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³Folic Acid for Pregnant Women in the First Trimester

Andi Maulana Kamri , Bayu Putra, Rachmat Kosman**Published:** N/A (see history)**DOI:** 10.7759/cureus.**Cite this article as:** Maulana Kamri A, Putra B, Kosman R (N/A) Folic Acid for Pregnant Women in the First Trimester. Cureus (): e. doi:10.7759/cureus.

⁴Abstract

Background: ⁶Pre-eclampsia is a condition of elevated blood pressure with proteinuria that occurs during pregnancy. Pre-eclampsia is a complication of elevated blood pressure and usually occurs after the 20th week of pregnancy. This can be fatal for both mother and baby if it occurs ⁷before birth. Several things can affect food intake during pregnancy ⁸. The goal of this study is to identify risk factors and effective doses of folic acid. Method: This study is an ¹¹observational study with a cohort design and retrospective data collection. ¹²Data was collected at Cahaya Ibu Pharmacy Store in Makassar from 164 patients. Result: Chi-square statistical analysis data showed a ¹³significant risk relationship between pregnant women and the development of hypertension compared with nonpregnant patients, with a p-value of 0.001. ¹⁶Her risk level for the event reaches twice, as evidenced by her odds ratio reaching 1.9 times. The results of Fisher's test data analysis show a relationship between patient age and

hypertensive status. The results show no ¹⁷significant association between the two, with a p-value of 0.523. The results show a significant association between reducing the risk of elevated blood pressure and taking folic acid. Conclusions: Using folic acid early in pregnancy planning is a great opportunity to ¹⁸reduce the incidence of pre-eclampsia. Triggering risk factors for pre-eclampsia include inadequate folic acid intake, duration of folic acid intake, and pregnancy status of patients with disease risk up to 98%. Starting at age 30, taking folic acid can reduce the risk.

²⁰Introduction

Pre-eclampsia is a condition of increased blood pressure accompanied by proteinuria that occurs during pregnancy, especially in the last trimester [1]. Preeclampsia is a complication where there is an increase in blood pressure which usually occurs at the age of 20 weeks of gestation and above. This can be fatal to the mother and also the baby ²¹if allowed to occur before birth. ²²Several things can influence food intake during pregnancy [2]. ²⁵Compliance with maintaining health use by pregnant women is essential during pregnancy [3]. ²⁷At the present time, the use of folic acid during pregnancy is very low realised by some mothers. In this study, ²⁹we will look at how effective the use of folic acid is for pregnant women in early pregnancy. This research will be a pioneer in increasing awareness and the use of folic acid at the beginning or before planning a pregnancy. This study aims to determine the effect of giving folic acid to pregnant women and to find out the ³¹best dose of folic acid for consumption by pregnant women [4].

Several previous studies have shown that pregnant women with preeclampsia ³³found lower blood levels of B12 than pregnant women of the same age but who did not have preeclampsia. Another interesting thing was found that the use of folic acid had no effect on increasing haemoglobin levels in the blood ³⁴which plays a role in the incidence of anemia in pregnant women. However, no one has suggested that there is a relationship between the use of folic acid and an increase in blood pressure. Although the incidence of anemia in pregnant women also has a special concern for pregnant women [5,6,7]. Research on folic acid is lacking, so researchers feel this study will be good additional data for clinicians and health practitioners alike. Some of the problems that became the focus of this study were the effect of folic acid administration on blood pressure in pregnant women at the end of the trimester and the best dose consumed by pregnant women to prevent preeclampsia. The benefits of this research can be used as a reference by clinicians in determining which folic acid is good for pregnant women to consume to maintain health during pregnancy.

35 Materials & Methods

A³⁶. Design Research

This research is observational with ³⁸a cohort design and retrospective data collection. The sample selection used a ³⁹purposive sampling method where every patient who used folic acid would certainly be included in the group. The research was conducted at the Cahaya Ibu pharmacy store, in the capital city of Makassar, from 1 August 2022 to 30 December 2022. This method is used because collecting data can not be for following up directly with the patient and the researcher must confirm patient vitamin history used.

B. Population

⁴¹The inclusion criteria for patients using folic acid, complete drug use data, blood pressure data, and patients with gestational age at 7 to 9 months. ⁴³Meanwhile, the exclusion criteria were patients who objected to being included in the group and a total of 164 patients. ⁴⁶Data analysis used a statistical program with a Chi-Square analysis test, Fisher's test, Pearson Correlation test and multivariate. The distribution of data on the normality of the relationship is also presented in graphical form to see the relationship between blood pressure, folic acid dose, and duration of folic acid use.

