Literature Review

jurnal SAGO gizi dan kesehatan

The importance of folate consumption during pregnancy in preventing neural tube defects: A Literature Review

Pentingnya konsumsi asam folat pada ibu hamil dalam mencegah neural tube defects: Literatur Review

SAGO: Gizi dan Kesehatan
2026, Vol. 7(1) 382-392

DOI: http://dx.doi.org/10.30867/gikes.v7i1.2605
https://ejournal.poltekkesaceh.ac.id/index.php/gikes
Poltekkes Kemenkes Aceh

Tiara Andhiny[1], Anita Rahmiwati[2], Novrikasari[3*]

Abstract

Background: Neural Tube Defects (NTDs) are severe congenital disorders that can result in lifelong disabilities. These malformations are largely preventable through adequate folic acid intake before conception and during early pregnancy. However, in many settings, including Indonesia, pregnant women's awareness and adherence to folic acid supplementation remain below optimal levels. Scientific evidence has long demonstrated that folic acid supports proper neural tube formation and lowers the risk of conditions such as spina bifida and anencephaly. However, there is limited discussion in existing reviews about contextual barriers, such as cultural perceptions, healthcare access, and policy limitations, that influence supplementation practices in low- and middle-income countries. This review aims to fill this gap by examining recent evidence on the preventive role of folic acid and exploring the factors that shape its effectiveness.
Objectives: This study aimed to evaluate and review the existing evidence on the role of folic acid consumption in preventing Neural Tube Defects (NTD) in pregnant women and to identify factors that influence its effectiveness.
Methods: This review was conducted using PubMed and Google Scholar with searches guided by standardized Medical Subject Headings (MeSH) terms: "Folic Acid," "Pregnant Women," and "Neural Tube Defects." The selection process followed the PRISMA guidelines, applying the following criteria: publication between 2020 and 2024, availability of full-text articles, and a primary focus on the relationship between folic acid and NTD prevention in pregnant women. The methodological quality of the included studies was assessed using the Joanna Briggs Institute (JBI) critical appraisal tool.
Results: The results of the six studies showed that folic acid deficiency significantly increased the risk of anencephaly and neural tube defects, whereas folic acid supplementation before and during pregnancy reduced the incidence of NTDs. Adequate folic acid levels in pregnant women also reduce the risk of spina bifida, although knowledge and compliance with folic acid consumption among pregnant women remain low. The methodological quality varied from moderate to high, although several studies did not adequately control for confounding factors.
Conclusion: Based on these findings, folic acid consumption is crucial for preventing NTDs. However, there is a need to improve education and compliance with folic acid consumption among pregnant women. Further research is required to understand the factors influencing compliance and to design more effective interventions to enhance awareness and implementation of folic acid consumption among pregnant women.

Keywords
Folic Acid, Pregnant Women, Neural Tube Defects

Abstrak

Latar Belakang: Neural Tube Defect (NTD) merupakanadalah kelainan bawaan yang serius dan dapat menyebabkan kecacatan seumur hidup. Kelainan ini sebagian besar dapat dicegah melalui asupan asam folat yang memadai sebelum

[1] Bidang Kajian Utama Gizi, Program Studi Magister Ilmu Kesehatan Masyarakat, Fakultas Kesehatan Masyarakat, Universitas Sriwijaya, Palembang, Sumatera Selatan, Indonesia. E-mail: tiaraandhinyyasin@gmail.com
[2] Bidang Kajian Utama Gizi, Program Studi Magister Ilmu Kesehatan Masyarakat, Fakultas Kesehatan Masyarakat, Universitas Sriwijaya, Palembang, Sumatera Selatan, Indonesia. E-mail: anita_rahmiwati@fkm.unsri.ac.id
[3] Bidang Kajian Utama Gizi Program Studi Magister Ilmu Kesehatan Masyarakat, Fakultas Kesehatan Masyarakat, Universitas Sriwijaya, Palembang, Sumatera Selatan, Indonesia. E-mail: novrikasari@fkm.unsri.ac.id

Penulis Koresponding:
Novrikasari: Bidang Kajian Utama Gizi, Program Studi Magister Ilmu Kesehatan Masyarakat, Fakultas Kesehatan Masyarakat, Universitas Sriwijaya, Palembang, Sumatera Selatan, Indonesia. E-mail: novrikasari@fkm.unsri.ac.id

