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Masters Program in Public Health, Universitas Sebelas Maret

Meta-Analysis

Meta-analysis Effect of Compliance with Folic Acid Supplement Consumption in Pregnant Women on the Risk of Birth Defects

Fathia Mutiara Zahra[1)], Frannesty Estu Winahyu[2)], Bhisma Murti[3)]

[1)]Study Program of Pharmacy, Universitas Sebelas Maret
[2)]Study Program of Acupuncture, Health Polytechnic, Ministry of Health Surakarta
[3)]Masters Program in Public Health, Universitas Sebelas Maret

ABSTRACT

Background: Low concentrations of folic acid supplement intake during pregnancy can cause birth defects in the baby. Therefore, this study was conducted to identify those associated with adherence to folic acid supplement consumption in pregnant women and provide a shadow for further research. The purpose of this study was to investigate the effect of birth defects and pregnant women's adherence to taking folic acid supplements during pregnancy.
Subjects and Method: This study uses the PRISMA flowchart to perform the meta-analysis. The article review process took place between 2017 and 2022 with PICO as follows, Population: Pregnant Women. Intervention: Folic acid consumption before and during pregnancy, Comparison: no folic acid consumption before and during pregnancy, Outcome: risk of birth defects, articles collected using databases such as PubMed, Google Scholar, and Science Direct used. The articles obtained will be filtered using the stages according to the PRISM flow diagram. The analysis was carried out using RevMan 5.3.
Results: A total of 9 articles, including 6 articles from the Asian continent, namely China, Japan, India, and Bangladesh, 2 articles from the Americas, namely Mexico and New York, and 1 from the African continent, namely Ethiopia. Wherefrom the meta-analysis of 9 articles, it is known that adherence to folic acid supplementation can reduce the risk of birth defects in pregnant women (aOR= 0.69; 95% CI= 0.50 to 0.96; p= 0.003).
Conclusion: Adherence to folic acid supplementation can help reduce the risk of birth defects in pregnant women.

Keywords: pregnant women, folic acid, birth defects

Correspondence:
Fathia Mutiara Zahra. Study Program of Pharmacy, Universitas Sebelas Maret. Jl. Ir. Sutami 36A, Surakarta 57126, Central Java. Email: efemzahra31@student.uns.ac.id. Mobile: +62815-67987661.

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BACKGROUND

Folic acid supplementation during the time of conception has long been known to reduce the incidence of birth defects. Folic acid (vitamin B9) is a supplement content that is widely used by pregnant women. This content is very important to maintain the fetus from trimester 1 to 3. Folic acid can be found in salmon, green vegetables, fruits, nuts, and milk. Multivitamin supplementation and fortification of grains such as wheat, cereals, and pasta. Consuming these foods is another way to increase folic acid intake in the general population (Qu, 2019). In the United States, folic acid fortification of grain products has been required since

January 1998, and in Canada since December 1998. About a third of women of reproductive age get the required daily amount of folic acid. In addition to supplementing pregnancy needs with other vitamins and minerals, folic acid has been shown to promote good outcomes for both mother and newborn.

In addition to preventing neural tube defects (NTD), folic acid supplementation during pregnancy appears to have a number of other benefits, including protection from congenital heart disease and oral clefts, and possibly premature birth. The method by which folic acid protects the fetus from structural abnormalities is unknown, but may involve regulation of homocysteine metabolism. Women with previous affected pregnancies are at greater risk for NTDs in future pregnancies than the general population (3-5% (Liu et al. 2017). Based on clinical trials (ACMG, 2011; CDC, 1991), these women recommended consuming 4,000 g FA daily (10 times the recommendation for the general population of potentially reproductive women) (Bibbins-Domingo et al, 2017).

Iron and folic acid supplementation programs should ideally be part of an integrated antenatal and neonatal care program that promotes adequate gestational weight gain, screening for anemia of all women at antenatal and postpartum visits, use of complementary measures to control and prevent anemia (e.g., control of anemia). hookworms), and a referral system for managing cases of severe anemia (WHO, 2012). During the first 3-4 weeks of pregnancy, birth abnormalities may appear. Women need folic acid even before they get pregnant, as more than half of all pregnancies in the United States are unplanned.