C. ⁴⁷Collecting Data

The researcher used the method of direct interviews with all patients to confirm data on vitamin history. Researchers used medical records of patients to ⁴⁹find inspection clinical asses, especially data on blood pressure. Data retrieval uses a nurse assistant⁵⁰ to check the truth. ⁵¹All data analysis uses statistical analysis to find and look for a relation.

Results

Some vitamins that play an important role in the process of pregnancy include ⁵³iron, 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 ⁵⁴at the end of pregnancy. Chi-Square statistical analysis data showed that there was a significant risk relationship between pregnant and the incidence of ⁵⁵increased

blood pressure compared to patients ⁵⁶ who were not pregnant with a p-value <0.001. The risk level of the event reaches 2 times as seen in the Odds Ratio reaching 1.9 times. The data analytic can see in Table 1:

Variable		Blood Pressure				P value	Odds Ratio
		⁵⁸ Normal		High			
		n	%	n	%		
Patient condition	⁶⁰ Pregnant	17	47	19	53	<0.001	1.9
	Not pregnant	116	90.6	12	9.4		
	Total	133	81.1	31	18.9		

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

When pregnancy is associated with age, where ⁶² according to the facts that patients over 30 years of age have a greater risk, the results of Fisher's test data analysis show a relationship between the patient's age and ⁶³ the condition of increased blood pressure. The result shows that there is no ⁶⁴ significant relationship between the two with a p-value of 0.523. ⁶⁵ 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 in particular can minimize this risk as presented in ⁶⁷ Table 2 data.

Variable		Blood Pressure				P value
		Normal		High		
		n	%	n	%	
Age	<30	88	80.7	21	19.3	0.523
	>30	45	81.8	10	18.2	
	Total	133	81.1	31	18,9	

Table 2: Fisher analysis between patient's age and blood pressure

There are two stages to the placental ⁶⁸illness pre-eclampsia. 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 aetiology 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. Corin, a transmembrane enzyme that locally activates atrial natriuretic peptide by zymogen modification, may also have an impact on trophoblast invasion and remodelling of spiral arteries. The physiology of decidualization has a good understanding of uterine NK (uNK), which may have a role in the aberrant placentation seen in pre-eclampsia. [10,11,12,13]. This was proven in the Pearson correlation test between the dose and the risk of blood pressure that might occur in patients. The results show that there is a significant relationship between reducing the ⁶⁹risk of increasing blood pressure with the consumption of folic acid at doses > 1000 µg and the use of high doses of folic acid can reduce the risk of increasing blood pressure during the late trimester of pregnancy in women ⁷⁰compared to patients who do not use folic acid or use folic acid. smaller doses of folate such as 400 µg.

The value of $r = 0.505$ shows a positive correlation analysis with very strong correlation strength besides the p-value which shows a significant meaning between the use of high doses of folic acid and an ⁷¹increase in blood pressure. This is evidence that the use of folic acid at a dose of 1000 µg has a clinical significance and positive impact in reducing the risk of pre-eclampsia. ⁷²The 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 pre-eclampsia. This can be seen in the graph to find the relationship between the effect of folic acid dose and duration of use with the incidence of increased blood pressure. We can see data in Table 3:

Variable	Blood Pressure		Pearson	P value
	Normal	High		

		n	%	n	%		
Folic acid dose	1000 µg	112	88.9	14	11.1	r = 0.505 n = 164	<0.001
	<1000 µg	20	83.3	4	16.7		
	Not use	1	7.1	13	92.9		

Table 3: Pearson correlation analysis between folic acid dose and blood pressure

It can be seen in ⁷³the graph that the use of folic acid at a dose of 1000 µg and use for more than 2 months during pregnancy planning is the golden time 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. ⁷⁴This 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%. Showed data in Table 4:

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
Time Period	-3.112	0.749	17.248	1	<0.001	0.045
Constant	3.277	2.364	1.922	1	0.166	26.499

Table 4: Logistic Regression Multivariate Analysis

Preeclampsia is characterized by the presence of proteinuria [1]. In another study, it was seen that there was a relationship between the incidence of mecobalamin deficiency during pregnancy, causing blood pressure disorders [6]. ⁷⁵The vitamin needs of pregnant women during pregnancy will significantly differ each month. Folic acid is a supplement that can reduce the risk of preeclampsia. Folic acid can

⁷⁶ reduce placental perfusion in general and usually does not occur in the first and second trimesters. Folic acid can prevent and restore endothelial dysfunction, apart from plasma homocysteine, folic acid can also prevent increased blood pressure until the second stage.