Diterima: 06/06/2025 Revisi: 31/07/2025 Disetujui: 20/08/2025 Diterbitkan: 21/04/2026

konsepsi dan selama trimester awal kehamilan. Namun, di banyak negara, termasuk Indonesia, kesadaran dan kepatuhan ibu hamil terhadap suplementasi asam folat masih di bawah tingkat optimal. Bukti ilmiah telah lama menunjukkan bahwa asam folat mendukung pembentukan tabung saraf yang normal dan mengurangi risiko kondisi seperti spina bifida dan anencephaly. Namun, pembahasan tentang hambatan kontekstual—seperti persepsi budaya, akses layanan kesehatan, dan batasan kebijakan—yang memengaruhi praktik suplementasi di negara-negara berpendapatan rendah dan menengah masih terbatas dalam tinjauan yang ada. Tinjauan ini bertujuan untuk mengisi celah tersebut dengan menganalisis bukti terbaru tentang peran pencegahan asam folat dan mengeksplorasi faktor-faktor yang memengaruhi efektivitasnya.

Tujuan: Artikel ini bertujuan untuk mengevaluasi dan mengkaji bukti-bukti yang ada mengenai peran konsumsi asam folat dalam mencegah Neural Tube Defects (NTD) pada ibu hamil, serta mengidentifikasi faktor-faktor yang mempengaruhi efektivitasnya.

Metode: Ulasan ini dilakukan menggunakan PubMed dan Google Scholar dengan pencarian yang dipandu oleh istilah Medical Subject Headings (MeSH) yang standar: “Asam Folat”, “Wanita Hamil”, dan “Cacat Tabung Saraf”. Proses seleksi mengikuti pedoman PRISMA, dengan menerapkan kriteria berikut: publikasi antara tahun 2020 dan 2024, ketersediaan artikel teks lengkap, dan fokus utama pada hubungan antara asam folat dan pencegahan cacat tabung saraf pada wanita hamil. Kualitas metodologis studi yang disertakan dievaluasi menggunakan alat penilaian kritis Joanna Briggs Institute (JBI).

Hasil: Studi dari 6 artikel menunjukkan bahwa defisiensi asam folat signifikan meningkatkan risiko anensefali dan kelainan tabung saraf, sementara suplementasi folat sebelum dan selama kehamilan dapat menurunkan kejadian NTD. Kadar folat yang cukup pada ibu hamil juga mengurangi risiko spina bifida, meskipun pengetahuan dan kepatuhan ibu terhadap konsumsi folat masih rendah. Kualitas metodologi bervariasi dari sedang hingga tinggi, meskipun beberapa studi tidak cukup mengontrol faktor-faktor pengganggu.

Kesimpulan: Berdasarkan temuan yang ada, konsumsi asam folat sangat penting untuk mencegah NTD. Namun, diperlukan peningkatan edukasi dan kepatuhan ibu hamil dalam mengonsumsi asam folat. Penelitian lanjutan diperlukan untuk memahami faktor-faktor yang mempengaruhi kepatuhan ini dan untuk merancang intervensi yang lebih efektif guna meningkatkan kesadaran dan penerapan konsumsi folat di kalangan ibu hamil.

Kata Kunci
Asam Folat, Ibu Hamil, Kelainan Tabung Saraf

Introduction

Since September 2014, the Ministry of Health has conducted sentinel monitoring of congenital anomalies in infants in several hospitals. By March 2018, 1,085 cases were reported, 956 of which met the inclusion criteria. The eight most common types of congenital abnormalities include clubfoot (talipes), lip and palate cleft (orofacial cleft), neural tube defect, abdominal wall defect, no anal opening (atresia ani), and urinary tract disorders such as hypospadias, epispadias, conjoined twins, and head size, which are much smaller than normal (microcephaly) (Kemenkes 2018). While this provides important local context, more recent global figures highlight that neural tube defects (NTDs) remain a pressing health concern. According to the World Health Organization (WHO, 2023), NTDs continue to affect hundreds of thousands of pregnancies annually, with the highest burden observed in low- and middle-income countries. Data from the United States Centers for Disease Control and Prevention (CDC, 2024) show that approximately 1,300 babies are born with spina bifida, 700 with anencephaly, and 350with encephaloceles annuallye. These updated statistics underscore that NTDs are not merely historical issues but ongoing challenges requiring sustained preventive action both globally and in Indonesia.