In view of this, a comprehensive study is needed that combines data from several major studies on the risk of birth defects in pregnant women with folic acid supplementation. With a systematic review of the main studies conducted by the previous authors, this study aims to estimate the magnitude of the risk of birth defects in pregnant women with folic acid supplementation before and during pregnancy.

SUBJECTS AND METHOD

1. Study Design

This research was conducted using a meta-analysis research design with the PRISMA flowchart guideline. Article searches were performed using the following databases: PubMed, Google Scholar and Science Direct. Some of the keywords used are: “Pregnant Woman” AND “Folic Acid” AND “Birth Defect”.

2. Inclusion Criteria

The inclusion criteria for this research article were articles 2017-2022 that used English, case-control and cohort study designs, adjusted Odds Ratio (aOR) relationship measures, subjects pregnant women taking folic acid with birth defects.

3. Exclusion Criteria

The exclusion criteria for this research article were the results of bivariate statistical analysis, and articles that did not use English.

4. Operational Definition of Variables

The articles included in this study were PICO-adjusted. The search for articles was carried out taking into account the eligibility criteria determined using the following PICO model: Population = Pregnant Women, Intervention= Folic acid consumption before and during pregnancy, Comparison= no folic acid consumption before and during pregnancy, Outcome= risk of birth defects.

Folic acid is a synthetic dietary supplement found in artificially enhanced pharmaceutical and dietary vitamins. Folate and folic acid are not biologically active. To

participate in cellular metabolism, both must be derived. The micronutrient form of folate that circulates in plasma and is involved in physiological processes is l-5-methyltetrahydrofolate (l-methylfolate). Folic acid is categorized as taking folic acid before and during pregnancy and not taking folic acid before and during pregnancy. The measurement scale is categorical.

Birth defects are determined by the physical status of the baby after birth which is diagnosed by a doctor. Birth defects are categorized as birth defects and not birth defects. The measurement scale is categorical.

5. Instruments

Research is guided by the PRISMA flow diagram and assessment of the quality of research articles using the Critical Appraisal Skills Program (CASP, 2018) tool for the design of case-control and cohort studies.

The 11 case-control study questions used are as follows:

1. Does the case control study clearly address the clinical problem?
2. Did the researcher use the correct method to answer the research question?
3. Was the case selected in the right way?
4. Were the controls selected the right way?
5. Is exposure accurately measured to minimize bias?
6. Has the researcher taken into account the influence of all potential confounding factors in the study? Has the researcher controlled for the influence of all potential confounding factors in the design or analysis of the data?
7. How big is the effect of exposure?
8. How precise is the estimation of the exposure effect?
9. Are the results reliable?
10. Are the results applicable to the local (local) population?
11. Are the results of this study compatible with other available evidence?

The 12 cohort study questions used are as follows:

1. Did the cohort study clearly address the clinical problem?
2. Were the cohorts (subjects in the exposed and unexposed groups) selected in the right way?
3. Is exposure accurately measured to minimize bias?
4. Was the outcome (mortality status) measured accurately to minimize bias?
5. Did the researcher identify all the important confounding factors? Did the researcher take confounding factors into account in the design and/or analysis?
6. Did the research subject complete the research time in full? Were the research subjects followed for a long time?
7. Are the results of this study reported in the aOR?
8. How precise are the results?
9. Are the results reliable?
10. Are the results applicable to the local (local) population?
11. Are the results of this study compatible with the available evidence?
12. What are the implications of this research for practice?

6. Data Analysis

Articles were analyzed using the Review Manager (RevMan) 5.3 application to calculate effect size and heterogeneity, and form the final results of the meta-analysis. The results of data processing are presented in the form of forest plots and funnel plots.

RESULTS

Process of searching article wascarried out by searching several journal databases PubMed, Sciencedirect, and Googlescholar. it can be seen using the PRISMA FLOW flowchart shown in Figure 1.

