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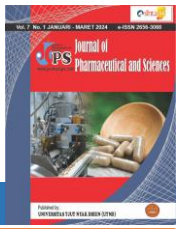

Folic Acid Supplementation in First-Trimester Pregnant Women for Preeclampsia Prevention: *A Retrospective Cohort Study*

Suplementasi Asam Folat pada Wanita Hamil Trimester Pertama untuk Pencegahan Preeklampsia: Studi Kohort Retrospektif

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Abstract

Preeclampsia is a disorder characterized by hypertension and proteinuria that manifests during gestation. Various vitamins can influence food consumption during pregnancy. Folic acid supplementation is known to reduce preeclampsia risk, yet adherence remains low among pregnant women. The objective of the research is to identify risk variables and dosage efficacy associated with folic acid utilization. This study employs an retrospective cohort study and utilizes retrospective data collection. Data was gathered from Cahaya Ibu Pharmacy Store in Makassar, encompassing a total of 164 patients. A chi-square statistical study indicated a substantial risk association between pregnant women and the onset of hypertension in comparison to nonpregnant individuals, with a p-value of 0.001. Pregnant women had twice the risk, as shown by an odds ratio of 1.9. The study of Fisher's test data indicates a correlation between patient age and hypertension condition. The findings indicate no substantial correlation between the two variables, with a p-value of 0.523. The findings indicate a substantial correlation between the mitigation of raised blood pressure risk and the consumption of folic acid. The early use of folic acid during pregnancy planning significantly diminishes the likelihood of preeclampsia. Risk factors for preeclampsia include insufficient folic acid consumption, the duration of folic acid supplementation, and the pregnancy status of individuals with a disease risk of up to 98%. Less at age 30 years old, the consumption of folic acid may reduce the risk.

Keywords: Hypertension; Folic Acid in Pregnancy; Risk Factors; Folic Acid Dosage; Pregnancy.

Abstrak

Preeclampsia adalah gangguan yang ditandai dengan hipertensi dan proteinuria yang muncul selama kehamilan. Berbagai vitamin dapat mempengaruhi konsumsi makanan selama kehamilan. Namun, banyak ibu yang mengabaikan untuk mengonsumsi suplemen asam folat untuk pencegahan. Tujuan penelitian ini adalah untuk mengidentifikasi variabel risiko dan efikasi dosis yang terkait dengan penggunaan asam folat. Studi ini menggunakan desain observasional dengan kerangka kohort dan memanfaatkan pengumpulan data retrospektif. Data dikumpulkan dari Apotek Cahaya Ibu di Makassar, mencakup total 164 pasien. Sebuah studi statistik chi-square menunjukkan adanya asosiasi risiko yang substansial antara wanita hamil dan onset hipertensi dibandingkan dengan individu yang tidak hamil, dengan nilai p sebesar 0,001. Wanita hamil memiliki resiko dua kali lipat, seperti yang ditunjukkan oleh rasio odds sebesar 1,9. Studi data uji Fisher menunjukkan adanya korelasi antara usia pasien dan kondisi hipertensi. Temuan menunjukkan tidak ada korelasi substansial antara kedua variabel tersebut, dengan nilai p sebesar 0,523. Temuan menunjukkan adanya korelasi yang signifikan antara mitigasi risiko tekanan darah tinggi dan konsumsi asam folat. Penggunaan asam folat sejak dini selama perencanaan kehamilan secara signifikan mengurangi kemungkinan

terjadinya preeklampsia. Faktor risiko untuk preeklampsia termasuk konsumsi asam folat yang tidak cukup, durasi suplementasi asam folat, dan status kehamilan individu dengan risiko penyakit hingga 98%. Kurang dari usia 30 tahun, konsumsi asam folat dapat mengurangi risiko.

Kata Kunci: HIpertensi, Asam folat pada kehamilan, Faktor resiko, Dosis asam folat, Kehamilan

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Introduction

Preeclampsia is a disorder characterized by elevated blood pressure and proteinuria that manifests during pregnancy, particularly in the third trimester [1]. Preeclampsia is a condition characterized by elevated blood pressure, typically manifesting at 20 weeks of gestation or later. This can be lethal to both the mother and the fetus if permitted to transpire prior to delivery. Various factors can affect food consumption during pregnancy [2]. Adherence to health maintenance by pregnant women is crucial during gestation [3].

