

The Effect of Hypertension on the Risk of Premature Birth: Meta Analysis with Binary Data

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ABSTRACT:

Hypertension in pregnancy is a condition where systolic blood pressure increases to more than 140 mmHg and diastolic more than 90 mmHg. Apart from endangering the mother, hypertension is also dangerous for the fetus. We conducted a meta-analysis of articles on the risk of premature birth in pregnant women with hypertension. The research method was carried out by searching for scientific articles in the PubMed and ScienceDirect databases to see if they contained control cases/cohorts of the influence of hypertension on premature birth with $N > 200$. From the search results, 8 eligible journals were selected, namely those containing the relevant independent variable hypertension. The results show that the risk of premature birth is influenced by pregnant women who experience hypertension = 3.971 (95% CI, 2.567; 6.144) with a random effect model because high heterogeneity was detected ($I^2 = 98.992\%$). This shows that hypertension experienced by pregnant women can increase the risk of premature birth by 4 times. Hopefully, these results can improve health policies that enable more appropriate treatment, and for pregnant women to carry out routine early examinations and maintain nutritional intake and a healthy lifestyle.

Keywords: Hypertension, premature birth, meta-analysis.

1. Introduction

Maternal Mortality Rate (MMR) is the number of maternal deaths per 1000 live births during a certain period, this is also an indicator of the success of a country's services. Many efforts have been made to reduce MMR and IMR in both developed and developing countries, such as Indonesia. However, in reality, Indonesia still has a high maternal mortality rate (MMR), namely 305 per 100,000 live births based on the results of the last Inter-Census Population Survey (Survei Penduduk Antar Sensus, SUPAS) conducted by BPS Statistics Indonesia in 2015, while the Sustainable Development Goals (SDGs) target in 2030 is 131 per 100,000 live births.

Many maternal deaths are associated with several causative factors including postpartum hemorrhage, hypertension that progresses to preeclampsia/eclampsia, sepsis, and abortion. According to Khosravi et al, hypertension in pregnancy is a state of systolic blood pressure that increases more than 140 mmHg and diastolic more than 90 mmHg [1]. In addition to endangering the mother, this hypertension is also dangerous to the fetus, namely the occurrence of inadequate placental oxygen transfer, Intrauterine Growth Restriction (IUGR), premature birth, placental abruption, stillbirth, and neonatal death. Not all mothers with preeclampsia understand and often seek help late when clinical symptoms develop into severe preeclampsia and result in the birth of a premature baby.

Premature births are still common in both at-risk and non-risk mothers. Premature birth is a birth that occurs when the gestational age is less than 37 weeks and has a high level of vulnerability because its organs have not developed perfectly so it requires intensive handling. Premature birth is the second leading cause of death in the world in children under five years old, after pneumonia. According to WHO data in 2018, Indonesia ranked 5th out of 10 countries with the largest number of premature births at 675,700 and ranked 9th out of 10 countries with the highest premature birth rate per 100 live births at 15.5%. The purpose of this study is to see the odds of premature birth caused by pregnancy with hypertension from various literatures.

2. Method

Meta-analysis is used to determine other risk factors or correct previous factors. This meta-analysis was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematics Review and Meta-Analysis) statement. Data analysis was carried out on relevant research results using Open Meta software. This analysis is to obtain an effect size calculation (odds ratio).

2.1. Qualification Criteria and Article Search

Qualification criteria were characterized earlier to a comprehensive search of the important literature. Articles were considered qualified if they met the following criteria.

1. Case-control/cohort study,
2. Research on premature birth cases,
3. Loading variable hypertension,
4. Minimum sample size of 200,
5. Year of publication of the article after 2017.

The article search was conducted electronically using databases from Pubmed and ScienceDirect. The search keywords used were "hypertension, premature birth, odds ratio" and open access articles were selected. No language restrictions were imposed. Authors independently assessed the titles and abstracts of retrieved articles. Full text was retrieved only for potentially qualified articles and evaluated against the inclusion criteria. Demographic and pattern characteristics and result data were extracted from qualified articles and organized. Journal titles, author names, and institutions were concealed to avoid duplication.