Preeclampsia continues to be a major global cause of maternal and newborn morbidity and mortality, and there is a continuous need to research efficient preventative measures. Early human and animal investigations have raised the possibility that folic acid may have a preventive effect against preeclampsia. We predicted that folic acid supplementation during pregnancy would reduce the risk of preeclampsia in a number of ways, including promoting healthy placental growth and development in the first trimester, lowering blood homocysteine levels, and enhancing systemic endothelial function [5]. Consuming folic acid in the run-up to conception lowers the chance of neural tube abnormalities (NTDs). Among others, mandated the folic acid fortification of white wheat flour and other enriched cereal products to lower the prevalence of NTDs. Since the introduction of fortification, the prevalence of NTDs has considerably decreased, and there is almost no evidence of widespread folate deficiency [7].

It is believed that serum folate can be transported to the placenta. Although it is advised, RBC-folate screening for women is not yet common. According to Daly et al., RBC-folate may be a stronger indicator of the risk of NTDs during the first trimester of pregnancy than serum folate. Within the first four weeks of supplementation, serum folate levels significantly increased in all of the women, although many of the participants (particularly in the 400 g/day group) did not reach an ideal RBC-folate level. Only <20% of women failed to reach the desired red blood cell folate level after 8 weeks when 800 g/day of folate was given. Women in both research groups with low baseline RBC-folate concentrations (population median) continued to have lower concentrations than women with higher baseline values. Low doses need to be used for a longer period of time (4-8 weeks) than higher doses [14].

It takes folic acid as a cofactor to keep homocysteine levels within a reasonable range. Unbalances in serum vitamin B12 and folic acid (folic acid/vitamin B12) are more strongly linked to ⁷⁷GDM. Folic acid is a crucial vitamin during pregnancy since it plays a role in DNA methylation and the manufacture of proteins and nucleic acids needed for cell replication and embryonic growth [15]. A safe and viable strategy that may provide pregnant women exposed to free radicals with a

way to reduce the risk of fetal growth decrease is higher-dose folic acid supplementation. The study's comparatively low attrition rate of 2% and strict adherence to the intention-to-treat principle are among its advantages [16].

Discussion

Correlation of Folic Acid with Preeclampsia

78 Pre-eclampsia risk can be decreased by taking folic acid. Folic acid is a fairly 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 pre-eclampsia 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 pre-eclampsia, 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. Pre-eclampsia develops as a result of 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, and lower the incidence of pre-eclampsia [17,18,19].

Folic Acid Mechanism

The placenta and developing foetus have rapidly dividing cells, which increases the need for folate during pregnancy. Poor nutritional status and insufficient consumption of micronutrients before and throughout pregnancy have been associated with unfavourable pregnancy outcomes. Due to its role as a methyl donor in one-carbon metabolism and its significance in DNA synthesis, folate is essential for the growth of a healthy foetus and placenta during pregnancy. Low folate intake during pregnancy can inhibit one-carbon metabolism in vivo and reduce foetal and placental growth. Folic acid supplementation is believed to aid in the prevention of preeclampsia by ensuring an adequate supply of folate necessary for cell division, angiogenesis, trophoblast invasion, and endothelial-dependent arterial relaxation during pregnancy. Furthermore, homocysteine methylation, which lowers serum homocysteine levels during pregnancy, is facilitated by folate. Women with higher serum homocysteine concentrations have

been found to have higher levels of the associated indicators, which are connected to endothelial dysfunction and oxidative stress in preeclampsia. Early in pregnancy, taking folic acid supplements offers a source of folate, which is essential for healthy placental implantation and blood supply. The reduction in maternal plasma folate levels later in pregnancy may be prevented by folic acid supplementation, ensuring that there is enough folate for the conversion of homocysteine to methionine. Folic acid dosage should be maintained after the first trimester because preeclampsia is known to be brought on by excessive plasma homocysteine levels [20,21,22]. The enzyme on which antifolates operate determines their mode of action. Even though there are many enzymes involved in the metabolism of folate, some of them stand out for their important contributions to folate's historical usage as a medication. Dihydropteroate synthase is one of the folate metabolism's most frequently studied enzymes. Despite the WHO's recommendation for a minimum dose of 400 µg, this dosage is exclusively for pregnant women to preserve their health.⁷⁹ The recommended dosage for lowering the risk of preeclampsia is 1000 µg [20,21,23].

