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Article

The Correlation of Retinol Level with Hemoglobin Level in Third Trimester of Pregnancy Woman

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A B S T R A C T

Bleeding is one of the highest causes of maternal death. Anemia is a major cause of bleeding. Anemia in pregnant women is caused by iron deficiency, meanwhile the achievement of giving Fe tablets is quite high. Factors for anemia due to lack of intake of vitamins A, C, B12 and folate.This study aims to determine the Correlation Retinol Level with Hemoglobin Level and Ferritin Level in Pregnant Women Thiird trimester. This study was conducted using cross sectional approach, from Juli 2017 – February 2018 at Lubuk Buaya Health Center, Andalas Health Center and UNAND Biomedical Laboratory using pregnant women in third trimesteras sample with consecutive sampling technique totalling 44 people. Independent variable is retinol level and dependent variable are hemoglobin and ferritin level. Examination using Hematology Analyzer for hemoglobin and ELISA reader for examination of retinol level and ferritin level. Data was performed using a computer program to analyze nprmally distributed data using pearson test and spearman test that are abnormally distributed. Mean of retinol level of respondent was 137,612±21,717 ng/ml, hemoglobin 10,916±0,880 gr/dl and ferritin level 26,681±30,829 ng/ml. From result of analysis pearson test showed that there was a significant correlation between retinol level and hemoglobin level in pregnant women with p=0,001 (p<0,05) dan r=0,473 and there was no significant correlation between retinol level and ferritin level in pregnant women p=0,158 (p>0,05) (r=0,216). The conclusion of this study is that there is a correlation of retinol level with hemoglobin level and no correlation of retinol with ferritin level.

I. INTRODUCTION

The highest maternal death is caused by bleeding. The main cause of bleeding in pregnant women is anemia in pregnant women, which is one of the main maternal mortality factors in Indonesia. Indonesia has the highest maternal mortality rate (MMR) compared to other ASEAN countries. MMR in Indonesia always goes down every year until 2007 to 228 per 100,000 live births. In 2012 the results rose to 359 per 100,000 live births and decreased to 305 maternal deaths per 100,000 live births (Kemenkes RI 2016).

Based on the 2015 Intercensal Population Survey (SUPAS), MMR in Indonesia is at 305 / 100,000 live births. This situation certainly requires joint work to reduce maternal and infant mortality in Indonesia as the target set in the Sustainable Development Goals (SDGs) (Badan Pusat Statistik 2015).

Health Service data Padang showed that maternal mortality rates in 2015 were 17, and continued to rise in 2016 with the case of mother's death of 20 people, The details of maternal death is composed of maternal deaths of four people and the death of postpartum mothers 16 people (Dinkes Kota Padang 2016)

Based on data from the Household Health Survey (SKRT) in 2012 the incidence of anemia in infants was 40.5%, pregnant women 50.5%, postpartum mothers 45.1%, young women aged 10-18 years 57.1% and ages 19-45 year 39.5%. stated that women have the highest risk of anemia, especially in adolescent girls(Kemenkes RI 2013).

Meanwhile, the data of West Sumatra Provincial Health Office showed that the prevalence of anemia among pregnant women in West Sumatra in 2014 amounted to 20.7%. This shows that anemia is still a public health problem in Indonesia, including in West Sumatra(Dinkes Prov Sumbar 2015).

Judging from the most common causes of anemia are nutritional deficiencies. Where about 75% of the causes of anemia in pregnant women are caused by iron deficiency which shows microcytic hypochromic erythrocytes on peripheral blood smears. The World Health Organization reports that the prevalence of pregnant women who have iron deficiency is around 35-75% and increases with pregnancy.

The main cause of anemia in pregnant women is due to iron deficiency of 43.1%. Anemia of pregnant women is not only associated with iron deficiency but also because of vitamin A ($p = 0.004$) and nutritional status (LILA) ($p = 0.003$). There is a close correlation between anemia during pregnancy with fetal death, abortion, congenital defects, low birth weight babies, reduced iron reserves in children or children born in nutritional anemia (Muthalib 2010).

The coverage of pregnant women in Indonesia who received Fe tablets in 2014 was 85.1%, the data has not reached the 2014 program target of 95%. Provinces in Indonesia in 2014 with the highest Fe3 coverage were in Bali Province (95%), while the lowest coverage was in West Papua Province (38.3%). West Sumatra Province reaches 81.1% which is still below Indonesia's achievement target. This achievement is expected to prevent anemia. However, from the data obtained, the incidence of anemia in Indonesia is still quite high (Kemenkes RI 2016).

