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Meta Analysis

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Meta-Analysis of Associations between Maternal Age, Low Hemoglobin Level during Pregnancy, Low Birth Weight, and Preterm Birth

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ABSTRACT

Background: Maternal age <19 years and anemia in pregnancy are often associated with adverse neonatal outcomes. This study aims to analyze the relationship between maternal age <19 years and anemia in pregnancy (Hb <11 g/dL) on the incidence of low-birth-weight (LBW) babies and premature birth.

Subjects and Method: This was a meta-analysis took cohort studies published in 2018-2022. The PICO formulation used: the population is pregnant women, the intervention consists of groups of pregnant women aged <19 years and pregnant women with anemia (Hb<11 gr/dL), comparison is the group of pregnant women aged 20-35 years and pregnant women are not anemic while Outcomes were LBW and premature birth. Search articles through databases: PubMed, springer, science direct and google scholar with the keywords "Adolescence pregnancy OR young OR Teenage AND Pregnancy AND neonatal outcome OR Low birth weight OR preterm birth OR Low weight", "Anemia OR Maternal anemia AND Neonatal outcome OR Preterm birth". Data analysis using the Review Manager (RevMan) 5.4 application.

Results: A total of 7 cohort articles on pregnancy aged <19 years and 5 cohort articles on anemia were analyzed. Articles come from Canada, Turkey, England, Russia, Finland, China, Chinese Taipei, Ethiopia, Zambia and Bangladesh. The sample sizes were n=43,399 (maternal age and LBW), n=55,049 (maternal age with premature birth), n=16,544,075 (anemia and premature birth). Pregnant women aged <19 years have a 1.63 risk of giving birth to LBW babies (aOR= 1.63; 95% CI= 0.96 to 2.78; p= 0.070) and 1.41 times giving birth to premature babies (aOR= 1.41; 95% CI= 0.78 to 2.56; p= 0.250). Pregnant women with anemia have a 1.60 times risk of giving birth to premature babies (aOR= 1.60; 95% CI= 1.10 to 2.32; p= 0.010).

Conclusion: The age of pregnant women <19 years does not have a significant effect on the occurrence of LBW and premature birth. Pregnant women with anemia increase the risk of premature birth.

Keywords: maternal age, anemia, low birth weight, premature birth.

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BACKGROUND

As many as 21 million pregnancies annually occur in adolescent groups (age 15-19 years) in several low- and middle-income countries. Teenage pregnancies are at higher risk of experiencing low birth weight (LBW), premature birth, and poor neonatal conditions (WHO, 2022). In 2003-2015 the prevalence of teenage pregnancy in Africa was 18.2%, while in 2016-2018 teenage pregnancy increased to 20.5% (Kassa et al., 2018). In Turkey from 2013-2016 there were 42,280 deliveries and 8.8% of them were adolescent deliveries (Karataşlı et al., 2019b). A cross-sectional study was conducted at a regional hospital in Northern Mexico looking at maternal and neonatal outcomes of adolescent and adult pregnancies. In the study, 34% consisted of teenage pregnancies (Minjares-Granillo et al., 2016). The results of another study by Daniels et al., (2017) who conducted a cohort study from January 2007-December 2015 at Mater Mother's Hospital (MMH) Brisbane, Australia stated that of the 8904 deliveries at MMH, 18.2% were adolescents.

Research in Canada in 2021 stated that during teenage pregnancies there was an increase in the prevalence of LBW by 56% and 23% for premature birth (DeMarco et al., 2021). One study from a hospital in Indonesia stated that the risk of premature birth was high for mothers aged 12-19 years (aOR=1.5; 95% CI= 0.88 to 2.53; p<0.001) (Indarti et al., 2020). Similar research was also conducted in sub-African countries in 2015-2018. 11.1% of the teenage pregnancy population also experienced an increased risk of prematurity (aOR= 1.14; 95% CI= 1.06 to 1.23; p= 0.001) (Serunjogi et al., 2021). Nonetheless, the opposite was reported by Fleming et al., (2013). In the study in Ontario, Canada, there were no significant differences in LBW and preterm birth between groups of teenage and adult pregnant women. The study has adjusted for confounding factors such as smoking, maternal parity, family economic income and education. Yuce's study (2015) in Turkey also reported that during the delivery of the adolescent group there was a decrease in several neonatal and maternal complications. Differences in neonatal outcomes between adult and adolescent mothers, especially in cases including LBW and premature births, have not been clearly reported.

In addition to the age factor of the mother, there are also conditions that lead to adverse birth outcomes. This condition is anemia. In more than 80% of countries in the world, the prevalence of anemia in pregnancy is >20%. The global prevalence of anemia in pregnancy is estimated to be 41.8% (Garzon et al., 2020). Anemia that lasts until the 3rd trimester is one of the causes of premature birth (OR= 1.85; 95% CI = 1.06 to 3.20) (Huang et al., 2015). Other studies mention similar results. Anemia of third trimester pregnant women causes an increased risk of prematurity (OR= 0.92; 95% CI= 0.55 to 1.56) (Young et al., 2019).

