SYSTEMATIC / NARRATIVE REVIEW ARTICLE

Normocytic Anemia in Pregnant Women: A Scoping Review

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ABSTRACT

Introduction: The iron supplementation program for pregnant women is the main program for tackling anemia in various countries, especially in developing countries in which daily diets may lack sufficient iron intake. In Indonesia, it is recommended that expectant mothers ingest 90 iron tablets during their pregnancy; however, the World Health Organization reports that 37% of pregnant women in the country continue to experience anemia. Iron deficiency anemia consistently emerges as the primary etiology for diagnosing anemia; however, it is important to recognize that anemia can stem from various factors beyond just lack of iron. In addition to iron deficiency, chronic illnesses and infections significantly contribute to the prevalence of anemia worldwide. Consequently, this literature review endeavors to uncover the underlying factors responsible for normocytic anemia among pregnant women, focusing on developing countries.

Materials and Methods: Eight search engines, specifically Proquest, EbscoHost, Scopus, Cochrane Library, Science Direct, Wiley Online Library, PubMed, Google Scholar, and Garuda, were utilized to identify primary articles. Three independent reviewers assessed abstracts and full articles based on specific inclusion and exclusion criteria. The data collected encompassed information regarding the population under study, research methods employed, and primary findings pertinent to the review's objectives. Fifteen studies, published between 2014 and 2023, that met the eligibility criteria outlined in the PRISMA-ScR.

Results: Among the 15 studies on normocytic anemia in pregnant women, malaria and HIV were the highest causes of normocytic anemia, followed by worm/intestinal parasite infections, chronic diseases, and bleeding.. In pregnant women, anemia of chronic disease and infection often coexists with iron deficiency anemia, both show decrease serum iron levels. Hence, other investigations need to be carried out to diagnose with certainty the cause of anemia in pregnant women.

Conclusion: Anemia is not a standalone disease but rather a symptom of various underlying diseases. Therefore, diagnosing anemia requires identifying the basic disease that causes anemia, rather than simply labeling it as anemia.

KEYWORDS:
Normocytic anemia, pregnant women, chronic disease, infection, bleeding

INTRODUCTION

Anemia is prevalent among pregnant women, particularly in developing countries, commonly attributed to insufficient iron levels.[1] The primary method for addressing anemia in these countries, particularly where daily iron intake through food is often inadequate, is the implementation of iron supplementation programs for pregnant women. For instance, in Indonesia, expectant mothers are advised to consume 90 iron tablets during their pregnancy. According to the World Health Organization (WHO), anemia affects a significant number of women between the aged of 15 and 49, as well as millions of children aged 6 to 59 months globally. It is estimated that anemia affects 40% of children aged 6 to 59 months, 37% of pregnant women, and 30% of women aged 15 to 49 years worldwide. In 2019, anemia affected 30% (539 million) of non-pregnant women and 37% (32 million) of pregnant women aged 15 to 49 years.[2] In Indonesia, the causes of anemia during pregnancy are multifactorial, but iron deficiency is generally considered the primary cause, as anemia diagnosis primarily relies on measuring hemoglobin levels. According to the 2018 Basic Health Research (Riskesdas) data, the prevalence of anemia in pregnant women in Indonesia has increased from 37.1% in 2013 to 48.9% in 2018, indicating a concerning annual rise in anemia cases among expectant mothers. Consequently, promptly addressing this issue is crucial, as maintaining good health is paramount.[3]

Normocytic anemia is characterized by red blood cells of normal size and shape and containing normal hemoglobin levels.[4] Despite this, individuals with normocytic anemia still experience anemia. The mean corpuscular volume (MCV) in normocytic anemia falls within the standard range of 80-100 fL. The primary cause of normochromic normocytic anemia is typically a chronic illness. The prevalence of anemia due to chronic diseases varies depending on the specific condition, with infection ranging from 18% to 95%, cancer from 30% to 77%, autoimmune disorders from 8% to 71%, and chronic kidney disease and inflammation from 23% to 50%.[1] In pregnancy, anemia is determined using the World Health Organization's classification, which considers a

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hemoglobin (Hb) level below 11 g/dl as indicative of anemia. The WHO classification further divides anemia into three degrees: mild anemia (Hb level 9.0-10.9 g/dL), moderate anemia (Hb level 7.0-8.9 g/dL), and severe anemia (Hb level less than 7.0 g/dL).[5]

Anemia is not a separate disease but a symptom of various underlying diseases.[6] Therefore, diagnosing anemia requires identifying the basic disease that causes anemia, rather than simply labeling it as anemia. This is important because the underlying disease is often hidden, so if this can be uncovered, it will lead clinicians to hidden dangerous diseases. Understanding the underlying cause is crucial for effective treatment. An approach to anemia patients requires an understanding of the pathogenesis and pathophysiology of anemia and skills in selecting, analyzing, and summarizing the results of anamnesis, physical examination, laboratory tests, and other supporting examinations.[6,7]

A scoping review was undertaken to enhance comprehension of the primary research domains about normocytic anemia in pregnant women, particularly in developing countries. The rationale for conducting a scoping review lies in the dearth of available data concerning normocytic anemia in pregnant women in developing countries such as Indonesia. This study aims to: 1) determine the prevalence of normocytic anemia in pregnant women, 2) determine the degree of normocytic anemia in pregnant women, and 3) identify the causes of normocytic anemia in pregnant women.

