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Hypertension in Pregnancy: A Nested Case-Control Study

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Abstract

Hypertension during pregnancy is the leading cause of maternal and neonatal morbidity and mortality. In Indonesia, 30 % of deaths are caused by hypertension. This study was conducted to analyze the risk factors for hypertension in pregnancy in mothers with high pregnancy risk. A nested case-control study design was employed, with data sourced from secondary records of obstetric medical documents from Gondosari Health Centre, Kudus Regency, Central Java Province, Indonesia, for the years 2021, 2022, and 2023. The number of hypertension cases was 46, and the number of controls was 92. The technique for collecting case data was based on reviewing the medical records of mothers with hypertension. In contrast, control data was taken by random sampling from mothers with high risk but who did not have hypertension. Statistical analysis used the chi-square (bivariate) and logistic regression (multivariate) tests. The study's results stated that significant factors for hypertension in pregnancy were gestational age of 20 weeks, obesity, and primigravida with p 0.037, p 0.044, and p 0.010. Pregnant women > 20 weeks have a risk of 2.267 times to experience pregnancy hypertension, obesity has a risk of 4.288 times to experience hypertension in pregnancy, and non-primigravida status is at a higher risk of hypertension in pregnancy than primigravida mothers by 0.252 times. Mothers who have these three factors together have a probability of 80.79% of experiencing hypertension during pregnancy. This study concluded that gestational age > 20 weeks, obesity, and non-primigravida were related to the risk of hypertension in pregnancy at the study site; mothers who had gestational conditions > 20 weeks, obesity, and non-primigravida had the highest likelihood of developing hypertension in pregnancy

Introduction

Hypertension during pregnancy is the leading cause in the world (WHO, 2023). Hypertension during pregnancy results in the deaths of 70,000 women each year, including half a million births and neonatal deaths, the majority of which occur in developing countries (WHO, 2023). According to the World Health Organization, hypertension disorders during pregnancy cause 14.5% of maternal deaths in Southeast Asia (Say *et al*., 2014). In Indonesia, 30% of the deaths are caused by hypertension (Kemenkes, 2021). Hypertension during pregnancy (HDP) is classified into three types. First, chronic hypertension occurs 20 weeks before pregnancy. Hypertension in pregnancy

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occurs after 20 weeks of pregnancy, and pre-eclampsia occurs after 20 weeks of pregnancy, accompanied by signs of proteinuria, thrombocytopenia, increased transaminase levels, renal insufficiency, pulmonary edema, or new-onset headache (Khadegi & Bello, 2021; Narkhede & Karnad, 2024). According to the available evidence, hypertension during pregnancy is related to blood type O, multiple pregnancies (Jilo *et al*., 2024), primary, having previous HDP, family history of hypertension, low level of maternal education (Meazaw *et al*., 2020), older gestational age, family history of Diabetes Mellitus (DM), Body Mass Index (BMI) > 25, alcohol consumption, lack of counseling nutrient consumption during antenatal, lack of fruit consumption, and vegetable consumption (Tesfa *et al*., 2020).

HDP is one of the conditions for women with high-risk pregnancies (Jordan & Murphy, 2009; Kipnis *et al*., 2022), and is associated with obstetric complications in the form of intrauterine growth retardation, prematurity, and intrauterine death (Regitz-Zagrosek *et al*., 2018; Wilson *et al*., 2024), stroke and ischemic heart disease (Ray *et al*., 2005; Sheehy *et al*., 2023), chronic kidney failure (Watanabe *et al*., 2020), and cognitive decline (Mielke *et al*., 2023). Complications that occur due to hypertension during pregnancy are usually found late, which happens due to inadequate health care-seeking behavior (Syairaji *et al*., 2024; Suparji *et al*., 2024). Therefore, early discovery through early detection solves the high pregnancy risk (Tjandraprawira & Ghozali, 2019). Early detection behaviors correlated with increased knowledge, finding that mothers who had a good understanding of pregnancy red flags were 6.657 times more likely to be worried about risky pregnancies earlier than those who did not understand them (Mardiyanti *et al*., 2019). It was also found that women who understood the danger signs of pregnancy were 3.470 times more likely to visit antenatal services (Belayhun *et al*., 2021). This proves that pregnant women have a sense of caution about the danger signs that cause maternal death.

