EVALUATION OF THE ANTIHYPERTENSIVE DRUGS IN PREECLAMPSIA PATIENTS TO CLINICAL OUTCOMES AT RSUD SEKARWANGI ON 2021 PERIOD

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ABSTRACT

Preeclampsia is a pregnancy complication with several symptoms, such as hypertension, proteinuria, and edema. Such symptoms occur in pregnant women after the gestational age reaches 20 weeks. Preeclampsia is divided into mild preeclampsia (PER) and severe preeclampsia (PEB). Antihypertensive drugs are used to lower blood pressure and proteinuria levels in patients with preeclampsia. The purpose of this study was to obtain a profile of antihypertensive drugs and monitor changes in clinical outcomes in patients with preeclampsia. This was a retrospective cross-sectional study using secondary data from the medical records of preeclampsia patients. Of the 54 patients who met the inclusion criteria with the age at which most preeclampsia was 21–35 years old, 33 (61.11%) patients and 32 (59.62%) patients had PEB. The most widely used antihypertensive drug was a combination of methyldopa and nifedipine, with 27 (50%) patients receiving combination therapy. After treatment with antihypersensitive drugs, 50 (92.60%) patients experienced a decrease in blood pressure, 45 (83.33%) patients experienced a decrease in proteinuria levels, and 45 (83.33%) patients had normal birth conditions. Antihypertensive treatment for preeclampsia patients has a relationship with a decrease in the patient's blood pressure (p-value = 0,007), but there was no relationship with a decrease in proteinuria levels (p-value = 0,660) and condition of baby birth (p-value = 0,446).

Keyword: Preeclampsia; Antihypertensive Drugs; Clinical Outcomes

INTRODUCTION

According to the WHO, one of the causes of mortality and morbidity in pregnant women is preeclampsia (PE), with the incidence of preeclampsia in developed countries being 6–7%, while in Indonesia about 3.8─5% (World Health Organization, 2020). Preeclampsia is defined as the presence of hypertension, proteinuria, or organ damage that occurs after 20 weeks of pregnancy, whereas eclampsia is defined as the development of seizures in women with preeclampsia (Phipps et al., 2019). Preeclampsia is mostly associated with more than 50.000 maternal death and more than 500,000 fetal deaths globally (Karrar and Hong, 2023).

Preeclampsia conditions may cause placental abnormalities, chronic ischemic placenta, blood vessel spasm, and decline in utero placental function, which leads to diminished nutrition supply and oxygen and impaired fetal growth (Haslan and Trisutrisno, 2022). According to the Indonesian Ministry of Health, the number of pregnant women's deaths hasincreased by 2021. From 4,627 cases in 2020 and raised to 2021, 7,389 and 1,077 cases, respectively, were caused by hypertension. The number of cases of maternal death due to hypertension during pregnancy in West Java Province was 212 and 19.68%, respectively.

Management of hypertension during pregnancy can be overcome pharmacologically and non-pharmacologically. Pharmacological management consists of administering antihypertensive drugs, while Dietary Approaches to Stop Hypertension (DASH) by performing exercise or physical activity, reducing sodium intake, avoiding smoking, alcohol,

and stress could be performed as a non-pharmacological approach. In pharmacological and non-pharmacological management, it is necessary to pay attention to the risks that can occur to the mother and baby to a minimum (Kuswadi, 2019), In research conducted by Yani (2021), regarding the evaluation of antihypertensive drugs using in preeclampsia inpatient at RSUD Prof. Dr. W. Z Johannes Kupang found that the most widely used antihypertensive drug was nifedipine, which was found in 28 (66.67%) of 42 patients.

The selection of drugs during pregnancy must consider the ratio of benefits and risks for the mother and fetus to produce safe and rational therapy with the best effectiveness, as measured by the achievement of clinical outcomes. The clinical outcome values could be predicted by the decrease in blood pressure and proteinuria levels as well as the baby's birth condition. Therefore, it is necessary to conduct research to evaluate the correlation between antihypertensive drugs and clinical outcomes in patients with preeclampsia.