Currently, the utilization of folic acid during pregnancy is significantly underutilized by certain moms. This study will examine the efficacy of folic acid for pregnant women throughout early gestation. This study aimed to enhance awareness and utilization of folic acid before or during pregnancy planning. This study is to ascertain the impact of folic acid supplementation in pregnant women and to identify the optimal dosage for their consumption [4]. Numerous prior research studies have indicated that pregnant women with preeclampsia exhibit reduced blood levels of B12 compared to their age-matched counterparts without the condition. It was discovered that the administration of folic acid did not influence the elevation of hemoglobin levels in the blood, which is pertinent to the occurrence of anemia in pregnant women. Nonetheless, no one has proposed a correlation between folic acid consumption and elevated blood pressure. The prevalence of anemia in pregnant women is a significant concern for this demographic [5–7].

Few studies in Southeast Asia have examined folic acid dosage and timing. Research on folic acid is insufficient, prompting experts to believe that this study will provide valuable supplementary data for clinicians and health practitioners alike. This study focused on the impact of folic acid supplementation on blood pressure in pregnant women during the final trimester and the optimal dosage for preventing preeclampsia. This research provides a reference for practitioners to ascertain the appropriate folic acid for pregnant women to sustain health during gestation.

Research Method Section

This study's data comprises two primary categories: patient condition characteristics and folic acid utilization by patients. The patient's condition data includes age, age at conception, blood pressure, and pregnancy status or involvement in a pregnancy program. This study employs an observational cohort design and utilizes retrospective data collection.

Materials and Analysis

The sample selection employed a consecutive sampling strategy, ensuring that every patient utilizing folic acid was included in the group. The study was performed in the Cahaya Ibu drugstore in Makassar from August 2022 to June 2023. The inclusion criteria for patients encompass the usage of folic acid, comprehensive

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drug utilization data, blood pressure measurements, and patients with a gestational age of 7 to 9 months. The exclusion criteria encompassed patients who declined participation, totaling 164 individuals.

The study encompassed the collection of instrumental data, which comprised information on prior folic acid usage, dosage, length of use, age at pregnancy or pregnancy program category, previous pregnancies, patient age, and physical examination data, including the patient's blood pressure. This study employs medical record data, patient interview consent forms, and data collection methods tailored to the study's requirements. This research was conducted with ethical approval from the Health Research Ethics Committee of Universitas Muslim Indonesia, Registration Number: UMI022210568.

The data analysis employed a statistical program utilizing chi-square analysis, Pearson correlation, and multivariate techniques, Include normality tests before parametric/non-parametric analyses. The graphical representation of data illustrates the normalcy of the relationship among blood pressure, folic acid dosage, and length of folic acid usage.

Results and Discussion

Patient's Characteristics

Several vitamins that play an important role in the process of pregnancy include iron, mecobalamin, and folic acid [8]. Folic acid is a B vitamin that plays a role in cell metabolism and DNA synthesis [9]. This research will focus on looking at the use of folic acid and the factors that influence the incidence of preeclampsia at the end of pregnancy. Chi-square statistical analysis data showed that there was a significant risk relationship between pregnancy and the incidence of increased blood pressure compared to patients who were not pregnant, with a p-value <0.001. The odds ratio of 1.9 indicates a nearly twofold increased risk. Although age >30 years was not significantly associated with hypertension in this study, genetic factors may still contribute to risk. An odds ratio of 1.9 suggests a 90% higher risk compared to the control group. The condition characteristic of patients is shown in Table 1.

Table 1. Chi-Square analysis between the patient's condition and blood pressure.

Variable		Blood Pressure		P-value	Odds Ratio
		Normal (%)	High (%)		
Patient condition	After pregnant	47	53	<0.001	1.9
	Before pregnant	90.6	9.4		
Ages	<30 years old	80.7	19.3	0.523	
	>30 years old	81.8	18.2		

a. "After pregnant" are patients consuming folic acid after entering the pregnancy period of the first trimester
b. "Before pregnant" are patients consuming before entering the pregnancy period of the first trimester