There are several meta-analytical studies that also discuss negative outcomes of maternal age <19 years and anemia during pregnancy on neonatal births that have been published previously. The study included primary articles, most of which did not adjust for confounding factors, the research only involved the results of primary studies from certain areas, and some conducted meta-analyses on studies other than cohorts. This meta-analysis study only involved primary studies with cohort designs and studies that included multivariate analysis results (including adjusted values). The purpose of this study was to estimate the effect of maternal age and anemia during pregnancy on the possibility of LBW and preterm birth.

SUBJECTS AND METHOD

1. Study Design

This study is a systematic review and meta-analysis involving several primary articles using a cohort study design. Primary studies come from electronic journal databases: science direct, google scholar, springer and PubMed. The keywords used in the article search process are: “Adolescent pregnancy OR Adolescence pregnancy OR young OR Teenage AND Pregnancy AND neonatal outcome OR Low birth weight OR preterm birth OR Low weight”, “Anemia OR Maternal anemia AND Neonatal outcome OR Preterm birth”, “Maternal Anemia OR Anemia AND Neonatal outcome OR Preterm birth AND cohort study”.

2. Steps of Meta-Analysis

1) Formulate research questions in the PICO format (Population, Intervention, Comparison, Outcome).
2) Search primary study articles from databases such as Science direct, Google Scholar, Springer, and PubMed.
3) Perform screening by determining inclusion and exclusion criteria and conducting critical assessments.
4) Perform data extraction and analysis using RevMan 5.3 Software
5) Interpret the results and draw conclusions.

3. Inclusion Criteria

The primary articles involved in the analysis are primary studies with a cohort study design, full text available in English, published between 2018-2022, reporting the results of calculating the adjusted odds ratio (aOR), including information on the age limit of the mother, both adolescents and adults, and hemoglobin levels.

4. Exclusion Criteria

Primary research, if the number of samples is <200, teenage pregnancies with certain risk factors, pregnancies in women with anemia and a history of previous preterm birth will be excluded.

5. Operational Definition of Variable

Maternal Age was mother’s age when pregnant, adolescent age if the age was less than 20 years old at the time of pregnancy and adult age if more than 20 years old.

Low Hemoglobin Level during Pregnancy was less than 11.5 gr/dL

Low Birth Weight was baby's birth weight is less than 2500 grams

Preterm Birth was the baby was born before the mother's gestation was 37 weeks.

6. Instrument

Primary studies that have been screened are subject to critical appraisal or study reviews to determine eligibility. The assessment instrument uses the Critical Appraisal Cohort Study for Meta-analysis Research published by the Magister in Public Health (2023).

7. Data Analysis

Article search results are collected with the help of the PRISMA diagram. Primary articles that match the determination of inclusion criteria and CASP assessment were analyzed using the Review Manager (RevMan) 5.4 application. The magnitude of the effect size and confidence interval (95% CI) is obtained from calculating the aggregate aOR value. The calculation of the estimated amount of heterogeneity (I^2) was carried out by choosing the random effect model approach because the estimated amount of heterogeneity was > 50%.

RESULTS

1. Study Characteristics

Search results on the electronic database obtained as many as 1,368 articles. Duplication removal was performed on 17 articles. After the initial screening, 1,255 articles were issued. Full text article reviews were conducted on 101 primary articles. A total of 89 articles were again excluded because they did not meet the inclusion criteria. The final results obtained were 12 cohort articles that were subjected to quantitative synthesis and meta-analysis. The cohort articles were published between

2018-2022. The search review process can be seen in PRISMA Flowchart in Figure 1 while the distribution of research areas is in Figure 2.

2. Relationship between maternal age during pregnancy and LBW

Six cohort studies were included in the meta-analysis of the effect of maternal age at pregnancy on the incidence of LBW.