RESEARCH METHODS

This was a non-experimental and descriptive study (with and without any intervention). This study was also performed retrospectively, and the data were collected in a cross-sectional manner.

The study population included 109 patients hospitalized and diagnosed with preeclampsia. The Slovin formula was used to calculate the sampling technique. The Slovin formula was used to determine the appropriate number of samples, and the sample size was determined based on the accessibility of the population. In this study, the Slovin formula was used because there was not enough information about the population.

The minimum sample used is based on the Slovin formula, as follows:

$$n = \frac{109}{1 + 109\,(0{,}12)}$$
$$= 52 \text{ sample}$$

The data used were secondary data in the form of medical records of patients with preeclampsia who met the inclusion criteria.

Inclusion Criteria :
1. Preeclampsia patients who gave birth at Sekarwangi Regional Hospital in 2021 and received antihypertensive drug therapy with the required information in their medical records.
2. Inpatient pregnant women undergoing treatment at Sekarwangi Regional Hospital for the 2021 period who were diagnosed with preeclampsia.

Exclusion Criteria :
1. Preeclampsia patients were excluded at RSUD Sekarwangi in 2021.
2. Patients with unclear, illegible, or incomplete medical records.
3. Medical records of patients with preeclampsia accompanied by other diseases, such as HIV, Covid-19, autoimmunity, diabetes mellitus, obesity, and any other disease that may interfere with the clinical outcome rather than preeclampsia itself.

Research Procedure
1. Ethical clearance process. This research was conducted under ethical clearance from RSUD Sekarwangi number 07/Tim Etik/VIII/2022.
2. Observation of the number and medical records of preeclampsia patients at Sekarwangi Regional Hospital for the period 2021.
3. Data were collected from the medical records of inpatient pregnant women who gave birth at RSUD Sekarwangi with pre-eclampsia. Data collection included diagnosis, medical treatment, blood pressure, proteinuria concentration before and after medication administration, and the baby's condition.

Selection of medical record data based on inclusion and exclusion criteria
Recording data on the data collection sheet
Documentation of the data that has been collected
Data analysis

Data Analysis
　　　Statistical analysis was performed using SPSS to analyze the research results. This analysis aimed to determine the relationships between several variables. The statistical analysis used was in accordance with the relationship test.
1. **Chi-Square Test**
   It was used to examine the correlation between the drugs used and clinical outcomes in preeclampsia patients.
2. **Paired Sample T-test Test**
   It was used to determine differences in blood pressure before and after treatment.
3. **Regresi Logistik Test**
   It was used to determine the correlation of confounding variables with the clinical outcomes of patients with preeclampsia.

RESULTS AND DISCUSSION
Primary Characteristic of Patients
　　　This study used medical record data from preeclampsia patients hospitalized at Sekarwangi Regional Hospital in 2021. Some of the primary characteristics that met the inclusion criteria were age, parity, gestational age, sex, and severity of preeclampsia. Based on age, 33 patients (61.11 %) were in the 21–35-year age group. In a study conducted by Syamsiah et al. (2022), pregnant women most often experience preeclampsia at the age of 21–35 years (54.5 %). According to Novianti (2016), the reproductive age of a woman is 20–35 years; ages <20 years and >35 years are also known as high-risk ages for experiencing complications during pregnancy, but preeclampsia could also occur at reproductive age, which can be due to genetic factors, parity, multiple pregnancies, and others.