The prevalence of anemia can be caused by several factors including low intake of iron and other nutrients such as vitamin A, vitamin C, folate, riboplafin and B12 which function to help iron absorption. Besides that, it can meet iron needs by consuming animal food sources as one of the sources of iron that is easily absorbed, consuming a plant-based food source which is a high source of iron but difficult to absorb (Briawan 2014).

The group of pregnant women given iron and vitamin A experienced a decrease in ferritin concentration and increased hemoglobin concentration due to an increase in erythropoiesis in the administration of iron and vitamin A every week.

Determination of hemoglobin as an iron status index has a number of disadvantages including dependence on age, sex, race, low sensitivity and specificity and other factors such as diurnal variation and smoking, therefore iron status index is used as iron reserves in the form of ferritin.

II. METHODS

This study was conducted at Lubuk Buaya Health Center, Andalas Health Center, and UNAND Biomedical Laboratory from July 2017 to February 2018. This study was a quantitative study with a cross sectional approach. The population was all pregnant women in the third trimester, the study sample was taken using Non Probability Sampling technique that is by consecutive sampling in accordance with the inclusion and exclusion criteria.

The material of study was a respondent's venous blood sample for examination of hemoglobin levels and using the respondent's serum for examination of retinol levels and ferritin levels. The study tool used questionnaire sheet containing the respondent's personal data and the results of the examination of retinol levels, hemoglobin levels and ferritin levels of respondents. Blood sampling was carried out at the Lubuk Buaya Health Center and Andalas Padang Health Center along with taking routine blood from the patient. 3 ml of blood collection on the mediana cubiti vein using vacutainer needle which is directly inserted into the vacuum blood tube. Direct hemoglobin examination was performed using a hematology analyzer and for examination of retinol and ferritin levels centrifuged for 15-20 minutes at a speed of 3000 rpm. The serum is then stored at -80°C until inspection at the Biomedical Laboratory of Andalas University. Retinol level examination used the Human RBP ELISA Kit and examination of ferritin levels used the Human Ferritin ELISA Kit

III. RESULT

This study was carried out from January until February 2018 by taking samples at the Lubuk Buaya Health Center and Andalas Health Center. Technique sampling was using consecutive sampling technique and obtained as many as 44 study subjects. Characteristics of respondents in this study included maternal age with a mean age of 29.34 ± 5.46 years, mean gestational age was 32.09 ± 3.17 weeks, mean maternal weight was 63.73 ± 7.99 kg and mean height mother is 159.09 ± 4.82 cm.

After univariate analysis, it was found that the distribution of data on the variable retinol levels of respondents with a mean of 137.61 ± 21.71 ng / ml, hemoglobin levels with a mean of 10.91 ± 0.88 gr / dl and ferritin levels with a mean of 26.68 ± 30, 82

ng / ml. The results of the normality test showed that the data on retinol levels, hemoglobin levels and ferritin levels were normally distributed (p> 0.05). Of the 44 respondents found 100% of respondents experienced low levels of retinol, 61.4% had normal hemoglobin levels and 54.5% had normal ferritin levels.

Correlation of Retinol with Hemoglobin Levels and Ferritin Levels in Pregnant Women

In this study also carried out bivariate analysis using correlation analysis to see the closeness of the correlation between the independent variables is the level of retinol with the dependent variable are hemoglobin levels and ferritin levels.

Tabel 1. Hasil Analisis Korelasi Kadar Retinol Dengan Kadar Hemoglobin Dan Kadar Ferritin

Variabel	r	r^2	p value
Hemoglobin Level	0,473	0,224	0,001
Ferritin Level	0,216	0,047	0,158

Table 1 shows that there is a significant correlation between the levels of retinol with hemoglobin levels and no significant correlation between the levels of retinol with ferritin levels in the third trimester pregnant women.

Correlation Retinol Levels with Hemoglobin Levels in Pregnant Women

The correlation between retinol levels and hemoglobin levels analyzed by Pearson test because the data on retinol levels and hemoglobin levels were normally distributed (p> 0.05). Based on the results of the analysis on Pearson correlation test found that there was a significant correlation between retinol levels and hemoglobin levels in third trimester pregnant women with p = 0.001 (p <0.05) and the correlation strength of these two variables was moderate (r = 0.473) with direction of positive correlation.