Neural tube defects (NTDs) are the second most prevalent congenital disorder after cardiac malformations in the United States and are associated with significant morbidity and mortality. According to *the Center for Disease Control* (CDC) estimates, the average annual prevalence of the two most common types of NTDs, anencephaly and spina bifida, reached 6.5 cases per 10,000 live births between 2009 and 2011 (Viswanathan et al., 2017). *Neural tube defects* (NTDs) have complex causes and are influenced by various factors, including genetic, lifestyle, and environmental factors. Although chromosomal anomalies may contribute to NTDs, cases associated with this factor account for only 2% to 16% of NTDs that occur in isolation. Several studies have suggested the involvement of genetic factors in the development of NTDs, as evidenced by the increased risk in certain ethnic groups, such as the Irish and Mexican peoples, and the high chance of recurrent NTDs in the siblings of affected individuals. In addition to genetic factors,

environmental factors, such as parental occupation, maternal obesity, and nutritional status, are also known to play a role in the occurrence of NTDs (Ebara, 2017).

Neural tube defects (NTD) are congenital disorders that occur when neural tube closure during the early stages of pregnancy is incomplete. This disorder can affect various important structures, such as the skull, spine, meninges, muscles, and skin. Conditions that fall under the NTD category include anencephaly, encephalocele, cranial meningocele, myelomeningocele, spinal meningocele, lipomeningocele, spina bifida, and several other brain disorders. Spina bifida and anencephaly are the two most common NTDs. Several factors are known to play a role in increasing the risk of NTDs, including maternal nutritional status during pregnancy, obesity, diabetes, folic acid consumption (either through supplements or fortified foods), environmental exposure to toxic substances, and genetic variations that differ between ethnic groups (Wulan & Simanjuntak, 2016).

A survey conducted by *the March of Dimes National* showed that folic acid can prevent *Neural Tube Defects* (NTD) by 70%. Conversely, pregnant women with folic acid deficiency are at a higher risk, with a 200% increase in NTD incidence. In addition, folic acid deficiency can cause neurological, psychological, and carbon metabolism disorders. One method for detecting folic acid deficiency is to monitor fetal brain growth and development during pregnancy, which can be evaluated based on the size of the baby's head at birth (Khairani, 2021). Folic acid is a synthetic form of folate, a part of vitamin B9 (Lourdes et al., 2024), which plays a crucial role in the early stages of fetal development, particularly in the formation of the central nervous system. Disruptions in this process can affect various aspects of fetal development, including the formation of bones of the head and face (such as cleft lip), hormonal system (menstrual disorders), learning ability, cognitive and motor function (paralysis or developmental delay), autonomic system (micturition and defecation disorders), and heart defects. Therefore, all women of reproductive age (12-45 years) with childbearing potential are recommended to take folic acid supplements as part of a multivitamin when undergoing a medical check-up (Douglas Wilson et al., 2015).

Folic acid supplementation in early pregnancy has been shown to reduce the risk of *neural tube defects* (NTD). According to the *Center for Disease Control* (CDC) in 2004, the mandatory fortification of cereal products with folic acid starting in 1998 reduced the number of pregnancies with NTD fetuses from 4,000 cases per year to approximately 3,000 cases per year. More than half of NTD cases can be prevented by daily consumption of 400 μg folic acid during the periconceptional period of pregnancy. In addition, there is evidence that folate deficiency is a global problem associated with brain development (Ars et al., 2019).

Although there is strong and consistent evidence regarding the preventive benefits of folic acid, most of the available literature, especially in the Indonesian context, tends to be descriptive. Much of this repeats well-known biological explanations without clearly outlining the research gaps. Few studies have identified what remains uncertain; for instance, how socio-cultural, economic, and health system conditions in Indonesia affect pregnant women's adherence to folic acid. In addition, thematic synthesis and critical comparison of previous findings are lacking, particularly in terms of connecting them to the national public health policies and practical applications. Consequently, the originality of many reviews is limited because they often rely on a small number of articles and fail to integrate them into a comprehensive analytical framework.

Considering the persistent challenges Indonesia faces in lowering the incidence of congenital disorders, it is essential to explore the factors influencing compliance and the specific knowledge gaps among Indonesian pregnant women. Therefore, this review seeks to present existing evidence and critically evaluate it in light of its relevance to local maternal health initiatives, offering both context-based insights and practical recommendations.