Table I. Primary Characteristic of Preeclampsia Patient In RSUD Sekarwangi in 2021 Period

Patient Characteristic	Patient Amount (n=54)	
	Amount	Percentage
Age		
< 20 years old	3	5.56%
21─35 years old	33	61.11%
> 35 years old	18	33.33%
Parity Number		
< 3	40	74.07%
> 3	14	25.93%
Gestational Age		
Trimester II	3	5.56%
Trimester III	51	94.44%
Kind of Pregnancy		
Single	51	94.44%
Twin	3	5.56%
Severity of Preeclampsia		
Mild Preeclampsia	22	40.74%
Severe Preeclampsia	32	59.26%

　　　Based on the number of parities, 40 (74.07%) patients experienced parity with <3. In a study conducted by Radjamuda and Montolalu (2014), 109 (52.7%) pregnant women with parity <3 and 98 (47.3%) with parity >3. The 2nd and 3rd parity is the safest parity, while 1st

parity and after 3rd parity are at risk of preeclampsia. After 3rd parity there was a decline in reproductive system function (Veftisia and Khayati, 2018).

Based on gestational age, 51 (94.44 %) patients experienced preeclampsia in the third trimester of pregnancy. In a study conducted by Lestariningsih (2018), the incidence of preeclampsia was mostly experienced by pregnant women with preterm gestational age or gestational age that had reached the third trimester (65 [74.71 %] of the patients).

Based on the type of pregnancy, preeclampsia was the most common in single pregnancies, with 51 (94.44%) patients, in research conducted by Parantika et al. (2021); there were 49 (87.5%) patients with single pregnancies and 7 (12.5%) patients with twin pregnancies who experienced preeclampsia. Preeclampsia can occur in single pregnancies due to several factors, such as a previous history of hypertension, the age of the pregnant woman who is at risk, or a lack of antenatal check-ups so that preeclampsia cannot be detected early. Preeclampsia is more at risk in pregnant women carrying twins, which is related to the larger mass of the placenta and the level of placental circulation. Excessive placental tissue is unlikely to receive adequate perfusion compared with mothers who experience singleton pregnancies (Yulianti, 2019).

Based on the severity of preeclampsia, which was most commonly affected, severe preeclampsia was dominant in 32 (59.26%) patients. Compared to other studies, the number of patients with severe preeclampsia was higher, with 27 (72.97%) experiencing severe preeclampsia and 10 (27.03%) experiencing mild preeclampsia (Purwanti, 2018). Severe preeclampsia often occurs due to a lack of awareness of carrying out pregnancy checks or Antenatal Care, so that patients are not aware that they have experienced mild preeclampsia to severe preeclampsia (Yulianti, 2019).

In Table II there provides an overview of the use of antihypertensive drugs in preeclampsia patients with the aim of lowering blood pressure and preventing complications in the mother and fetus during pregnancy and delivery.

Table II. Preeclampsia Inpatient Antihypertensive Drug Use at RSUD Sekarwangi in 2021 Period

Antihypertensive Drug Types	Patients Amount (n=54)	
	Amount	Percentage
Single		
Methyldopa	24	44,45%
Nifedipine	2	3.70%
Combination		
Methyldopa, nifedipine	27	50%
Methyldopa, amlodipine	1	1,85%

From the results of the data describing the use of antihypertensive drugs in preeclampsia patients who were hospitalized at the Sekarwangi Regional Hospital for the period 2021, the most frequently used combination therapy was methyldopa and nifedipine, with 27 (50%) patients, while the single therapy most widely used was methyldopa with 24 (44.45%) patients.

In a study conducted by Purwanti et al. (2018), the most widely used combination antihypertensive drug was a combination of methyldopa and nifedipine in 22 (95.65%) patients. The combination of methyldopa and nifedipine could manage hypertension in pregnancy from mild to severe stages, and be effective in preventing the occurrence of eclampsia. Combination therapy is based on the patient's severity and is used when the blood pressure is too high, reaching more than 160/100 mmHg (Yulianti, 2019).

In this study, a Paired Sample T-test was performed to determine whether the antihypertensive treatment provided could cause changes in blood pressure, as listed in Table III. Based on this study, we found that the highest average decrease in blood pressure

resulted from the combination of methyldopa and nifedipine, with an average decrease in systolic blood pressure of 30.92 mmHg and an average decrease in diastolic blood pressure of 16.29 mmHg. When using a single antihypertensive drug, methyldopa, it was found that the average decrease in systolic blood pressure was 26.92 mmHg and the average decrease in diastolic blood pressure was 9.58 mmHg. In a study conducted by Nurmainah et al. (2021), the greatest decrease in blood pressure was observed when using antihypertensives, a combination of methyldopa, and nifedipine.