Tabel 2. Hubungan Kadar Retinol dengan Kadar Hemoglobin Ibu Hamil

	Variable	n	Mean±SD	p
Retinol Levels With Normal Hemoglobin	**Retinol Levels Normal Hemoglobin Levels**	27	144,46±23,03 11,45±0,67	0,317
Retinol Levels With Low Hemoglobin	**Retinol Levels Low Hemoglobin Levels**	17	126,73±14,14 10,05±0,24	0,001

The 44 pregnant women studied, as many as 27 pregnant women obtained with normal hemoglobin level and after analysis using Pearson correlation test showed that no significant correlation exists at levels of retinol and hemoglobin levels in pregnant women who had normal hemoglobin with p = 0.317 .

While 17 pregnant women with anemia were analyzed using Pearson test showed that there was a significant correlation on

retinol levels and hemoglobin levels in anemic pregnant women with p = 0.001.

Correlation Retinol Levels with Ferritin Levels in Pregnant Women

The correlation between retinol levels and ferritin levels was carried out by Pearson test because the data of retinol levels and ferritin levels were normally distributed (p> 0.05). Based on the Pearson correlation test results showed that there was no significant correlation between retinol levels and ferritin levels in pregnant women with p = 0.158 (p> 0.05) and the strength of the correlation of these two variables was weak (r = 0.216) with a positive correlation direction .

Tabel 3. Hubungan Kadar Retinol dengan Kadar Hemoglobin Ibu Hamil

	Variable	n	Mean±SD	p
Retinol Levels With Normal Ferritin	**Retinol Levels NormalFerritin Level**	24	144,55±22,01 41,95±35,10	0,114
Retinol Levels With LowFerritin	**Retinol Levels Low Ferritin Levels**	20	129,28±18,61 8,35±3,33	0,297

The 44 pregnant women studied, 24 pregnant women with normal ferritin levels and after analyzing using the Spearman test found that there was no significant correlation with retinol levels and ferritin levels in pregnant women who had normal ferritin levels with p = 0.114.

In line with the results of an analysis of 20 pregnant women with low ferritin levels using Pearson test showed that there was no significant correlation with retinol levels and ferritin levels in pregnant women who had low ferritin levels with p = 0.297.

IV. DISCUSSION

Univariate Analysis

The results of this study found retinol levels with an mean of 137.61 ± 21.71 ng / dl. According to Almatsier (2009), vitamin A is a yellow crystalline alcohol and fat soluble. Serum retinol examination is an established biochemical indicator to determine the status of vitamin A. Vitamin A is transported from the liver into the blood plasma if it is bound to Retinol Binding Protein (RBP). This RBP is also synthesized in the liver / liver. Almost all retinol, is the circulation of vitamin A in serum that is bound to RBP, so that the concentration of RBP in the blood can be used as an indicator of vitamin A status. Retinol testing in pregnant women can help determine vitamin A status in pregnant women which is useful for the mother's condition at the time pregnancy where vitamin A can help reduce the risk of infection, the incidence of anemia, reproductive disease and maternal survival up to two years postpartum.

The mean hemoglobin level of pregnant women is 10.91 ± 0.88 gr / dl. Hemoglobin is a metal protein that transports iron-containing oxygen in red blood cells in mammals and other animals. Hemoglobin will carry oxygen from the lungs to the entire tissue and bring carbon dioxide back to the lungs. In pregnant women this hemoglobin will carry oxygen to the fetus in the uteroplacental cycle. So it is necessary to do this hemoglobin examination to determine the hemoglobin level in the blood that can carry oxygen to the red blood cells.The mean ferritin level of pregnant women was 26.68 ± 30.82 ng / dl. Ferritin is an important protein in iron metabolism. Under normal conditions, ferritin stores iron which can be recovered for use as a necessity. In excess

iron, the body's iron stores are greatly increased and far more ferritin is found in the tissues, such as the liver and spleen. Ferritin examination is a parameter and sensitive to determine iron reserves of healthy people. Low serum ferritin is an early sign of iron deficiency and the results of serum ferritin can assess the state of iron deficiency in pregnancy(Pearce 2010).

