

Meta-Analysis: The Effect of Anxiety During Pregnancy on the Risk of Premature Birth and Low Birth Weight in Infants

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ABSTRACT

Background: Pregnancy can be defined as the process of meeting spermatozoa with the ovum which is followed by attachment of the embryo to the uterine wall, in the process of pregnancy according to some or almost all women it becomes a happy process or causes anxiety due to the occurrence of many physiological and psychological changes, so that if it is not treated seriously then will have an impact on the baby such as premature birth and low birth weight. This study aims to estimate the magnitude of the effect of anxiety during pregnancy on premature birth and low birth weight with a meta-analysis study.

Subjects and Method: This was a meta-analysis and systematic review conducted with PRISMA flow diagrams. Population= pregnant women, Intervention= anxiety, Comparison= not anxious, Outcomes= premature birth and low birth weight. Search articles through journal databases include: Google Scholar, PubMed, Science Direct. The articles used in this study are articles that have been published from 2000-2021. The keywords to search for articles were as follows: "antenatal anxiety" OR "pregnancy anxiety" OR "anxiety during pregnancy" OR "anxiety disorder" OR anxiety OR pregnancy AND "Perinatal outcomes" OR "adverse birth outcome" OR "neonatal outcome" OR "low birth weight" OR "Low Birth Weight" AND "preterm birth" OR "preterm infant". The inclusion criteria were full text with a cohort study design, articles in English, analysis used multivariate with adjusted odds ratio. Eligible articles were analyzed using the Revman5 application.

Results: 10 observational studies showed that anxiety during pregnancy increased the risk of preterm delivery by 1.49 times compared with no anxiety (aOR=1.49; 95% CI 1.33 to 1.66; p<0.001). A meta-analysis of 7 observational studies showed that anxiety during pregnancy increased the risk of low birth weight by 1.55 times compared with no anxiety (aOR=1.55; 95% CI 1.26 to 1.91; p<0.001).

Conclusion: Anxiety during pregnancy increases the risk of premature birth and low birth weight.

Keywords: Pregnancy, anxiety, premature birth, low birth weight

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BACKGROUND

The process of pregnancy according to some or almost all women is a process that is happy, fun, hopeful at the same time can

cause anxiety. Happiness is because it will produce offspring as a complement and perfection of women, while the anxiety or anxiety that arises can be caused by fear of

bad things that might happen to him during pregnancy or during the delivery process.

Anxiety in pregnancy is an emotional reaction that occurs in pregnant women related to the mother's concerns about the welfare of herself and her fetus, the continuity of pregnancy, childbirth after childbirth and when it has become a mother (Dunkel Schetter and Tanner, 2012), while according to Alipour et al., (2012) depression or anxiety is the most common psychiatric disorder during pregnancy and postpartum and the symptoms can range from mild to severe.

According to Mansur (2011) nearly 80% of pregnant women experience disappointment, rejection, anxiety, anxiety, depression and moodiness and the incidence of mental disorders by 15% that occurs in primigravida mothers, namely in the first trimester, while according to Grigoriadis et al., (2018) there are increased anxiety during pregnancy with a prevalence of 15.2% for anxiety disorders and 22.9% for anxiety symptoms, Taryn et al found that the prevalence of anxiety disorders during pregnancy was 6.6%-16.8% (Tarayn et al., 2009).

Based on the data above, it reflects that the prevalence of anxiety during pregnancy is still very high and several studies explain that there is an increase in anxiety during pregnancy, so that anxiety in pregnant women if not treated seriously will have a prolonged impact on the baby such as the risk of being born with low birth weight. (LBW) and premature birth, this is because pregnant women who experience anxiety will experience changes in the hypothalamus that cause pituitary-adrenal axis activity. In the prenatal period, it is associated with increased maternal HPA axis activity, where mothers who experience high levels of anxiety during pregnancy will cause

an increase in stress hormones such as cortisol, cortisol. The release of these hormones can cause changes in immunological function and blood flow in the uterus so that there is a risk of low birth weight in infants and premature birth (Ding et al., 2014).

