exclusion criteria. The instruments were the respondent data assessment sheet, FFQ questionnaire, blood sampling equipment, and hematology analyzer. The instrument for taking primary data which is zinc and folic acid intake used FFQ. Examination of hemoglobin levels was carried out by an analyst and researcher at the Laboratory of Lubuk Kilangan Health Center.

Univariate analysis was analyzed to describe variables such as characteristics of respondents and shown on the frequency distribution table. Analysis of bivariate used Pearson correlation test ($p<0.05$). This research has received ethical approval from The Research Ethics Committee of the Medical Faculty Andalas University.

RESULTS AND DISCUSSIONS

RESULTS

Results of Univariate Analysis

Table 1. The Characteristics of Third Trimester Pregnant Women

Characteristics	n=64	%
Age (Year)		
20-35	48	75.0
>35	16	25.0
Gestational age		
28-33 weeks	54	8..4
34-40 weeks	10	15.6
Parity		
Nulliparous	14	21.9
Primiparous	22	34.4
Multiparous	28	43.8
Education		
Elementary School	5	7.8
Junior High School	4	6.3
Senior High School	36	56.2
College	19	29.7
Profession		
Working	11	17.2
No working	53	82.8

The characteristics of third trimester pregnant women were shown on table 1 and known that most pregnant women were 20-35 years (75.0%), gestational age was 28-33 weeks (84.4%). Most of them were multiparous (43.8%), had a high school education (56.2%), and not working (82.8%).

Table 2. Mean Level of Zinc and Folic Acid Intake and Hemoglobin Levels

Variables	n	Mean ± SD	Min	Max
Zinc intake (mg)	64	7.35 ± 3.205	2.49	16.90
Folic acid (mcg)	64	215.56 ± 110.3278	62.98	491.89
Hemoglobin levels (mg/dL)	64	11.08 ± 1.1326	7.60	13.60

Based on table 2 known that the mean level of zinc and folic acid intake had not reached the minimal standard for the third trimester of pregnancy which was zinc 12 mg/day and folic acid 600 mcg/day but the hemoglobin levels has reached the minimum standard which was 11g/dL. Based on Figure 1 known that most pregnant women had less zinc (89.10%) and folic acid intake (100 %) and also has low hemoglobin levels (51.56%).

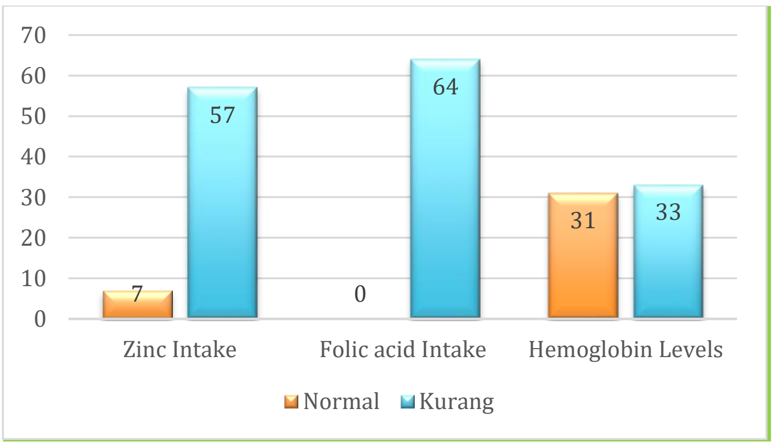

Figure 1 The Distribution of The Third Pregnant Women based on Intake status and Hemoglobin Levels

Results of Bivariate Analysis

Based on Table 3, known that there was a positive correlation between zinc intake with hemoglobin levels in third trimester of pregnancy

Table 3. Correlation between Zinc Intake with Hemoglobin Levels

Variables	**n**	*r*	*p-value*
Zinc intake (mg) Hemoglobin Levels (mg/dL)	64	0.303	0.015

Table 4. Correlation between Folic Acid Intake with Hemoglobin Levels

Variables	**n**	*r*	*p-value*
Folic acid intake (mcg) Hemoglobin Levels (mg/dL)	64	0.349	0.005

Based on Table 4, known that there was a positive correlation between folic acid intake with hemoglobin levels in third trimester of pregnancy

Discussions

a. Correlation between Zinc Intake with Hemoglobin Levels in Third Trimester of Pregnancy

This research found that there was a significant correlation between zinc intake with hemoglobin level, with a correlation value of 0.303 which indicates a positive correlation. Zinc is a mineral that plays a role in health and plays a role in metabolism, the immune system, and other biological processes (Grüngreiff, Gottstein and Reinhold, 2020). Almost 90% of zinc intake will be metabolized, while the rest will be stored as reserves which are important in maintaining the body's zinc status (Saaka, 2012).