Bivariate Analysis

Correlation Retinol Levels with Hemoglobin Levels in Pregnant Women

Pearson correlation statistical test results showed that there was a significant correlation between retinol levels and hemoglobin levels in pregnant women with p value = 0.001 ($p < 0.05$) and the correlation strength of these two variables was moderate ($r = 0.473$) with a positive correlation direction.

Pregnant women observed that there was an increase in hemoglobin levels at 26-28 weeks higher for mothers who were given iron supplementation plus vitamin A than pregnant women who were given iron alone. The positive correlation found between low retinol and the occurrence of anemia and iron deficiency reinforces the findings of experimental and epidemiological studies. It is believed that changes in the nutritional status of vitamin A do not interfere with the process of iron absorption, but by mobilization in the liver(Lu, et al. 2017).

The another experiment using mice and cell culture, found an association between vitamin A levels and protein gene transcription factors related to iron bioavailability. The results show that serum retinol deficiency increases hepcidin expression and directly affects liver mobilization from iron storage needed for erythropoiesis (Citelli M 2012)

This process of erythropoiesis starts from multipotential stem cells which will form unipotential stem cells which will each form one type of cell such as erythrocytes. Hemoglobin is the most important element in plasma erythrocytes. The hemoglobin molecule consists of groups of globin, protoporfuin and iron. Disorders of globin production only occur due to gene disorders. But in producing erythrocytes is influenced by various elements, one of which is vitamin A. There are several essential processes in the body that are in dire need of vitamin A such as in the metabolic process, hematopoiesis, erythropoiesis, regulation of cell differentiation and play a role in the immune system. One of the functions of vitamin A is its role in the process of forming red blood cells through its interaction with iron.

Based on the results of the study as many as 17 pregnant women with anemia were analyzed using Pearson correlation test found that there was a correlation on retinol levels and hemoglobin levels in pregnant women in the third trimester of anemia with a value of $p = 0.001$.

The 27 pregnant women with normal hemoglobin levels analyzed using Pearson correlation test showed that there was an insignificant correlation with retinol levels and hemoglobin levels in pregnant women with normal hemoglobin with $p = 0.317$. This means that when retinol levels are low, hemoglobin levels will decrease.

It was concluded that mothers with low levels of retinol will also decrease hemoglobin levels, because vitamin A can help mobilize iron from the liver and help the erythropoiesis process to produce hemoglobin. Where iron with retinol will be transported by Retinol Binding Protein

(RBP) and transferin which will later be synthesized in the liver so that in case of vitamin A deficiency it will affect the mobilization of iron from the liver or the incorporation of iron into erythrocytes and cause hemoglobin deficiency. This is also related to its function to synthesize proteins, where when vitamin A deficiency will affect bone cell growth which is where the formation of eritroit is in the bone marrow.

In addition, it is also due to being involved in the catabolism process of proteins in the liver, namely Fe storage and mobilization. Where an increase in erythropoietin can affect Hb as long as vitamin A is high or as long as vitamin A can interact with Fe, to keep it dissolved in the intestinal lumen and prevent inhibiting factors from absorbing Fe, the iron available in Ferri (Fe3 +) will be reduced to ferro (Fe2 +) by ferireductase found on the surface of enterocytes (Bakta 2015).

Enterocytes are present on the surface of the proximal duodenum which contributes to iron absorption. The presence of Vitamin A in the diet makes it easier to reduce ferri to ferro. This low hemoglobin level can also be caused by other symptoms such as megaloblastic anemia due to vitamin B12 deficiency and hypoplastic anemia due to lack of spinal cord which can make new blood cells (Citrakesumasari 2012).

But from the results of the study also found mothers with low levels of retinol but have normal hemoglobin levels due to other factors that influence the formation and maturation of erythrocytes which will later affect their own hemoglobin such as iron, zinc, vitamin C, vitamin B12, vitamin B6 and folate (Berdanier CD 2008). In this case the factor is not examined, perhaps the pregnant woman is due to other factors that are normal.

Correlation Retinol Levels with Ferritin Levels in Pregnant Women

Pearson correlation statistical test results showed that there was no significant correlation between retinol levels and ferritin levels in pregnant women with $p = 0.158$ ($p > 0.05$) and the strength of the correlation between these two variables was weak ($r = 0.216$) with a positive correlation direction .

Ferritin concentration decreased significantly in the group given iron with vitamin A in the short term. Administration of vitamin A and iron every week will increase hemoglobin concentration but reduce serum ferritin concentration due to increased iron mobilization from iron stores in the body and increased erythropoiesis.