⁸⁰ Conclusions

⁸¹ The use of high doses of folic acid such as 1000 µg can and consumption before pregnancy or in the first trimester can reduce the risk of increased blood pressure events at the end of pregnancy. Even so, the use of folic acid early in pregnancy planning is a golden time to reduce the incidence of pre-eclampsia. Some of the risk factors that trigger pre-eclampsia are the lack of consumption of folic acid, the period of the folic acid use, and also the gestational condition of the patient with an incidence risk of up to 98%. Age over 30 years the risk can be lowered with the use of folic acid.

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Author response: Cost-Effectiveness Folic Acid (B9) compared Methyltetrahydrofolate Use for Preventive Preeclampsia in Makassar, Indonesia

4 Reviewer beta: Please present the abstract into multiple sub sections

Author response: Background: Pre-eclampsia is a condition of elevated blood pressure with proteinuria that occurs during pregnancy and complication of elevated blood pressure and usually occurs after the 20th week of pregnancy. This could be fatal for mother after birth and baby if it occurs before birth. The goal of this study is to investigation risk, cost effective, and effective doses of folic acid. Method: This study is an observational study with cohort design with random simple sampling data collection. Data was collected at Cahaya Ibu Pharmacy Store in Makassar from 164 patients. Result: Chi-square statistical analysis data showed a significant risk relationship between pregnant women and the development of hypertension compared with nonpregnant patients, with a p-value of 0.001. Her risk level for the event reaches twice, as evidenced by her odds ratio reaching 6.9 times. The results cost analytic showed folic acid having equal effect for woman for reduce risk of preeclampsia than methyltetrahydrofolate. Conclusions: Using folic acid early in pregnancy

planning is a great opportunity to reduce the incidence of preeclampsia. The ICER value was obtained at \$0.293 so an increase in the cost of that amount was needed to improve the effectiveness of therapy by patients using folic acid compared to patients with Methyltetrahydrofolate therapy. That's mean Folic acid (B9) more cost effective compared than Methyltetrahydrofolate.

5 Reviewer theta: no mention of pre-eclampsia in title

Author response: I did it

6 Reviewer eta: It seems like these sentences could be merged into one. Pay attention to correctly define preeclampsia. It is not just "elevated BP with proteinuria". Also it is not a "complication" of elevated blood pressure: although preexisting hypertension is a major risk factor, preeclampsia per se has unique pathophysiology and is acknowledged as different medical condition.

Author response: Thank you, I did it

7 Reviewer eta: could be fatal for the mother after birth too.

Author response: Thank you, I did it

8 Reviewer gamma: This goal is not clearly written. Risk factor for what, and effective doses of folic acid for what.

Author response: Thank you, I have change it

9 Reviewer eta: Please be more specific about the study objectives. What exactly is under investigation? How is folic acid relevant?

Author response: Thank your suggestion , I have did

10 Reviewer theta: for what- prevention of pre-eclampsia?

Author response: For lowering risk for mother after birth and baby

11 Reviewer theta: clarify the study design

Author response: Yes, Cohort with random simple sampling

12 Reviewer gamma: what kind of data? should be mentioned.

Author response: Yes, I did

13 Reviewer eta: So, pregnant women suffer from hypertension more often than nonpregnant patients? Please define how folic acid (and/or its doses) are relevant to this conclusion.

Author response: Yes, like I explain in my paper

14 Reviewer eta: State clearly if this has to do with hypertension alone or preeclampsia.

Author response: Yes, Like my explain

15 Reviewer theta: no mention of such group

Author response: I have did and change

16 Reviewer eta: Who are you referring to?

Author response: Patient use folate

17 Reviewer eta: statistically significant

Author response: I have change

18 Reviewer eta: Is the preeclamsia percentage or the gestational hypertension percentage lower?

Author response: Preeclampsia

19 Reviewer epsilon: Introduction is all over the place. The author should properly structure and frame the introduction.

Author response: I will change

20 Reviewer beta: The introduction isn't properly framed. Consider rewriting the introduction to answer the following questions: Background, Research gap, why is this gap important to study, why is important to study now, and finally aims & objectives.

