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Masters Program in Public Health, Universitas Sebelas Maret
Meta-Analysis

Meta-Analysis: The Effect of Anemia in Pregnant Women on the Risk of Postpartum Bleeding and Low Birth Weight

Fahmi Adhimukti[1)], Uki Retno Budihastuti[2)], Bhisma Murti[1)]

[1)]Masters Program in Public Health, Universitas Sebelas Maret
[2)]Study Program of Obstetric and Gynecology, Universitas Sebelas Maret

ABSTRACT

Background: Anemia in pregnancy usually occurs in the 1st and 3rd trimesters with Hb levels below 11g% and in the 2nd trimester with Hb levels less than 10.5g%. The prevalence of anemia in pregnant women around the world ranges from 41.8% to 43.8%, which means that around 56-59 million pregnant women suffer from anemia. Factors that cause anemia that often appear in pregnant women are malnutrition and iron deficiency, so that iron anemia in pregnancy can result in increased maternal mortality rates (MMR). Anemia during pregnancy can result in fetal death, abortion, birth defects, low birth weight and can cause bleeding during labour.
Subjects and Method: Meta-analysis was carried out using the PRISMA flowchart and the PICO model (Population: pregnant women, Intervention: anemia, Comparison: no anemia, Outcome: LBW and postpartum hemorrhage). The databases used are PubMed, Research Gate, Science Direct, and Google Scholar with the keywords "maternal anemia" AND "postpartum hemorrhage" AND cohort, "maternal anemia" AND "low birth weight" AND cohort. There were 17 cohort studies published in 2012-2022 that met the inclusion criteria. The total sample in this meta-analysis was 719,172. Analysis was performed with Revman 5.3.
Results: Seventeen articles with cohort study originating from China, Taiwan, Japan, India, Bangladesh, England, Scotland, North America and the United States involving 719,172 pregnant women. A meta-analysis of 9 cohort studies showed that anemia in pregnant women increased the risk of giving birth to LBW babies 1.35 times compared to pregnant women who were not anemic (aOR= 1.35; 95% CI = 1.05 to 1.75; p=0.020). A meta-analysis of 8 cohort studies showed that anemia in pregnant women increased the risk of postpartum hemorrhage 1.99 times compared to pregnant women who were not anemic (aOR= 1.99; 95% CI = 1.24 to 3.18; p=0.004).
Conclusion: Anemia in pregnant women can increase the risk of LBW babies and postpartum hemorrhage.

Keywords: pregnant women, anemia, LBW, postpartum hemorrhage, and meta-analysis.

Correspondence:
Fahmi Adhimukti. Masters Program in Public Health, Universitas Sebelas Maret. Jl. Ir. Sutami 36A, Surakarta 57126, Central Java, Indonesia. Email: fahmiadhimukti13@gmail.com. Mobile: +628-5743155133.

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BACKGROUND

Anemia is a global health problem that is common and widespread and affects 56 million women worldwide and two thirds of them are in ASIA (Soh et al., 2015). Anemia is a sign of a disease and not a disease in itself. Anemia is a condition where the amount of hemoglobin in the blood is less than normal (Dinkes, 2021).

Anemia in pregnancy usually occurs in

the 1st and 3rd trimesters with Hb levels below 11g% and in the 2nd trimester with Hb levels less than 10.5g%. Factors causing anemia include non-adherence of pregnant women in consuming iron tablets, namely mothers not consuming iron tablets and the habit of consuming coffee and tea together at mealtimes so as to reduce iron absorption in the body which results in reduced benefits of iron. (Tarwoto and Wasnidar, 2013).

The global prevalence of anemia in pregnant women is 28-36 million. The highest number of anemia sufferers is in the Asian continent, namely 12-22 million people, and the lowest in Oceania or the Pacific region, around 100-200 people. Globally, the Asian continent, especially Southeast Asia, has the highest anemia rate in pregnant women, reaching 48.2% (Ikeanyi and Ibrahim, 2015).