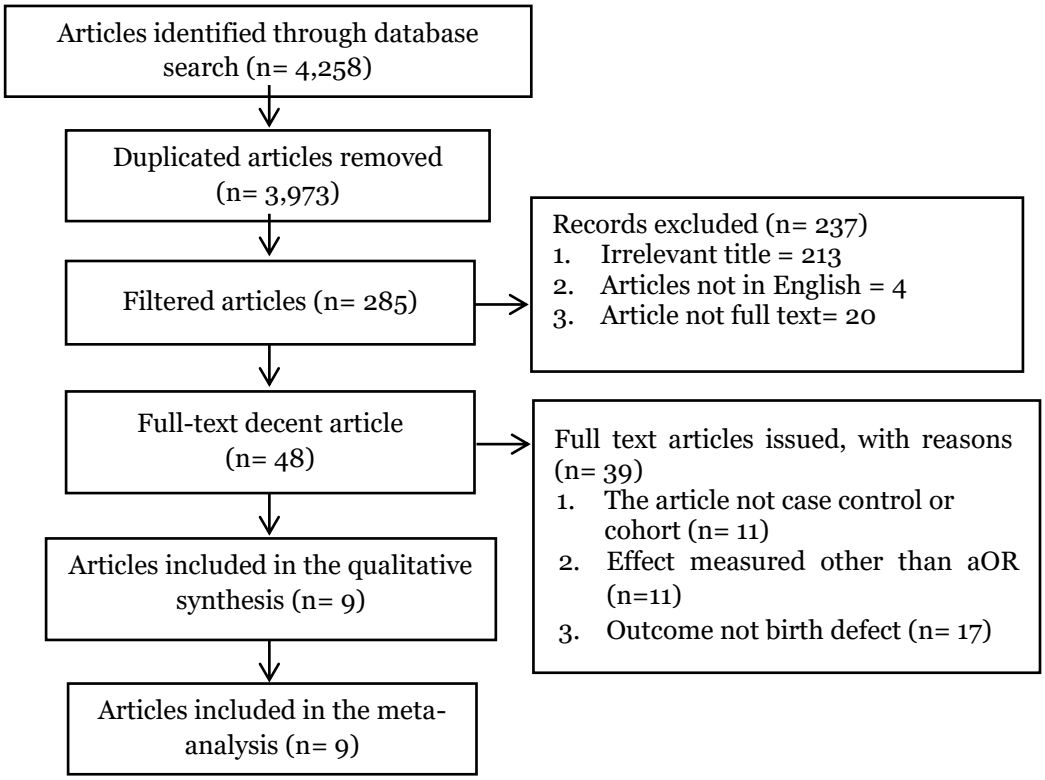

Figure 1. Results of Prisma Flow Diagrams

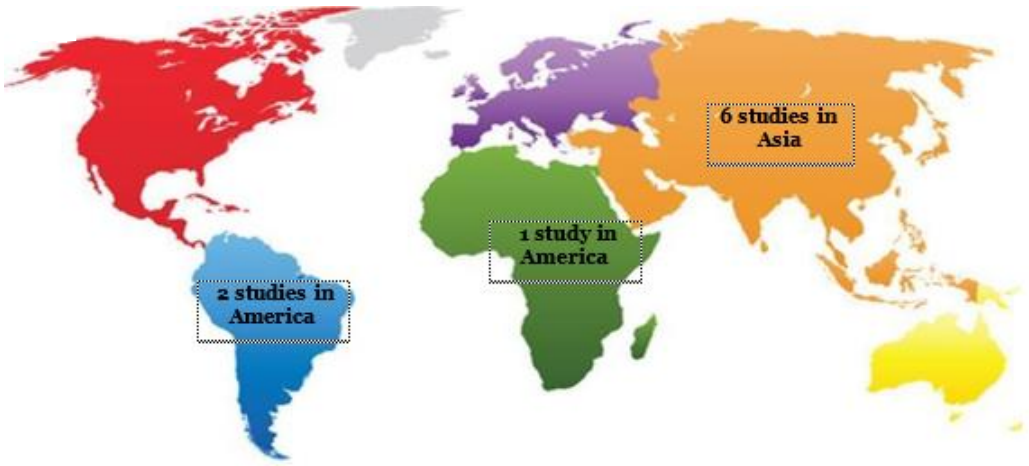

Figure 1. Resarch Distribution Map

Table 1. Results of Quality Assessment of the Cohort Study of the Effect of Compliance with Folic Acid Consumption on Birth Defects in Pregnant Women.