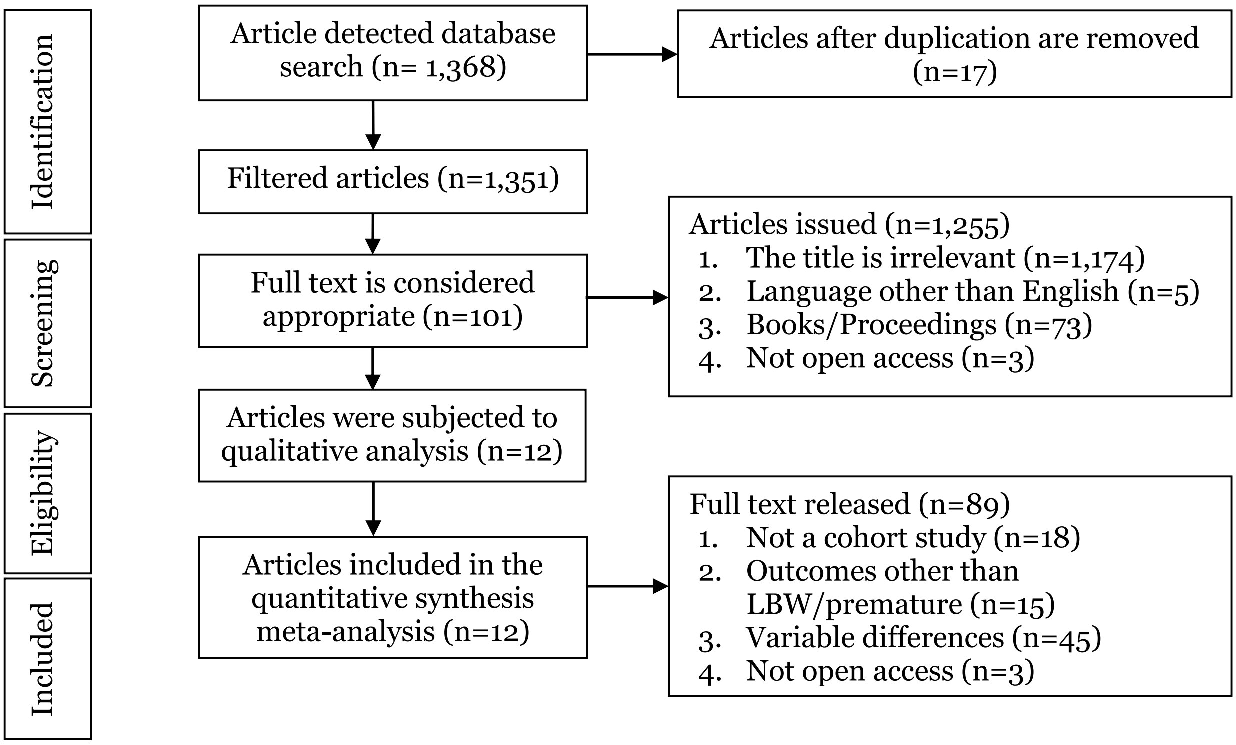

Figure 1. PRISMA Flow Diagram Results

Figure 2 summarizes the distribution of the cohort primary articles included in the meta-analysis. The following are the results of critical appraisal for the cohort study.

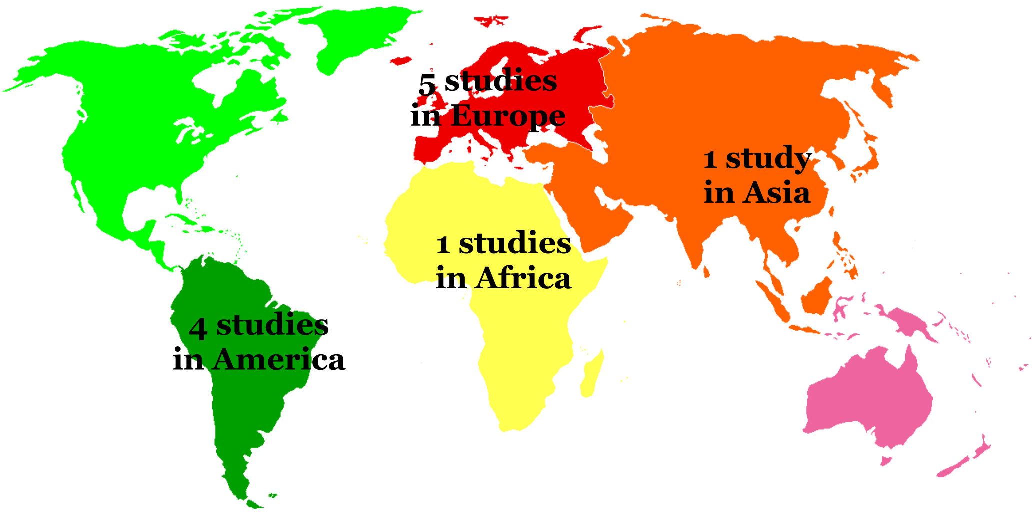

Figure 2. Map of the Research Area

Table 1. Critical appraisal results of primary cohort studies on the relationships between maternal age at pregnancy, anemia, LBW, and preterm birth