Methods

This study used a *literature review* design, which is a method of searching for literature through relevant *databases*. The search for articles in this study was conducted using national sources obtained from Google Scholar and PubMed databases. Search terms applied in both English and Indonesian included variations of "folic acid," "folate," "pregnant women," "periconception," and "neural tube defect," combined using Boolean operators. The search was restricted to studies published between 2020 and 2024, available in full

text, and written in English or Indonesian. Articles were eligible for inclusion if they were original empirical studies examining folic acid intake through supplements or fortified foods in relation to neural tube defects or closely related perinatal outcomes, involving human participants who were pregnant or of reproductive age. The exclusion criteria were non-empirical publications, animal or laboratory studies without direct clinical relevance, studies not reporting outcomes related to neural tube defect prevention, duplicates, retracted papers, and inaccessible full texts.

The selection process, summarized in the PRISMA flow diagram, began with title and abstract screening, followed by a full-text review of the remaining articles. Disagreements between the two independent reviewers were resolved by consensus, and the reasons for exclusion were noted. Five studies met the inclusion criteria, a limited number which reflected a narrow time frame and stringent eligibility requirements. Data from the included studies were extracted using a standardized form to capture bibliographic details, journal indexing and ranking, study design, setting, participant characteristics, timing and dosage of folic acid intake, outcomes, and reported effect sizes. Methodological quality and risk of bias were assessed using the Joanna Briggs Institute (JBI) critical appraisal tools appropriate for each study design, with ratings of low, moderate, or high concern informing the interpretation of the findings. Given the heterogeneity of study designs and outcomes, results were synthesized narratively using a thematic approach that grouped evidence by supplementation timing, dosage, adherence, and clinical outcomes, with attention to the influence of study quality on the strength of the conclusions.The selection of studies in this literature review was done using the PRISMA diagram with the following scheme:

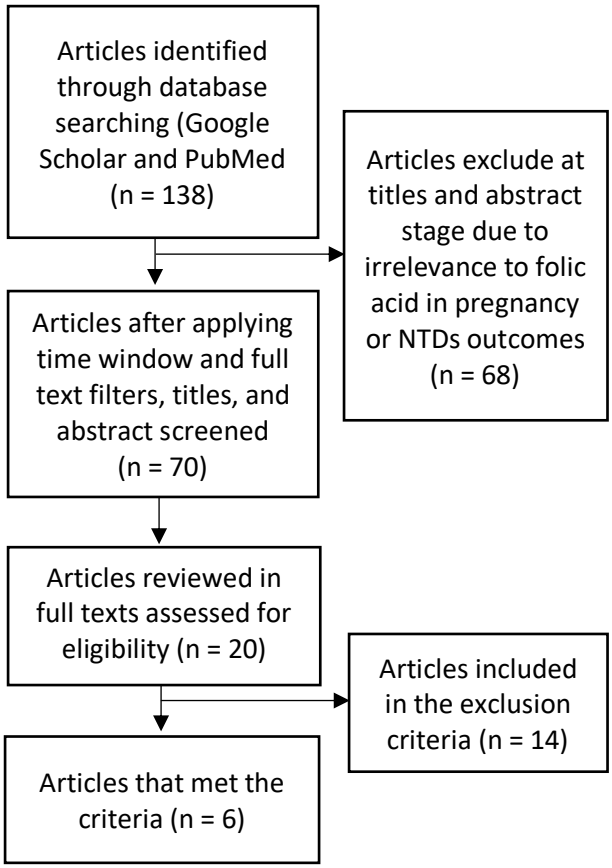

Figure 1. PRISMA Flo Diagram

Results

The analysis of this review identified five studies, four national and one international, which are summarized in Table 1.