2.2. Meta-analysis with Binary Data

The most common meta-analysis is binary data where the number of successes is considered in a sequence of independent studies each of which succeeds with probability p [2]. The purpose of the meta-analysis is to combine treatment effect or effect size (ES) estimates across similar studies. If the estimated treatment effect or effect size is not given, but there are more respondents than the total number of treatments and controls, the effect size for each study should be calculated, and the effects combined to assess consistency across studies and calculate a summary effect.

Effect Size

Effect size is a value that reflects the magnitude of the treatment effect or in general the strength of the correlation between two variables. Effect size can describe the relationship between two variables [3]. Treatment effect is denoted δ to match the notation in [2]. Then the hypothesis is:

$$H_0: \delta = 0 \text{ vs } H_1: \delta > 0 \quad (1)$$

1. Fixed Effect Model

Fixed effect model assumes that all factors give the same effect size across all studies. This model can be written:

$$\hat{\delta}_i = \delta + \epsilon_i, \delta_i \sim N(\delta, \hat{\sigma}_i^2) \quad (2)$$

2. Random Effect Model

The random effects model assumes the effect size $\hat{\delta}_{iR}$ of each study i is the estimation of the effect size δ_{iR} and the variance σ_i^2 , and subsequently δ_{iR} of all K studies follow the distribution $N(\delta, \tau^2)$. Random effect model can be written:

$$\hat{\delta}_i = \delta + v_i + \epsilon_i, v_i \sim N(0, \tau^2), \hat{\delta}_{iR} \sim N(\delta, \hat{\sigma}_i^2 + \tau^2) \quad (3)$$

Analysis with Odds-Ratio

Odds ratio (OR) associated with an event is defined as the ratio of the odds of the event in one study group to odds of events in other study groups [3].

Table 1: Binary Table 2x2

	<i>Event</i>	<i>Non-event</i>	<i>Total event</i>
Experimental	A_i	C_i	n_1
Control	B_i	D_i	n_2

Odds ratio is used in many statistical analysis methods, especially in logistic regression, used as a measure of effect size in analyzing categorical data in the form of a 2x table (Table 1) including meta-analysis of binary data. To estimate normal distribution in using odds ratio, it is common to convert odds ratio into log scale.

$$\log OR = \ln(OR), \quad OR = \frac{AD}{BC} = \frac{\hat{p}_E / (1 - \hat{p}_E)}{\hat{p}_C / (1 - \hat{p}_C)} \quad (4)$$

$$\text{The variance of logOR become: } \text{Var}(\log OR) = \frac{1}{A} + \frac{1}{B} + \frac{1}{C} + \frac{1}{D} \quad (5)$$

$$\text{The standard error is } SE_{\log OR} = \sqrt{\text{Var}_{\log OR}} \quad (6)$$

Then transformed back to the original form of odds ratio:

$$OR = \exp(\log OR) \quad (7)$$

$$\text{Lower limit: } LL_{OR} = \exp(LL_{\log OR}) \quad (8)$$

$$\text{Upper limit: } UL_{RR} = \exp(UL_{\log OR}) \quad (9)$$

Heterogeneity

Heterogeneity i is defined as the difference in research characteristics used by several studies. Hypothesis testing for the heterogeneity test is given as follows.

$$H_0: \tau^2 = 0 (\theta_1 = \theta_2 = \dots = \theta_i = \theta) \text{ vs}$$

$$H_1: \tau^2 \neq 0 (\text{at least there is one } \theta_i \neq \theta, i = 1, 2, \dots)$$

We used DerSimonian and Laird's test statistic, which said that H_0 will be rejected if the value of Q is greater than $\chi^2_{(k-1, \alpha)}$. It means the variance of the population effect size is heterogeneous, or the population effect size is not the same in all studies. This test is used to determine the variance of the effect size, if the variance is heterogeneous, it is better to use the random effect method [3].

The result obtained from the meta-analysis is a forest plot with the combined value of the odds ratio and fixed effect or random effect of each study. The combined odds ratio value will show the purpose of this study, which is to find out how big the risk factors of the variables that have been studied. Meta-analysis which includes the calculation of odds ratio, effect size, summary effect, and heterogeneity was conducted using OpenMeta [Analyst] software.