Author response:

Preeclampsia is a pregnancy disorder characterised by elevated blood pressure and proteinuria, particularly in the final trimester [1]. Preeclampsia is a condition characterised by elevated blood pressure that often manifests at or above 20 weeks of gestation. If this is allowed to happen before delivery, it might be deadly for both the mother and the child. Food consumption during pregnancy might be influenced by a number of factors [2]. It is crucial for expectant mothers to adhere to the maintenance of health use during their pregnancy [3]. Currently, very few mothers are aware that taking folic acid during pregnancy is beneficial. We will examine the efficacy of folic acid supplementation for early pregnancy in this study. This study will lead the way in raising folic acid awareness and usage before or at the start of pregnancy planning. The purpose of this study is to ascertain the impact of providing folic acid to expectant mothers and to ascertain the optimal dosage of folic acid that they should take [4].

According to a number of earlier research, pregnant women with preeclampsia than pregnant women without the condition at the same age. An intriguing finding was that folic acid supplementation had no effect on raising blood haemoglobin levels, which are a factor in the prevalence of anaemia in pregnant women. Nobody has, however, raised the possibility that taking folic acid and raising blood pressure are related. While pregnant women also have a particular concern over the occurrence of anaemia [5,6,7].

An analytical method called economic assessment is used to compare two or more methods in terms of costs and results. Cost Effectiveness Analysis is one type of example used in pharmacoeconomic research (CEA). For pharmacosocial research comparing two or more health interventions with varying degrees of efficacy, the relatively straightforward CEA method is frequently utilised. When a drug's ACER value is lower than another drug's and its ICER value indicates a rise in cost per unit of outcome, the data are analysed using CEAs (Cost Effectiveness Analyses), which are based on ACER (Average Cost Effectiveness Ratio) and ICER (Incremental Cost Efficiency Ratio). In this instance, cost effectiveness involves both cost optimisation and the lowest cost [8,9]. Some vitamins that play an important role in the process of pregnancy include iron, mecobalamin, and folic acid [10]. Folic acid is a B vitamin that plays a role in cell metabolism and DNA synthesis [11].

Therapeutic policy makers can find options that are more affordable for each clinical outcome they achieve by doing research that makes use of this comparison. The least expensive option for a given treatment goal may not always imply the most cost-effective one. The cost-effectiveness of treating patients with methyltetrahydrofolate and generic folate (B9) vitamins will then be analysed based on this study. Because there isn't much research on folic acid, the researchers believe this study will provide useful extra information for doctors and other healthcare professionals. The effect of folic acid administration on blood pressure in the final trimester of pregnancy and the optimal dosage for pregnant women to take in order to prevent preeclampsia were among the issues that became the focus of this study. Clinicians can utilise the research's benefits as a guide to determine which forms of folic acid are safe for expectant mothers to take in order to preserve their health throughout the pregnancy.

21 Reviewer theta: if allowed to is a wrong way of writing

Author response: I have repair it

22 Reviewer theta: why suddenly a jump from pre-eclampsia to food intake when it is not being assessed in the study?

Author response: I have erase this sentences

23 Reviewer theta: compliance for what?.....maintaining health use means?

Author response: I have erase

24 Reviewer theta: why suudenly a jump from pre-eclampsia to food intake when it is not being assessed in the study?

Author response: I have erase

25 Reviewer zeta: Rephrase this line. Meaning is not clear

Author response: I did it

26 Reviewer theta: meaning of sentence is not clear

Author response: I did it

27 Reviewer gamma: Please explain first what the benefit of folic acid in pregnancy. Then you can analyze how effective it is, and what the parameter of effectiveness.

Author response: I have addition cost effective and analytic blood pressure

28 Reviewer eta: What exactly do you mean by this?

Author response: I did it

29 Reviewer gamma: effective for what ? not clear

Author response: I did it

30 Reviewer theta: how effective in term of what- prevention of birth defects/pre-eclamsia/anemia/.....????

Author response: in analytic data

31 Reviewer eta: for what?

Author response: I did

32 Reviewer theta: sentences need to be written in a meaningful and comprehensible way with the correct use of grammar

Author response: I did

33 Reviewer eta: had

Author response: I did

34 Reviewer eta: you mean folic acid deficiency? please state clearly

Author response: I did it

35 Reviewer beta: Mention about the IRB approval. IRB Name, Approval number, waiver number (if waiver received)

Author response: This research have approval from committee ethical clearance Universitas Muslim Indonesia with number UMI022210568.

36 Reviewer zeta: Study design is not clear. How sample size calculation was done. Methodology is not appropriately written.

Author response: I did repair

37 Reviewer theta: clarify the research design

Author response: I did it

38 Reviewer gamma: Is it real cohort study? why don't use control group who don't take folic acid for comparison ? Without control group, it is difficult to draw conclusion about the effect of folic acid to prevent pre-eclampsia.

