CAUSES OF MICROCYTIC ANEMIA IN THIRD TRIMESTER PREGNANT WOMEN: A SCOPING REVIEW

**Ira Jayanti [1]*, Agussalim Bukhari [2],
Deviana Soraya Riu [3] and Rahmawati Minhajat [4]**

[1] Doctoral Study Program in Medical Sciences, Hasanuddin University, Indonesia.
[1] Guna Bangsa Yogyakarta College of Health Sciences, Master's Midwifery Study Program.
*Corresponding Author Email: ira.jayanti33@gmail.com
[2] Department of Nutrition, Faculty of Medicine, Hasanuddin University, Indonesia.
[3] Department of Obstetrics & Gynecology, Faculty of Medicine, Hasanuddin University, Indonesia.
[4] Division of Hematology and Oncology, Department of Internal Medicine,
Faculty of Medicine, Hasanuddin University, Indonesia.
[4] Department of Histology, Faculty of Medicine, Hasanuddin University, Indonesia.

Abstract

Purpose: This review focuses on microcytic anemia which has the aim to describe the causes of microcytic anemia in pregnant women. Method: Scoping review adapting the Arksey and O'Malley Framework. It was found that 20 out of 120 articles were selected based on inclusion and exclusion criteria. Results: The results of a review of this article found that there is still a high prevalence of anemia in developing countries and also in Indonesia, and pregnant women who experience anemia have the most Hb levels between 10 - 10.9 g/dl which are categorized as mild anemia and the highest cause of anemia in developing countries and Indonesia is microcytic anemia caused by iron deficiency andβThalassemia. Conclusion: The most common cause of anemia in developing countries and Indonesia is iron deficiency anemiaβThalassemia.

Keywords: Microcytic Anemia and Third Trimester Pregnant Women, Iron Deficiency, and βThalassemia.

INTRODUCTION

Anemia in pregnancy is an important public health problem in the world. The World Health Organization (WHO) estimates that more than half of pregnant women in the world have hemoglobin levels that indicate anemia (<11.0 gr/dl).

Data from the World Health Organization (WHO), reports that around 32.4 million pregnant women suffer from anemia worldwide, and 0.8 million suffer from severe anemia. The highest prevalence was in Africa (44.6%), followed by Asia with a prevalence of 39.3%. As many as 50% of anemia cases are caused by iron deficiency micronutrient deficiency (folic acid, riboflavin, and vitamin B12). Acute and chronic infections (Malaria and tuberculosis), as well as disorders affecting hemoglobin synthesis.

Microcytic anemia refers to the formation of small red blood cells as a result of poor hemoglobinization characterized by a Mean Corpucular Volume (MCV) < 80 Fl. While macrocytic anemia is a type of anemia with a larger than average volume of red blood cells. The complete blood count showed a mean corpuscular volume (MCV) > 100 fL.[33]

The condition of anemia in pregnant women must be detected as early as possible and given appropriate management. Calculation of the prevalence of anemia in pregnant women is useful for knowing the number of pregnant women who are at risk and require appropriate attention and treatment to prevent mothers from giving birth

to babies with iron deficiency anemia which will inhibit the growth of brain cells and other body cells which can manifest in the form of stunting. [26]

This systematic review discusses the incidence of microcytic anemia. However, it is more specific to the causes of microtic anemia in pregnancy, which is caused by iron deficiency and thalassemia.

METHOD

Scoping review is a literature review that aims to explore the extent of available evidence by mapping the concepts underlying the research area, sources of evidence and types of evidence available [27]. Use of this methodology is appropriate to practice, education, policy and research issues relevant to healthcare practitioners enabling the assessment of scientific evidence [28]. The preparation of this scoping review adapted the framework of Arksey and O'Malley (2005) which was further developed by Levac (2010) [29]. with five stages namely: identifying research questions, identifying relevant articles, selecting or selecting studies, chatting and compiling data, summarizing and reporting results.