In pregnancy anemia often occurs because the blood of pregnant women undergoes hemodilution (dilution) with an increase in volume of 30% to 40%, which peaks at 32 to 34 weeks of gestation. Anemia during pregnancy can result in fetal death, abortion, birth defects, low birth weight and can cause bleeding during labour. This condition causes high perinatal mortality rates, as well as maternal mortality and morbidity (Manuaba, 2012). The biggest cause of anemia is anemia due to iron deficiency. Iron is the most important component in the formation of hemoglobin which plays a role in transporting oxygen to blood cells for the metabolism of glucose, fat and protein into energy (Ministry of Health RI, 2017).

Anemia in pregnant women can affect pregnancy, namely: the occurrence of abortion, premature delivery, inhibition of fetal growth and development in the uterus, and hyperemesis gravidarum. Dangers to the fetus include abortion, intrauterine death, low birth weight, and birth defects can occur. The WHO, states that 40% of maternal deaths in developing countries are related to anemia in pregnancy and most of them are caused by iron deficiency and acute bleeding and it is not uncommon for the two to interact with each other which in turn is at risk for abortion, premature parturition or low birth weight. (LBW) (Syaifudin, 2014).

Anemia increases the frequency of complications in pregnancy and childbirth, the risk of maternal death, the rate of prematurity, low birth weight, and prenatal mortality (Larumpaa, Suparman and Lengkong, 2017).

In this study, the authors were interested in conducting a meta-analytic study regarding the effect of anemia in pregnant women on the risk of LBW and postpartum hemorrhage using a meta-analysis.

SUBJECTS AND METHOD

1. Study Design

The meta-analysis was performed using the PRISMA flowchart using PubMed, Science Direct, Research Gate and Google Scholar databases. The keywords used were “maternal anemia” AND “low birth weight” AND cohort, “maternal anemia” AND “postpartum hemorrhage” AND cohort. There were 17 studies with cohort research designs published in 2012-2022 that met the inclusion criteria. Analysis was performed with RevMan 5.3.

2. Steps of Meta-Analysis

The meta-analysis was carried out in five steps as follows:

1. Formulate research questions in the PICO format (population, intervention, comparison, outcome).
2. Search for primary study articles from various electronic databases including PubMed, Research Gate, Science Direct, and Google Scholar.
3. Conduct screening and critical appraisal (Critical Appraisal) of primary research articles.

4. Perform data extraction and synthesize effect estimates into RevMan 5.3.
5. Interpret and conclude the results.

3. Inclusion Criteria

Full-text paper research articles using a cohort study design. The relationship measure used is OR. Analysis using multivariate with adjusted Odds Ratio (aOR). The research subjects were pregnant women. Intervention in the form of anemia pregnant women. Outcome is LBW and postpartum hemorrhage.

4. Exclusion Criteria

Articles published before 2012 and after 2022, paid or inaccessible articles, and not multivariate analysis studies.

5. Operational Definition of Variables

Anemia in pregnant women is the condition of the body of pregnant women with a hemoglobin level in the blood <11 g% in the 1st and 3rd trimesters or a hemoglobin level <10.5 g% in the 2nd trimester.

Postpartum hemorrhage is blood loss ≥500 ml after vaginal delivery or ≥ 1000 ml after cesarean section.

Low Birth Weight is a baby with a birth weight of less than 2500 grams.

6. Instrument

Quality assessment in this study used a critical assessment checklist for cohort studies published by CASP (Critical Appraisal Skills Programme).

7. Data Analysis

The articles in this study were collected using the PRISMA diagram and analyzed using the Review Manager 5.3 application by calculating effect sizes and heterogeneity to determine the combined research model and form the final results of the meta-analysis.

RESULTS

The search results for articles regarding the effect of anemia in pregnant women on the risk of LBW and postpartum hemorrhage yielded 17 articles with cohort studies which can be seen in Figure 1 PRISMA meta-analysis diagram.