Author response: I did it

39 Reviewer theta: purposive sampling for cohort studies- High chances of bias are there.

Author response: I did with randomly simple sampling

40 Reviewer theta: sampling technique?

Author response: Random simple sampling

41 Reviewer zeta: Inclusion and exclusion criteria are out of my understanding!! If title mentions folic acid in first trimester then how can inclusion criteria include patients with gestational age 7 to 9 months?? Please clarify. And if outcome was assessed at the end of the pregnancy then it is not clearly mentioned in methodology..

Author response: I did repair

42 Reviewer theta: clarify the inclusion exclusion criteria

Author response: I did with patients not have complete blood pressure test

43 Reviewer gamma: The exclusion criteria is not clearly written. I don't know the meaning of the sentence.

Author response: I did

44 Reviewer eta: 164 were excluded or finally included?

Author response: Finally

45 Reviewer theta: represent in separate subsection

Author response: I did

46 Reviewer theta: purposive sampling for cohort studies- High chances of

bias are there

Author response: Yes, I have repair

47 Reviewer zeta: Consider rephrasing lines

Author response: I did, thanks

48 Reviewer kappa: Direct Interview ?please use right word.

Author response: interviews

49 Reviewer theta: meaning?

Author response: I did

50 Reviewer theta: how?

Author response: I did in paper

51 Reviewer theta: redundant line

Author response: I fix it

52 Reviewer theta: part of introduction

Author response: I fix it

53 Reviewer eta: iron is not a vitamin

Author response: I fix it

54 Reviewer eta: doesn't need to be stated

Author response: I fix

55 Reviewer eta: so, not preeclamsia

Author response: I fix it

56 Reviewer gamma: how did the authors can get the data of non-pregnant woman, while the inclusion criteria is woman with gestational age at 7 - 9 months ? I thinks it is also wrong design. If we want to see the effect of folic acid, it should be compared with the group with no folic acid, not with the non pregnant woman. The control or comparator group should be the pregnant woman without taking folic acid.

Author response: I explain in method

57 Reviewer eta: were non pregnant women included? also, i believe this is not the correct comparison (pregnant vs non pregnant) it should be pregnant + folic acid vs pregnant without folic acid

Author response: I fix, thank you for suggestion

58 Reviewer eta: define blood pressure values for normal and for high (mmHg)

Author response: I have it

59 Reviewer theta: highly biased study as pregnancy is a state that raises the risk of high BP and pre-eclampsia

Author response: I did

60 Reviewer epsilon: Comparison should be between Pregnant women on folic acid vs Pregnant women without folic acid. Please do not include non - pregnant women as it will change the entire study

Author response: I fix it

61 Reviewer theta: comparison group is inappropriate

Author response: I fix it

62 Reviewer eta: which facts?

Author response: I fix it

63 Reviewer eta: hypertension

Author response: I fix it

64 Reviewer eta: statistically significant

Author response: I fix it

65 Reviewer eta: Please rewrite this sentence. I do not understand its meaning.

Author response: I fix it

66 Reviewer eta: No comment on folic acid is presented in Table 2.

Author response: I fix it

67 Reviewer gamma: table 2 don't say anything about folic acid. How the author can correlate the result on Table 2 with the use of folic acid ?

Author response: I fix it

68 Reviewer eta: Not the best term. Use "medical condition" instead

Author response: I fix it

69 Reviewer eta: incidence of hypertension/hypertensive disorders

Author response: I fix it

70 Reviewer eta: were such patients included in the study as a comparison group? if not, no conclusion can be made

Author response: I fix it

71 Reviewer eta: maybe: DECREASE in the incidence of hypertension?

Author response: I fix it

72 Reviewer eta: If you dont consume folic acid, the probability of becoming

hypertensive is almost 100%? Were women planning pregnancy included in the study?

Author response: I fix it

73 Reviewer gamma: which graph ?

Author response: I fix it, I erase

74 Reviewer gamma: How authors can obtain the data of non-user of folic acid while the inclusion criteria is woman who take folic acid ? Apart from this, the number of subject in each groups were not comparable. Author should mention from the beginning about the pregnancy status and use of folic acid of the research subjects.

Author response: I fix it

75 Reviewer eta: Why is that?

Author response: I explain

76 Reviewer eta: therefore folic acid intake poses a risk for preeclampsia?

Author response: I explain with ACER and ICER analytic

77 Reviewer eta: gestational diabetes mellitus

Author response: I fix it

78 Reviewer eta: It is suggested in this study that...

Author response: Thank you

79 Reviewer gamma: is the recommendation derived from this study or from literature? Please discuss the implication of this study.