1. Identify research questions

Question development is an important step that forms the basis of the entire review protocol in determining search strategies, inclusion and exclusion criteria and data extraction [30,32]. In this review, the Population, Exposure, Outcome, Study Design (PEOS) framework was used to assist in identifying the key concepts in the focused review. The PEOS framework can be seen in the table below.

Table 1: PEOS Framework

P(Population)	E (Exposure)	O (Outcomes)	S (Study Design)
Pregnant Women Pregnant Women in Trimester III Pregnant Women with Anemia	Microcytic Anemia Iron deficiency Thalassemia	Causes type	All research studies/study designs related to third trimester pregnant women with Microcytic Anemia

So the research question in this review is the cause of microcytic anemia in third trimester pregnant women?

2. Identify relevant articles

There are three steps in identifying relevant articles. The first step is to determine the database. The databases used are PubMed, SciencesDirect, EBSCO and Google Scholar. The second step, determine the inclusion and exclusion criteria. Articles were filtered according to inclusion criteria published 2017-2023, articles published in English, primary research articles (original research), and no country-specific criteria, cross-sectional and descriptive research methods that describe data on hemoglobin levels, and describe Types of anemia and causes of anemia experienced by pregnant women. For the exclusion criteria, namely opinion articles, peer reviews, thesis manuscripts and theses. The third step is to determine which keywords are focused based on the framework.

Table 2: Article search keywords

Databases	Keywords Search
PubMed	(microcytic anemia) OR ("cause microcytic anemia") OR ("type cause microcytic anemia") AND (women pregnant with iron deficiency) OR ("women pregnant third trimester with thalassemia")
Science Direct	("microcytic anemia") OR ("cause microcytic anemia") OR ("type cause microcytic anemia") AND (women pregnant with iron deficiency) OR ("women pregnant third trimester with thalassemia")
EBSCO	("microcytic anemia") OR ("cause microcytic anemia") OR ("type cause microcytic anemia") AND (women pregnant with iron deficiency) OR ("women pregnant third trimester with thalassemia")
Google Scholar	(microcytic anemia) OR ("cause microcytic anemia") OR ("type cause microcytic anemia") AND (women pregnant with iron deficiency) OR ("women pregnant third trimester with thalassemia")

3. Selection / selection of articles

The screening process is used to assess the relevance of the research identified in the search according to the desired literature characteristics. From the search using 4 databases as many as 120 articles. Then the articles were filtered based on duplication, abstract and title as well as full text reading. So that found 19 articles that will be reviewed. Furthermore, a critical appraisal was carried out using the Quality Assessment tool from Hawker and the total quality classification of articles and the article screening process were contained in PRISMA [31]. Flowchart in figure 1.

4. Data charts

Based on the 19 selected articles, data charting was then carried out to include several key points from the articles such as author, location, research objectives, methodology, number of samples from the findings of the study.
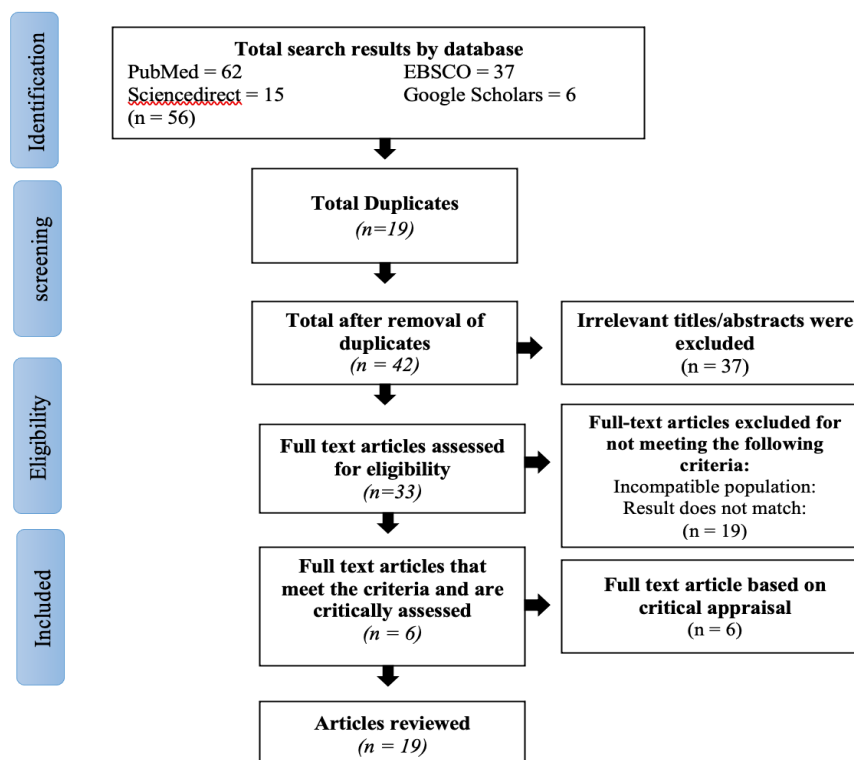
5. Compiling, Summarizing and Reporting Results