In 2023, the Maternal Mortality Rate in Indonesia was recorded at 305/100,000 live births. And in 2024, the Indonesian government made the Maternal Mortality Rate (MMR) the third "Major Project" of national development, with an MMR target of 183/100,000 live births. Towards the Sustainable Development Goals (SDGs) target in 2030, efforts continue to be made nationally. Although Indonesia is expected to achieve more than the SDGs target, reaching the MMR target of below 70 per 100,000 live births takes hard work (Syairaji *et al*., 2024). Indonesia must make several efforts to reduce MMR. An increased understanding of pregnancy danger indicators is needed to help women become more aware of potential threats and to seek medical help immediately. Therefore, efforts are required to find more appropriate risk factors to help increase public awareness in recognizing the risks of pregnancy and childbirth hazards in Indonesia. The findings of high-risk pregnancies can be known through early detection and appropriate predictors, so that women can detect high-risk pregnancies early on their own through community case studies that have a high-risk incidence rate. Indonesia has the 4th largest population and birth rate in the world, located between the United States and Australia, and has 17,508 islands. Java is one of the provinces on the island of Java, with the 3rd highest population density in Indonesia. Kudus Regency is one of 29 districts in Central Java with a high population density of 2,014 people per square kilometer (BPS, 2023). Therefore, this study aims to analyze the determinants of hypertension during pregnancy among pregnant women who have a high risk of pregnancy in the community primary services (Gondosari Health Center).

Method

The research design employed is a nested case-control study, a type of research where case and control data are collected from the cohort population over time (Saefurrohim *et al*., 2022). The place of this research is at the Gondosari Health Center, which is the health center with the highest cases of high risk of pregnancy in the Kudus Regency area in 2021, 2022, and 2023 respectively in 2021 (24.93%), 2022 (29.59%), and 2023 (41.07%) (DDK Kudus, 2021), (DDK Kudus, 2022), (DDK Kudus, 2023). The data used in this study were secondary data collected retrospectively from a database of obstetric

service documents, specifically the Monitoring of the Maternal and Child Health Local Area (PWS KIA) of the Gondosari Health Center, Kudus Regency, Central Java, Indonesia, in 2021, 2022, and 2023.

The population of this study was 1119 high-risk pregnant women at the Gondosari Health Centre in 2021, 2022, and 2023. The number of cases in this study is pregnant women who experience hypertension in pregnancy, a total of 46 respondents. While the control in this study is pregnant women who have a high risk of pregnancy but do not experience hypertension in pregnancy which amounted to 1073 respondents, control data collection was carried out by random sampling technique based on numbers using the excel format "RANBETWEEN", several ratios of 1: 2 = 46: 92 respondents were taken, the control was also matched based on commute time for health, gestational age, age of pregnant women, interval between pregnancies, number of children, pregnant status, nutritional status, the history of SC, anemia status, history of abortion and status of diabetes. Selection of a 1:2 ratio based on considerations, Susan Lewallen, MD (1998) (Lewallen, 1998), which states control of more than two for each case in the case control study, statistically does not provide meaningful information. Figure 1 shows the flow of research respondents.