MATERIALS AND METHODS

The process of conducting this scoping review aligns with the framework proposed by Arksey H and O'Malley,[8] which serves as a methodological blueprint for conducting comprehensive reviews. This approach suggests that scoping reviews can effectively explore the breadth, depth, and characteristics of existing literature, thereby identifying research areas lacking sufficient attention. Additionally, this type of review can be utilized to inform future systematic reviews, synthesize and disseminate current knowledge, as well as identify gaps, and provide direction for future research endeavors.

The operational methodology described in the 2020 PRISMA ScR statement is utilized for reporting purposes.[9] This methodology outlines the most effective approach for identifying, selecting, evaluating, and synthesizing studies from both systematic and scoping reviews. The process consists of five stages: formulating research questions, identifying relevant studies, selecting studies, mapping data, compiling, summarizing, and reporting the findings.

Identify research questions

Our research questions were formulated based on the Population Concepts and Context (PCC) framework endorsed by the Joanna Briggs Institute.[10] The PCC framework is widely acknowledged for its efficacy in adequately addressing the specific requirements of a scoping review, offering a broader approach compared to a systematic review.[11]

There are three formulations of questions: 1) What is the incidence rate of normocytic anemia in pregnant women? 2) What are the causes of normocytic anemia in pregnant women?

Identify relevant studies

The first step is that determining the database:
There are a total of nine electronic databases commonly utilized in academic research, namely Proquest, EbscoHost, Scopus, Cochrane Library, Science Direct, Wiley Online Library, PubMed, Google Scholar, and Garuda (Digital Reference Garba), an online reference search platform curated by the Indonesian Ministry of Research, Technology, and Higher Education.

The second step is that determining inclusion and exclusion criteria
The screening process utilized in this study was based on the framework developed by Arksey H and O'Malley (2005) and further refined by Levac D.[8,12] The team conducted independent screenings of titles and abstracts using predetermined criteria outlined in Table I to determine inclusion or exclusion. Abstracts that passed this initial screening were then evaluated to assess their eligibility for detailed evaluation. Subsequently, four reviewers independently obtained and evaluated complete articles aligned with the eligible abstracts, ensuring they were pertinent to the research inquiries and adherence to the inclusion criteria (Table II).

The third step is namely the search strategy
The data search strategy consisted of primary studies published from 2014-2023 and the eight databases used. The search terms used were "anemia", "normocytic", "pregnant women", "chronic disease", "infection", and "bleeding". The most recent search was carried out on August 16, 2023.

Study selection

The selection and assessment of studies to determine the quality of the articles were carried out by four reviewers. 15 studies were evaluated from a rating scale of 0-3, based on the following criteria: 1) Study design: studies using cross-sectional, case-control, or cohort = 1, otherwise = 0; 2) Sample size: large = 1, small = 0; 3) there are supporting laboratory tests such as serum Fe, Ferriti, TIBC, peripheral blood smear, stool specimen examination etc = 1, otherwise = 0; 4) There is a degree of anemia and identify the cause of anemia = 1, if not = 0 (JBI, 2021). The average value of these scores was presented as the final score, the scores were then grouped as follows: 1=Poor; 2=Moderate; 3-4=High.

Charting and summarizing the data

Based on the 15 articles that met the inclusion criteria and were selected, data mapping was then carried out to determine the articles' important key points: author, year of publication, purpose, sample, participant characteristics, research design, causes of anemia, and research findings.

Compile, summarize, and report results

There are 15 pieces of literature used in this scoping review. Levac et al. (2010) employed a methodology that involves compiling, summarizing, and reporting review findings. This

Table I: PCC Framework (population, concept, and context)

Population (P)	Pregnant women
Concepts (C)	Causes of normocytic anemia (chronic disease, infection, bleeding)
Contexts (C)	The study was conducted in a developing country

Table II: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Quantitative study human studies Original article Published between 2014-2023 Native language and English	Review articles, Case reports animal studies

Table III: Search strategies and research threads for databases

Search strategy	Search strategy
Keywords used: Anemia, normocytic, pregnant women, chronic disease, infection and bleeding	236 from primary sources and five from auxiliary databases
Example 1: A Scopus search using (anemia OR anemia) AND (Normocyte OR normocytic) AND infection AND (pregnancy OR pregnant OR gestation OR gestational) returns 78 records	
Example 2: A PubMed search using (anemia OR anemia) AND (Normocyte OR normocytic) AND ("infection OR malaria OR HIV OR typhoid OR hepatitis OR tuberculosis OR "post hemorrhagic" OR "acute bleeding" OR Hemolysis OR inflammatory OR bowel OR intestinal) AND (pregnancy OR pregnant OR gestation OR gestational) resulted in 125 records	
Duplicate records are removed	197 remaining after duplicates were removed
Number of studies deleted for not meeting study objectives (n=58)	139 remaining
Studies (n=118) were deleted for reasons	21 studies remaining
The study does not have full text (n=6)	15 studies were left for final analysis

was achieved through describing article characteristics and applying thematic analysis.