Table 1. Results of Article Analysis

Researcher and Year	Title	Research Design, Sample and Location	Main Findings, Methodological Quality, Relation to Other Studies and Thematic Synthesis
Aditya, 2021	Effect of Folic Acid Adequacy on Congenital Patients in Newborns at Gatot Soebroto Army Central Hospital	Descriptive. A total of 90 newborns with congenital conditions and their mothers were included. Gatot Soebroto Army Central Hospital, Jakarta	Adequate maternal folic acid intake significantly reduced risk of congenital anomalies High Clinical setting with biochemical assessment; lacked adjustment for genetic predisposition. Reinforces Erdiana (2021) and Herdiyantini et al. (2024) on the preventive role of folic acid. Hospital-based evidence supports broader public

			health recommendations and underscores clinical validation.
Rahayu, 2024	Pregnant women's knowledge about taking folic acid during pregnancy	Descriptive (*Case-Control*). 150 pregnant women in 2nd trimester. Central Java, Indonesia	Of the respondents, 58% had good knowledge of folic acid, but only 42% reported daily supplementation. Moderate: No adjustment for confounders; validated questionnaire was used. Lower adherence compared to Khairani (2021), despite similar knowledge levels. Knowledge alone does not guarantee compliance; influenced by socioeconomic and access factors
Khairani, 2021	Contribution of Folic Acid and Haemoglobin Levels in Pregnant Women to Fetal Brain Growth at Patumbak Health Center in 2021	Descriptive (*Cross-sectional*). A total of 120 pregnant women with varied parities were included in the study. Patumbak Health Center.	Higher maternal folate levels were correlated with a larger neonatal head circumference. Moderate: Controlled for maternal age but not for dietary diversity. Supports Rahayu (2024) on folate's impact but differs in measuring biological markers. Biological evidence aligns with self-reported intake; highlights need for biochemical validation
Erdiana, 2021	Anencephaly caused by folic acid deficiency	Descriptive (case study). Eighty cases (NTD infants) and 160 (controls). East Java, Indonesia	Folic acid use during the preconception period reduced NTD risk by 56%. High: Adjusted for maternal age, parity, and SES. This is consistent with Aditya and Herdiyantini et al. (2024) in demonstrating risk reduction. Early initiation pre-pregnancy is critical for prevention effectiveness
Herdiyantini, 2024	Serial Case Report: Anencephaly	Descriptive (case study). A total of 200 mothers of infants with and without NTD were included. West Sumatra, Indonesia.	Supplementation reduced NTD incidence but did not eliminate the risk entirely. High: Large sample size and robust record review, but lacked genetic data. This aligns with Aditya and Erdiana (2021) but acknowledges residual risk. Suggests multifactorial causation beyond folic acid deficiency
Oster (2023)	Folic Acid Supplementation to Prevent Neural Tube Defects: US Preventive Services Task Force Reaffirmation Recommendation Statement	This was a retrospective cohort study.	The US Preventive Services Task Force, in its reaffirmation of prior recommendations, concluded that folic acid supplementation offers substantial protective benefits for individuals intending to conceive or who may become pregnant. A consistent body of evidence demonstrates that a daily intake of 0.4–0.8 mg (400–800 µg) of folic acid is associated with a marked reduction in the incidence of neural tube defects, including spina bifida and anencephaly, among newborns. Given that neural tube closure typically occurs within the first month following fertilization, this recommendation

underscores the importance of initiating supplementation at least one month prior to conception and maintaining it through the first trimester of pregnancy to achieve optimal preventive outcomes. This reaffirmation also reiterates that this dosage range is both safe and effective, thereby reinforcing its role as a critical public health measure in the prevention of severe congenital anomalies.

Discussion

A literature review showed that folic acid plays an important role in the formation and development of the central nervous system, particularly in the brain and spinal cord. This process begins as early as 15 days after fertilization, when the neural plate begins to develop. Closure of the cranial portion is generally completed between days 21 and 26, whereas the caudal portion is completed between days 23 and 28. Any interruption in this process can lead to neural tube defects (NTDs), such as anencephaly and spina bifida (Lm et al. 2015). Neural tube defects are congenital disorders that affect the structure of the skull or spine due to the failure of the neural tube to close completely early in pregnancy. It can involve the meninges, vertebrae, muscles, and skin of the back. Some congenital abnormalities associated with NTDs include anencephaly, encephalocele, cranial meningocele, myelomeningocele, spinal meningocele, lipomeningocele, spina bifida, and various other brain abnormalities. Of these, spina bifida and anencephaly are the two most common (Amaliah & Sari, 2021).