The total number of articles in the initial search process was 1,144 from the PubMed, Science Direct, Research Gate and Google Schoolar databases. Furthermore, the deletion of duplicate articles as many as 67 articles and 1077 articles were filtered. From a total of 176 eligible full text articles, 17 were included in the synthesis meta-analysis. Full text articles included in the exclusion criteria are due to the following reasons: (1) The intervention from the study was not anemia in pregnant women, but an intervention with a history of anemia during labor and the puerperium; (2) The outcome of the study was not LBW but premature birth, abortion, and neonatal death. And the outcome is not postpartum hemorrhage but disturbances during the delivery process for example prolonged parturition and disorders during the puerperium such as uterine sub involution, and (3) Does not include the aOR value as the result of multivariate logistic regression.

Figure 2 shows the distribution area of the primary study articles in 4 continents, namely 7 articles on the Asian Continent (China, Taiwan, Japan, India, and Bangladesh), 2 articles on the European Continent (England and Scotland), 2 articles on the Australian Continent, and 3 Continental articles North America, and 2 articles on the South American Continent.

Assessment of the quality of the study was carried out quantitatively and qualitatively, this study used the Cohort Study Checklist published by CASP (Critical Appraisal Skills Programme). Critical appraisal which consists of 12 questions. Each "yes" answer is given a score of 1, and a "no" answer is given a score of 0.

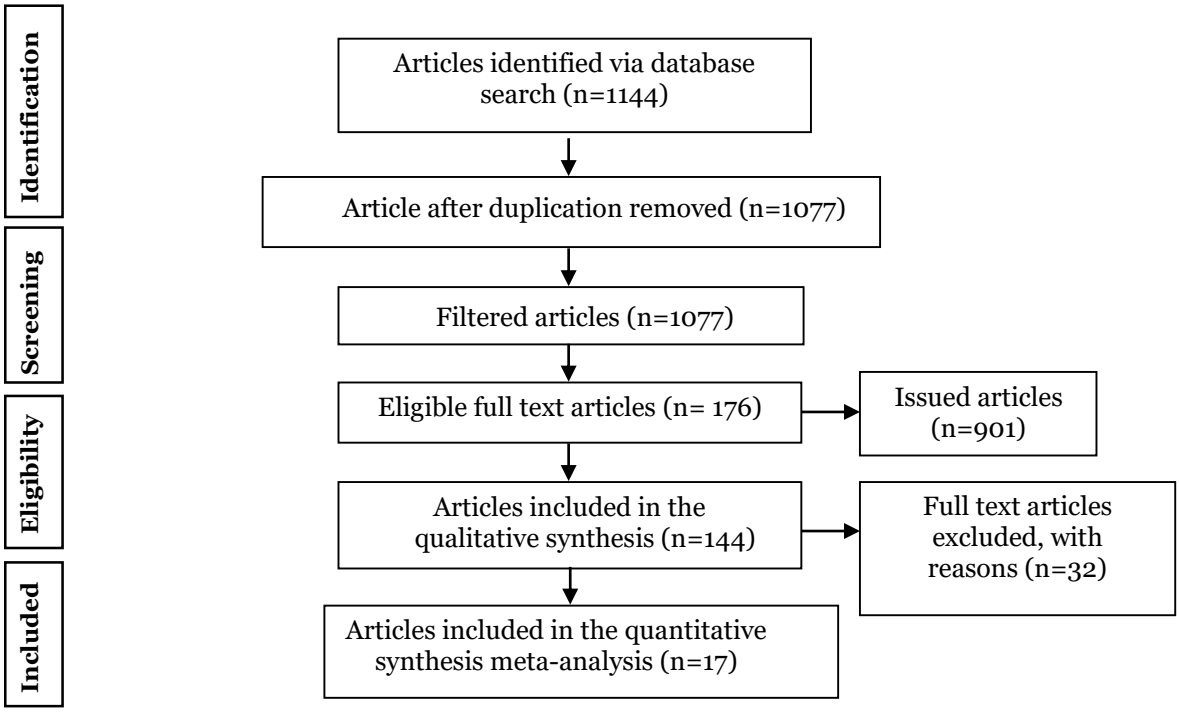

Figure 1. PRISMA flowchart diagram

Figure 2. Map of the meta-analysis area

Table 1 describes the assessment of study quality by cohort study checklist. Based on the answers from the quality assessment, a total score of answers ranging from 11 to 12 scores was obtained, this indicates that the quality of the article is feasible for meta-analysis.