According to what was done by (Levac) to Compile, summarize and report the results of the review can be done by describing the characteristics of the article and thematic analysis [29].

Table 3: Data Charting

No	Title/Researcher, Year	Objective	Method	Participants	Results
A1	Prevalence and aetiologies of anemia among first trimester pregnant women in Sri Lanka; the need for revisiting the current control strategies (Amarasinghe., GS. et al, 2022).	To explore the prevalence of etiological factors that significantly contribute to anemia in pregnancy in Sri Lanka	Cohort Study	First trimester pregnant women registered in the public maternal care program in Anuradhapura district.	Of the 3127 participants, 14.4% had anemia. 331 had mild anemia. There were 243 (54%) who had microcytic anemia, 114 (25.3%) with normochromic-normocytic anemia, 80 (17.8%) with normocytic hypochromic anemia, and 2 (0.45) with macrocytic anemia. From the incidence of microcytic anemia, iron deficiency was 41.9%, B12 deficiency was 23.8% and ovalocytosis was 0.9%.
A2	Common morphologic type of anemia among pregnant teenagers in Western Uganda (Hassan., SM. et al. 2022).	To determine the type of anemia among pregnant adolescents	Cross Sectional Study	288 pregnant adolescents aged 13-19 years	The majority of anemia in pregnant women is microcytic 40 (53.3%) with iron deficiency, normocytic 25 (33.3%) and 10 (13.3%) with macrocytic anemia.
A3	Comparative Study of Anemia of Inflammation in Pregnant and Non-Pregnant Women (nisasa., F. et al. 2022)	To compare the prevalence of Inflammatory Anemia (AI in pregnant and non-pregnant women)	Cross Sectional Study	Pregnant women aged 7-13 weeks with Hb levels <10 g/dl.	The results of 300 participants were 133 pregnant women and 167 non-pregnant women and the results were 17% with inflammatory anemia due to inflammation and 23% with thalassemia.