2.3. Research Variable

Premature Birth

According to the WHO, premature birth is characterized as a baby born alive before gestation is complete, which is 37 weeks. The category of premature birth based on gestational period are extreme premature (< 28 weeks), very premature (28 - 32 weeks), and moderate to late premature (32 -37 weeks). The cause of premature birth is various. Most cases occur spontaneously, but several of them are caused by early induction of giving birth or caesarean birth, either for medical or non-medical reasons. Regular causes of premature birth are multiple pregnancies, infections, and chronic conditions such as diabetes and high blood pressure. But, on some cases, often no cause is identified.

Hypertension

According to Khosravi et al, hypertension in pregnancy is a state of systolic blood pressure that increases more than 140 mmHg and diastolic more than 90 mmHg. This hypertension is divided into four groups, (1) gestational hypertension, namely the state of maternal blood pressure 140/90 mmHg or more in pregnancy 20 weeks and above, (2) chronic hypertension, namely hypertension that already exists before pregnancy or occurs before 20 weeks of pregnancy, (3) preeclampsia / eclampsia, namely conditions of increasing blood pressure accompanied by edema and proteinuria, (4) preeclampsia accompanied by chronic hypertension [1]. In addition to endangering the mother, hypertension is also dangerous to the fetus in the womb, namely the occurrence of inadequate placental oxygen transfer, intrauterine growth restriction (IUGR), premature birth, placental abruption, stillbirth, and neonatal death.

2.4. Research Hypothesis

The following is the hypothesis for *effect size*:

$H_0 : \delta = 0$ (population effect size has a significant effect on the observed effect size)

$H_1 : \delta > 0$ (population effect size does not significantly affect the observed effect size)

The following is the hypothesis for heterogeneity:

$H_0 : \tau^2 = 0 (\theta_1 = \theta_2 = \dots = \theta_{10} = \theta)$ (homogeneous variance)

$H_1 : \tau^2 \neq 0$ (minimal ada satu $\theta_i \neq \theta, i = 1, 2, \dots, 10$) (heterogeneous variance)

2.5. Sensitivity Analysis

This research collects previous journals by sorting out studies that are deemed lacking in methodological quality, questionable feasibility studies, or results. The results of this research will be accurate if this process does not provide significantly different outcomes than the original analysis.

3. Hasil Dan Pembahasan

3.1. Search Process

The process of searching for study materials can be seen in Figure 1.