Primary Study	Criteria												Total
	1	2	3	4	5	6	7	8	9	10	11	12	
Liu et al. (2019)	1	1	1	1	1	1	1	1	1	1	1	1	12
Ito et al. (2019)	1	1	1	1	1	1	1	1	1	1	1	1	12
Mao et al. (2017)	1	1	1	1	1	1	1	1	1	1	1	1	12

Note: Answer 1= Yes; Answer 0= No

Table 2. Results of Quality Assessment of Case Control Studies The Effect of Compliance with Folic Acid Consumption on Birth Defects in Pregnant Women.

Primary Study	Criteria											Total
	1	2	3	4	5	6	7	8	9	10	11	
Xu et al. (2021)	1	1	1	1	1	1	1	1	1	1	1	11
Petersen et al. (2019)	1	0	1	1	1	1	1	1	1	1	1	10
Mendonca et al. (2019)	1	1	1	1	1	1	1	1	1	1	1	11
Atlaw et al. (2019)	1	1	1	1	1	1	1	1	1	1	1	11
Kancherla et al. (2017)	1	1	1	1	1	1	1	1	1	1	1	11
Rivera et al. (2018)	1	1	1	1	1	1	1	1	1	1	1	11

Note: Answer 1= Yes; Answer 0= No

figure 1. Research related to effect of compliance with folic acid supplement consumption in pregnant women on the risk of birth defects of 9 articles from the initial search process yielding 4,285 articles, after the deletion process, articles were published with 285 requirements for full-text review more carry on. A total of 9 articles that met the quality assessment were included in the quantitative synthesis using a meta-analysis.

It can be seen in Figure 2 that the research articles come from two continents that is the Asian continent, namely China, Japan, India and Bangladesh, 2 articles from the Americas, namely Mexico and New York, and 1 from the African continent, namely Ethiopia.

An assessment of the quality of the articles used in this study can be seen in table 1 and table 2.

Then Table 3 shows that 9 articles from case control and cohor study provide evidence about effect of compliance with folic acid supplement consumption in pregnant women on the risk of birth defects. Then in table 2 it can be seen about the details of the articles used in this study, such as the study population, intervention, comparison, and the results of each study. All articles used in this study are case control and cohor design.

Based on the results of the forest plot (figure 3) shows that adherence to folic acid supplement consumption in pregnant women reduces the risk of birth defects by 0.69 times compared to pregnant women without folic acid consumption (aOR= 0.69; 95% CI= 0.50 to 0.96), and the results were statistically significant (p= 0.030). With subgroup analysis, the cohort study design obtained results (aOR = 0.92; 95% CI= 0.74 to 1.13) these results were not statistically significant (p= 0.410) , then for the case-control study design the results were obtained (aOR = 0.55; 95% CI =0.50 to 0.99) the results were statistically significant (p= 0.050).

In (Figure 4) it can be seen about the Funnel Plot from the results of the data analysis that has been carried out, where it can be seen that the shape of the funnel plot is asymmetrically distributed. This asymmetrical funnel plot distribution indicates that there is a potential for bias with an overestimated effect characterized by an asymmetric distribution between the right and left plots. There are 6 plots on the right, 3 plots on the left so there is a publication bias. The plots on the right and left of the graph have a standard error (SE) between 0 and 0.70.