RESULTS

studies fail to provide information on the severity of anemia in their investigations. In comparison, four studies merely provide a general overview of the causes of normocytic anemia in pregnant women. Malaria infection is the predominant cause of normocytic anemia in pregnant women, followed by HIV, worm/intestinal parasite infections, chronic disease and bleeding, and urinary tract infections.

Quality assessment of study findings

Of the 15 studies reviewed, 12 studies[7,13–21,23,26], were rated as high quality, scoring between 3 and 4, which accounts for 80% of the total One study[22], 6.7% got a score of 2, indicating medium quality. The remaining two studies[24,25] representing 13.3%, were rates as low quality with a score of 1.

DISCUSSION

Significant factors leading to anemia in developing nations include deficiencies in micronutrients, infectious illnesses, hemoglobin disorders, and maternal hemorrhaging. Regarding morphological traits, iron deficiency anemia commonly exhibits microcytic characteristics, while anemia of chronic disease manifests as normocytic. Conversely, macrocytic anemia is commonly linked to vitamin B12 and folate deficiencies or the toxic effects of drugs and alcohol. (7). Normochromic normocytic anemia, the most prevalent form, is primarily associated with chronic diseases, with estimated prevalence rates of the underlying causes being infection (18%-95%), cancer (30%-77%), autoimmune disorders (8%-71%), chronic kidney disease, and inflammation (23%-50%).[1] In a comprehensive analysis of anemia's global burden from 1990 to 2010, hookworm, schistosomiasis, and malaria emerged as the top three causes.[27]

Of the 15 studies, there were seven studies[7,13,14,16,18,23,24] that have an incidence of normochromic normocytic anemia above 50%. This is in line with the findings in India

Table IV: Findings of Normocytic Anemia Study in Pregnant Women (2014-2023)

No	Study (year)	Objective	Sample size	Participant characteristics	Study design	Causes of Anemia	Results
1	Melku et al (2014)(13)	To evaluate the frequency and factors influencing maternal anemia, a study was conducted.	Of the 302 pregnant women, 50 (16.5%) pregnant women were diagnosed with anemia	Pregnant women receiving prenatal care at Gondar University Hospital in Ethiopia.	Cross-sectional	A significant occurrence of anemia was observed among mothers who were HIV-positive (38.7%), had hookworm infections (30%), and experienced chronic illnesses (27.3%).	Out of the 50 pregnant women diagnosed with anemia, the majority (76%) exhibited normocytic normochromic anemia, while 64% experienced mild anemia. Additionally, 30% of the women were classified as having moderate anemia, and a smaller proportion (6%) were diagnosed with severe anemia.
2	Alemayehu et al (2016)(14)	To ascertain the occurrence, severity, and factors influencing the presence of anemia in pregnant women.	Out of a total sample of 360 pregnant women, approximately 36.1% (130 individuals) were found to have anemia.	South Sudanese refugee pregnant woman, Pugnido, western Ethiopia	Cross-sectional	This study reveals that intestinal parasite infections accounted for 73% of anemia cases in pregnant women.	Among 130 pregnant women with anemia, the majority (56.2%) had normocytic normochromic anemia, while 89.2% experiencing mild anemia, 8.5% having moderate anemia, and 2.3% suffering severe anemia.
3	Adamu et al (2017) (7)	The objective of this study was to analyze the frequency and geographic distribution of various degrees and classifications of anemia, as well as investigate the potential risk factors associated with different levels of severity in anemia.	264 pregnant women with anemia	Pregnant women who live in rural and urban areas in Malawi, Africa	Cross-sectional	In this study, it was found that individuals with HIV infection experience the development of anemia at various levels of severity.	In a sample of 264 pregnant women, 61.7% of them were observed to have normocytic anemia. Within this group, 71.1% exhibited mild anemia, while the remaining 28.9% presented with moderate to severe anemia.
4	Anchang Kimbi J et al (2017)(15)	To examine the correlation between red blood cells anomalies and the etiology of anemia, a comprehensive assessment was required.	Out of the total population of 279 pregnant women, a significant proportion of 159 individuals (57%) were diagnosed with anemia during their pregnancy.	Pregnant women were recruited at the first antenatal visit at the Mutengene and Muea Integrated Medical Center, Cameroon.	Cross-sectional **Study design**	The research identified malaria infection as the cause of anemia in 2.3% of anemia cases in pregnant women.	Normocytic anemia was observed in 43.2 percent of pregnant women.

Table IV: Findings of Normocytic Anemia Study in Pregnant Women (2014-2023)