A4	The prevalence of anemia and iron deficiency among pregnant Ghanaian women, a longitudinal study (Ruth A Pobee., et al. 2021)	To determine the prevalence of anemia and ID during pregnancy in the Central region of Ghana	Cross Sectional Study	Pregnant women in trimesters 1, 2 and 3	The prevalence of iron deficiency anemia is 16%, 20% and 38%, while pregnant women with inflammatory anemia are 29%, 6% and 2%.
A5	Anemia Prevalence after Iron Supplementation among Pregnant Women in Midwives Practice of Primary Health Care Facilities in Eastern Indonesia (Seu., MMV. et al. 2019)	To determine the prevalence of anemia and types of anemia after iron supplementation in pregnant women	Cross Sectional Study	Pregnant women who have been given iron supplementation	Out of 102 pregnant women, 34.3% had anemia detected. 14.7% suspected due to iron deficiency and 19.6% suspected dueBeta Thalassemia.
A6	Prevalence Of Beta-Thalassemia Trait In Pregnant Women Attending Antenatal Clinic (Jain U, et al. 2021)	To determine the prevalence of beta thalassemia in pregnant women	Retrospective study	Pregnant women aged 18-45 years	Of the 94 pregnant women, 55.31% experienced anemia. And of all pregnant women who experienced anemia, 87.23% were diagnosed with iron deficiency anemia and 4.25% with beta thalassemia minor anemia, and around 8.51% had anemia with iron deficiency and beta thalassemia.
A7	Prevalence of Anemia and Associated Factors Among Pregnant Women Attending Ante Natal Care in Arba Minch Public Health Institutions, South Ethiopia (Gutema Waye., B. et al. 2020)	Knowing the prevalence of anemia and its causal factors in pregnant women who come to antenatal care at the Arba Minch Health Center.	Cross Sectional Study	374 pregnant women who visited the Minch Health Center.	The results of the study found that the prevalence of anemia among 374 pregnant women was 28.8%. Which consisted of 75.7% mild anemia, 23.3% moderate anemia, and 1% mild anemia. Morphologically, 75.5% of anemic pregnant women had normochromic normocytic anemia, 23.3% had hypochromic microcytic anemia, and 1% had normochromic

				macrocytic anemia.
A8	Anemia in Ugandan pregnant women: a cross-sectional, systematic review and meta-analysis study (Bongomin., F. et al. 2021)	To determine the prevalence and factors associated with anemia of pregnancy	Cross Sectional Study	263 pregnant women who came to the treatment clinic at the Kawempe National Referral Hospital.	The prevalence of anemia was 14.1% and 21 (56.8%) had microcytic anemia.
A9	Study of prevalence of anemia among pregnant women attending antenatal checkups in a rural teaching hospital in Telangana, India (. S., 2018)	To evaluate the prevalence of anemia in pregnant women attending antenatal check-ups at the Teaching Rural Hospital in Telagana	Cross sectional observational study	Pregnant women attending antenatal check up at the Teaching Rural Hospital in Telagana	The prevalence of anemia is 20%. Of the 600 cases, there were 140 (23.3%) pregnant women with mild anemia, 340 (56.6%) with moderate anemia, 20% with severe anemia. With the most common iron deficiency anemia.
A10	Factors associated with maternal anemia among pregnant women in Rural India (Singal., N. et al. 2018)	To determine the risk factors associated with anemia in pregnant women at MIR during the study period with special reference to the severity of the disease.	-	Pregnant women who are anemic and not anemic	A total of 200 pregnant women with anemia, 70% with moderate anemia and 30% with severe anemia. And the results obtained were 82.5% who had hypochromic microcytic anemia with nutritional insufficiency.
A11	Frequency of Beta Thalassemia and Iron Deficiency Anemia in Moderate Anaemic Pregnant Patients Visiting to Tertiary Care (Zulfiqar., B. 2017)	To screen iron deficiency anemia patients, thalassemiaβ or combined iron deficiency anemia and thalassemiaβ	Cross Sectional Observational Study	140 pregnant women aged 18-45 years	Of the 140 pregnant women, 128 (91.4%) had iron deficiency anemia, 4 (2.8%) only had Beta Thalassemia and 8 (5.7%) had a combination of IDA and Beta Thalassemia.
A12	Assessment of some nutritional blood parameters during pregnancy at southern Abobo hospital (Abidjan, Côte d'Ivoire) (Paul Aristide., AJ. et al. 2018)	To evaluate the effects of metablosime variations on blood biomarkers.	Cross Sectional Study	150 pregnant women from trimester 1 to 3 with an age range of 18-35 years	The prevalence of anemia is 36% in the first trimester, 44% in the second trimester, and 56% in the third trimester. And the incidence of hypochromic