While low birth weight can be interpreted as a baby born with a weight of <2500 grams (Bailey, 2012), in babies who experience low birth weight are more at high risk of experiencing growth delays, infectious diseases so that indirectly babies who experience low birth weight Low birth weight has a risk of neonatal death of 60% to 80% of the total neonatal mortality, while the overall prevalence of low birth weight is 15.5% or about 20 million low birth weight babies born each year and 96.5% of them occur in developing countries (Bailey, 2012) and in addition the impact on pregnant women who experience anxiety (anxiety), which will pose a risk for premature birth. While preterm birth can be defined as the birth of a baby before 37 weeks of age, almost 7.5%-12% in various regions of the world and reaches the highest rate in developing countries giving birth to premature babies (Taheri et al., 2018).

While prematurity itself is a mortality factor associated with the incidence of mortality and morbidity in some infants who die in the first 28 days of life, on the other hand, premature babies are also susceptible to head compression due to the soft skull bones and immaturity of brain tissue, so that premature babies will experience head compressions. 5 times more risk of intracranial bleeding, in addition, babies born prematurely will also be at risk for the occurrence of respiratory distress syndrome (RDS) which causes 44% of babies to die in infants less than 1 month old (Imron et al., 2012).

Several studies have been conducted to determine the effect of anxiety during pregnancy on the incidence of low birth weight in infants and premature events, one of which is the study of Nasreen et al., (2019) which said that the results obtained in this study were the proportion of neonates with low birth weight. low with mothers experiencing anxiety during pregnancy was not different from the control group who did not experience anxiety during pregnancy, namely by the amount of 42% and 51%, respectively. However, research (Field et al., 2003) states that babies born to mothers who have anxiety will have a higher risk of giving birth to babies under 2,500 grams compared to newborns to mothers who are not anxious.

The results of the study by Pavlov et al., (2014) showed that anxiety disorders during pregnancy had a higher rate of preterm birth compared to the comparison group, namely pregnant women who did not experience anxiety disorders.

Meanwhile, Andersson et al., (2004) explained that the results of the study did not find a relationship between depression and/or anxiety on premature birth.

SUBJECTS AND METHOD

1. Study Design

The study design used in this research is a systematic review and meta-analysis, using PRISMA flow diagram guidelines. Search articles through journal databases including PubMed, Google Scholar, and Science Direct. The articles used in this study are articles that have been published from 2000-2021. The keywords to search for articles were as follows: “antenatal anxiety” OR “pregnancy anxiety” OR “anxiety during pregnancy” OR “anxiety disorder” OR anxiety OR pregnancy AND “Perinatal outcomes” OR “adverse birth outcome” OR “neonatal outcome” OR “low birth weight”

OR “Low Birth Weight” AND “preterm birth” OR “preterm infant”.

1. Inclusion Criteria

In this study, the inclusion criteria were full text articles using a cohort study design in English, the analysis used was multivariate with adjusted odds ratio. The study subjects were pregnant women. The intervention was anxiety and the outcome was preterm birth and low birth weight.

2. Exclusion Criteria

Exclusion criteria in this study included articles published before 2000, female respondents with term births and abortions, primary studies that had meta-analyses conducted and articles using other than English language.

3. Operational Definition

In formulating research problems, PICO is used. Population is pregnant women. Intervention is anxiety with comparison that is not anxious, outcomes are premature birth and low birth weight.

Anxiety is an emotion and subjective experience experienced during pregnancy which is characterized by feelings of fear that are not clear and not supported by situations caused by various responses that occur during the pregnancy process.

Premature is a baby born at the age of 22-37 weeks.

Low Birth Weight is the first baby's weight after birth which was measured during the first hour after birth with a weight of <2500 grams.

4. Instrument

An assessment of the quality of research articles is carried out using the Critical Appraisal of a Cohort Study (CEBMA, 2014)

5. Data Analysis

Articles were collected using the PRISMA diagram and analyzed using the Review Manager 5.4 application by calculating effect size and heterogeneity to determine

the combined research model and form the final result of the meta-analysis.