No	Study (year)	Objective	Sample size	Participant characteristics	Study design	Causes of Anemia	Results
5	Tunkyi K & Moodley J (2018)(16)	The objective of this study was to ascertain the frequency of anemia during the initial antenatal consultation and at 32-34 weeks of gestation, as well as to assess the impact of this condition on maternal and perinatal outcomes.	Out of the total sample size of 2000 pregnant women, 854 individuals (42.7%) were found to have anemia.	Pregnant women who visit African regional hospitals	Cohort Study	The occurrence of anemia in pregnant women with HIV is significantly higher compared to the uninfected population, with a prevalence of 64.6%.	In a study of 854 pregnant women with anemia, the majority (68.9%) displayed normocytic normochromic anemia, while 81.34% were diagnosed with mild anemia, 18.06% exhibited moderate anemia, and 0.6% had severe anemia.
6	Feleke and Feleke (2018)(17)	The objective of this study was to ascertain the prevalence and contributing factors of anemia in women during pregnancy and lactation.	Out of a total of 550 pregnant women, 187 individuals (34%) exhibited symptoms of anemia.	Pregnant and breastfeeding women who come to visit health facilities in the city of Bahir dar Etophia	Comparative cross-sectional	Pregnant women afflicted with malaria face a 3.61-fold increase in the likelihood of experiencing anemia, while those infected with hookworms face a 3.37-fold increase in the risk of developing anemia.	Among the population of pregnant women, approximately 34% were found to have anemia. Specifically, 7.45% exhibited normocytic hypochromic anemia, while 0.4%. had normochromic anemia
7	Adebo et al (2019)(18)	To ascertain the occurrence rate of anemia among pregnant women and elucidate its underlying causes.	Among the sample of 200 pregnant women, half of them (50%) were diagnosed with anemia.	pregnant women who carry out antenatal checks at the University Hospital of Abomey Calavi/So-Ava, Benin, West Africa	Cross-sectional descriptive analytic	Among a cohort of 200 pregnant women, half of them, or 100 individuals, were diagnosed with anemia.	A substantial portion of pregnant women, specifically 60%, experience normocytic anemia, while 83% exhibit mild anemia. Moreover, 15% of pregnant women experience moderate anemia, and a small proportion, specifically 2%, exhibit severe anemia.

Table IV: Findings of Normocytic Anemia Study in Pregnant Women (2014-2023)

No	Study (year)	Objective	Sample size	Participant characteristics	Study design	Causes of Anemia	Results
8	Okia et al (2019) (19)	A significant proportion of pregnant women, specifically 60%, exhibit normocytic anemia, while 83% experience mild anemia. Additionally, it should be noted that a considerable proportion of pregnant women, specifically 15%, are confronted with moderate anemia, while a negligible percentage of 2% endure severe anemia.	Out of the total sample of 163 pregnant women, a subset of 12 individuals (7.4%) were found to have anemia.	Pregnant woman having antenatal checkup at Itojo hospital, Ntungamo district, southwest Uganda	Cross-sectional	The present study found a significant positive association between urinary tract infection and anemia in pregnancy (p=0.002, CI 3.5-6.7). Furthermore, a history of postpartum hemorrhage was also found to be significantly associated with anemia in pregnant women (p=0.03).	The prevalence of anemia in the sample population was found to be 7.4%, with normochromic normocytic anemia accounting for 8.3% of cases. The majority of individuals (91.7%) presented with mild anemia, while 8.3% had severe anemia. Notably, none of the pregnant women in the study were found to have moderate anemia.
9	Schmiegelow et al (2019) (20)	To examine the potential links between preconception factors and hemoglobin (Hb) levels in the initial stages of pregnancy, a research study was conducted.	A total of 261 pregnant individuals were included in the study, with hemoglobin levels assessed in 226 of them.	The study was carried out in 48 rural communities located in the districts of Korogwe and Handeni in the northeastern region of Tanzania.	Cohort study	This study revealed that malaria infection accounted for 14.6% of anemia cases in pregnant women, while HIV and intestinal worm infection accounted for 2.4% and 6.7% respectively.	Among the cohort of 226 pregnant individuals, 46.5% of women experienced anemia during the initial stages of pregnancy, while 41.9% exhibited normochromic normocytic anemia.
10	Berhe, et al (2019)(21)	The aim of this study was to ascertain the incidence and etiology of anemia among expectant mothers.	Out of the total sample size of 304 pregnant women, a subset of 24 individuals (7.9%) were identified as having anemia.	Pregnant women who make antenatal visits at Adigrat General Hospital, northern Ethiopia	Cross-sectional	The presence of a history of bleeding has a notable correlation with the occurrence of anemia, as indicated by an odds ratio of 3.4 (95% confidence interval: 1.16-10.2, p=0.026).	Out of the total population of pregnant women, approximately 7.9% were diagnosed with anemia. Among these individuals, 25% exhibited normocytic anemia, while the remaining 75% were split between mild (62.5%) and moderate (37.5%) anemia.
11	Wirahartati, Herawati and Wande (2019)(22)	The categorization of anemia in pregnant women with consideration to hemoglobin levels and erythrocyte index.	A sum of 94 pregnant individuals experiences the condition of anemia.	The data obtained are secondary data from patient medical records from April to December 2016	Retrospective descriptive study	This paper addresses the topic of iron deficiency anemia, a form of anemia that can occur in various contexts.	A total of 34.04% of pregnant women were found to have normochromic normocytic anemia, while 29.8% exhibited mild anemia. Moreover, 61.7% of the pregnant population displayed moderate anemia, and 8.5% suffered from severe anemia.