Author response: I fix it

80 Reviewer epsilon: The study does not do a good job in highlighting the aim. Author must revise the entire study.

Author response: I fix it

81 Reviewer gamma: Actually, it can not be concluded from this study because the research design is not so valid. There is no good comparison between doses, and between the user and non-user of folic acid. It is also not clear, when the subject start taking the folic acid in their pregnancy, while they are now in 7-9 months gestation age.

Author response: I fix it

Reviewer Questionnaire Comments (Old Version):

Reviewers who started their review prior to the release of new, expanded reviewer questionnaire were prompted to reply to the following two questions only. Please revise accordingly, but you do not need to respond directly to these comments. The new, expanded reviewer questionnaire replies are in the next section and will require your response for each comment.

Provide a brief summary of the main research question, claims, and conclusions of the study. How does this research fit within the existing literature?

Reviewer beta: Pre-eclampsia is a condition of elevated blood pressure with proteinuria that occurs during pregnancy. To identify risk factors and effective doses of folic acid, the authors have conducted a retrospective cohort study. The study concludes that using folic acid early in pregnancy planning is a great

opportunity to reduce the incidence of pre-eclampsia. Triggering risk factors for pre-eclampsia include inadequate folic acid intake, duration of folic acid intake, and pregnancy status of patients with disease risk up to 98%.

Provide a brief assessment of the research process and presentation while noting any obvious flaws or areas of weakness. Are the conclusions consistent with the evidence presented?

Reviewer beta: A retrospective cohort study with the aim to identify risk factors and effective doses of folic acid. Writing and presentation have to improve. The major flaw is the lack of IRB approval. If IRB approval isn't sorted, it is unethical to get the patient data and do the study.

Reviewer Questionnaire Comments

1. Are the objectives of the study clearly stated?

Reviewer gamma: The study did not use an appropriate design to answer questions regarding the effectiveness of folic acid in preventing preeclampsia in pregnant women, so the aim of this study was not answered accurately.

Reviewer epsilon: The language and presentation of the study may benefit from clearer organization and more concise descriptions. Improving the clarity and visual representation of the data in the tables could significantly enhance the overall impact of the article. Employing a more reader-friendly approach to convey the findings would likely result in a broader understanding and appreciation of the significance of folic acid supplementation.

Reviewer zeta: Objectives of the study are not clearly mentioned. Authors are not clear about their goal and objectives which is a pre-requisite for any study.

Reviewer eta: No, they are not. Starting from the title and the introduction, the reader cannot fully understand what the main objective of this study is.

Reviewer theta: No. The researchers are themselves not clear on what they want to study. The comparison group and sampling technique chosen bring in high bias to the study.

Reviewer kappa: objective is not clearly stated.

2. Are the study methods reported in sufficient detail to allow for their

replicability and/or reproducibility?

Reviewer gamma: The cohort study design used is not very clear and lacks consistency in its explanation. To see the effectiveness of folic acid in a study cohort, it should be compared to a control group that did not use folic acid. However, in this study the inclusion criteria were pregnant women who used folic acid. However, the results are also inconsistent, because one table states that there are several subjects who did not use folic acid. It's a bit confusing. Apart from that, even if there are subjects who do not use folic acid, the number is also very small compared to those who do, so it is not comparable, and will reduce the statistical power of the calculations.

Reviewer epsilon: The study's language and structure could be enhanced for better clarity and conciseness. Improving the organization and providing more succinct descriptions would contribute to a more impactful article. Additionally, clearer visual representation of the data in the tables could enhance overall comprehension. Adopting a reader-friendly approach to present the findings may lead to a broader understanding and increased appreciation of the significance of folic acid supplementation.

Reviewer zeta: The methodology in the present study lacks clarity, with insufficient explanation of key elements. Notably, the absence of information regarding sample size calculation raises concerns about the robustness and statistical validity of the findings. The study design remains unclear, lacking sufficient detail to comprehend the approach taken to investigate the research questions. A more comprehensive and transparent explanation of the methodology is essential and will enhance the overall clarity and credibility of the research.

Reviewer eta: No, the study design seems to be problematic. The objective is not clearly defined, the population studied and the data extraction methods are not so well defined in order to draw safe conclusions.

Reviewer theta: No. The methodology is too much flawed. all the sections including study design, sample size estimation, sampling technique are flawed. There is no mention of ethical clearance by any statutory body.