					microcytic anemia is 20%, followed by 16% hypochromic normocytic anemia. In this study the incidence of hypochromic microcytic anemia was caused by iron deficiency.
A13	Anemia prevalence, severity, types, and correlations among adult women and men in a multiethnic Iranian population: the Khuzestan Comprehensive Health Study (KCHS) (Akbarpour., E. et al. 2022)	To illustrate the prevalence, severity, most common types, and major determinants of anemia	Cross Sectional Study	Pregnant women with Hb level < 13 gr/dl with an age range of 20-65 years.	The prevalence rate of anemia is 10.86%. The most common rate of mild anemia was 7.71%, and only 0.17 for severe anemia. The type of cause of anemia was 50.65% with number cytic anemia together with microcytic, and 30.29% with hypochromic microcytic anemia.
A14	Prevalence of Maternal Anemia in Pregnancy: The Effect of Maternal Hemoglobin Level on Pregnancy and Neonatal Outcome (Youssry., MA. et al. 2018)	To assess the prevalence of anemia in pregnant women, and to evaluate the effect of anemia severity on perinatal outcomes.	Retrospective Cohort Study	Pregnant women with a gestational age of 20 weeks and over.	Of the 2,654 pregnant women who met the criteria, 42% had anemia, consisting of 83.3% with mild anemia and 16.7% with moderate and severe anemia. And as much as 92.8% of the causes of anemia are iron deficiency and 7.2% are caused by sickle cell traits, and thalassemia.
A15	Association of Colecalciferol, Ferritin, and Anemia among Pregnant Women: Results from Cohort Study on Vitamin D Status and Its Impact during Pregnancy and Childhood in Indonesia (Judistiani., RTD. et al. 2018)	To determine whether 25(OH) vitamin D (cholecaciferol) status is associated with ferritin, anemia and its changes during pregnancy.	Cohort Study	Pregnant women with single pregnancies with a gestational age of 10-14 weeks.	Of the 193 samples, 96.5% had hypovitaminosis D and about 151 (75.5%) had deficiency and 42 (21%) had deficiency in the first trimester. As many as 17 (23.6%) experienced anemia due to

					chronic disease, and 24 (10.3%) experienced anemia due to acute malaria attacks.
A16	Prevalence of Anemia and its Associated Factors among Pregnant Women Attending Antenatal Care (ANC) In Mizan Tepi University Teaching Hospital, South West Ethiopia (Zekarias., B. et al. 2017)	To determine the prevalence and determinants of anemia in pregnant women who come to the Antenatal Care at Mizan Tepi University Teaching Hospital.	Cross Sectional Study	An anemic pregnant woman who comes for antenatal care at Mizan University Teaching Hospital.	The prevalence of anemia is 23.5%. Of the 72 pregnant women, the results showed that 43 (59.7%) had mild anemia, 24 (33.3%) had moderate anemia, and 5 (7%) had severe anemia.
A17	Non-nutritional and disease-related anemia in Indonesia: A systematic review (Bukhari, A. et al. 2020)	To examine the contribution of non-nutritional anemia to the incidence of anemia in Indonesia.	Descriptive Cross Sectional Study	Pregnant women with anemia	Very low prevalence of anemia (19.3%), ID (20.1%) and IDA (6%) of 77 women with anemia, 24 (31.2%) had ID, 20 (26.0%) had related genes thalassemia, and 33 (42.9%) has an unknown underlying factor.
A18	Role of Mentzer index for differentiating iron deficiency anemia and beta thalassemia trait in pregnant women (Tabassum., S. et al. 2022)	To observe the role of the Mentzer index for differentiating iron deficiency anemia (IDA) and beta thalassemia traits (βTT) in pregnant women.	Cross Sectional Study	100 pregnant women with microcytic anemia	Out of 100 pregnant women, 87 were diagnosed with IDA anemia and 13 with Beta Thalassemia anemia.
A19	Prevalence of anemia and iron deficiency anemia in Chinese pregnant women (IRON WOMEN): a national cross-sectional survey (Tan, J. et al. 2020).	To determine the prevalence of anemia and IDA and their risk factors in pregnant women in China.	Cross Sectional Survey Study	There were 12,403 pregnant women in the first, second and third trimesters	Of the 12,403 pregnant women in total, 19.8% experienced anemia and 13.9% were caused by IDA. The prevalence of anemia is 24.0% and IDA is 17.8%.