Table IV: Findings of Normocytic Anemia Study in Pregnant Women (2014-2023)

No	Study (year)	Objective	Sample size	Participant characteristics	Study design	Causes of Anemia	Results
12	Waye et al (2020)(23)	To ascertain the frequency of anemia among pregnant women and identify associated factors, this study aimed to investigate the prevalence of this condition and its potential determinants.	Out of the total sample size of 312 pregnant women, 90 individuals, constituting 28.8 percent, were identified as having anemia.	Pregnant woman having antenatal checkup at Arba Minch Health Facility South Ethiopia	Cross-sectional	The prevalence of anemia was significantly higher among pregnant women who had experienced blood loss during childbirth, with an adjusted odds ratio (AOR) of 3.66 (95% confidence interval [CI]: 1.56-8.70). Similarly, pregnant women infected with malaria had a significantly higher likelihood of anemia, with an AOR of 6.10 (95% CI: 2.26-16.43).	Among the population of pregnant women, a total of 28.8% were found to have anemia. Within this subset, 75.5% of cases exhibited normochromic normocytic anemia, while 55.5% were classified as mild, 43.3% as moderate, and a mere 1.1% as severe.
13	Eunika Alicia Valentina (2021)(24)	To mitigate the occurrence of high-risk pregnancies in Indonesia in the future, it is crucial to have a comprehensive understanding of the prevalence of anemia and hemoglobin levels among multiparous pregnant women.	Out of a total of 50 pregnant women, 26 individuals (constituting 52% of the sample) were found to have anemia.	Medical record data for multiparous pregnant women at Citra Medika Hospital, Sidoarjo, Indonesia	Retrospective descriptive study	Hemodilution has been identified as the underlying factor contributing to normochromic normocytic anemia.	Among the cohort of pregnant women, a total of 52% were diagnosed with anemia. Within this group, 34.8% exhibited normochromic normocytic anemia, while mild anemia was observed in 46% of cases. Moderate anemia was identified in 50% of pregnant women, whereas severe anemia was present in only 4% of the individuals.
14	Princess Wande and Mahatini (2021)(25)	Knowing the description of the erythrocyte index in pregnant women with anemia	43 pregnant women with anemia	Data on medical records of anemic pregnant women at the Abiansemal I Community Health Center, Bandung Regency	Retrospective descriptive study	The causes of normochromic normocytic anemia are only described in general terms, possibly due to hemolytic anemia, anemia of acute renal failure, post-hemorrhage, and chronic disease.	There were 62,8% normochromic normocytic anemia, 72.1% mild degree, 27.9% moderate degree and no severe anemia
15	Bansal et al (2023)(26)	To investigate systematically the causes of anemia in pregnancy	Out of 2000 pregnant women, there were 500 (25%) pregnant women with anemia	Pregnant women having antenatal check up in North India	Cross-sectional	The examination of peripheral blood revealed that the primary cause of normochromic normocytic anemia among patients was predominantly attributed to anemia of chronic disease, accounting for 51.6% of cases.	Of the 25% of pregnant women with anemia, 24.4% were normochromic normocytic anemia,