Reviewer kappa: Author did not use right method to achieve aim and objective.

3. In their discussion section, have the authors clearly emphasized the strengths and limitations of their study/theory/methods/argument?

Reviewer gamma: The author does not explain the strengths and limitations of this research, even though there is quite a lot that needs to be said. For example, the number of subjects is not comparable between groups of folic acid users and non-users, different folic acid dosage groups, etc.

Reviewer epsilon: The authors of the article have not provided a well-defined elucidation of the strengths inherent in their work. A comprehensive identification and articulation of the strengths are crucial for establishing the credibility and reliability of the research. Clear delineation of the study's robust methodologies, rigorous data collection procedures, and the judicious selection of statistical analyses would contribute to a more convincing portrayal of the study's strengths. Furthermore, an explicit discussion on the limitations and potential biases mitigated by the chosen methodologies would not only enhance the transparency of the research but also highlight the conscientious efforts undertaken by the authors. In essence, a more explicit and nuanced exposition of the study's strengths is imperative to bolster the overall integrity and impact of the article.

Reviewer zeta: In the current study, the authors have overlooked a crucial aspect by not adequately highlighting the strengths and limitations of their work. This omission is significant as it denies the reader a comprehensive understanding of the study's validity and the extent to which its findings can be generalized. A thorough discussion of the strengths and limitations is essential for providing a balanced perspective and ensuring the credibility and applicability of the research outcomes. It is recommended that the authors address this oversight by incorporating a thoughtful analysis of both the strengths and limitations in their study, contributing to the overall robustness of their work.

Reviewer eta: There are certain limitations of the study that arise throughout the whole text. However, they are not emphasized on. Whether pregnant or non pregnant women were included, when was folic acid administered and for how long, detailed results of the study etc.

Reviewer theta: Results are flawed, so there is no point in assessing the discussion section.

Reviewer kappa: methodology is not properly used so discussion is not clearly defined.

4. Are the interpretation of results and study conclusions supported by the data and the study design?

Reviewer gamma: Due to the lack of validity of the research design, the accuracy of the results cannot be accepted.

Reviewer epsilon: The interpretation of results and study conclusions appears to be well-founded, supported by both the data and the study design. However, it is important to acknowledge that further research is needed in this particular field to develop a universal Standard Operating Procedure (SOP). While the current study provides valuable insights, the complexities of the topic suggest that a broader and more extensive investigation is necessary to establish a comprehensive SOP that can be universally applied. Additional studies could explore different variables, populations, or contexts, contributing to a more robust understanding of the subject matter. This acknowledgment underscores the study's role as a stepping stone in the ongoing quest for a standardized approach, emphasizing the need for continued research efforts to refine and validate the findings.

Reviewer zeta: The results and conclusions of the article exhibit inconsistency, requiring a realignment of the concluding statements to accurately reflect the study findings. Numerous sentences lack clarity and need to be rephrased to enhance their meaning. The overall composition of the article appears vague, and improvements are necessary for a more precise and coherent presentation of the research findings.

Reviewer eta: Not quite. There are some not well supported conclusions.

Reviewer theta: No. The points have been mentioned in previous questions

Reviewer kappa: interpretation is not good.

5. Does the article have flaws which should prohibit its publication?

Reviewer gamma: Yes, the results are less convincing because the design is not strong enough. Grammatically, it still needs a lot of improvement.

Reviewer epsilon: The primary flaw observed in the article pertains to its writing style. The author should employ a more engaging language to effectively convey and represent the data. By adopting a more dynamic and captivating writing approach, the article could enhance its accessibility and appeal to a broader audience. Utilizing language that is both informative and engaging not only facilitates better comprehension but also sustains the reader's interest throughout the content. This improvement in writing style would contribute to a more effective communication of the research findings, ultimately maximizing the impact and reach of the article.

Reviewer zeta: Major corrections are warranted for this article, particularly in the areas of the title, methodology, and conclusion sections. The title requires refinement for better clarity and specificity. The methodology section lacks adequate explanation and transparency, especially concerning the sample size calculation and study design. Furthermore, the conclusion section needs substantial improvement to align with the study's findings and to provide a more concise and accurate summary of the research outcomes. Overall, comprehensive revisions are essential to enhance the overall quality, coherence, and impact of the article.

Reviewer eta: It needs to be reviewed by the authors and corrections should be made. If the corrections are not made, it should not be published due to its limitations.

Reviewer theta: Definitely. Faulty Introduction, Unclear Objectives, Flawed methodology

Reviewer kappa: proper methodology is not used