The independent variables in this study include; travel time to health services (categorized to be > 30 minutes and 30 minutes); pregnancy (categorized into > 20 weeks and < 20 weeks); age of pregnant women (categorized by age < 20 years >35 and ages 20 – 34); interval between pregnancies, (categorized < 2 years and > 2 years); number of children (categorized into ≥4 and <4); gravidity (categorized into primigravida and non-primigravida); nutritional status (categorized as obesity and non-obese); the history of Section Caesaria (SC) (categorized as having a history of SC and not having a history of SC); anemia status (categorized as anemia and non-anemia); the history of abortion (categorized as having a history of abortion and not having a history of abortion); Diabetes Mellitus status (categorized as DM and non-DM); the bound variables in this study are hypertension in pregnancy (categorized as hypertension in pregnancy and non-hypertension in pregnancy). The data was analyzed using bivariate analysis with chi-square or Fisher, p-value<0.05. and multivariate with logistic regression on variables that meet the p-value <0.25 criteria. Based on the result of the logistic regression, the regression equation can be formulated as follows: y (hypertension in pregnancy) = - 0.838 (gestational age > 20 weeks) + 1.456 (Nutritional status of obesity) + -1.402 (gravidities primigravida). The above equation can be used to calculate the probability of hypertension in pregnancy using the formula:

$$p = \frac{1}{1 + \exp(-(y))}$$

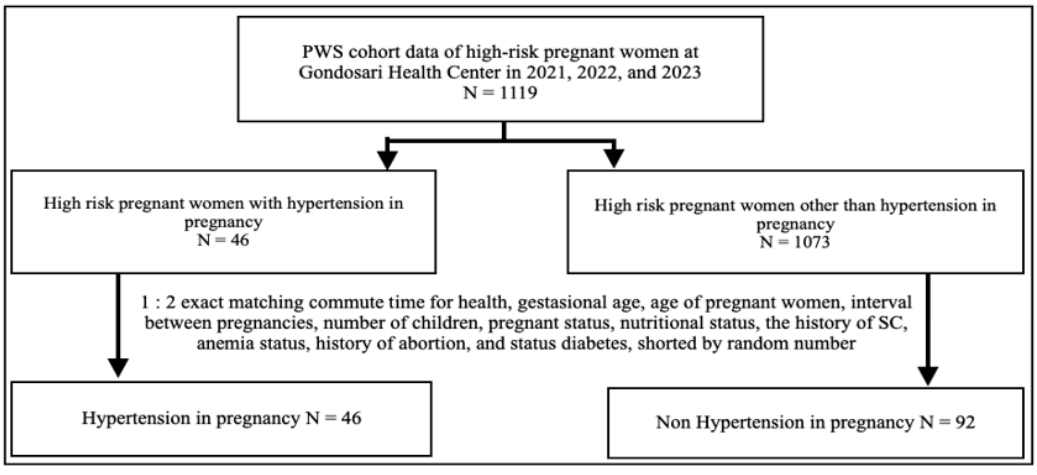

FIGURE 1. Flow Chart Sampling Process

Result and Discussion

The characteristics of respondents of those at risk and those not at risk of hypertension in pregnancy are presented in Table 1. Hypertension cases of 33.33%, Commute time for health> 30 minutes 11.59%, Gestational age > 20 weeks 34.78%, Age of pregnant women <21 year and >35 year 31.88%, Interval between pregnancies < 24 months 9.42%, Number of children ≥4 person 14.49%, Pregnant status; primigravida 25.36%, Nutritional status; obesity 7.25%, The history of Section Caesaria (SC); having history of SC 11.59%, Anemia status; anemia 8.70%, History of abortion; having history of SC 11.59%, Diabetes Mellitus (DM) 4.35%. The results of bivariate analysis are also shown in Table 1, where the significant variables for HDP are gestational age and gravida status with hypertension (p<0.05), with an unadjusted odds ratio at gestational age 2.327 (95% CI 1.115 – 4.854) and Gravida Status 0.252 (95% CI 0.90 – 0.703). Multivariate analysis was carried out on candidate variables with a p < of 0.25, and the results of the study are shown in Table 2, gestational age variables, nutritional status and gravidity were significant to HDP with a p value of < 0.05, the most dominant risk factor for HDP occurred in the nutritional status variable (obesity) with an OR of 4,288 (95% CI 1,038 - 17,711). There is also a protective factor in HDP, gravidity (non-primigravida), with an OR of 0.246 (0.084 - 0.717). Results of probability calculation (Table 3) showed some probability of HDP occurring: First, mothers with >20 weeks of gestation, obesity, and primigravida are likely to experience HDP of 50.87%.