RESULTS

Research from primary studies related to the effect of anxiety during pregnancy on premature birth and low birth weight in pregnant women consists of 13 articles from 1

African continent (Ghana), 2 Asian studies (Israel and Bangladesh), 4 American studies (Peru and Bangladesh). three studies from the United States) and 6 studies from the European continent (Sweden, Norway, France, three studies from Germany).

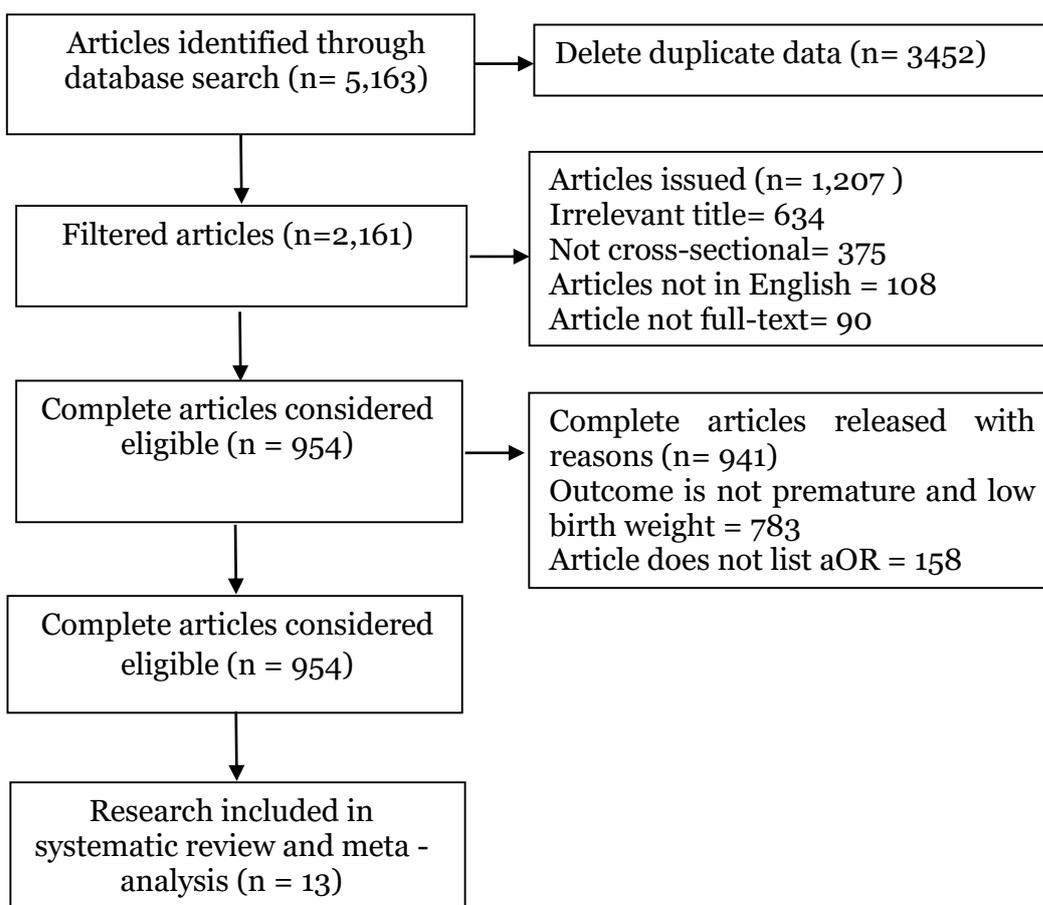


Figure 1. PRISMA flow diagram

Figure 1 shows the region of the articles taken according to the inclusion criteria. Furthermore, the researchers conducted an assessment of the quality of the articles. The results show that anxiety during pregnancy has an influence on premature birth and low birth weight. The search for articles was carried out using a database based on the PRISMA flow diagram in Figure 1 after the study quality assessment was carried out, as

many as 13 articles were divided into 2 categories according to the independent variables. Of the 13 articles, there were 3 articles, each of which included 2 interventions, so that 10 articles were obtained for premature and 7 articles for low birth weight.