Zinc and iron have interactions. Zinc acts as a cofactor for the amino acid levulinic dehydrase which plays a role in the synthesis of transferrin in the heme synthesis process (Linder, 2006). Zinc deficiency results in impaired heme synthesis. The interaction between iron and zinc occurs in two mechanisms. Direct interactions occur through absorption and in the transport pathways of iron and zinc, both of which are transported by the same transporter (Atmasier, 2015).

Zinc deficiency is caused by several factors. In several countries, low food quality is the main determinant of inadequate consumption of micronutrients. Zinc absorption in the body is around 5-40% and food is not the only determinant of absorption, but also zinc bioavailability (Wieringa et al., 2016). Zinc in high levels and has easily absorbed properties is zinc derived from animal food ingredients. The zinc content of vegetable origin generally binds to oxalates, tannins, and phytates (Tarini et al., 2021)

In this study, it was found that 57 people, or 89.1% of third-trimester pregnant women had low zinc intake. The reason for this is thought to be related to the type of food consumed. Third trimester pregnant women in this study consumed more plant foods containing phytate. This result in line acwith the theory which states that animal foods do not contain a lot of phytates so that zinc can be absorbed optimally. Fiber and phytic acid will inhibit zinc bioavailability (Iqbal and Ali, 2021).

Findings from the results of research in the field obtained information that the food consumption of pregnant women in the third trimester at the Lubuk Kilangan Health Center tends to come from vegetables, which contain low amounts of zinc. This is thought to be the cause of most pregnant women having low levels of ferritin and zinc intake. The above needs to be a concern because topographically, the working area of the Lubuk Kilangan Health Center is an area with access to the seaside which is far enough so that access to foods high in zinc content such as clams, oysters and fresh fish is quite difficult.

The risk that can occur in pregnant women who experience zinc deficiency during pregnancy is growth retardation in infants by affecting the development of the immune system. During pregnancy, some enzymes and growth hormones require zinc, such as placental alkaline phosphatase, which stimulates DNA synthesis and cell proliferation. Zinc has also been shown to play a role in IGF-I. activity (Jyotsna, Amit and Kumar, 2015).

Zinc deficiency during pregnancy is also associated with complications and disorders in the fetus, such as growth disorders, congenital malformations, low birth weight, prematurity, delayed development, impaired immune system and erythropoiesis (Karimi et al., 2012). Research shows that zinc supplementation during pregnancy reduces the risk of preterm delivery, especially in low-income countries (Agedew et al., 2022).

Another mechanism that can explain the correlation between zinc intake and ferritin levels is through erythropoiesis, erythropoietin, and insulin growth factor-1 (IGF-1) which are required in the early stages to initiate hematopoiesis. IGF-1 is a hormone produced by the liver by Growth Hormone (GH). Several minerals, namely zinc, magnesium, and selenium are important determinants of IGF-1 bioactivity (Maggio et al., 2013).

GH and IGF-1 will decrease when zinc deficiency occurs. Erythropoietin then regulates erythrocyte production by delaying DNA degradation and preventing erythroid progenitor cells from undergoing apoptosis (Obeng, 2021). When a multipotent cell transforms into a proerythroblast, erythropoietin binds to the erythropoietin receptor and causes the release of GATA-1, a zinc-finger protein transcription factor whose function regulates various genes involved in erythrocyte synthesis(Katsumura et al., 2013).

GATA-1 and FOG-1 which are cofactors of GATA-1 form a complex and interact to regulate the transcriptional activity for erythroid differentiation. Protoblasts then turn into several cells including erythroblasts (Chlon & Crispino, 2012). Zinc is required by GATA-1 and FOG-1 to bind to the zinc-finger protein. When there is a deficiency of zinc intake, the activity of the GATA-1 transcription factor in hematopoiesis will decrease so that hemoglobin production also decreases(Suzuki et al., 2014).