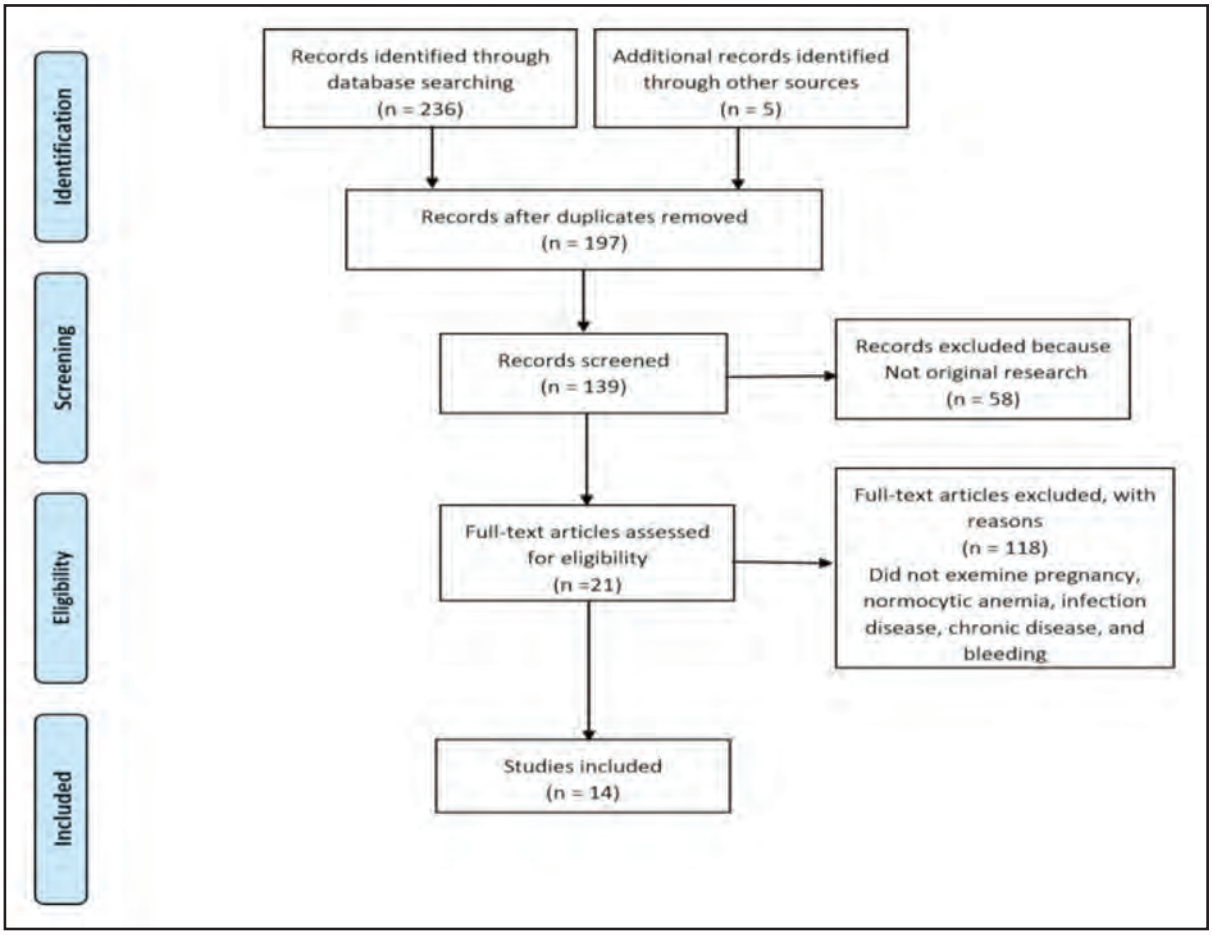

Fig. 1: The PRISMA flowchart shows the results of the search strategy, the inclusion and exclusion criteria of the articles

conducted by[28] And[29]. This is due to lack of health awareness, extreme poverty, a large number of families, and overcrowding which causes recurrent infections and antepartum bleeding. However, this contrasts with findings from[30] and[31], where microcytic anemia is more dominant; this is due to iron supplementation and slow early detection of anemia, which also causes a high incidence of anemia. This is in line with research conducted in[17,19–22,26].

For the degree of anemia from 15 studies, nine studies [7,13,14,16,18,19,21,23,24], in which most degrees of mild anemia are compatible with[32], and four studies did not include the degree of anemia[15,17,20,26]. Most types of normocytic anemia are mild. Physiologically, the lowest hemoglobin levels in pregnant women occur during the second trimester of pregnancy, averaging Hb 10.5 g/dL. In the first and third trimesters, the hemoglobin level is around 11 g/dL. Normocytic anemia is characterized by low Hemoglobin (Hb) levels but normal Mean Corpuscular Volume (MCV). In the third trimester, Hb levels tend to rise again after the decrease in the second trimester. This pattern means that women with normocytic anemia usually experience mild anemia, rather than moderate or severe levels.[22] Physiological anemia is a commonly employed term to denote the reduction in hemoglobin concentration during a typical pregnancy. This decrease is attributed to expanding plasma volume beyond normal levels towards the end of gestation, despite a concurrent increase in red blood cell mass. As a result, normocytic anemia is manifested.[24] In pregnancy, anemia can also be associated with the cause of normocytic anemia.

Malaria

According to five studies, normocytic anemia is primarily attributed to malaria infection, with a prevalence of 33.3% [15,17,18,20,23], all of which are in the countries of the African continent, namely Cameroon, Ethiopia, Benin, Tanzania, and Africa. The anemias associated with malaria discussed in this review demonstrated a notable reduction in the hematological index. Malaria-induced inflammatory anemia leads to alterations in iron absorption and distribution, leading to prolonged iron storage in a form that restricts its availability for maternal use and potentially hinders its transfer to the fetus.

Mothers infected with malaria have a 3.61 times higher risk compared to mothers who do not have a history of malaria infection.[17] The reduction in red blood cell count results from Plasmodium species engulfing the host red blood cells. Malaria, caused by the Plasmodium parasite, is predominantly prevalent in Africa and contributes significantly to the mortality rates in this region. Conversely, Plasmodium vivax is primarily observed outside sub-Saharan Africa, such as Cameroon, Ethiopia, and Tanzania.[15,17,20] According to Basic Health Research[3] in Indonesia, the most

severe prevalence of anemia caused by malaria infection is observed in Papua New Guinea (89.7%). In particular, the island of Papua has the most severe prevalence of anemia compared to other islands in Indonesia. The prevalence of malaria infection in Indonesia is 0.37%.[3]

Based on a study conducted in Mumbai, India, pregnant women show a higher prevalence of malaria compared to other groups. This condition can lead to various adverse outcomes, including abortion, intrauterine fetal death, premature delivery, and even maternal death.[33] The susceptibility of pregnant women to malaria infection can be attributed to changes in their immune system during pregnancy, specifically alterations in cellular and humoral immunity, potentially influenced by elevated cortisol levels. In malaria-endemic regions[15,20], many pregnant women infected with malaria parasites do not exhibit typical disease symptoms (asymptomatic). Yet, it still poses risks to both the mother and the developing fetus. Moreover, deficiencies in essential micronutrients such as iron and folic acid exacerbates malaria infection among pregnant women. The Plasmodium parasite resides within red blood cells, utilizing hemoglobin for its growth and replication, subsequently rupturing the host's erythrocytes. Infected erythrocytes with surface changes and deformities are easily recognized and cleared in the spleen. In addition, malaria can cause digestive system inflammation, interfering with iron absorption in the digestive tract and the release of iron from hepatocytes.[27,34]

Human Immunodeficiency Virus (HIV)