Research Quality Assessment

Assessment of research quality uses a critical appraisal tool from the center for evidence based management which can be seen (table

- 1). The criteria for evaluating articles with a cohort study design are as follows:
 1. Does this study address a clearly focused problem?
 2. Is the cohort research method appropriate to answer the research question?
 3. Are there enough subjects to establish that the findings did not occur by chance?
 4. Was the cohort selection based on objective and validated criteria?
 5. Is the cohort representative of the defined population?
 6. Was the follow-up done in sufficient time?
 7. Are objective and unbiased outcome criteria used?
 8. Is the result measurement method validated?
 9. Are effect sizes practically relevant?
 10. Is there a given confidence interval?
 11. Have confounding factors been taken into account?
 12. Can the results be applied to your research?
- After assessing the quality of the study, as many as 13 articles were divided into 2 categories according to the dependent variable. Of the 13 articles, there were 3 articles, each of which included 2 interventions, so that 13 articles were included in the quantitative synthesis of meta-analysis using RevMan 5.4.

Table 1. Quality Assessment of Cohort Design Research

Primary Study	Criteria												Total
	1	2	3	4	5	6	7	8	9	10	11	12	
Anderson <i>et al.</i> (2004)	1	1	1	1	1	1	1	1	1	1	1	1	12
Berle <i>et al.</i> (2005)	1	1	1	1	1	1	1	1	1	1	1	1	12
Bindt <i>et al.</i> (2013)	1	1	1	1	1	0	1	1	1	1	1	1	12
Gelaye <i>et al.</i> (2020)	1	1	1	1	1	1	1	1	1	1	1	1	12
Nareen <i>et al.</i> (2010)	1	1	1	1	1	1	1	1	1	1	1	1	12
Huyer <i>et al.</i> (2020)	1	1	1	1	1	0	1	1	1	1	1	1	11
Ibanez <i>et al.</i> (2012)	1	1	1	1	1	1	1	1	1	1	1	1	12
Mannisto <i>et al.</i> (2010)	1	1	1	0	0	1	1	1	1	1	1	1	10
Martini <i>et al.</i> (2010)	1	1	1	1	1	1	1	1	1	1	1	1	12
Pavlov <i>et al.</i> (2014)	1	1	1	1	1	1	1	1	1	1	1	1	12
Rauchfuss and Maier (2014)	1	1	1	1	1	1	1	1	1	1	1	1	12
Xiong <i>et al.</i> (2008)	1	1	1	1	1	1	1	1	1	1	1	1	12
Yonkers <i>et al.</i> (2017)	1	1	1	0	1	1	1	1	1	1	1	1	12

1. The Effect of Anxiety on Prematurity

a. Forest Plot

The interpretation of the results of the meta-analysis process can be seen through the forest plot. From Figure 2, it can be seen that there is low heterogeneity ($I^2 = 0\%$ $p = 0.57$), so the forest plot data analysis uses a fixed effect model. Then it was found that there was an effect of anxiety on premature birth 1.49 times compared to mothers who did not experience significant anxiety (aOR= 1.49; 95% CI= 1.33 to 1.66; $p < 0.001$).

b. Funnel Plot

A funnel plot is a plot that depicts the estimated effect size of each study against an estimate of its accuracy which is usually the standard error. Figure 3 shows that there is a publication bias which is indicated by the asymmetry plots. The plot on the left of the graph appears to have a standard error between 0 and 0.8 and the plot on the right has a standard error between 0 and 0.6. Bias also occurred from the imbalance of the distance between the studies on both the right and left sides of the funnel plot.