Based on studies in animals given low-dose vitamin A supplements will experience increased absorption of iron in the small intestine and there is a buildup of iron in the storage area in the body such as the liver and spleen. Conversely if given high doses of vitamin A it will experience a decrease in iron reserves in the liver.

One of the biological mechanisms of vitamin A deficiency can cause anemia is modulation of erythropoiesis. During experiencing vitamin A deficiency, iron absorption is increased and iron absorption in the bone marrow is disrupted. During vitamin deficiency, iron trapped in the liver and spleen and is not effectively removed for erythropoiesis by the bone marrow and affects the osmotic fragility of erythrocytes.

The 24 pregnant women who had normal ferritin levels analyzed using the Spearman correlation test showed that there was no significant correlation with retinol levels and ferritin levels in pregnant women who had

normal ferritin levels with p = 0.114. In pregnant women with low retinol levels have normal ferritin levels because when there is a low level of vitamin A iron will be trapped in the liver and the spleen and ineffective released by the bone marrow so that iron reserves will remain stored and even an increase will occur. It can be concluded that when vitamin A levels are low, iron (ferritin) reserves in the liver will also increas.

While the 20 pregnant women who had a low ferritin levels after Pearson correlation test showed that there is no significant correlation to the levels of retinol and ferritin levels in pregnant women with low ferritin levels with p = 0.297. In pregnant women with low retinol levels but also low ferritin levels due to other factors that can affect ferritin levels, in this case no study was conducted such as the difference in age of pregnant women, maternal consumption patterns that can affect iron absorption other than vitamin A long bleeding conditions, in women with a history of severe menstrual bleeding, long-term gastrointestinal bleeding, and intestinal disorders that cause a decrease in iron absorption (Hillman 2011).

Giving iron intake to pregnant women from food sources alone does not meet iron requirements during pregnancy so iron supplements are needed. Iron supplementation during pregnancy can consistently increase hemoglobin levels and ferritin levels in pregnant women. But there are other factors that can affect the ferritin levels of pregnant women to decline so expect pregnant women also consume foods that contain food that can help to increase the absorption of non-hemoglobin iron optimally (Almatsier 2009).

Pregnant women are advised to consume iron because iron functions for hematopoiesis in hemoglobin synthesis. From the study conducted, it was found that retinol can affect several processes that will affect iron, namely the process of iron absorption, especially non-iron iron, can affect bone cell growth, the process of erythropoiesis itself and iron mobilization from the liver. So that pregnant women need intake containing retinol or vitamin A in addition to iron (Fe tablets). Not only retinol, protein intake must also be increased because proteins function to regulate osmotic pressure in the blood. In this case protein is useful to help transport retinol to the tissues, where retinoic acid will be transported in plasma in a state bound to aporetinol binding protein (Retinol Binding protein / RBP). Giving albumin can only be given according to the doctor's advice, but pregnant women can get it from foods such as chicken, turkey, duck, peas, almonds, tofu, soy milk, eggs and wheat.

Beef, duck meat, liver, egg yolks, milk, cheese, sea fish, green and orange vegetables (spinach, long beans, kale, mustard greens, tomatoes, carrots, broccoli, peppers), nuts and fruit brightly colored fruits are foods that have iron, vitamin A and protein at the same time, so that pregnant women can consume them in order to meet and help the hematopoiesis process.

V. CONCLUSION

The average level of retinol in the third trimester of pregnant women is low, the mean hemoglobin level is normal and the mean ferritin level is normal. There is a correlation between retinol levels and hemoglobin levels in pregnant women in the third trimester and there is no correlation

between retinol levels and ferritin levels in third trimester pregnant women.

It is expected that health care workers can improve nutritional counseling related to easily absorbable foods that contain lots of vitamin A and reduce foods that inhibit iron absorption.

For further study, it is expected that the results of this study can be used as a comparison if further study is conducted on retinol levels or hemoglobin and ferritin levels which are closely related to the effects on iron such as food recall in order to see intake that can affect retinol levels and iron levels itself. It also considers other factors that affect hemoglobin levels and ferritin levels in pregnant women such as vitamin C, B12, and iron absorption inhibiting factors, and can conduct study in first trimester pregnant women to labor to see differences or see the correlation between retinol levels and hemoglobin levels and ferritin levels during pregnancy.

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