The study description in Table 2 shows the effect of anemia in pregnant women on the risk of LBW. There are 9 articles with a total sample of 158,006 pregnant women with anemia.

The study description in Table 3 shows the effect of anemia in pregnant women on the risk of postpartum hemorrhage. There are 8 articles with a total sample of 561,166 pregnant women with anemia.

Table 1. Assessment of article quality by cohort design

Primary Study	Indicator of Question												Total
	1	2	3	4	5	6	7	8	9	10	11	12	
Biswas et al. (2019)	2	2	2	2	2	2	2	2	2	2	2	2	24
Carpenter et al. (2021)	1	0	2	2	2	2	2	2	2	2	2	2	23
Chu et al. (2020)	2	2	2	2	2	2	2	2	1	2	2	2	22
Jwa et al. (2015)	2	2	2	2	2	2	2	2	2	2	2	2	24
Nair et al. (2016)	2	2	2	1	2	2	2	2	2	2	1	2	23
Sun et al. (2021)	2	2	2	2	2	2	2	2	2	2	2	2	24
Shi et al. (2022)	2	2	2	2	2	2	2	2	2	2	2	2	24
Masukume et al. (2015)	1	2	2	1	2	2	2	2	2	1	2	2	21
Rukuni et al. (2016)	2	2	2	2	2	2	2	2	2	2	2	2	24
Harrison et al. (2021)	2	2	2	2	2	2	2	2	2	2	2	2	24
Butwick et al. (2017)	2	2	2	2	2	2	2	2	2	2	2	2	24
Detlefs et al. (2022)	2	2	2	2	2	2	2	2	2	2	2	2	24
Pinheiro et al. (2021)	2	2	2	2	2	2	2	2	2	2	2	2	24
Gonzales et al. (2012)	2	2	2	2	2	2	2	2	2	2	2	2	24

Note: 2= Yes, 1= Can't tell; 0=No

Note:

1. Does this research have a clear research focus?
2. Was the cohort research process clearly defined?
3. Is exposure measured accurately so as to minimize bias?
4. Are the results measured accurately to minimize bias?
5. Did the authors identify any important confounding factors? We're confounding factors considered in the design or analysis?
6. Was the follow-up of the subject complete? Was the follow-up period sufficient?
7. Are the results of research using HR?
8. Are the research results accurate?
9. Do you believe the results of this study?
10. Can this research be applied to local populations?
11. Are the results of this study in accordance with the existing evidence?
12. Do the results of this study have implications?

Table 2. Description of the cohort study on the effect of anemia in pregnant women on the risk of LBW (n=158.066)

Author (year)	Country	Sample	PICO			
			P Population	I Intervention	C Comparison	O Outcome
Biswas et al. (2019)	India	998	Pregnant mother	Anemia with Hb level <11 g/dL	Not anemic	LBW babies
Carpenter et al. (2021)	Bangladesh	51,665	Pregnant mother	Anemia with Hb levels in TM 1 and 3 <11 g/dL	Not anemic	LBW babies
Chu et al. (2020)	Taiwan	32,234	Pregnant mother	Hb at TM 2 <10.5 g/dL	Not anemic	LBW babies
Jwa et al. (2015)	Japan	1,986	Pregnant mother	Anemia with Hb level 9.7 g/dL≤Hb≤10.8 g/dL	Not anemic	LBW babies
Masukume et al. (2015)	New Zeland, Australia, UK, Ireland	5,906	Pregnant mother	Anemia with Hb level <11 g/dL	Not anemic	LBW babies
Nair et al. (2016)	India	1,007	Pregnant mother	Anemia with Hb level <10.7 g/dL	Not anemic	LBW babies
Harrison et al. (2021)	US	10,217	Pregnant mother	Anemia with Hb level <11 g/dL	Not anemic	LBW babies
Rukuni et al. (2016)	Scotland	7,475	Pregnant mother	Anemia in TM 1 and 3 with Hb level <11 g/dL	Not anemic	LBW babies
Sun et al. (2021)	China	46,578	Pregnant mother	TM 2 Hb <10.5 g/dL	Not anemic	LBW babies