TABLE 1. Characteristics of the Study Population and Case-Control Bivariate Analysis Results

Variable	Total Population		Hypertension (Case)		No Hypertension (Control)		P-value
	N=136	%	N=46	%	N=92	%	
Hypertension							
yes	46	33.33					
no	92	66.67					
Commute time for health							
>30 minutes	16	11.59	6	13.0	10	10.87	0.925
≤30 minutes	122	88.41	40	87.0	82	89.13	
Gestational age							
>20 weeks	48	34.78	22	47.8	26	28.26	0.037*
<20 weeks	90	65.22	24	52.2	66	71.74	
Age of pregnant women							
<21 year and >35 year	44	31.88	16	34.8	28	30.43	0.747
21-35 years	94	68.12	30	65.2	64	69.57	
Interval between pregnancies							
< 24 months	13	9.42	5	10.9	8	8.70	0.760
≥ 24 months	125	90.58	41	89.1	84	91.30	
Number of children							
≥4 person	20	14.49	7	15.2	13	14.13	1.000
<4 person	118	85.51	39	84.8	79	85.87	
Pregnant status							
Primigravida	35	25.36	5	10.9	30	32.61	0.010*
Non primigravida	103	74.64	41	89.1	62	67.39	
Nutritional status							
Obesity	10	7.25	6	13.0	4	4.35	0.084
Non obese	128	92.75	40	87.0	88	95.65	

Variable	Total Population		Hypertension (Case)		No Hypertension (Control)		P-value
	N=136	%	N=46	%	N=92	%	
The history of Section Caesaria (SC)							
Having a history of SC	16	11.59	7	15.2	9	9.78	0.511
Not having a history of SC	122	88.41	39	84.8	83	90.22	
Anemia status							
Anemia	12	8.70	1	2.2	11	11.96	0.061
Not anemia	126	91.30	45	97.8	81	88.04	
History of abortion							
Have had an abortion	19	13.77	7	15.2	12	13.04	0.930
Never had an abortion	119	86.23	39	84.8	80	86.96	
Diabetes Mellitus (DM)							
DM	6	4.35	2	4.3	4	4.35	1.000
Non-DM	132	95.65	44	95.7	88	95.65	

*p<0,05; considered statistically significant.

TABLE 2. Multivariate Analysis of Hypertension During Pregnancy Results

Variable	P-value	95% CI		
		AOR	Lower Bound	Upper Bound
Gestational age	0.037*	2.267	1.051	4.889
Nutritional status	0.044*	4.288	1.038	17.711
Pregnant status	0.010*	0.246	0.084	0.717
Constan	0.002	0.433		

Abbreviations: AOR, Adjusted Odds Ratio; CI, Confidence Interval
*p<0,05; considered statistically significant

TABLE 3. Result of Probability Calculation in Several Scenarios of Hypertension During Pregnancy (HDP) (N = 138)

SR	GA	NS	*G*	*y*	*(-)y*	*exp (-y)*	*1+exp (-y)*	*p*	*HDP Probability (%)*
A	1	1	1	0.035	-0.035	0.965605	1.965605	0.509	50.87
B	1	1	0	1.437	-1.437	0.23764	1.23764	0.808	80.79
C	1	0	0	-0.019	0.019	1.019182	2.019182	0.495	49.52
D	0	0	0	-0.838	0.838	2.311739	3.311739	0.302	30.19
E	1	0	1	-1.421	1.421	4.14126	5.14126	0.195	19.45
F	0	1	1	-0.784	0.784	2.190216	3,190216	0.313	31.34
G	0	0	1	-2.24	2.24	9.393331	10.39333	0.096	9.62
H	0	1	0	0.618	-0.618	0.539021	1.539021	0.650	64.97