When pregnancy is associated with age, where according to the facts, patients over 30 years of age have a greater risk of preeclampsia, the results of test data analysis show a relationship between the patient's age and the condition of increased blood pressure. The result shows that there is no significant relationship between the two, with a p-value of 0.523. While age was not statistically significant in this cohort, larger studies may clarify its role in preeclampsia risk. This does not mean that it is permissible for people over 30 years of age to get pregnant and have a risk because, in this case, the genetic factor is also a special consideration, but the use of folic acid can minimize this risk as presented. There are two stages to the placental illness preeclampsia. An overabundance of anti-angiogenic factors is followed by an aberrant placentation in the first trimester, which is known as "motherhood syndrome" in late second and third pregnancies. The placenta's upregulation of hypoxia-inducible transcription factors (TFs) and the presence of a gene profile linked with hypoxia point to hypoxia as a major etiology of preeclampsia. Normal placentation results from hypoxia that follows oxygenation of the mother's bloodstream, and intermittent hypoxia and reoxygenation brought on by inadequate spiral arterial invasion might result in oxidative stress. Our findings align with prior evidence that folic acid reduces endothelial dysfunction, but further research is needed to confirm its role in placental angiogenesis. A transmembrane enzyme that locally activates atrial natriuretic peptide by zymogen modification may also have an impact on trophoblast invasion and remodeling of spiral arteries. The physiology of decidualization has a good understanding of uterine NK (uNK), which may have a role in the

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aberrant placentation seen in preeclampsia [10–13]. This was proven in the Pearson correlation test between the dose and the risk of blood pressure that might occur in patients.

Prevention Probability.

The results of the calculation of the probability of occurrence for patients who are planning a pregnancy and do not consume folic acid either in the early trimester or before pregnancy have a probability of up to 98.06% to experience an increase in blood pressure at the end of the trimester, which is certainly at risk of experiencing preeclampsia. This can be seen in the graph to find the relationship between the effect of folic acid dose (folic acid supplements available in Indonesia have strengths of <400µg, 400–1000µg, >1000µg) and duration of use (how many weeks to use) with the incidence of increased blood pressure. We can see multivariate analysis on Table 3 showing the relation of all variables. It can be seen in the graph that the use of folic acid at a dose of 1000 µg for more than 8 weeks during pregnancy planning is the optimal timing to reduce the incidence of increased blood pressure at the end of the trimester. It appears that patients who do not use or use folic acid at a dose of <1000 µg have a risk of experiencing an increase in blood pressure in late pregnancy. This can be seen from the probability of an increase in blood pressure for patients who do not consume folic acid at all, both early in pregnancy and during pregnancy planning, reaching 98%. This risk estimate may be influenced by unmeasured confounders like obesity, hypertension, and diabetes mellitus.

Table 2. Logistic Regression Multivariate Analysis.

Variabel	Coefisien	S.E	Wald	df	P Value	OR
Age patient	0.437	0.685	0.407	1	0.523	1.548
Patient type	-1.708	1.302	1.722	1	0.189	0.181
Dose	-2.471	1.769	1.951	1	0.162	0.085
Gestational age	-0.352	1.494	0.55	1	0.814	0.703
Duration of supplementation	-3.112	0.749	17.248	1	<0.001	0.045
Constant	3.277	2.364	1.922	1	0.166	26.499

Note: Patient type: 'Before pregnant' = preconception users, 'After pregnant' = first-trimester users; duration of supplementation is patients duration use folic acid before pregnancy.

Preeclampsia risk can be decreased by taking folic acid. Folic acid is an affordable supplement, making it the ideal choice for persons from moderate to poor socioeconomic backgrounds. It has been demonstrated that folic acid consumption during pregnancy decreases aberrant trophoblast invasion into the uterus in patients with preeclampsia and does not impact neonatal weight as a result. resulted in a significant decrease in the number of postnatal cases requiring NICU care. Homocysteine levels, which are connected to the risk of preeclampsia, are also thought to be reduced by folic acid. Early to mid-pregnancy impaired placental perfusion marks the start of the first stage. Generalized endothelial dysfunction then follows, which is frequent in late pregnancy. Preeclampsia develops as a result in the final trimester. Reduced homocysteine release causes endothelial dysfunction, which folic acid can restore. This suggests that folic acid is crucial for pregnant women in their first and second trimesters. While folic acid has direct mechanisms to promote placental implantation and endothelial function, it also lowers homocysteine levels, which can lessen maternal endothelial damage, which lowers the incidence of preeclampsia [14–16].