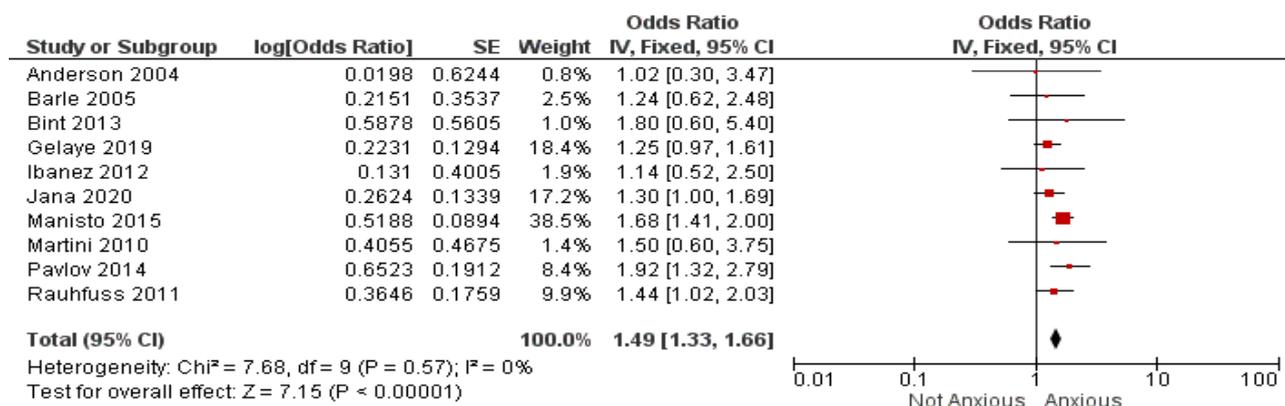


Figure 2. Forest plot of the effect of anxiety during pregnancy on preterm birth

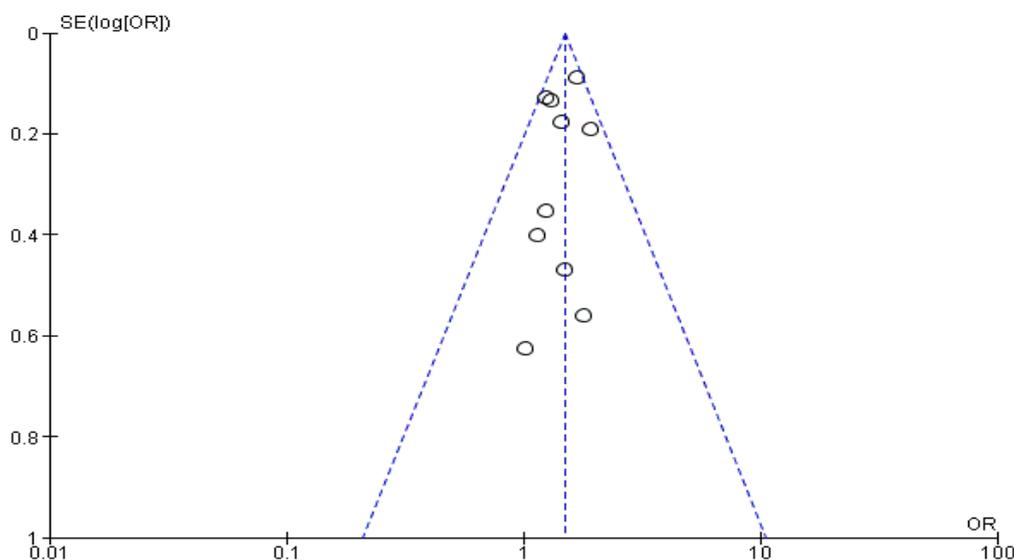


Figure 3. Funnel plot of the effect of anxiety during pregnancy on preterm birth

2. Anxiety on the Low Birth Weight

a. Forest plot

The interpretation of the results of the meta-analysis process can be seen through the forest plot. From Figure 4, it can be seen that there is low heterogeneity ($I^2=8\%$; $p=0.37$), so the forest plot data analysis uses fixed effects. Then it was found that there was an effect of anxiety during pregnancy on low birth weight, pregnant women who experienced anxiety increased low birth weight 1.55 times compared to pregnant women who

did not experience anxiety significantly (aOR= 1.55; 95% CI= 1.26 to 1.91; $p < 0.001$).

b. Funnel plot

A funnel plot is a plot that describes the estimated effect size of each study on its estimated accuracy, which is usually a standard error. Figure 5 shows that there is a publication bias which is indicated by the asymmetry of the plot on the left and the right, where there are 2 plots on the left and 4 plots on the right. The plot on the left of the graph appears to have a standard error between 0 and 0.2 and the plot on the right between 0.2 and 1.