Table III. Blood Pressure Altering Before and After the Use of Antihypertensive Drug in Preeclampsia Inpatient at RSUD Sekarwangi

Antihypertensive Drugs	Amount of Patients (n=54)	Systolic Blood Pressure Average (mmHg)		Δ	P-value	Diastolic Blood Pressure Average (mmHg)		Δ	P-value
		Pre	Post			Pre	Post		
Single									
Methyldopa	24	153.75	130.83	26.92		97.91	88.33	9.58	
Nifedipine	2	145	125	20		9	90	5	
Combination									
Methyldopa, Nifedipine	27	163.70	132.78	30.92	0.00 0	104.44	88.15	16.29	0.00 0
Methyldopa, Amlodipine	1	150	130	20		100	90	10	

Notes :
Pre : Blood pressure before treatment of anti hypertensive drug
Post : Blood pressure after treatment of anti hypertensive drug

The combination of methyldopa and nifedipine is widely used, one of which is because blood pressure in preeclampsia patients is quite high. Most of the 54 patients who met the inclusion criteria were categorized as having severe preeclampsia, characterized by a blood pressure of ≥ 160/110 mmHg. Use of this antihypertensive combination has a different mechanism. This is due to increasing the efficacy or benefits that complement each other and produce a greater reduction in blood pressure than using a single antihypertensive drug (Lestariningsih, 2018). In preeclampsia patients, single or combination antihypertensive drug therapy can be administered as long as it does not cause side effects, and the option depends on the patient's initial blood pressure and the absence of complications. If a single antihypertensive drug is used at a low dose, but the reduction in the patient's blood pressure does not reach the target, the dose of the drug can be increased or another antihypertensive can be used. The side effects of drugs can usually be avoided by using low doses, either alone or in combination with antihypertensive drugs. The purpose of combination antihypertensive drugs is to accelerate the reduction of blood pressure so that complications do not occur due to high blood pressure, with doses that are safe for the mother and fetus (Queensland Government, 2015).

The Antihypertensive Drug Evaluation to Clinical Outcome in Preeclampsia Patients
In this study, we assessed the reduction in blood pressure and proteinuria levels as well as the condition of the baby at birth. Blood pressure parameters and proteinuria levels decreased if they decreased after antihypertensive treatment until discharge from the hospital. In contrast, it is stable if there is no change in blood pressure and proteinuria levels from the time the patient is admitted to the hospital until discharge from the hospital.

However, in the case of an infant birth, it could be declared normal if the baby's weight was more than 2500 grams and there was no fetal growth restriction or fetal death.

Data on blood pressure of preeclampsia patients were collected from the first time the patient came to the hospital and was hospitalized. At the time the patient was discharged from the hospital, evaluation of the use of antihypertensive drugs was carried out using the chi-square analysis test to determine the correlation between antihypertensive drugs and blood pressure in preeclampsia patients.

Table IV. The Correlation of Antihypertensive Drugs to Preeclampsia Patient Blood Pressure

Blood Pressure	Patients Amount (n=54)		
	Amount	Percentage	P-value
Decreased	50	92,60%	0,007
Constant	4	7,40%	

As shown in Table IV, there were 50 (92.60%) patients whose blood pressure decreased and 4 (7.40%) patients whose blood pressure remained constant after antihypertensive treatment. In a study conducted by Nurmainah et al. (2021), 6.45% of preeclampsia patients had normal blood pressure, 29.03% had prehypertension, 40.32% had stage 1 hypertension, and 24.19% had stage 2 hypertension. In preeclampsia, both severe and mild cases have a blood pressure reduction target of 130–150 mmHg for systolic blood pressure and 80–90 mmHg for diastolic blood pressure. The use of drugs should consider safety, effectiveness, and rationality to achieve desired therapeutic targets based on the severity of hypertension (Togarikar, 2017).