Article	Questions														Total
	1a	1b	1c	1d	2a	2b	3a	3b	4a	4b	5a	6a	6b	7	
Abebe et al. (2020)	2	2	2	2	2	2	2	2	1	1	2	2	2	2	26
Dowle et al. (2018)	2	2	2	2	2	2	2	1	2	2	2	2	2	2	27
Genc et al. (2021)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Kartasli et al. (2019)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Kassa et al. (2019)	2	2	2	2	2	2	2	1	1	2	2	2	2	2	26
Usynina et al. (2018)	2	2	2	2	2	2	2	2	0	2	2	2	2	2	26
Moraes et al. (2018)	2	2	2	2	2	2	2	1	1	1	2	2	2	2	25
Kabir et al. (2022)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Chu et al. (2020)	2	2	2	2	2	2	2	1	2	2	2	2	2	2	27
Shi et al. (2022)	2	2	2	2	2	2	2	1	2	2	2	2	2	2	27
Ronkainen et al. (2019)	2	2	2	2	2	2	2	2	1	2	2	2	2	2	27
Smith et al. (2019)	2	2	2	2	2	2	2	1	2	1	2	2	2	2	26

Description of Critical Appraisal Criteria:

1. Formulation of research questions in the acronym PICO
   a. Is the population in the primary study the same as the population in the PICO meta-analysis?
   b. Is the operational definition of intervention, namely the exposed status in the primary study, the same as the definition intended in the meta-analysis?
   c. Is the comparison, namely the unexposed status used by the primary study, the same as the definition intended in the meta-analysis?
   d. Are the outcome variables examined in the primary studies the same as the definitions intended in the meta-analysis?
2. Methods for selecting research subjects
   a. Is at the start of the study, the target population and accessible population has not experienced it the outcome being studied?
   b. Were the groups differentiated at the start of the study? exposed group and unexposed group
3. Methods for selecting research subjects
   a. Did the target population and accessible population not experience the outcomes studied at the start of the study?
   b. Was there a distinction between the exposed group and the unexposed group at the start of the study?
4. Design-related bias
   a. Is there no possibility of "Loss-to Follow-up Bias" in primary studies?
   b. Whether primary study researchers have made efforts to prevent or overcome such bias (e.g., selecting highly motivated subjects, subjects who are easy to track, or providing incentives to subjects so they do not drop out)
5. Methods for controlling confusion

Whether the primary study researcher has made efforts to control the influence of confounding (for example, conducting a multivariate analysis to control the influence of a number of confounding factors, or performing matching).

6. Statistical analysis methods
   a. Did the researcher analyze the data in this primary study with a multivariate analysis model (e.g., multiple linear regression analysis, multiple logistic regression analysis, Cox regression analysis?
   b. Does the primary study report effect sizes

or relationships resulting from multivariate analysis (e.g., adjusted OR, adjusted regression coefficient)

7. Conflict of interest

Is there no possibility of a conflict of interest with the research sponsor, which could cause bias in concluding the research results?

Scoring Instructions:

1. Total number of questions = 14 questions.
2. The answer "Yes" to each question gives a score of "2". The answer "Undecided" gives a score of "1". The answer "No" gives a score of "0".
3. Maximum total score= 14 questions x 2= 28.
4. Minimum total score = 14 questions x 0 = 0. So, the range of total scores for a primary study is between 0 and 28.
5. If the total score of a primary study is >= 24, then the study can be included in the meta-analysis. If the total score of a primary study was <24, then the study was excluded from the meta-analysis.

Table 3. Summary of cohort articles from primary study sources with sample size (n=43,399)

Author (Year)	Country	Sample	Population	Intervention	Comparison	Outcome
Dowle et al. (2018)	English	4,332	Pregnant mother	Age <19 years	Age 20-34 years	LBW
Moraes et al. (2018)	Zambia	1,328	Pregnant mother	Age 10-15 years	Age 20-24 years	LBW
Usynina et al. (2018)	Russia	35,104	Pregnant mother	Age <19 years	Age 20-34 years	LBW
Kassa et al. (2019)	Ethiopia	1,116	Pregnant mother	Age 15-19 years	Age 20-34 years	LBW
Abebe et al. (2020)	Ethiopia	618	Pregnant mother	Age <19 years	Age <27 years	LBW
Genc et al. (2022)	Türkiye	901	Pregnant mother	Age ≤16 years	Age 25-35 years	LBW

Table 4. Data of adjusted odds ratio (aOR) and 95% confidence interval (CI 95%) effect of maternal age at pregnancy on the incidence of LBW

Author	aOR	Lower Limit	Upper Limit
Genc et al. (2022)	4.75	2.26	9.21
Moraes et al. (2018)	1.42	0.42	4.83
Usynina et al. (2018)	0.72	0.55	0.95
Kassa et al. (2019)	2.14	1.36	3.36
Abebe et al. (2020)	2.22	1.13	4.36
Dowle et al. (2018)	1.10	0.81	1.50

The forest plot in Figure 3 shows the effect of maternal age during pregnancy on the incidence of low birth weight. However, statistically the effect does not show a significant relationship. Mothers aged <19 years during pregnancy had a 1.63 risk of giving birth to babies with low birth weight (aOR= 1.63; 95% CI= 0.96 to 2.78; p= 0.070). The heterogeneity calculation also shows high results, namely I^2= 86% so that the calculation of the estimated magnitude is chosen using the random effect model.