Table 3. Description of the cohort study on the effect of anemia in pregnant women on the risk of postpartum hemorrhage (n=561,166)

Author (Year)	Country	Sample	PICO			
			P Population	I Intervention	C Comparison	O Outcome
Butwick et al. (2017)	US	35,614	Pregnant mother	Anemia with Hb levels of 10.9 g/dL to 10 g/dL	not anemic	Postpartum bleeding
Detlefs et al. (2022)	US	7,416	Pregnant mother	Anemia with Hb level <11 g/dL	Not anemic	Postpartum bleeding
Gonzales et al. (2012)	peruvian	1,804	Pregnant mother	Anemia with Hb level <11 g/dL to 7 g/dL	Not anemic	Postpartum bleeding
Harrison et al. (2021)	US	10.217	Pregnant mother	Anemia in TM 1 and 3 with Hb level <11 g/dL	Not anemic	Postpartum bleeding
Nair et al. (2016)	India	1,007	Pregnant mother	TM 2 Hb <10.5 g/dL	Not anemic	Postpartum bleeding
Borovac-Pinheiro et al. (2021)	Brazil	270	Pregnant mother	Anemia with Hb level <11 g/dL	Not anemic	Postpartum bleeding
Rukuni et al. (2016)	Scotland	7,475	Pregnant mother	Anemia with Hb level <11 g/dL	Not anemic	Postpartum bleeding
Shi et al. (2022)	China	497,363	Pregnant mother	Anemia with Hb level ≤10 g/dL	No anemia	Postpartum bleeding

The forest plot in Figure 3 shows that anemia in pregnant women increases the risk of LBW and the effect is statistically significant. Pregnant women with anemia have a risk of giving birth to LBW babies 1.35 times compared to pregnant women who are not anemic (aOR= 1.35; 95% CI = 1.05 to 1.75; p=0.020). The forest plot also shows high heterogeneity of effect estimates between primary studies in this meta-analysis (I^2= 89%; p<0.001), so the calculation of effect estimates uses the Random Effect Model (REM) approach.

The funnel plot in Figure 4 shows that the distribution of effect estimates between studies is more or less symmetrical, that is, the distribution of effect estimates to the right and left of the vertical line of the average effect estimates is the same. Thus, this funnel plot shows no publication bias.