Abbreviations: SR, Scenario respondents; GA, Gestational age; NS, Nutritional status; G, Gravidity
Gestational age: 1 = > 20 weeks, 0 = ≤ 20 weeks; Nutritional status: 1 = obesity, 0 = non obese; Gravidity: 1 = primigravida, 0 = non primigravida; *p<0,05; considered statistically significant

The findings of this study showed that maternal factors such as time to health services, maternal age, birth distance, number of children, parity, cesarean history, anemia, abortion history, and diabetes status do not show a significant relationship with HDP, only the variables of gestational age, nutritional status and gravidity have significance and are predictors of HDP (Table 2). The gestational age variable > 20 weeks in this study was significant

with HDP p value 0.019 OR 2.267 (95% CI 1.051 - 4.889), which means that in this study, mothers with a gestational age > 20 weeks were 2,267 times more likely to experience HDP than mothers with a gestational age of 20 weeks. Gestational age is the number of days or weeks from the first day of the last normal menstrual period in women with regular menstrual cycles (Marc & Vangeenderhuysen, 2015). Sibai (2002) states that during normal pregnancy, there is an increase in metabolism, increasing cardiac output of 30-50%, accompanied by a decrease in systemic vascular resistance and an increase in plasma volume. Khedagi & Bello (2021) explained that in the second trimester of pregnancy (14 to 27 weeks) there is excessive sympathetic activity after 20 weeks of pregnancy, this condition is related to the risk of gestational hypertension or preeclampsia, due to a decrease in systemic vascular resistance, relaxin decreases to intermediate values after the circulation of the uterocente is formed, so that the absorption of vascular resistance becomes low. In addition, arterial pressure reaches the nadir during the second trimester, while cardiac output increases to 45% above the start at 24 weeks. Pregnancy hypertension occurs in mothers with a gestational age of 19 – 23 weeks, based on research by Gibbone *et al* (2021), caused by functional changes in the heart that then progress to preeclampsia in the following weeks. A previous study corroborates these findings in 1345 pregnancies with a gestation age of 24 weeks in which respondents were identified as having early or advanced preeclampsia; the results of the study found an increase in left ventricular mass and a higher diastolic functional index compared to those whose pregnancies were uncomplicated (Valensise *et al*., 2008). The findings of this study are inconsistent with previous studies in Southern Ethiopia that did not find a relationship between gestational age and hypertension in pregnancy (Jilo *et al*., 2024), but consistent with research Mwanri *et al* (2015) in Tanzania which declared a gestational age > 20 weeks significant with hypertension in pregnancy with an OR of 1,10 (95% CI 1,02 - 1,20). Another finding that causes gestational hypertension in pregnant women > 20 weeks is the existence of predictors in the form of plasma levels of SERPINC1, SERPINA5, CFHR5, clusterin, CK18, and HRG in the plasma of pregnant women who experience gestational hypertension after gestational age > 20 weeks, where these plasma levels are not found in pregnant women without hypertension (Zhou *et al*., 2024).

The obesity variable in this study is at risk of experiencing an increase in HDP. A study by Ali *et al*. (2020) showed that the majority of housewives in Central Java are either pre-obese or obese, with overweight individuals following in number. Previous studies showed that due to the excess adipose tissue owned by obese women, this tissue is rich in pro-inflammatory cytokines and complementary proteins. Systemic inflammation during pregnancy due to excess adiposity impacts the development of the placenta, thus giving rise to antiangiogenic factors. This condition explains why obesity contributes to the pathogenesis of HDP (Schiavone *et al*., 2024). Another study in Soppeng, South Sulawesi, also showed a significant relationship between nutritional status and the incidence of hypertension with p-value<0.05 (Maria *et al*., 2023). The results of this study are that obesity contributes to an increase in HDP with a p value of 0.044 OR 4.288 (95% CI 1.038 – 17.711). This means that obese mothers have a total of 4,288 times the risk of experiencing HDP compared to non-obese mothers. The results of this study are in line with previous research which stated that obesity is at risk for HDP by OR=3.77 (95% CI 3.45 – 4.13) (Sun *et al*., 2024), research in China and Sweden also stated obesity as a risk factor for HDP with OR 5.12 dan 3,49 (Yang *et al*., 2021).