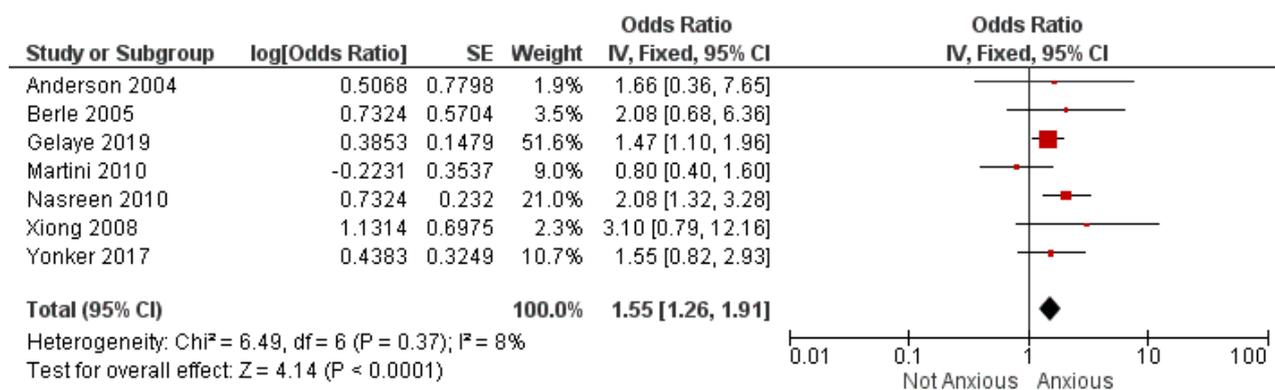


Figure 4. Forest plots the influence of anxiety during pregnancy on low birth weight

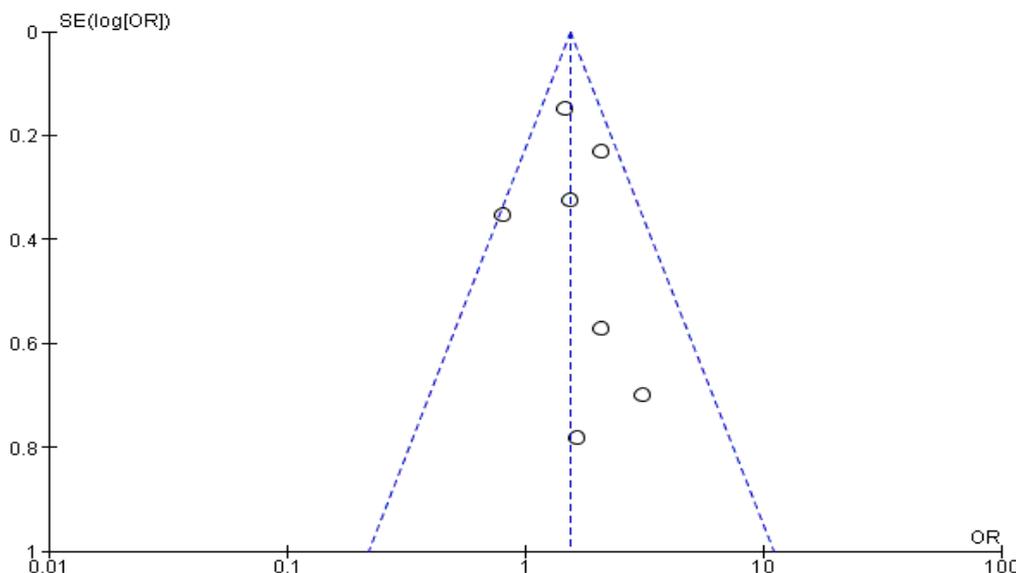


Figure 5. Funnel plots of the influence of anxiety during pregnancy on low birth weight

DISCUSSION

This systematic review and meta-analysis study raised the theme of the effect of anxiety during pregnancy on the incidence of prematurity and low birth weight in infants. The independent variable was anxiety during pregnancy and the dependent variables analyzed were premature birth and low birth weight. This intervention was designed to reduce the incidence of preterm birth and low birth weight caused by anxiety during pregnancy with an observational cohort study design. Research that discusses preterm birth

and low birth weight is considered important because premature birth and low birth weight are a problem in increasing infant mortality rates, both in developing and developed countries.