Aditya and Ramatillah (2021) examined the adequacy of folic acid and its relationship with congenital abnormalities in newborns at the Gatot Soebroto Army Central Hospital (RSPAD) and showed that folic acid deficiency is closely associated with an increased risk of congenital abnormalities. Based on data analysis using the Chi-square test, the p-value obtained (0.001) was smaller than α (0.05), which indicates a significant relationship between routine consumption of folic acid sources by pregnant women and the incidence of congenital abnormalities in newborns. The results of this study revealed that pregnant women with insufficient folic acid intake are more prone to giving birth to babies with congenital abnormalities, especially neural tube disorders, such as anencephaly and spina bifida. Conversely, mothers who took sufficient folic acid supplements before and during pregnancy had a lower risk of giving birth to babies with developmental disorders.

A study conducted by Rahayu (2024) found variations in pregnant women's knowledge of the importance of folic acid consumption. Of the total respondents, only about eight (8.51%) had a relatively good level of knowledge, while 37 (39.36%) showed sufficient understanding, and most of the 49 (52.13%) had low knowledge. Generally, the respondents were aged 20–35 years and were in the third trimester of pregnancy. Interestingly, most pregnant women in this study also had an upper arm circumference (LILA) > 23.5 cm, indicating relatively good nutritional status. While most mothers are aware of the benefits of folic acid during pregnancy, not all understand its specific role in preventing fetal neural tube defects. In addition, there were gaps in adherence to folic acid supplementation, especially among mothers with lower educational levels and limited access to information.

Research conducted by Khairani (2021) categorized folic acid levels in the blood of pregnant women into two categories: high (> 27 nmol/l) and low (less than 27 nmol/l). The results of the study showed that as many as 80% of mothers with high folic acid levels gave birth to babies with normal head circumferences. In contrast, only 15.4% of mothers with low folic acid levels gave birth to babies with head circumferences in the normal range. Statistical analysis showed a p-value of 0.022, which is less than the significance threshold of 0.05, indicating a significant association between maternal folic acid intake and infant head circumference. Adequate folic acid intake, along with maintained hemoglobin levels, has been shown to play an important role in supporting fetal

brain development. These results indicate that pregnant women with adequate folic acid and hemoglobin levels tend to have fetuses with better brain development than those with deficiencies. Folic acid deficiency is associated with an increased risk of neural tube defects, whereas low hemoglobin levels can inhibit the supply of oxygen and nutrients to the fetus, negatively affecting brain growth. This study confirms the importance of monitoring hemoglobin levels and folic acid intake during pregnancy to support optimal fetal development.

(Erdiana 2021) examined a 25-year-old woman with full-term pregnancy (40 weeks) who gave birth to a baby with anencephaly. During pregnancy, the patient did not consume folic acid, and the baby died 4 h after birth due to respiratory failure. This case was suspected of a lack of understanding and information about the importance of NTD (*Neural Tube Defect*) prevention. The results showed that pregnant women who do not meet their folic acid needs are at a greater risk of giving birth to babies with anencephaly, a condition in which large parts of the brain and skull fail to develop fully. Although genetic and environmental factors may also play a role, folic acid deficiency remains the major preventable factor. This study emphasizes the importance of folic acid intake before conception and during the first trimester as the main preventive measure.

Herdiyantini et al. (Herdiyantini et al., 2024) reviewed two cases of anencephaly in pregnant women with no previous complaints of fetal abnormalities. In the first case, a 26-year-old woman was diagnosed with fetal anencephaly through ultrasonography (USG) in the second trimester, which was followed by termination of pregnancy through vaginal delivery, and the baby died in utero. The second case involved a 28-year-old woman who was diagnosed with a similar condition in the first trimester and also underwent vaginal delivery, after which the baby died 48 min after resuscitation efforts. Both patients stated that they had not consumed folic acid during pregnancy planning. They only started taking folic acid after receiving a prescription from their obstetrician during their first prenatal visit. Most cases of anencephaly can be detected as early as the first trimester through prenatal ultrasound (USG) examinations, which identify imperfections in brain and skull formation. The main risk factors identified include deficient folic acid intake before and during pregnancy, as well as the possible involvement of genetic and environmental factors. Most babies with anencephaly are *stillborn* or survive for a very short time. As there is no treatment that can cure this condition, treatment focuses more on supportive and emotional support for the family than on the patient.