After malaria, HIV stands as the second most common cause, comprising 26.6% of the review findings across several African continent including Tanzania, Ethiopia, Malawi, and Africa[7,13,16,20], with the highest prevalence in Africa at 64.6%. Anemia is the strongest predictor of mortality within the first year post-HIV diagnosis. The risk of death is higher with increasing severity of anemia, as evidenced by studies conducted in developing countries like Africa.[7,16] A study conducted in Indonesia revealed that the average prevalence of anemia in individuals with HIV/AIDS is 57.5%. However, at DR. Wahidin Sudirohusodo Hospital in Makassar, Indonesia, the prevalence of anemia in HIV/AIDS patients was notably higher at 89.6%. This higher prevalence can be attributed to the generally severe nature of the disease among patients referred to the hospital. Among the 58 HIV/AIDS patients studied, 52 (80%) were found to have anemia. Out of the cases examined, the majority (80.7%) showed normochromic normocytic anemia. A smaller percentage exhibited hypochromic microcytic anemia (9.6%), macrocytic hypochromic anemia (3.8%), normochromic microcytic anemia (3.8%), and normocytic hypochromic anemia (1.9%). These results are consistent with international studies, suggesting that normochromic normocytic anemia is the most commonly observed form of anemia among individuals with HIV/AIDS.[1]

Anemia is a prevalent hematological complication in individuals with HIV infection. Typically, the condition is characterized by normochromic normocytic features, including a low count of immature red blood cells, normal iron levels, and a compromised response to erythropoietin.[35]

The etiology of anemia in HIV-infected individuals can be broadly classified as a result of an inefficient hematopoiesis process, which can be attributed to factors such as malnutrition, co-infections, neoplasms, reduced erythropoietin production, and the use of antiretroviral drugs. Other mechanisms contributing to anemia may involve heightened erythrocyte destruction and blood loss from gastrointestinal or genitourinary bleeding.[36] The pathogenesis of anemia associated with HIV infection is intricate and multifaceted. Notably, opportunistic infections or malignancies commonly associated with HIV infection can further induce anemia. Diagnosing anemia in regions where infectious diseases like malaria and helminthiasis are prevalent poses a challenge, as these conditions can independently cause anemia without HIV infection, complicating the diagnostic process.[37]

The real impact of anemia is fatigue. This is exacerbated by pregnancy. Fatigue in HIV infection is associated with physical functional impairment, psychological distress, and decreased quality of life. Although the cause of fatigue in anemia is multifactorial, it is suspected that anemia is the most influential cause of fatigue. Fatigue is seen in disruptions of daily routines, work productivity, and sleep pattern.[36]

Intestinal worm and parasitic infections

Apart from HIV, infections with worms and intestinal parasites are also the most common cause after malaria, according to the review[14,17,20] by 26.6% This occurs in African countries like Ethiopia, West Ethiopia, and Tanzania, with the highest prevalence in West Ethiopia, as high asa 73%. According to the World Health Organization, worms are infested with one or more intestinal parasitic roundworms belonging to the intestinal nematode class, including whipworms, hookworms, and Ascaris.[38] Intestinal nematodes responsible for causing helminthiasis typically belong to the Transmitted Helminths (STH) group, which consists of worms that require specific soil conditions for their infective stage to occur. Examples of STH nematode species that contribute to helminthiasis include roundworms (Ascaris lumbricoides), hookworms (Ancylostoma duodenal and Necator americanus), threadworms (Strongyloides stercoralis), and whipworms (Trichuris trichiura). The pinworm (Oxyuris vermicularis) is another non-STH nematode that commonly infects individuals.[39]

Helminthiasis remains highly prevalent worldwide, especially in tropical and sub-tropical climates, including Indonesia. Worm disease, categorized as one of the 17 Neglected Tropical Diseases (NTDs), pertains to tropical illnesses that receive inadequate attention from the government. The prevalence of helminthiasis fluctuates between 40% and 60% across all age groups. Alarmingly, a substantial population of 195 million individuals in Indonesia reside in areas endemic to worm infestation. Moreover, the overall prevalence of worm infections remains remarkably elevated in Indonesia, particularly among socioeconomically disadvantaged groups with heightened susceptibility to this ailment.[40,41] The high prevalence of helminthiasis does not only occur in Indonesia. Other countries with conditions similar to Indonesia also

experience the same thing as research in North West Ethiopia, with a prevalence of helminthiasis in pregnant women of 32% in the Dembecha District[42] and 70.6 % in the Mecha District.[43]

The presence of intestinal worms exacerbates anemia by increasing blood loss. This disruption in iron equilibrium occurs due to the release of a greater amount of iron compared to the amount supplied.[44] Consequently, alterations in intestinal iron absorption, iron metabolism, and intestinal bleeding can result in iron deficiency anemia. Furthermore, the impairment of the intestinal mucosa obstructs the absorption of essential nutrients, specifically micronutrients like iron, thereby detrimentally affecting the host's physical condition, nutritional status, and immune system.[45]

The presence of anemia in pregnant women contributes to an elevated susceptibility to complications throughout pregnancy and delivery. Anemia in expectant mothers is closely linked to heightened rates of mortality and morbidity among both the maternal and neonatal populations, encompassing the likelihood of spontaneous abortion, fetal demise, preterm birth, and lower birth weight.[2] Worm infestations can be contracted via the consumption of improperly washed food contaminated with worm eggs, the ingestion of water containing worm eggs, the influence of socioeconomic and environmental factors, and inadequate personal hygiene practices.[46]