In this systematic review, there are 13 intervention studies identified worldwide from 2000 to 2020. This systematic review and meta-analysis research uses research that has controlled for confounding factors or confounding factors that can be seen from the inclusion criteria of the previous primary

studies used, namely the results of the analysis of the inclusion criteria of the previous primary study used, namely the results of multi-variate analysis in the form of adjusted odds ratio (aOR). Confounding factors themselves can be interpreted as combining the estimated relationship between exposure and disease or with exposure, so that confounding factors can affect the relationship or effect of exposure to the occurrence of the disease that is estimated by the study is not the same as the actual relationship or effect that occurs in the target population in other words the results the study is not correct (Murti, 2018).

Processing data on the relationship between anxiety during pregnancy with premature birth and low birth weight in infants using the Review Manager 5.4 application with the generic inversion of variance method. This method is a method used to analyze data in the form of level data, time to event, hazard ratio, ordinal scale, adjusted estimate and average difference or average ratio, the results of systematic reviews and meta-analysis will be presented in the form of forest. plots and funnel plots. A forest plot is a diagram that shows an overview of the information from each of the studies examined in the meta-analysis and estimates of the overall results (Murti, 2018). The forest plot also shows visually the magnitude of variation (heterogeneity) between study results. The funnel plot shows the relationship between the effect size of the study and the sample size or the standard error of the effect size of the various studies studied, the possibility of publication bias caused in the funnel plot can be seen from the asymmetry of the number of studies on the right and left sides depicted through the plot in the figure (Murti, 2018).

1. Anxiety during pregnancy on premature birth

There are 10 articles with a cohort study design as a source of meta-analysis of the

relationship between anxiety during pregnancy and prematurity. The results of the meta-analysis on the forest plot showed that pregnant women who experienced anxiety significantly increased preterm birth by 1.49 times compared to pregnant women who did not experience anxiety during pregnancy significantly (aOR= 1.49; 95% CI= 1.33 to 1.66; $p < 0.001$). In this study, there is a publication bias shown by the funnel plot with the asymmetric distribution of the plot. Publication bias on the effect of anxiety during pregnancy on premature birth is because there are studies that have a small number of samples so that the SE value is large. Anderson et al. (2004), Bint et al. (2013) and Martini et al. (2010) have SE values of SE= 0.624, SE= 0.561 and SE= 0.467 (SE values > 0.50), causing the distribution in the funnel plot to be asymmetrical which causes publication bias. These results are consistent with the theory expressed by Murti (2018) where the variables that influence the occurrence of publication bias include sample size, type of design, sponsorship, conflict of interest and prejudice about the observed relationship. The strength of this study is that it can confirm that this type of meta-analysis can provide strong evidence about the influence of anxiety during pregnancy on the incidence of preterm birth. The results of this study are supported by other studies conducted by Berle et al (2005) at Umea University Hospital and Sunderby Central Hospital, which stated that pregnant women who experience anxiety have 1.02 times the risk of premature birth compared to mothers without anxiety (aOR= 1.02; 95% CI= 0.30 to 3.4; $p = 0.050$).

Gibson-Smith et al. (2015) states that antenatal anxiety is associated with several adverse perinatal outcomes. head circumference and small gestational age significantly. According to Maryunani (2016) there are many cases of preterm labor as a result of pathogenic processes which are biochemical

mediators that have an impact on the occurrence of contractions and cervical changes, one of which is psychological stress including anxiety. Anxiety itself can be caused by stressors that arise from the environment when the body is faced with serious stressors, one part of the brain, namely the amygdala, will conduct an assessment (Stuart, 2015), the amygdala itself will stimulate other parts of the sympathetic nervous system, so that the sympathetic nerves will produce a physiological stress response, namely through the limbic-hypothalamic-pituitary-adrenal axis (LHPA), so that LHPA will produce corticotrophine releasing hormone (CRH) and glucocorticoid (GCs) hormones (Systems et al., 2018). The hormone CRH itself plays an important role in regulating the pituitary-adrenal mic, therefore mothers who experience high levels of anxiety during pregnancy will cause an increase in stress hormones such as cortisol and corticolamine. The release of the hormone cortisol can cause changes in immunological function, thereby increasing the risk of infection (Ding et al., 2014).