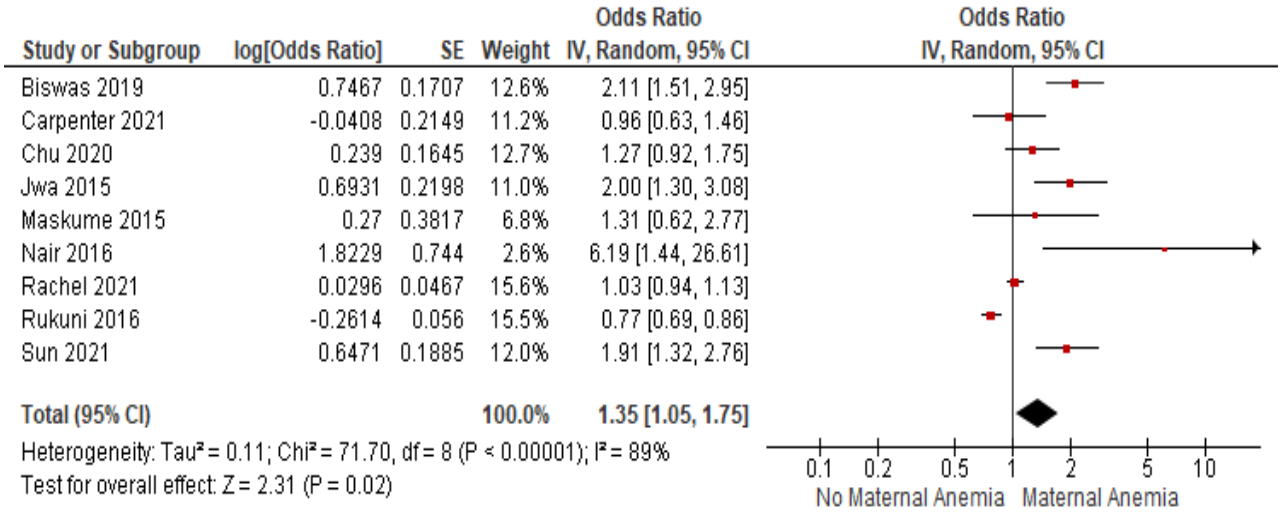

Figure 3. Forest Plot of the effect of anemia in pregnant women on the risk of LBW

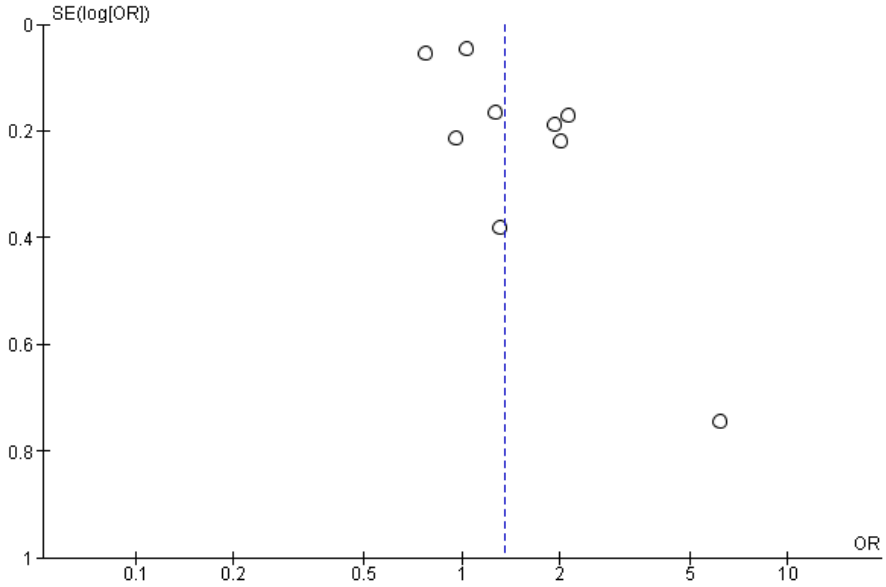

Figure 4. Funnel plot of the effect of anemia in pregnant women on the risk of LBW

The forest plot in Figure 5 shows that anemia has an effect on an increased risk of postpartum hemorrhage and this effect is statistically significant. Pregnant women with anemia have the possibility of approaching the risk of postpartum hemorrhage 1.99 times compared to pregnant women who are not anemic (aOR= 1.99; 95% CI= 1.24 to 3.18; p = 0.004). The forest plot also shows the heterogeneity of effect estimates between primary studies which were meta-analyzed (I^2= 100%; p<0.001) so that the calculation of the average effect estimate uses the Random Effect Model (REM) approach.

The funnel plot in Figure 6 shows that the effect estimates are more distributed to the left than to the right of the average vertical line of effect estimates, thus indicating publication bias. Because the effect distribution is located more to the left of the estimated average vertical line as opposed to the location of the estimate (diamond shape) which is located to the right of the null hypothesis in the forest plot image, the publication bias reduces the previous effect estimate (under estimate).