Chronic Disease

After the prevalence of HIV and intestinal worm and parasite infections, a review conducted in Ethiopia and India found that chronic disease accounted for 13.3% of the findings in Ethiopia and 27.3% in India[13,26]. Anemia of Chronic Disorder (ACD), also known as anemia of chronic disease or chronic inflammation, is identified as the second most common type of anemia globally, following iron deficiency anemia.[47] Typically lasting over three months, the chronic disease contributes to anemia through three main mechanisms. Firstly, the production of red blood cells in the bone marrow is suppressed due to inflammatory mediators impacting iron homeostasis, resulting in limited iron availability for erythropoiesis and subsequent development of anemia. Secondly, inflammation affects the production and activity of erythropoietin, the hormone responsible for regulating red blood cell formation, primarily through cytokine inhibition and reduced expression of erythropoietin receptors on erythroid progenitors, as well as limited iron availability. Thirdly, impaired iron utilization in the body prevents stored iron in the bone marrow from effectively producing new red blood cells. Anemia of chronic disease often progresses slowly and mildly, leading to few or no noticeable symptoms. When symptoms do arise, such as fatigue, weakness, or pallor, they are typically attributed to the underlying disease rather than the anemia itself.[48,49] As a result, laboratory tests are necessary for a definitive diagnosis of Chronic Disease Anemia.

Hepcidin, a hormone synthesized by the liver, is crucial in maintaining iron balance within the body. Its synthesis is elevated in Anemia of Chronic Disease (ACD) cases and reduced in instances of Iron Deficiency Anemia (IDA). Frequently, ACD and IDA occur simultaneously, and their manifestations can be indistinguishable upon visual examination of the peripheral blood sample. Furthermore, the diagnosis of IDA and ACD is commonly conducted through laboratory tests such as measuring serum iron levels, Total Iron Binding Capacity (TIBC), transferrin saturation, and ferritin concentrations.[50]

Anemia in chronic diseases,whether infectious or non-infectious diseases, is the result of a combination of several factors, including genetics, behavior, and the environment.[1] According to a study in India[26], Chronic diseases as comorbidities among pregnant women include chronic liver disease, chronic kidney disease, heart disease, essential hypertension, diabetes mellitus, tuberculosis, and autoimmune disorders. The same study reported that half of pregnant women in India experience chronic diseases such as diabetes, hypertension, tuberculosis, respiratory disease, malaria, and cardiovascular disease. Studies show that mothers who have two or more chronic diseases during pregnancy have a higher chance of experiencing delivery-related complications such as seizures and excessive vaginal bleeding.[33]

Bleeding

The next cause of maternal health issues is bleeding or post-hemorrhagic events, 13.3% of cases found in the African continent, including Uganda, both southern and northern Ethiopia.[19,21,23] This high percentage is often due to a history of previous postpartum bleeding, abortion, and bleeding during pregnancy, all of which cause anemia in pregnant women.

Based on the World Health Organization (WHO) findings, approximately 40% of maternal fatalities in developing nations can be attributed to anemia during pregnancy. Most instances of anemia in pregnancy result from acute hemorrhaging and inadequate nutritional conditions.[51] Field[52–54] research in Indonesia has demonstrated that pregnant women with suboptimal nutritional status are prone to experiencing chronic energy deficiency (CED). Furthermore, anemia during pregnancy can contribute to postpartum hemorrhage, a leading cause of maternal mortality, with a staggering mortality rate of 58%, particularly prevalent in developing countries.[2] Although women survive after experiencing postpartum hemorrhage, they can later experience severe blood loss (severe anemia) and prolonged health problems. This is what will affect anemia in women in subsequent pregnancies. Anemia that occurs during pregnancy will likely impact the process of childbirth, the postpartum period, and the health of the newborn.

Acute or rapid blood loss can give rise to severe initial symptoms, particularly when anemia occurs abruptly due to sudden blood loss from various causes such as injury, surgical procedures, childbirth, or the rupture of blood vessels. The sudden depletion of significant quantities of blood can lead to two major complications: First, a decrease in blood pressure arises due to insufficient fluid volume within the blood vessels. Second, the body experiences a sharp decline in its oxygen supply, owing to the rapid reduction in the

number of red blood cells responsible for carrying oxygen. Consequently, these circumstances can precipitate adverse events, such as heart attacks, strokes, or even death.[55]

Chronic blood loss is a more prevalent occurrence compared to sudden blood loss. Chronic bleeding refers to the long-term and ongoing bleeding from any part of the body. While significant bleeding events like nosebleeds and hemorrhoids are easily noticeable, smaller blood losses might go unnoticed. For instance, it may be difficult to detect small traces of blood in the stool, referred to as occult or hidden blood loss. Prolonged and gradual bleeding can lead to substantial blood loss over time if left unaddressed. This gradual bleeding is commonly associated with gastrointestinal or urinary tract disruptions, as well as heavy menstrual periods.[19] This type of chronic bleeding typically results in low iron levels, exacerbating the severity of anemia.[55]

CONCLUSION

Anemia is not a standalone disease but a symptom of various underlying conditions. Therefore, diagnosing anemia requires more than just identifying its presence; it necessitates determining the root cause. This review article explores five causes of normocytic anemia in pregnant women, most of which occur in African continent countries. The most common causes include malaria, HIV, worm infections and intestinal parasites, chronic disease, and bleeding.

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