Figure 4, the funnel plot above shows that the distribution of effect estimates is quite symmetrical. the number of plots is the same between the right and left sides of the vertical line. Symmetrical funnel plots indicate no publication bias.

a. Forest plot

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Abebe 2020	0.7975	0.3445	15.9%	2.22 [1.13, 4.36]
Dowle 2018	0.0953	0.1561	20.0%	1.10 [0.81, 1.49]
Genc 2022	1.5581	0.379	15.1%	4.75 [2.26, 9.98]
Kassa 2019	0.7608	0.2313	18.6%	2.14 [1.36, 3.37]
Moraes 2018	0.3492	0.6245	10.0%	1.42 [0.42, 4.82]
Usynina 2018	-0.3285	0.1374	20.3%	0.72 [0.55, 0.94]
Total (95% CI)			**100.0%**	**1.63 [0.96, 2.78]**

Heterogeneity: Tau² = 0.34; Chi² = 36.66, df = 5 (P < 0.00001); I² = 86%
Test for overall effect: Z = 1.81 (P = 0.07)

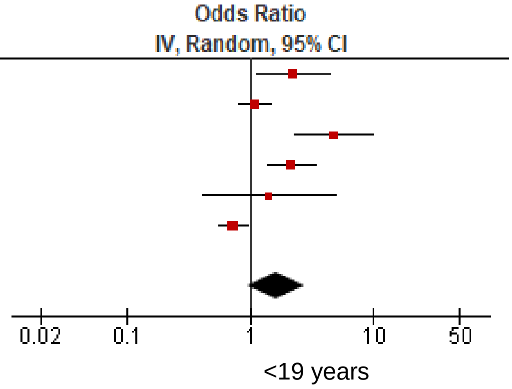

Figure 3. Forest plot of the relationship between the age of pregnant women and LBW

b. Funnel plot

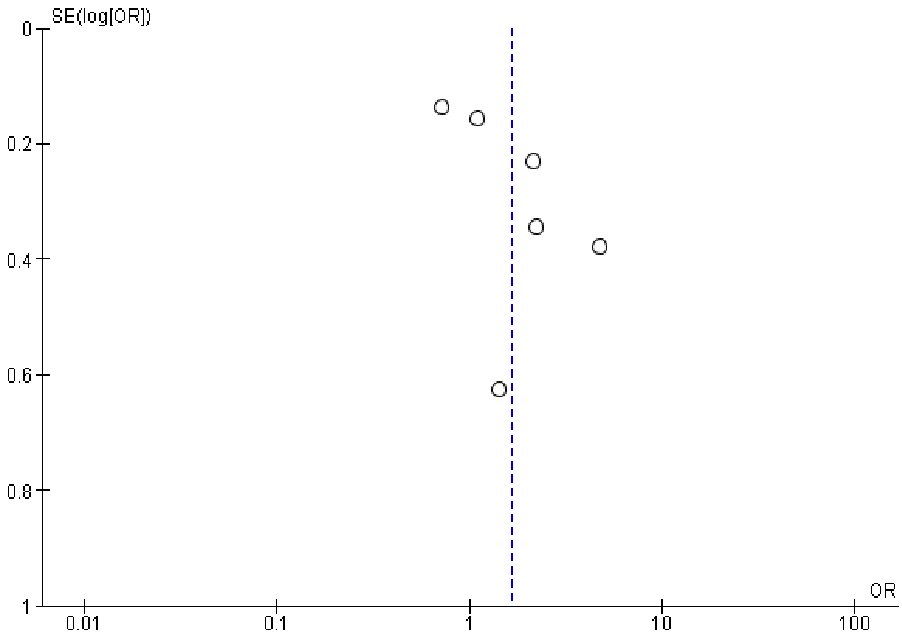

Figure 4. Funnel plot of the relationship between the age of pregnant women and LBW

3. Relationship between maternal age during pregnancy and premature birth

There were six cohort study articles included in the meta-analysis of the effect of maternal age at pregnancies on preterm birth.

The forest plot in Figure 5 shows the effect of maternal age during pregnancy on premature birth. However, statistically the effect is not significant. Mothers aged <19 years during pregnancy had a 1.41 risk of giving birth to premature babies (aOR= 1.41; 95% CI= 0.78 to 2.56; p= 0.250). Heterogeneity calculations show high results I^2 = 93% so that the calculation of the estimated magnitude chosen uses the random effect model.