RESULTS

Article Characteristics

This review is based on articles published between 2016 and 2022. Articles come from developed and developing countries. Of the 19 articles used for review, 15 articles used a cross-sectional study design, 2 articles used a cohort study design, 2 articles used a retrospective cohort study design.

Thematic Analysis

Based on a review of 19 articles, three main themes emerged from the scoping review regarding the causes of anemia in third trimester pregnant women, namely the prevalence of anemia in pregnant women, the percentage of anemia in pregnant women, the magnitude and type of causes of microcytic anemia.

Table 3: Thematic Analysis

themes	subtheme	References
Prevalence of anemia in pregnant women	1. Microcytic Anemia 2. Normocytic Anemia 3. Macrocytic Anemia	Articles 1, 2, 6, 7, 10, 12, 13
Degree of anemia of pregnant women	1. Mild Anemia 2. Moderate Anemia 3. Severe Anemia	Articles 6, 7, 9, 10, 13, 14, 15, 16,
Types of causes of microcytic anemia in pregnant women	1. Iron Deficiency (IDA) 2. βThalassemia (βST)	Articles 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19

Theme 1: Prevalence of anemia in pregnant women

Of the 19 articles, there are 6 articles that explain the prevalence of anemia which describes that the average prevalence of anemia in developing countries is still at a very high rate, which is below 60%. The highest prevalence was in the Indian region which reached 55.31%, then in the African region which reached 36% and 28.8%. In West Uganda, the prevalence reached 26%. Followed by Sri Lanka 14.4% and Khuzestan 10.86%.

Microcytic anemia is characterized by reduced red blood cells, with a hemoglobin concentration of less than 11.0 g/dl which is categorized as anemia. Depending on the Mean Corpuscular Volume (MCV), anemia is classified as microcytic if the MCV is less than 82 fl. Anemia is defined as a condition or condition in which there is a decrease in hemoglobin concentration, hematocrit or red blood cell mass at the same age, sex and geographic location, resulting in a low amount of available oxygen to support body activities. Normocytic anemia if the MCV is between 82 fl and 98 fl. Macrocytic anemia is characterized by enlarged red blood cells, and an MCV value of more than 98 fl. [7].

Theme 2: Degree of anemia in pregnant women

In developing countries, there are several studies which explain that the incidence of anemia is also influenced by the degree of anemia. There are 7 articles that review the incidence of anemia at each degree of anemia. Based on the results of laboratory examinations that pregnant women who experienced the most anemia had an average Hb between 10-10.9 g/dl (mild anemia) including in the Jeddah region of Saudi Arabia it was found at 83.3%, both in the Ethiopia and South West regions Ethiopia by 75.5% and 43.3%, in India 25.5% and 23.3%, and finally in Khuzestan 7.7%. The moderate anemia group with Hb 7-9.9 gr/dl has the highest incidence of anemia in the Indian

region reaching 70% and 56.6%, then in the South West Ethiopia region with 33.3% and 23.3%. Severe anemia is anemia with Hb levels <7 gr/dl,

Based on WHO, anemia in pregnancy is enforced if the hemoglobin (Hb) level is <11 g/dl. While the center of disease control and prevention defines anemia as a condition with Hb levels <11 g/dl in the first and third trimesters, Hb <10.5 g/dl in the second trimester, and <10 g/dl in postpartum. [24]

Mild anemia is anemia in pregnant women called mild if the mother's hemoglobin level is 10.9g/dl to 10g/dl. Moderate anemia is defined as anemia in pregnant women called moderate if the mother's hemoglobin level is 9.9g/dl to 7.0g/dl. Meanwhile, severe anemia (Hgb <7g/dl) during pregnancy has been associated with major complications or death in the mother and fetus, such as increased premature birth, maternal and newborn mortality, and low newborn health. [7.21]

- **Anemia in pregnancy**: The hemoglobin level is below 11 g/dl during the first and second trimesters and 10.5 during the second trimester of pregnancy.