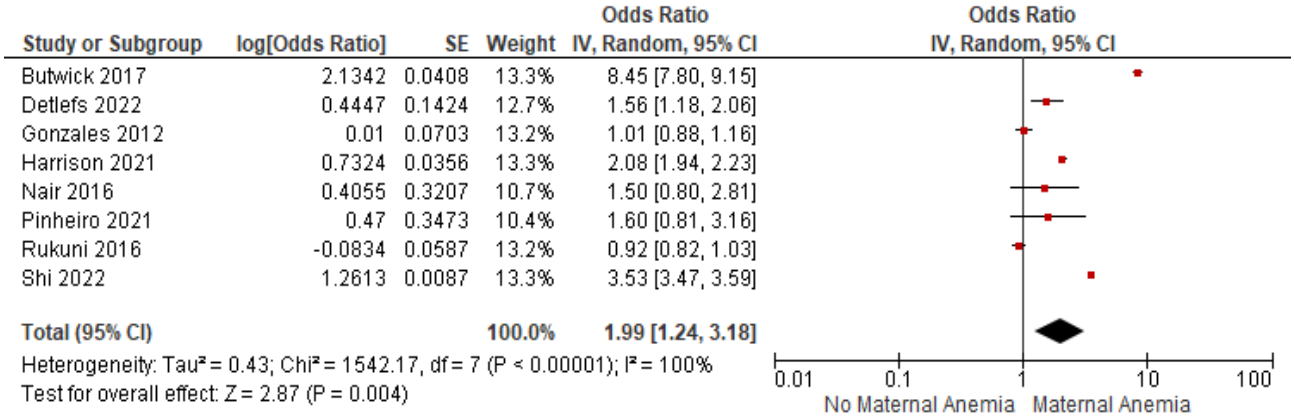

Figure 5. Forest plot of the effect of anemia in pregnant women on the risk of postpartum hemorrhage

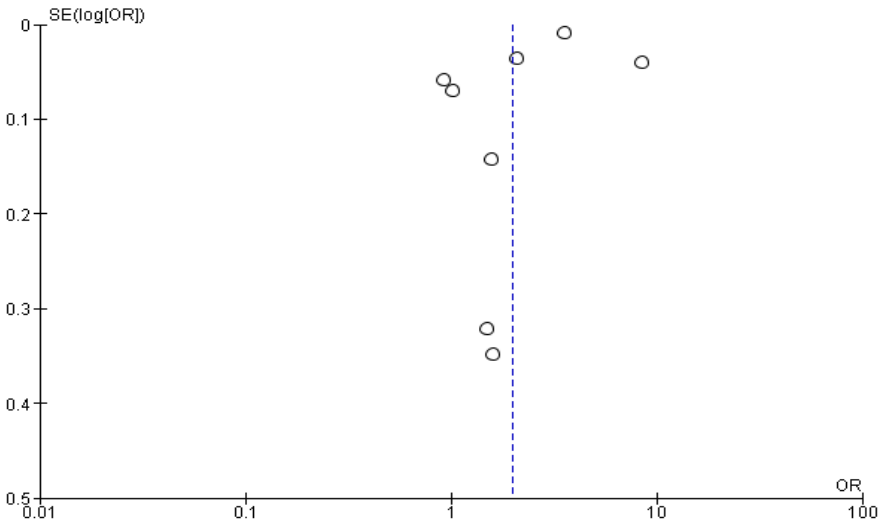

Figure 6. Funnel plot of the effect of anemia in pregnant women on the risk of postpartum hemorrhage

DISCUSSION

The effect of anemia in pregnant women on the risk of LBW

Low Birth Weight or often abbreviated as LBW is the condition of a baby born weighing less than 2,500 grams (Manuaba, 2015). LBW itself can be divided into two groups, namely premature and dysmature. Premature babies are babies born with a gestational age of less than 37 weeks and have a weight in accordance with the weight for the gestation period, while premature babies are babies born with a weight less than the normal weight for pregnancy and during the pregnancy the baby is small (Jumiarni and Mulyani, 2012)

In this study there were eight observational research articles of cohort studies taken from various countries in the world including India, Bangladesh, Taiwan, Japan, New Zealand, United States, Scotland, and China. The results of this meta-analysis explain that pregnant women who are anemic are more at risk of giving birth to babies with LBW babies than pregnant women who are not anemic. This study used a cohort study showing that anemia in pregnant women can increase the risk of LBW babies 1.35 times compared to pregnant women who are not anemic and statistically significant (aOR= 1.35; 95% CI= 1.05 to 1.75, p= 0.020). The heterogeneity of the effect estimates between primary studies showed (I^2 = 89%; p<0.001) so the analysis used the Random Effect Model (REM).