Table 5. Summary of cohort articles from primary study sources with sample size (n= 55,049)

Author (Year)	Country	Sample	Population	Intervention	Comparison	Outcome
Dowle et al. (2018)	United Kingdom	4,591	Pregnant mother	Age <19 years	Age 20-34 years	Premature birth
Usynina et al. (2018)	Russia	35,110	Pregnant mother	Age <19 years	Age 20-34 years	Premature birth
Karataşlı et al. (2019)	Türkiye	12,687	Pregnant mother	Age <15 years	Age 25-30 years	Premature birth
Kassa et al. (2019)	Ethiopia	1,114	Pregnant mother	Age 15-19 years	Age 20-34 years	Premature birth
Abebe et al. (2020)	Ethiopia	618	Pregnant mother	Age <19 years	Age <27 years	Premature birth
Genc et al. (2022)	Türkiye	926	Pregnant mother	Age ≤16 years	Age 25-35 years	Premature birth

Table 6. Data on adjusted odds ratio (aOR) and 95% confidence interval (95%CI) for the effect of maternal age during pregnancy on preterm birth

Author	aOR	95% CI	
		Lower Limit	Upper Limit
Genc et al. (2022)	7.54	5.12	9.43
Usynina et al. (2018)	0.94	0.76	1.17
Karatsli et al. (2019)	0.34	0.19	0.65
Kassa et al. (2019)	1.65	1.09	2.49
Abebe et al. (2020)	2.87	1.49	5.52
Dowle et al. (2018)	1.10	0.78	1.56

Figure 6 of the funnel plot above shows that the distribution of effect estimates is quite symmetrical because the number of plots is the same between the right and left sides of the vertical line. The symmetrical funnel plot illustrates the absence of publication bias.

a. Forest plot

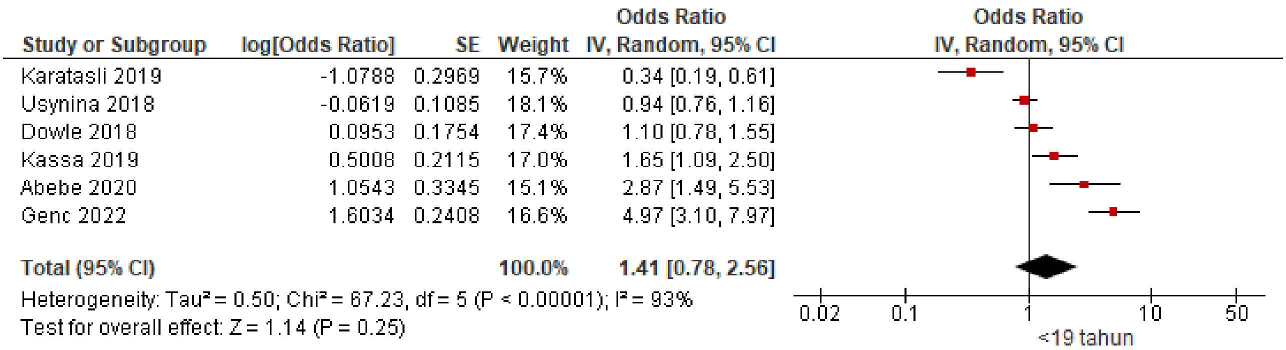

Figure 5. Forest plot of the relationship between age at pregnancy and preterm birth

b. Funnel plot

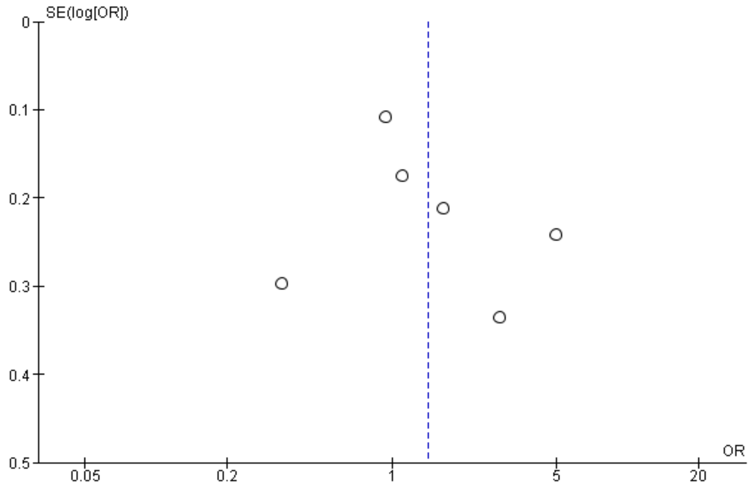

Figure 6. Funnel plot of the relationship between maternal age during pregnancy and premature birth

Table 7. Summary of cohort articles from primary study sources by sample size (n=16,554,075)