Table 3. Description of Primary Research included in the Meta-Analysis

No	Author (Year)	Country	Study Design	Sample		Population (P)	Intervention (I)	Comparison (C)	Outcome (O)	aOR (95 % CI)
				Total	Folic Acid (%)					
1	Xu et al. (2021)	China	Control case	8070	294 (29.7)	Pregnant women aged <25 years and >35 years	Consumption of Folic Acid during pregnancy	Do not consume folic acid before and after pregnancy	Risk of Birth Defects with cleft lip syndrome	0.41 (0.31-0.54)
2	Petersen et al. (2019)	New York	Control case	1,726	12 (27.9)	Pregnant women with UK over 12 weeks	Consumption of Folic Acid during pregnancy every day is 400 g-1000 g	Do not take folic acid before pregnancy	Risk of Birth Defects with Neural Tube Damage Syndrome (NTD)	0.89 (0.24-2.93)
3	Mendonca et al. (2019)	Bangalore, India	Control case	318	106 (32.6)	Pregnant women who take supplements during the periconception period	Consumption of Folic Acid before and after pregnancy	Do not consume folic acid before and after pregnancy	Risk of Birth Defects Nonsyndromic orofacial cleft	0,96 (0,93-0,99)
4	Atlaw et al. (2019)	Ethiopia Tenggara	Control case	462	232 (50.2)	Mothers after delivery with neural tube defects and ten consecutive births without NTD	Consumption of Folic Acid before and after pregnancy	Do not consume folic acid before and after pregnancy	Risk of Birth Defects NTD	0.095 (0.031-0.285)
5	Kancherla et al. (2017)	Bangladesh	Control case	106	65 (61.3)	Pregnant women and children with and without myelomeningocele	Consumption of Folic Acid before and after pregnancy	Do not consume folic acid before and after pregnancy	Risk of Birth Defects with Myelomeningocel	0.43 (0.18-1.02)
6	Rivera et al. (2018)	Mexico	Control case	420	48 (11.4)	Pregnant women who follow ANC	Consumption of folic acid before pregnancy	Do not take folic acid before pregnancy	Risk of Birth Defects with cleft lip syndrome	1.3 (0.6-2.9)

Table 3. Continue.

No	Author (Year)	Country	Study Design	Sample		Population (P)	Intervention (I)	Comparison (C)	Outcome (O)	aOR (95 % CI)
7	Liu et al. (2019)	China	Cohort	247,831	130,142 (52.5)	Data from deliveries at 20 complete gestational weeks, including live births, stillbirths and pregnancy terminations, and all structural congenital anomalies, regardless of gestational week, were recorded.	Consumption of Folic Acid before and after pregnancy	Do not consume folic acid before and after pregnancy	Risk of Birth Defects Reduction of limbs	0.87 (0.59-1.29)
8	Ito et al. (2019)	Prefektur Hokkaido Jepang	Cohort	14,896	3.315 (22,6)	Pregnant Women with UK 13 weeks	Consumption of folic acid in the first trimester	Do not take folic acid in the first trimester	Risk of Birth Defects with Nerve Cell Damage Syndrome	0,99 (0,74-1,32)
9	Mao et al. (2017)	China	Cohort	10087	7317 (72.5)	Pregnant women who meet the requirements who come to the hospital to give birth	Consumption of Folic Acid before and after pregnancy	Do not consume folic acid before and after pregnancy	Risk of Congenital Heart Birth Defects (CHD)	0.81 (0.51-1.29)