This study is in line with the results of the meta-analysis of Aditianti and Djaiman (2020) which stated that the effect of anemic pregnant women on LBW was 1.49 times higher than that of women who were not anemic (OR=1.49; 95% CI=1.26 to 4.60, p<0.001). This is in accordance with the research of Rahadinda et al. (2022) which states that pregnant women with anemia are 8 times at risk of giving birth to babies with LBW compared to pregnant women who are not anemic.

Anemia during pregnancy can cause low birth weight, premature birth, and death in perinatal, neonatal and mother (Haider et al., 2013; Rasmussen, 2001). This can be caused by impaired transfer of hemoglobin through the placenta to the fetus, resulting in impaired fetal weight gain and thus LBW (Novianti, 2018). Supplementation of iron tablets in pregnant women is associated with the incidence of LBW. Mothers who consume blood supplement tablets for less than 90 days are almost 3 times more likely to give birth to LBW babies than mothers who consume more than 90 days (Bhaskar et al., 2015)

Effect of anemia in pregnant women on the risk of postpartum hemorrhage

Postpartum hemorrhage is bleeding that exceeds normal physiological limits when the baby is born. Normally, the volume of maternal physiological bleeding during childbirth reaches 500 ml without causing disruption to homeostasis. Therefore, traditionally, bleeding in excess of 500 ml was classified as postpartum hemorrhage, and bleeding in excess of 1000 ml should be treated immediately. (Schuurmans, 2008).

In this study there were nine observational research articles of cohort studies taken from various countries in the world including California, Texas, Peru, the United States, India, Brazil, Scotland, and China. The results of this meta-analysis explain that pregnant women who experience anemia have a 1.99 times greater risk of giving birth with postpartum hemorrhage compared to pregnant women.

Who are not anemic. This study used a cohort study showing that anemia in pregnant women can increase the risk of postpartum hemorrhage 1.99 times compared to pregnant women who are not anemic

and statistically significant (aOR 1.99, 95% CI 1.24 to 3.18, p=0.004). The results of the forest plot showed heterogeneity in the estimation of the effect of anemia on pregnant women between primary studies that were carried out by meta-analysis (I^2= 100%; p<0.001).

Antepartum and postpartum hemorrhage is more common in anemic women and is more often fatal because anemic women cannot tolerate blood loss. This is in accordance with research conducted by Hidayah in 2018 where pregnant women who experience anemia are 4.35 times more likely to experience postpartum hemorrhage.

Anemia in pregnant women reduces the mother's immune system and increases the frequency of complications of pregnancy and childbirth. In addition, it also causes an increased risk of postpartum hemorrhage. Fatigue in anemic patients is caused by energy metabolism in muscles that cannot function properly due to lack of oxygen (Manuaba, 2012). The lower the hemoglobin level or the more severe the anemia in pregnant women, the greater the risk of postpartum hemorrhage (Kaima, 2015). Women who give birth with severe anemia are at increased risk of postpartum hemorrhage because the uterus is deprived of oxygen, glucose, and essential nutrients and does not work efficiently during labour. As a result of the lack of oxygen bound in the blood, the uterine muscles do not contract adequately, causing uterine atony which results in postpartum hemorrhage (Cuningham, 2013).

The limitation of this research is that there is research bias because it only uses 4 databases, namely Google Scholar, PubMed, and Science Direct, thus ignoring research from other databases. As well as language bias where the selected articles are only published in English, thus ignoring articles published in other languages.

AUTHOR CONTRIBUTION

Fahmi Adhimukti as the main researcher who chose the topic, conducted a search for data collection in this study. Uki Retno Budihastuti and Bhisma Murti conducted data analysis and reviewed research documents.

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This study is self-funded.

CONFLICT OF INTERESTS

There is no conflict of interest in this study.

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