Author (Year)	Country	Sample	Population	Inter-vention	Compa-rison	Outcome
Chu et al. (2018)	Chinese Taipei	12,844	Pregnant mother	Anemia (Hb <9.9 g/dL)	Not anemic	Premature birth
Ronkainen et al. (2019)	Finlandia	18,074	Pregnant mother	Anemia (Hb<11 g/dL)	Not anemic	Premature birth
Smith et al. (2019)	Canada	444,745	Pregnant mother	Anemia (Hb= 7-8.9 g/dL)	Not anemic	Premature birth
Kabir et al. (2022)	Bangladesh	2,259	Pregnant mother	Anemia (Hb < 11 g/dL)	Not anemic	Premature birth
Shi et al. (2022)	China	16,076,153	Pregnant mother	Anemia (Hb= 7-9 g/dL)	Not anemic	Premature birth

Table 8. Data on adjusted odds ratio (OR) and 95% confidence interval (95%CI) on the effect of anemia during pregnancy with preterm birth

Author	aOR	95% CI	
		Lower Limit	Upper Limit
Chu et al. (2018)	1.31	0.98	1.77
Ronkainen et al. (2019)	1.60	1.26	2.02
Smith et al. (2019)	2.26	2.02	2.54
Kabir et al. (2022)	2.03	1.01	4.25
Shi et al. (2022)	1.18	1.17	1.19

4. Relationship between anemia during pregnancy and premature birth

There were five cohort study articles included in the meta-analysis of the effect of anemia during pregnancy on preterm birth. The forest plot in Figure 7 shows the effect of anemia on preterm birth. Statistically, the effect shows a significant relationship. Mothers who experience anemia during pregnancy have a 1.60 times risk of giving birth to premature babies (aOR= 1.60; 95% CI= 1.10 to 2.32; p= 0.010). The results of the heterogeneity calculation also show a fairly high value of I^2 = 97% so that the calculation of the estimated magnitude is chosen using the random effect model.

Figure 8 of the funnel plot above shows that the distribution of effect estimates is quite symmetrical because the number of plots is the same between the right and left sides of the vertical line. A symmetrical funnel plot indicates that there is no publication bias.

a. Forest plot

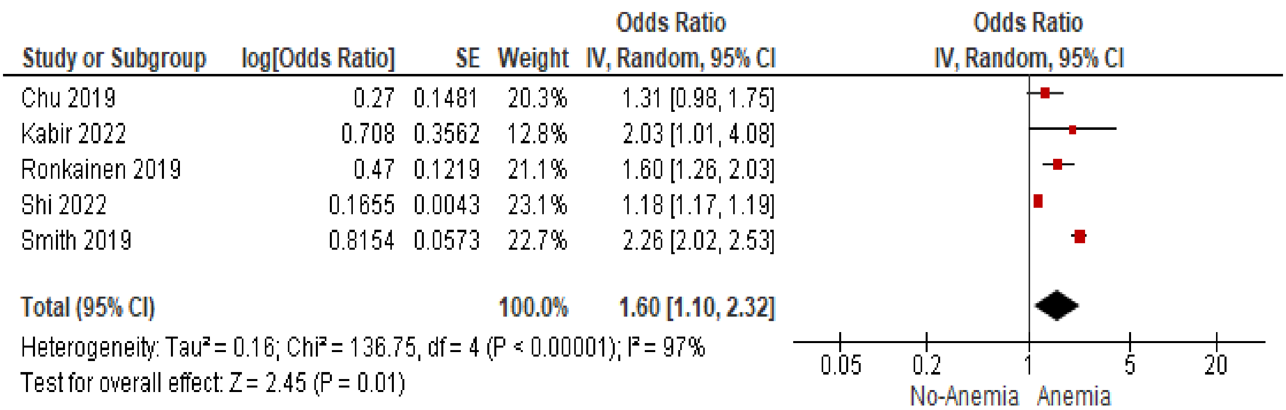

Figure 7. Forest plot of the relationship between anemia during pregnancy and preterm birth

b. Funnel plot

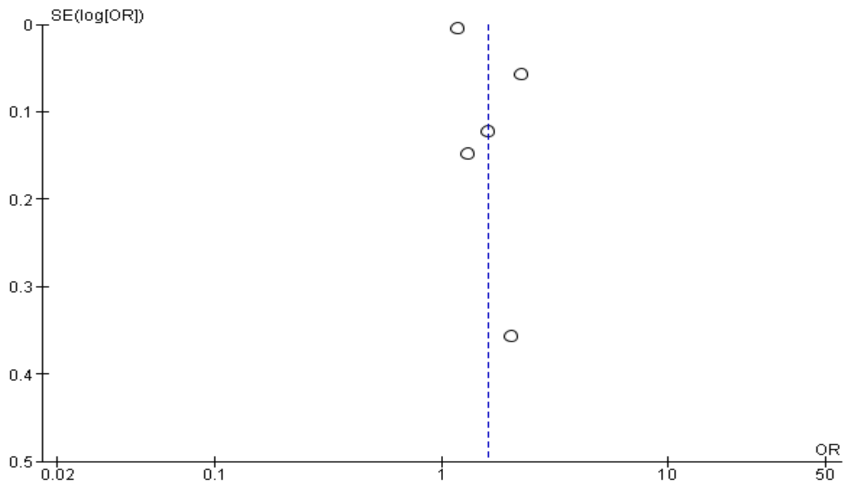

Figure 8. Funnel plot of the relationship between anemia in pregnancy and preterm birth