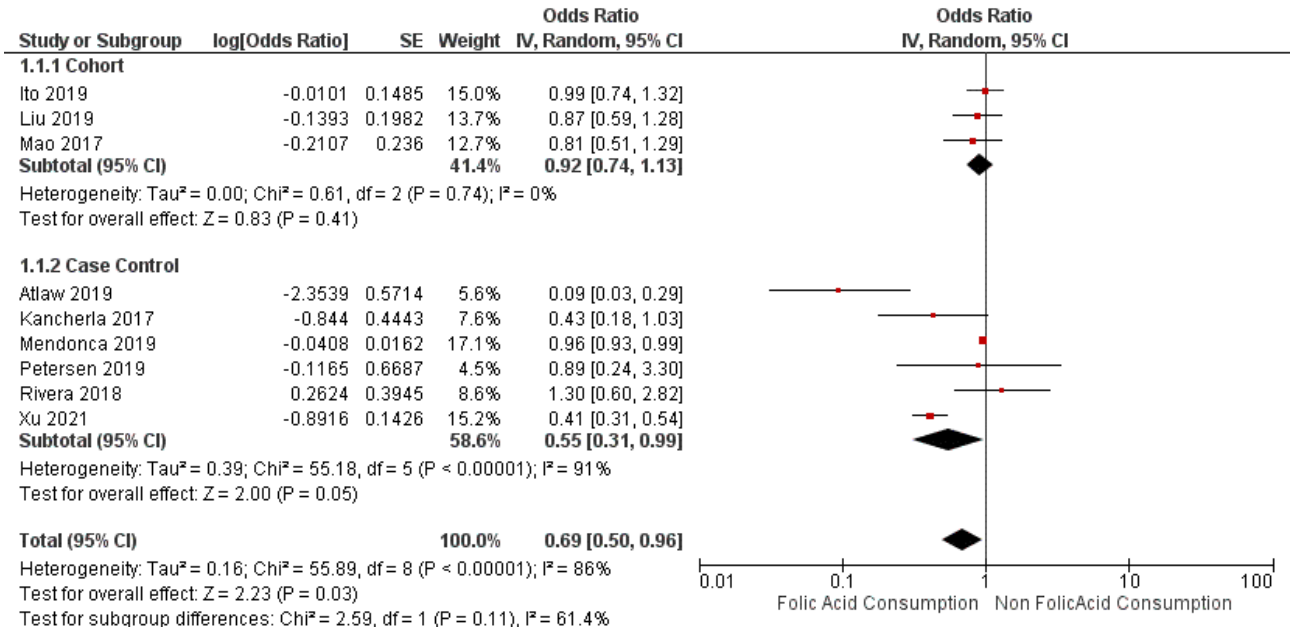

Figure 4. Forest plot of the Effect of Folic Acid Consumption on Birth Defects in Pregnant Women

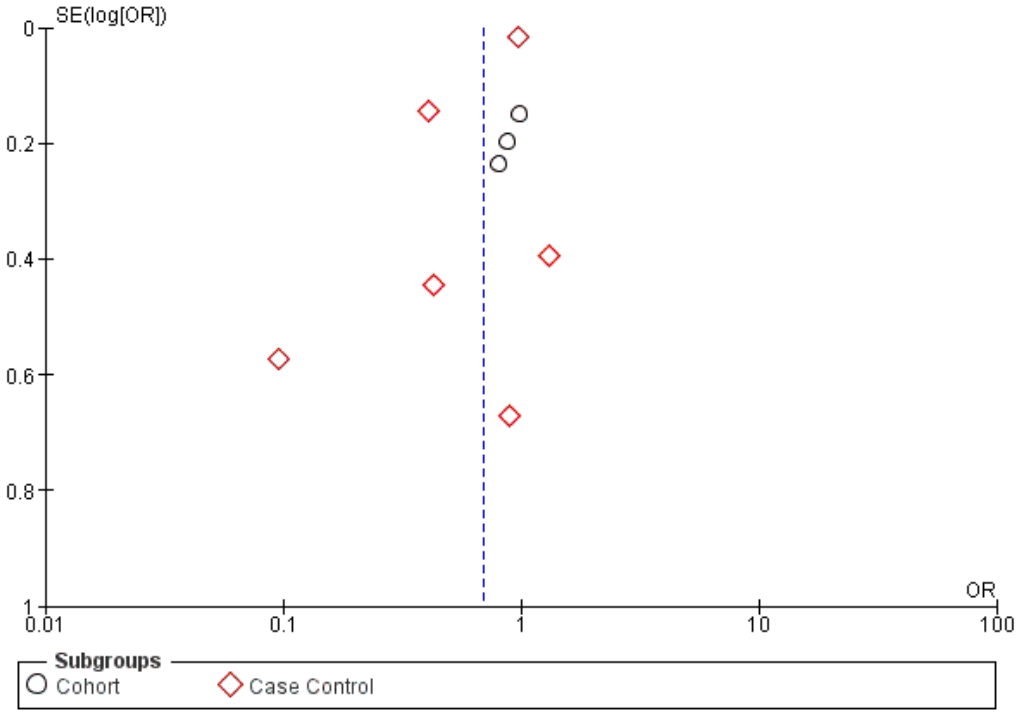

Figure 4. Funnel plot of the Effect of Folic Acid Consumption on Birth Defects in Pregnant Women

DISCUSSION

This study is a meta-analysis on the effect of taking folic acid supplements on the risk of birth defects in pregnant women. This study contains the consumption of folic acid supplements in pregnant women which are considered important because they are considered a high risk group for the incidence of birth defects.