- **Mild anemia**: Hemoglobin level from 10-10.9 g/dl.

- **Moderate anemia**: Hemoglobin level of 7-9.9 g/day.

- **Severe anemia**: A hemoglobin level of 7 g/dl. [16]

Theme 3: Causes of anemia in pregnant women

Iron Deficiency

In developing countries, the cause of anemia in pregnant women is microcytic anemia caused by iron deficiency. Almost all studies describe that the highest incidence of anemia is caused by iron deficiency as in the Jeddah Saudi Arabia region as much as 92.8%, then in the Pakistan region 91.4%. India is a country where the population also has 87.23% of pregnant women caused by iron deficiency, as well as in the Uganda region 53.3% incidence of anemia due to iron deficiency, in the Sri Lanka region the incidence of anemia due to iron deficiency is 41.9%, and still in the Asian region, namely China, the incidence of anemia due to iron deficiency is 24%. Then in the South Abobo region 20% and finally in the central part of Ghana as much as 14.7%.

In research conducted in Indonesia, especially in the eastern part by Seu (2019) that out of 102 pregnant women there were 19.6% who had iron deficiency anemia, and there was one systematic review conducted by Bukhari in 2020 that out of 77 women there were around 31.2 % due to iron deficiency.

Anemia due to micronutrient deficiency (iron deficiency) is a common cause of anemia in pregnancy. During pregnancy the rate of erythropoiesis increases, so that during erythropoiesis there are factors that must be met such as iron for the synthesis of heme/part of Hgb/, during pregnancy an additional 1000 mg of iron is needed, other nutrients such as vitamin B12 for RNA synthesis, folic acid (vitamin 9) for the next stage of DNA synthesis, also trace elements such as zinc for protein metabolism & nucleic acid metabolism and others can be required for erythropoiesis. If there is a deficiency of micronutrients or poor nutrition it will cause anemia. [7.25]

βThalassemia (βST)

Several studies in developing countries showed that in the Pakistan region where the incidence of anemia due to thalassemia was 7.2% and 2.8%, followed in the Shivpuri

region of India as much as 4.25%. In the territory of Indonesia, there is one study that discusses the incidence of thalassemia and one that conducts a systematic review. Meanwhile, Bukhari (2020) wrote in a systematic review that out of 77 pregnant women, 26% had the Thalassemia gene.

Beta Thalassemia is the most common hereditary type of hemoglobin opathies found in Pakistanis and so far more than 200 variables have been diagnosed [11]. Beta Thalassemia Trait (BTT) patients are usually asymptomatic and unaware of their carrier status unless diagnosed by testing. [11]

DISCUSSION

In the scoping review, I found 19 articles discussing the causes of anemia in pregnant women, of the 19 articles, 16 were conducted in developing countries and 3 others were in Indonesia. Of the 16 articles, several facts were found which described that the most common cause of anemia in pregnant women was microcytic anemia caused by iron deficiency and the second was Beta Thalassemia. In addition, several articles also explain that the incidence of nomrocytic anemia is also very large. This is also in line with research conducted in Indonesia, although there are not many, but the highest cause of anemia is microcytic anemia, which is in the first place due to iron deficiency and the second most common cause is thalassemia. So far in Indonesia, the implementation of efforts to prevent anemia in pregnant women through the administration of Fe tablets still needs to be reviewed based on the causes of anemia. Because if the cause of anemia is not iron deficiency, it will be difficult to prevent or treat by administering Fe tablets. So it needs further screening and diagnosis to support efforts to prevent anemia in pregnant women.

CONCLUSION

This scoping review resulted in several conclusions including that the prevalence of anemia is still very high and reaches 55%, especially in developing countries. The incidence of anemia in pregnant women at most has Hb levels between 10-10.9%, namely with a mild degree of anemia. And the highest cause of microcytic anemia is iron deficiency and thalassemia.

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