Vaginitis is one of the most common infections experienced by pregnant women, so that vaginitis is one of the predictors of preterm birth, as evidenced in a group of 88 primiparous pregnant women who experienced anxiety, which had a higher frequency of chorioamnionitis which had an impact on premature birth (Rauchfuss & Maier, 2011).

2. Anxiety During Pregnancy on Low Birth Weight

There are 7 research articles with cohort studies as a source of meta-analysis of the effect of anxiety during pregnancy on low birth weight in pregnant women. The results of the meta-analysis on the forest plot showed that pregnant women who experienced anxiety during pregnancy could increase low birth weight 1.55 times compared to pregnant women who did not

experience anxiety significantly (aOR= 1.55; 95% CI= 1.26 to 1.91; $p < 0.001$). In this study, there is a publication bias shown by the funnel plot with the result that the plot distribution is not symmetrical. The funnel plot shows the standard error relation of effect size from several studies studied. Publication bias on the effect of anxiety during pregnancy on low birth weight in pregnant women is because there are studies that have a small number of samples so that the SE value is large. The primary research article by Anderson et al. (2004), Berlee et al. (2005) and Xiong et al. (2008) have SE values of SE= 0.78, SE= 0.57 and SE= 0.69, namely SE values > 0.50 , causing the distribution in the funnel plot to be asymmetrical and causing publication bias.

According to Murti (2018), the variables that influence the occurrence of publication bias include sample size, type of design, sponsorship, conflict of interest and prejudice about the observed relationship. The strength of this study is that it can confirm that this type of meta-analysis can provide strong evidence about the influence of anxiety during pregnancy on the incidence of preterm birth. This meta-analysis study provides strong evidence that anxiety during pregnancy can increase births with low birth weight. This study was supported by Nasreen (2010) conducted by Bangladesh with the aim of knowing the independent effect of maternal antepartum depression and anxiety symptoms on LBW births in women in rural districts of Bangladesh. 2.08 times compared to pregnant women who did not experience significant anxiety (aOR = 2.08 ; 95% CI = 1.32 to 3.29).

A similar study explaining the effect of anxiety during pregnancy on low birth weight conducted by Yonkers et al (2017) found that pregnant women who experience anxiety have a risk of giving birth to babies with low birth weight by 1.55 times compared to those

who do not experience anxiety during pregnancy (aOR= 1.55; 95% CI= 0.82 to 2.92).

Chandra et al. (2021) in their study stated that antepartum mental disorders can increase the risk of low birth weight. Anxiety has been shown to be associated with hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, when triggered by the stressor of the HPA axis, it stimulates cortisol secretion throughout the body. Mood disturbances can lead to increased release of CRH from the placenta via the action of catecholamines and cortisol, thereby increasing permeability to gluco-corticoids.

A number of known mechanisms by which antepartum mental disorders can contribute to an increased risk of low birth weight, anxiety are evidenced by hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis. When triggered by stressors, the HPA axis will stimulate the secretion of cortisol and glucocorticoids throughout the body where glucocorticoid hormones are involved in the mobilization of energy stores (Gelaye et al., 2020). In addition, placental 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2) is another potential mechanism contributing to adverse birth outcomes. 11 β -HSD2 which catalyzes the inactivation of maternal corticosterone to inert 11-dehydrocorticosterone which serves as a physiological barrier to maternal glucocorticoids. Maternal anxiety is negatively correlated with the activity of MRNA 11 β -HSD2 in its place which suppresses placental function (Ding et al., 2014).

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AUTHORS CONTRIBUTION

Amalia Ulfah Suparno is the main researcher who chooses the topic, conducts a search for data collection in this study. Uki Retno Budihastuti and Bhisma Murti conducted

data analysis and review of research documents.

CONFLICT OF INTEREST

There is no conflict of interest in this study.

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