The primary studies that met the criteria were 9 articles originating from 6 from the Asian continent, 2 from the Americas, and 1 from the African continent. This study shows that adherence to consumption of folic acid supplements statistically affects the reduction of birth defects in infants. The forest plot results show that the magnitude of the effect of adherence to folic acid supplement consumption on birth defects in pregnant women is 0.96, which increases the reduction in the risk of birth defects (aOR= 0.69; 95% CI= 0.50 to 0.96; p= 0.003). 86% so that the data spread is declared Random Effect Model.

The results of the forest plot analysis also showed that adherence to folic acid supplement consumption in pregnant women reduced the risk of birth defects using a subgroup analysis, with a cohort design the results obtained (aOR = 0.92; 95% CI = 0.74 to 1.13) these results were not statistically significant (p= 0.041), the heterogeneity of the research data showed I^2= 0% , then for the case control design the results were obtained (aOR = 0.55; 95% CI = 0.50 to 0.99) the results were statistically significant (p = 0.005) with the heterogeneity of the research data showing I2 = 91%. Compliance with folic acid supplement consumption can reduce the risk of birth defects in pregnant women as a whole from all articles indicated by the results of (aOR = 0.69; 95% CI=0.50 to 0.96 with I^2= 86%; p= 0.003 statistically significant.

According to research by Ito, et al. (2018) Folic acid supplementation in preconception and during the first trimester reduces the risk of delivering a baby with neural tube defects (NTDs). Folate is an integral part of one-carbon metabolism, which produces pyrimidines and purines for DNA synthesis and sadenosylmethionine. Thus, folic acid is very important for cell proliferation and or the survival of body tissue cells. Folic acid can affect cell proliferation at an early stage of development, thereby promoting posterior neural tube closure (Ito et al., 2018). This is supported by the research of Atlaw et al. (2019) concluded that folic acid supplementation was identified to protect NTDs, because health facilities need to consider folic acid supplementation for women of reproductive age group and encourage women of reproductive age to conduct medical consultations before pregnancy properly and correctly.

The results of Mendonca et al. (2019) showed that a statistically significant protective association was found for separate folic acid supplements (not combined with iron or multivitamins) taken in the periconception period and all gaps combined (adjusted odds ratio (aOR= 0.62; 95 %CI= 0.45 to 0.86) and CL/P (aOR: 0.57; 95% CI, 0.38 to 0.86). Higher levels of dietary folic acid were found to be associated with reduced risk for all clefts (OR= 0.98; 95% CI= 0.96 to 0.99), CL/P (OR: 0.98; 95% CI= 0.96 to 0.99), and CP (aOR= 0.96; 95% CI= 0.93 to 0.99) (Mendonca et al., 2019).

The results of this study are also supported by the research of Mao et al. 2017, which showed that compared with nonusers of folic acid supplements, prepregnancy supplement users had a reduced overall risk of CHD (OR= 0.42; 95% CI= 0.21 to 0.86, p= 0.025) after adjusting for potential confounders. A protective effect was observed for certain CHD subtypes (OR= 0.37; 95% CI= 0.16 to 0.85 for large artery malformations; 0.26, 0.10 to 0.68 for cardiac septal malformations; 0.34, 0.13 to 0.93 for atrial septal defects). A similar protective effect was also seen for some CHD (OR= 0.49; 95% CI= 0.26 to 0.93, p= 0.004) compared to the middle quartile of dietary folate intake, lower dietary folate intake (Mao et al., 2017).

AUTHOR CONTRIBUTION

Fathia Mutiara Zahra and Frannesty Estu Winahyu were the main researchers who chose the topic, searched for and collected research data. Bhisma Murti analyzes data and examines research documents.

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This study is self-funded.

CONFLICT OF INTEREST

There is no conflict of interest in this study.

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