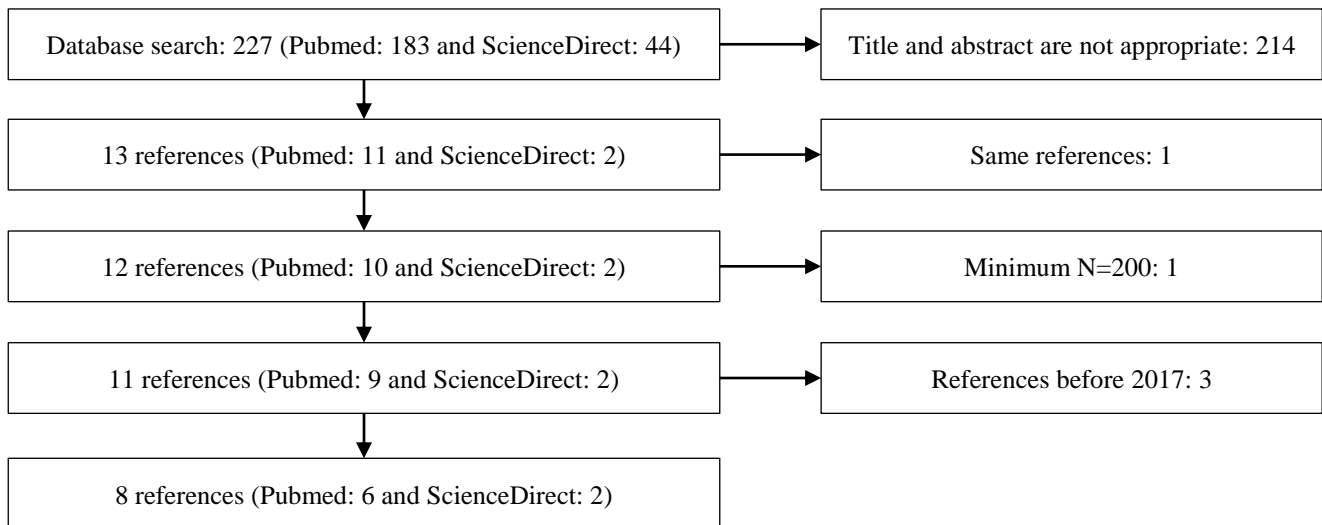


Figure 1: Article Search Process Flowchart

Based on the keyword search, 227 references were obtained in both databases, 183 references from Pubmed and 44 references from ScienceDirect. Then, there were 214 references with titles and abstracts that did not match the research topic, leaving 13 references. There was 1 reference that was the same from both databases so that the number of references that could be used was 11 references. From the inclusion criteria given, there were 4 references that did not meet the criteria of $N = 200$ or publication year after 2017, so the total references used in

this study were 8 references, 6 from Pubmed and 2 from ScienceDirect. The following is a summary of the articles used.

Table 2: Summary of Hypertension-influenced Premature Birth Studies

Researcher	Year of Publication	Study Design	Location	Premature Birth		Normal Birth	
				Hypertension	Control	Hypertension	Control
Jiang et al. [4]	2018	Case control	China	161	1008	36	1281
Yang et al. [5]	2018	Cohort	Taiwan	6460	5455	22553	110597
Vieira et al.[6]	2018	Case kontrol	Brazil	32	38	39	168
Stern et al.[7]	2020	Cohort	United States	2283	8683	14755	141242
Rohlfing et al.[8]	2020	Case control	California	88	323	20	437
Mekuriyaw et al.[9]	2020	Case control	Ethiopia	35	100	32	238
Wakeyo et al.[10]	2020	Case kontrol	Southern Ethiopia	16	44	20	160
Gejo et al.[11]	2021	Case control	Southern Ethiopia	16	55	9	133

3.2. Effect of Hypertension on Premature Birth

Effect size was obtained based on information from 8 previous studies. Effect size reflects the size of the impact of hypertension on premature birth. Based on Table 3, there are 8 studies that produce a positive effect size, which means that from these 8 studies, the tendency of premature birth increases for pregnant women who have hypertension.

Table 3: Effect Size and Combined Estimation with Fixed Effect Meta Analysis

Researcher	Effect size	Lower limit of 95% confidence interval	Upper limit of 95% confidence interval
Jiang et al. [4]	5.683	3.923	8.233
Yang et al. [5]	5.807	5.586	6.037
Vieira et al.[6]	3.628	2.020	6.513
Stern et al.[7]	2.517	2.396	2.644
Rohlfing et al.[8]	5.953	3.588	9.877
Mekuriyaw et al.[9]	2.603	1.527	4.437
Wakeyo et al.[10]	2.909	1.392	6.080
Gejo et al.[11]	4.299	1.792	10.313

After obtaining the effect size from these studies, meta-analysis modeling can then be carried out. First, using a fixed effect model assumes that there is one true fixed effect size underlying the analysis and assumes that differences in observed effects are due to sampling error [3]. The hypothesis testing for the combined effect estimate's significance of the fixed effect model is as follows.

$H_0 : \delta = 0$ (the population effect size has a significant effect)

$H_1 : \delta > 0$ (the population effect size does not significantly affect the observed effect size)

Based on the test results, the combined effect estimate is 4.215 (4.090;4.344) with $p - value < 0.001$ which is smaller than $\alpha = 0.05$. Thus, we reject H_0 which means that the combined effect of the fixed effect model has a significant effect on the observed effect size. Furthermore, heterogeneity testing needs to be done to determine the variance of the research characteristics used. The test hypothesis used is as follows.