According to the chi-square test, there was no correlation between antihypertensive drugs and blood pressure in preeclampsia patients, with a p-value of 0.007 (<0.005). According to Chambali et al. (2019), the effectiveness of an antihypertensive drug in preeclampsia patients can be seen from the patient's quality of life and patient compliance in using antihypertensive drugs, as well as the success of reducing blood pressure, which can be measured and seen after administering interventional therapy. A decrease in blood pressure in preeclampsia patients can occur in systolic and diastolic BP, which plays a role in measuring blood pressure. The choice of antihypertensive type is also very influential in achieving the target of reducing blood pressure in preeclampsia patients with several conditions experienced by the patient.

Table V. The Correlation of Antihypertensive Drugs to Protein Value in Preeclampsia Patients

Proteinuria Level (Dipstick Test)	Patients Amount (n=54)		
	Amount	Percentage	P-value
Decreased	45	83,33%	0,660
Constant	9	16,67%	

As shown in Table V, there were 45 (83.33%) patients who showed a decrease in proteinuria levels and 9 (16.67%) patients who remained constant after antihypertensive treatment. Data collection on proteinuria levels of preeclampsia patients was carried out when the patient came to the hospital and was hospitalized, and when the patient was discharged from the hospital, evaluation of the use of antihypertensive drugs was conducted using the chi-square test to determine the relationship or influence on proteinuria levels in preeclampsia patients.

In a study conducted by Togakirar (2017), patients with severe preeclampsia who received methyldopa and nifedipine alone experienced improvements in proteinuria levels. The percentage of patients who experienced improvements in proteinuria after the use of methyldopa and nifedipine was 90% and 88 %, respectively (Subiastutik et al.,

2019).

From the Chi-Square test, a p-value of 0.660 or $> \alpha$ 0.05 was obtained, it can be concluded that the use of antihypertensive drugs that have been carried out has no correlation with proteinuria levels in preeclampsia patients. Data collection on the birth condition of babies from mothers with preeclampsia was carried out on babies who were born and examined by a doctor. Evaluation of the use of antihypertensive drugs was carried out using the chi-square test to determine the correlation between the use of antihypertensive drugs and the condition of the baby's birth in mothers with preeclampsia.

Table VI. **The Correlation of Antihypertensive Drugs to Baby Birth Condition**

Baby Birth Condition	Amount of Patients (n=54)		
	Amount	Percentage	P-value
IUFD	2	3,70%	
Low Birth Weight	7	12,97%	0,446
Normal	45	83,33%	

In Table VI, there were 45 (83.33%) patients with normal birth conditions, 7 (12.97%) patients with low birth weight babies, and 2 (3.70%) patients with birth conditions who had Intrauterine Fetal Death. Compared with previous research conducted by Subiastutik (2019) on the RSUD dr. Soebandi Jember January–December 2017, ot was found from total of 105 preeclampsia patients, 4 (3.81%) babies experienced IUFD.

In babies born from mothers with preeclampsia, spasm of the decidual spiral arterioles will occur, which will result in decreased blood flow to the placenta, following disruption of placental function, resulting in fetal hypoxia. If the pregnancy lasts long enough to term, there is a risk of Intrauterine Growth Restriction (IUGR) and Intrauterine Fetal Death (IUFD). Apart from preeclampsia, IUGR and IUFD can occur due to several factors, including maternal, placental, and fetal factors (Sitorus and Amalia, 2020).

Meanwhile, LBW mainly occurs in premature births, which are caused by incomplete growth of the baby's organ systems. This incident can occur due to genetic factors, lack of blood flow to the baby, or placental dysfunction, such as preeclampsia. The baby is confirmed as LBW if it has a birth weight less than 2500 grams regardless of gestation period, while birth weight is the weight of the baby weighed within one hour after birth (Suryani, 2020).