The status of gravida primigravida in this study is a variable that contributes to an increase in the risk of HDP p value 0,010 OR 0,246 (95% CI 0.084 – 0.717), OR<1 is defined as a protective risk factor, which means that mothers with non-primigravida are more at risk of developing hypertension in pregnancy than mothers with primigravida. Previous research that is not in line with this study, namely a study at Abbotabad Hospital on 134 patients with gestational hypertension, found that hypertension in pregnancy is more experienced by primigravida mothers

by 76% with a gestational age of > 20 weeks compared to non-primigravida mothers (Faiza *et al*., 2023). Also, the findings of another study stated that primigravida mothers were more at risk of developing HDP compared to mothers with non-primigravida status (Meazaw *et al*., 2020; Zhou *et al*., 2024; Hinkosa *et al*., 2020). The study, which is in line with the findings of this study, is a study in Ghana of 500 pregnant women, found that mothers with multigravida are more at risk of developing HDP with OR 4,53 (95% CI 1,42–14,42) compared to mothers with primigravida (Boachie-Ansah *et al*., 2023). A study that corroborates the occurrence of HDP in non-primaries is the result of a survey in eight health facilities in seven Nigerian states, which found that about 61.2% of hypertension disorders do not resolve after childbirth (Ishaku *et al*., 2021). This can be interpreted that when hypertension does not heal in the first pregnancy, it can lead to chronic hypertension in the subsequent pregnancy, thus increasing the cumulative burden on the mother and multigravida.

Table 3 showed that mothers with a gestational age of> 20 weeks, obese but not primigravida, are likely to experience HDP of 80.79%. Mothers with a gestational age of > 20 weeks, who are not obese and who are not primigravida, are likely to experience HDP of 49.52%. Mothers with a gestational age of 20 weeks, not obese, and not primigravida are likely to experience HDP of 30.19%. Mothers with a gestational age of > 20 weeks, who are not obese and primigravida, are likely to experience HDP of 19.45%. Mothers with 20 weeks of gestation, obesity, and primigravida are likely to experience HDP of 31.34 %. Mothers with a gestational age of 20 weeks, not obese, and primigravida are likely to experience HDP of 9.62%. Mothers with a gestational age of 20 weeks, obesity, and non-primigravida are likely to experience HDP of 64.97%. The strength of our study was the use of a cohort with a period of 3 years in the highest high-risk group in the population. We also matched the hypertension group in pregnancy and the control group at a ratio of 1:2 to commute time for health, gestational age, age of pregnant women, interval between pregnancies, number of children, pregnant status, nutritional status, the history of SC, anemia status, history of abortion, and status of diabetes in at-risk groups. This is done to evaluate whether the findings are consistent in individuals with different characteristics. The limitation of this study is that the data used, namely secondary data, misses some variables that are relevant to socio-demographic factors, such as maternal education level, maternal height, maternal smoking status, religion, occupation, family history of hypertension, and antenatal care history, as well as pre-pregnancy blood pressure.

Conclusion

Women with HDP have a greater risk of morbidity and mortality than women who have normal blood pressure. Gestational age >20, obesity, and non-primigravida are risk factors for HDP, and the highest probability occurs if the mother has these three risk factors. Based on the findings of this study, recommendations that can be given are screening, counseling, and education in pre-conception care services to prevent hypertension before pregnancy, and during pregnancy, strengthening antenatal care services with counselling and treatment of complications from the beginning of pregnancy.

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