Discussion

Preeclampsia is defined by the occurrence of proteinuria [1]. A separate investigation indicated a correlation between mecobalamin deficiency during pregnancy and the occurrence of blood pressure issues [7]. The vitamin requirements of pregnant women will vary with each month during gestation. Folic acid is a vitamin that may diminish the likelihood of preeclampsia. Folic acid may diminish placental perfusion overall and typically does not manifest during the first and second trimesters. Folic acid can prevent and ameliorate endothelial dysfunction; in addition to its effect on plasma homocysteine levels, it can also inhibit the elevation of blood pressure up to the second stage. Preeclampsia remains a significant global contributor to maternal and neonatal morbidity and mortality, necessitating ongoing research into effective preventive strategies. Preliminary studies on humans and animals suggest that folic acid may have a protective effect against preeclampsia. We anticipated that folic acid supplementation during pregnancy would mitigate the risk of

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preeclampsia by various mechanisms, including fostering healthy placental growth and development in the first trimester, reducing blood homocysteine levels, and improving systemic endothelial function [6].

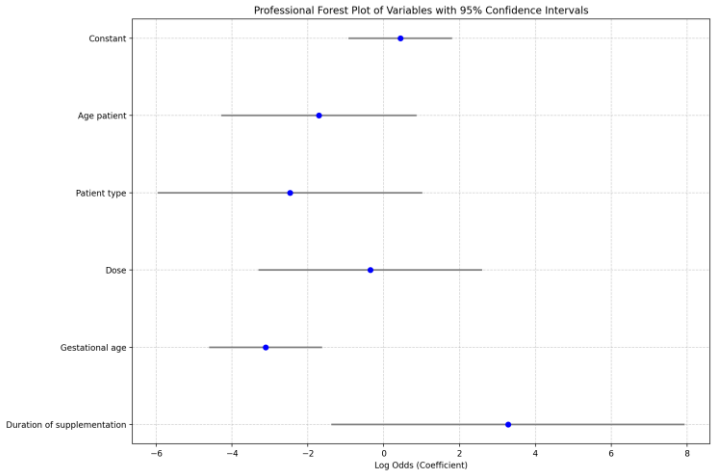

Figure 1. Forest plot for multivariate analysis test, it indicates that the effect of age on the outcome might not be statistically significant, although the point estimate suggests a negative association.

Ingesting folic acid prior to conception reduces the risk of neural tube defects (NTDs). Among other measures, authorized the fortification of white wheat flour and other enriched cereal products with folic acid to reduce the incidence of neural tube defects (NTDs). Following the implementation of fortification, the incidence of neural tube defects (NTDs) has significantly diminished, and there is virtually no indication of widespread folate shortage. Serum folate is thought to be transportable to the placenta. Despite recommendations, RBC-folate screening for women is not yet prevalent. Daly et al. suggest that RBC-folate may serve as a more robust predictor of NTD risk during the first trimester of pregnancy compared to serum folate. During the initial four weeks of supplementation, serum folate levels markedly elevated in all women; however, numerous participants, especially in the 400 g/day group, failed to achieve optimal RBC-folate levels. Fewer than 20% of women did not achieve the target red blood cell folate level after 8 weeks of receiving 800 g/day of folate. Women in both research cohorts with low baseline RBC-folate concentrations (population median) maintained lower concentrations compared to those with elevated baseline values. Lower doses must be administered over an extended duration (4–8 weeks) compared to higher doses [17].

Folic acid serves as a cofactor to maintain homocysteine levels within an acceptable range. Imbalances in blood vitamin B12 and folic acid are more significantly associated with gestational diabetes mellitus (GDM). Folic acid is an essential vitamin during pregnancy since it contributes to DNA methylation and the synthesis of proteins and nucleic acids required for cellular replication and embryonic development. A secure and effective approach that may enable pregnant women exposed to free radicals to mitigate the risk of diminished fetal growth is increased folic acid supplementation. The study's relatively low attrition rate of 2% and rigorous compliance with the intention-to-treat principle are notable advantages [18-20].

Conclusions

Consumption prior to pregnancy or during the first trimester may mitigate the chance of elevated blood pressure occurrences in the latter stages of pregnancy. The administration of folic acid during early pregnancy planning is an optimal period to diminish the occurrence of preeclampsia. Certain risk factors that precipitate preeclampsia include insufficient folic acid intake, the duration of folic acid supplementation, and the patient's gestational status, with an incidence risk reaching 98%. The risk for individuals over 30 years can be mitigated with the administration of folic acid. The optimal time to start consuming folic acid is 8 weeks before pregnancy. Early folic acid supplementation should be encouraged in prenatal care.

Conflict of Interest

All author declare no conflict of interest in this research.

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