Following Chi-Square test, a p-value of 0.446 or $> \alpha$ 0.05 was obtained, it can be concluded that the use of antihypertensive drugs has no correlation on the condition of the baby's birth in preeclampsia patients.

In this study, a multiple logistic regression test was performed to determine whether confounding variables could influence the clinical outcomes of patients with preeclampsia. The confounding variables were patient age, gestational age, parity, and the type of pregnancy experienced by the patient.

Table VII. **Analysis of Confounding Variables to Clinical Outcome in Preeclampsia Inpatient**

Variable	P-value		
	Blood Pressure Reduction	Proteinuria Reduction	The Baby State
Patient age	0.593	0.874	0.988
Maternal age	0.999	0.138	0.871
Parity	0.999	0.854	0.222
Kind of Pregnancy	0.999	0.999	0.999

In

Table **VII**, the results of the multiple logistic regression test show that there is no correlation between confounding variables (patient age, maternal age, parity number, and type of pregnancy) and the clinical outcome of preeclampsia patients (p-value > 0.05). The limitation of this study is that it was conducted retrospectively, and the data were dependent on medical records. There is a possibility that some of the data were'nt recorded properly. To obtain better results, we suggest that this study should be conducted prospectively.

CONCLUSION

In this study, it was concluded that antihypertensive treatment had a correlation with the decrease in blood pressure (p = 0.007), while there was no correlation between antihypertensive treatment and decrease in proteinuria levels (p = 0.660) and the condition of the baby's birth (p = 0.446). The results of this study indicate that the use of antihypertensive medication effectively decreases blood pressure in preeclampsia patients; however, there are also many factors that could be considered, but this has not been analyzed in this study (e.g., patient compliance and rationality of the drug). On the other hand, we should consider any other additional treatment and other factors that could help decrease proteinuria levels and prevent deterioration of the baby's condition.

REFERENCES

Chambali, M. A., Meylina, L., dan Rusli, R. (2019), "Analisis Efektivitas Biaya Penggunaan Obat Antihipertensi pada Pasien Preeklampsia di RSUD Abdul Wahab Sjahranie Periode 2018", *Proceeding of Mulawarman Pharmaceuticals Conferences*, Vol. 10, hal. 32–37.

Haslan, H. dan Trisutrisno, I. (2022), "Dampak Kejadian Preeklamsia dalam Kehamilan terhadap Pertumbuhan Janin Intrauterine", *Jurnal Ilmiah Kesehatan Sandi Husada*, Vol. 11 No. 2, hal. 445–454.

Karrar, S. A. dan Hong, P. L. (2023), "Preeclampsia", *StatPearls [Internet]*, StatPearls Publishing.

Kuswadi (2019) *Penatalaksanaan Hipertensi Pada Kehamilan dan Laktasi*. Yogyakarta: RSUP Dr. Sardjito Yogyakarta.

Lestariningsih, L. (2018), "Pengaruh Usia Kehamilan terhadap Risiko Pre Eklamsi–Eklamsi pada Kehamilan", *Medika Respati: Jurnal Ilmiah Kesehatan*, Vol. 13 No. 1, hal. 37–41.

Novianti, H. (2016), "Pengaruh Usia dan Paritas terhadap Kejadian Pre Eklampsia di RSUD Sidoarjo", *Journal of Health Sciences*, Vol. 9 No. 1.

Nurmainah, N., Hadad, F.M. and Andrie, M. (2021) 'Profil Proteinuria dan Tekanan Darah pada Pasien Preeklampsia Berat yang menggunakan Antihipertensi', *Indonesian Journal of Clinical Pharmacy*, Vo. 10 No. 2, p. 79.

Parantika, R. W., Hardianto, G., Miftahussurur, M., dan Anis, W. (2021), "Relationship between Obesity, Twin-pregnancy and Previous History of Preeclampsia with Preeclampsia", *Indonesian Midwifery and Health Sciences Journal*, Airlangga University, Vol. 5 No. 3, hal. 307–316.