DISCUSSION

1. Relationship between Mother's Age at Pregnancy and Low Birth Weight

Of the six primary studies that were included in the analysis, not all carried out age classification, so that the age category of adolescents was used by WHO, namely age 10-19 years. From Figure 3 we can see that the results of the meta-analysis did not show a significant relationship between maternal age <19 years and LBW. Research by Dowle et al., (2018) and Usynina et al., (2018) has a large study sample. However, the results of the relationship analysis are not significant. Studies with large samples whose results do not show a significant relationship tend to draw an effect size close to the zero line (Retnawati et al., 2018) (Figure 3).

This included primary study takes the value of the adjusted odds ratio (aOR). This value is the result of multivariate analysis between variables that have been adjusted for confounding factors. Pregnancy in adolescence is faced with several conditions. In Australia, pregnant adolescents tend to be in families with economic, educational and health limitations. The LBW rate for teenage pregnancies is 8.9%. Imbalance in socioeconomic conditions in adolescents, exposure to cigarettes, alcohol, lack of antenatal care also have an impact on maternal and neonatal health later (Mann et al., 2020).

Nonetheless, in the study of Dowle et al., (2018) it was reported that it had limitations in conducting an analysis with possible confounding factors so that this also provided opportunities for different effect size values.

2. Relationship between maternal age during pregnancy and premature birth

The results of the RevMan 5.4 analysis in this meta-analysis stated that maternal age <19 years (adolescent pregnancy) had a 1.41 risk of giving birth to a premature baby (aOR= 1.41; 95% CI= 0.78 to 2.56; p= 0.250). Although it provides a risk for preterm birth, it is statistically less significant. The same is mentioned in another study. Research states that mothers who are still teenagers (15–19 years) are 1.20 times at risk of experiencing preterm labor (aOR= 1.20; 95% CI= 0.60 to 2.30; p=0.600) (Jeena et al., 2020). Adolescents tend to be gynecologically immature (eg, short cervix (25 mm), small uterine volume) and susceptibility to subclinical infections. Adolescent adaptation disorders with changes in pregnancy physiology that appear can trigger preterm birth (Simon et al., 2002). However, the knowledge factor, access to health facility services, especially health care during pregnancy and adequacy of nutrition, are things that are closely related between teenage pregnancies and premature births. Some of these things continued to cause inhibited intrauterine growth (Diabelková et al., 2023). Other studies also support that factor analysis of inadequate access to prenatal care by pregnant adolescents has an effect on preterm birth (Elias et al., 2022).

3. Relationship between anemia during pregnancy and premature birth

There were five cohort study articles that were included in the meta-analysis of the effect of anemia during pregnancy on premature birth with a sample size of n= 16,554,075. The results of the RevMan 5.4 analysis show that there is an effect of anemia in preterm birth. Statistically the effect is significant. Mothers who experience anemia during pregnancy have a 1.60 times risk of giving birth to premature babies (aOR= 1.60; 95% CI= 1.10 to 2.32; p= 0.010). In fact, severe anemia during pregnancy increased the risk of preterm birth 3.27 times (aOR= 3.27; 95% CI= 2.21 to 4.84). In addition, premature birth is associated with neonatal death (aOR=10.60; 95% CI= 9.28 to 12.10) (Gurung et al., 2020). In cases of anemia during pregnancy, especially due to iron deficiency, it will cause disruption in the transport of hemoglobin in the blood. As a result, the transfer of O_2 to the placenta and fetus is also hampered. In addition, it makes less functioning enzymes and cell tissues. Disruption of myometrial contractions and dysfunction of the placenta triggers premature birth (Jaleel and Khan, 2008).

AUTHOR CONTRIBUTION

Ima Kusumawati as the main researcher chose the theme, conducted a primary article search, processed the results and compiled interim results. Bhisma Murti and Eti Poncorini Pamungkasari provided a review of the results of the analysis, selected articles, gave directions in preparing the results of the analysis and discussion.

FUNDING AND SPONSHORSHIP

This study is self-funded.

CONFLICT OF INTEREST

There is no conflict of interest in this study.

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