$H_0 : \tau^2 = 0(\theta_1 = \theta_2 = \dots = \theta_{10} = \theta)$ vs

$H_1 : \tau^2 \neq 0$ (at least there is one $\theta_i \neq \theta, i = 1, 2, \dots, 10$)

Based on the results of heterogeneity testing, the statistic $Q = 694.324$ with $p - value < 0.001$, thus we reject H_0 because the $p - value < \alpha$. It can be concluded that the variance is not homogeneous. In addition, it is obtained information that the index (I^2) shows high heterogeneity 98.992, which means that 98.992% of the total variance is not homogeneous.

The variability of the observed effect size can be attributed to the heterogeneity among the effect size populations. Since the variance is heterogeneous and the index (I^2) indicates high heterogeneity, the random effect model is more appropriate. The hypothesis testing for the pooled effect estimate's significance of the random effect model is as follows.

$H_0 : \delta = 0$ (the population effect size of the random effect model has a significant effect on the observed effect size)

$H_1 : \delta > 0$ (the population effect size of the random effect model does not significantly affect the observed effect size)

Based on the test results, the combined effect estimate is 3.971 (2.567;6.144) with $p - value < 0.001$ which is smaller than $\alpha = 0.05$. thus, we reject H_0 which means that the combined effect of the random effect model has a significant effect on the observed effect size. The random effect model can be written as $\hat{y}_i = 3.971 + v_i + \epsilon_i$.

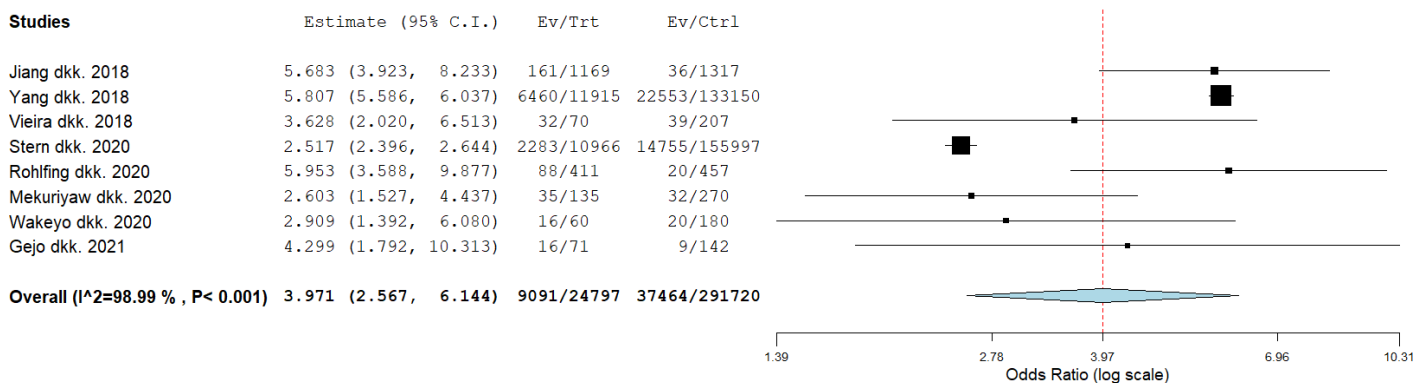


Figure 2: Forest Plot of Random Effect Model

Meta analysis can be visualized in the form of a forest plot in Figure 2. The weight given to each effect size is more balanced from study to study than in the fixed effect model. In random effect model, it is assumed that the effect size population variance around the combined effect, so the effect size population of the 8 studies ranged from 2.567 to 6.144 with an estimated combined effect of 2.795. From the 8 studies used, it shows that pregnant women who experience hypertension are at risk of giving birth to premature babies 3.971 times higher than mothers who do not experience hypertension.

4. Conclusion

Based on the results of a meta-analysis with binary data using a random effect model, it was concluded that hypertension in pregnant women is four times more at risk of premature birth than pregnant women who do not have hypertension. It is hoped that these results can improve health policies that allow more appropriate

treatment. For pregnant women to routinely conduct early examinations to avoid pregnancy complications, as well as maintain nutritional intake and a healthy lifestyle.

5. References

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