Phipps, E. A., Thadhani, R., Benzing, T., dan Karumanchi, S. A. (2019), "Pre-eclampsia: Pathogenesis, Novel Diagnostics, and Therapies", *Nature Reviews Nephrology*, Nature Publishing Group UK London, Vol. 15 No. 5, hal. 275–289.

Purwanti, N. U. (2018), "Profil Penggunaan Antihipertensi pada Pasien Pre-eklampsia di Rumah Sakit Umum Yarsi Pontianak Tahun 2018", *Jurnal Mahasiswa Farmasi Fakultas Kedokteran UNTAN*, Vol. 4 No. 1.

Queensland Government. (2015), "Hypertensive Disorders of Pregnancy", Queensland Clinical Guidelines.

Radjamuda, N. dan Montolalu, A. (2014), "Faktor-Faktor Risiko yang Berhubungan dengan Kejadian Hipertensi pada Ibu Hamil di Poli Klinik Obs-Gin Rumah Sakit Jiwa Prof.

Dr. VL Ratumbuysang Kota Manado", *JIDAN (Jurnal Ilmiah Bidan)*, Vol. 2 No. 1, hal. 33–40.

Sitorus, M. F. dan Amalia, L. (2020), "Hubungan antara Penggunaan Antihipertensi pada Pasien Preeklamsia terhadap Insidensi Asfiksia Neonatal dan Berat Badan Lahir Rendah di RSUP Dr. Hasan Sadikin Bandung", *Indones J Clin Pharm*, Vol. 9 No. 4, hal. 280.

Soma-Pillay, P., Nelson-Piercy, C., Tolppanen, H., dan Mebazaa, A. (2016), "Physiological Changes in Pregnancy: Review Articles", *Cardiovascular journal of Africa*, Clinics Cardive Publishing, Vol. 27 No. 2, hal. 89–94.

Subiastutik, E., Maryanti, S. A., dan Hafiyah, S. (2019), "Pengaruh Ibu Bersalin dengan Preeklamsia terhadap Kejadian Resiko Tinggi pada Bayi Baru Lahir di RSD Dr. Soebandi Jember Tahun 2017", *Jurnal Kesehatan*, Vol. 7 No. 1, hal. 5–9.

Suryani, E. (2020), *Bayi Berat Lahir Rendah dan Penatalaksanaannya*, Strada Ekspres, Blitar.

Syamsiah, S., Putri, R., dan Suciawati, A. (2022), "Faktor- Faktor yang Berhubungan dengan Kejadian Preeklamsia Berat pada Ibu Bersalin di RS Medika Dramaga Bogor", *Open Access Jakarta Journal of Health Sciences*, Vol. 1 No. 3, hal. 119–124, doi: 10.53801/oajjhs.v1i3.30.

Togarikar, S. M. (2017), "Efficacy of Methyldopa versus Nifedipine in Mild and Severe Pregnancy Induced Hypertension", *International Journal of Reproduction, Contraception, Obstetrics and Gynecology*, Vol. 6 No. 10, hal. 4544–4549.

Veftisia, V. dan Khayati, Y. N. (2018), "Hubungan Paritas dan Pendidikan Ibu dengan Kejadian Preeklampsia di Wilayah Kabupaten Semarang", *Siklus: Journal Research Midwifery Politeknik Tegal*, Vol. 7 No. 2, hal. 336–339.

World Health Organization. (2020), "Maternal Mortality the Sustainable Development Goals and the Global Strategy for Womens, Childrens and Adolescents Health".

Yani, Y. A. (2021), "Evaluasi Penggunaan Obat Antihipertensi Pasien Preeklampsia di Instalasi Rawat Inap RSUD Prof. Dr. WZ Johannes Kupang", *CHMK Pharmaceutical Scientific Journal*, Vol. 4 No. 1, hal. 242–248.

Yulianti. (2019), "Efektivitas Penggunaan Obat Antihipertensi pada Preeklampsia di Instalasi Rawat Inap RSUD Kajien Kabupaten Pekalongan Periode Januari─Desember tahun 2018".