The results of this study are also in line with research on pregnant women in Ghana, women with low zinc levels have a 3-fold risk of suffering from iron deficiency (Saaka, 2012). Other studies also reported that zinc supplements could increase the levels of IGF-1, which correlated with increased levels of hemoglobin and the number of erythrocytes. Previous studies have also reported that zinc is used in the biosynthesis of protoporphyrin IX which is a hemoglobin precursor when an iron deficiency occurs ((Nishiyama et al., 2015), (Kaneko et al., 2020), (Takahashi, 2022).

b. Correlation between Folic Acid Intake with Hemoglobin Levels in Third Trimester of Pregnancy

This research found that there was a significant correlation between folic acid intake with hemoglobin (Hb) levels, with a coefficient correlation of 0.349 which indicates a positive correlation. Anemia is a condition of decreased Hb, hematocrit, and erythrocyte counts below. Nutritional anemia often occurs in developing countries and is caused by a deficiency of nutrients. Nutrients play a role in the formation of hemoglobin, either due to lack of consumption or absorption disorders.

Deficiency of protein, iron, pyridoxine (vitamin B6), vitamin B12, vitamin C, Vitamin E, and folic acid are the cause of nutritional anemia (Akhtar & Hassan, 2012)Folate is a set of essential nutrients that participate in the synthesis of DNA and proteins (Ballestín et al., 2021). Folic acid also is a generic term for multiple forms of the essential B vitamin. Folate naturally occurs in foods. Folic acid is much more bioavailable than folate naturally occurring in foods and when ingested is converted by dihydrofolate reductase to the dihydrofolate and then the tetrahydrofolate form of folate (Rodwell et al., 2020).

Megaloblastic or macrocytic anemia is caused by folate deficiency. The effect of this deficiency in the first trimester of pregnancy leads to neural tube defects. Folate deficiency in pregnancy also has been associated with low birth weight, preterm delivery, and fetal growth retardation (Delchier et al., 2016). Folate deficiencies are well known to severely impair fetal development, leading to neural tube defects (NTDs) and an increased risk of mental retardation and cretinism, respectively(Medlock & Dailey, 2022). Folic acid supplementation increased the level of folic acid, reduced the level of HCY of brain tissue in offspring and reduced the wrong incorporation of uracil into telomeres (Zhou et al., 2022).

The correlation between folic acid intake with hemoglobin could be explained by folic acid plays a role in metabolizing amino acids which are also needed for the formation of erythrocytes and leukocytes (Akhtar & Hassan, 2012). Folate deficiency will cause interference with the maturation of the erythrocyte nucleus in the replication of DNA and the process of cell division (Prakash & Yadav, 2015).. This situation will affect the performance of body cells including cells that play a role in hemoglobin synthesis. Therefore, iron and folic acid supplementation is recommended during pregnancy to prevent complications.

Folic acid intake is obtained through the consumption of food. Various foodstuffs have good folic acid content from the consumption of meat, fruits, vegetables, and cereals. It was found information through FFQ that the source of folic acid intake for pregnant women is more from vegetable consumption. The types of vegetables that are most often consumed by pregnant women are spinach and cassava leaves. Most pregnant women consumed vegetables 3-4 times a week. Good sources of folic acid come from animal foods and this thing could be the reason why most pregnant women had less folic acid intake and anemia. This research also found that none of the pregnant women fulfilled their daily requirement of folic acid. This is evidenced by data showing that daily intake of folic acid is still under the RDA standard. The increased need for folic acid is not matched by the fulfillment intake was the cause of anemia. This result was in line with some previous studies (Meilinda Sembiring et al., 2020) , (Tamrin et al., 2019).

Optimal adherence to consuming iron and folic acid supplementation is the main effective strategy for preventing and controlling anemia in pregnancy caused by iron and folate deficiency (Yusrawati et al., 2019). WHO recommends pregnant women should receive and consume a standard dose of 30-60mg iron and 400 µg folic acid daily starting as early as possible throughout pregnancy to prevent and control anemia caused by deficiencies of micronutrients (WHO, 2012). Pregnant women should consume iron and folic acid supplements to have a normal hemoglobin concentration during pregnancy so could prevent anemia.

CONCLUSION

The results of the bivariate test showed that there was a significant correlation between zinc and folic acid intake with hemoglobin levels in third-trimester pregnant women in the LubuK Kilangan Health Center, Padang City. Pregnant women are expected to be able to fulfill the nutritional needs of zinc and folic acid because they have been proven to be correlated factors of the incidence of anemia. In addition, real effort and action are needed to encourage regular consumption iron and folic acid supplementation to prevent anemia and minimize the impact. Future research can explore several other factors related to hemoglobin levels with various research approaches and designs.

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