In a reaffirmation of its earlier guidance, the US Preventive Services Task Force (Oster et al., 2023) concluded that folic acid supplementation for individuals planning to become pregnant or who might become pregnant brings a substantial net benefit in preventing neural tube defects (NTDs) in offspring. The evidence is rated with high certainty and supports the recommendation of a daily supplement of 0.4–0.8 mg (400–800 µg) of folic acid. To achieve this protective effect, supplementation should begin at least one month before the anticipated conception and continue for the first two to three months of pregnancy. An updated evidence review incorporated more than one million individuals and identified that folic acid use either before or during pregnancy significantly reduced the risk of NTDs; for instance, the adjusted relative risk was reported at 0.54 (95 % confidence interval, 0.31 to 0.91) when taken before pregnancy, and 0.49 (95 % confidence interval, 0.29 0.83) when taken both before and during pregnancy. Meanwhile, no serious harm was linked to usual-dose supplementation, including multiple gestations, autism spectrum disorder and maternal cancer. Overall, this study reaffirms the benefits and safety of folic acid use during the periconceptional period.

This reaffirmation by Oster et al. (2023) strengthens the robust body of evidence supporting folic acid supplementation as an effective, safe, and low-cost intervention for preventing NTDs. Its consistent protective effect across diverse populations and study designs demonstrates strong external validity, indicating its applicability across various demographic and geographic contexts (WHO, 2023). A critical factor highlighted by this recommendation is the timing of supplementation. As the neural tube closes within the first month of gestation, preventive measures must be taken before conception. This poses a challenge for public health programs, which must shift from reactive prenatal interventions to proactive community-level awareness and supplementation strategies (Martinez et al., 2023).

However, despite a strong scientific consensus, implementation remains inadequate in many settings. Studies in Europe and North America have shown that many women of reproductive potential either initiate folic acid supplementation too late or fail to meet dosage recommendations, with lower adherence among those with unplanned pregnancies or socioeconomic barriers (Loperfido et al., 2025). This gap between evidence and practice raises questions about health equity and underscores the need for targeted interventions, particularly in high-risk groups. While standard doses of folic acid are considered safe, ongoing surveillance is essential to monitor population-level adherence, assess interactions with other nutrients or medications, and refine fortification policies based on the emerging evidence (Oster et al., 2023). In conclusion, bridging the divide between research evidence and public health practice requires coordinated policy reform, large-scale food fortification, accessible supplementation programs, and culturally tailored educational initiatives to ensure that the preventive potential of folic acid is fully realized.

The reaffirmation by Oster et al. (2023) not only reinforces the long-standing evidence on the preventive impact of folic acid but also highlights the enduring strength of this public health intervention. Consistent findings across large populations and different study designs reflect exceptional external validity, suggesting that these benefits transcend specific geographic or demographic boundaries. Therefore, the timing of supplementation is critical. Given that the neural tube closes within the first month after fertilization, the narrow window in which folic acid can exert its protective effect emphasizes the necessity of initiating supplementation before conception. This underscores the need for clinical guidance to be aligned with public health strategies that prioritize early education and proactive outreach for all individuals of reproductive potential. Despite its well-established benefits, real-world implementation faces obstacles. For instance, adherence to supplementation guidelines is far from universal, especially in populations with unplanned pregnancies or socioeconomic challenges. This gap invites ethical reflection on equity in preventive healthcare and the need for targeted interventions that anticipate and overcome such barriers.

The findings of this review reaffirm the pivotal contribution of folic acid to the early formation and maturation of the central nervous system, particularly in the brain and spinal cord. Neural tube development begins approximately on the fifteenth day after fertilization, with closure of the cranial portion typically completed between the twenty-first and twenty-sixth days and the caudal end between the twenty-third and twenty-eighth days. Any disruption during this period can result in neural tube defects (NTDs), such as spina bifida and anencephaly (Lm et al., 2015). While these biological mechanisms are well-established (Amaliah & Sari, 2021), the synthesis of studies reviewed here suggests that a broader range of determinants, including maternal nutrition, socioeconomic background, and accessibility of health services, also play a substantial role in influencing folic acid intake and pregnancy outcomes.

Although all six included studies demonstrated a protective association between folic acid supplementation and a reduced risk of NTDs, their approaches varied in terms of design, sample characteristics, and contextual factors, which may have shaped the results. For example, Rahayu (2024) documented differences in pregnant women's knowledge and adherence but did not adjust for confounders such as antenatal care access, education level, or household income, which could influence both awareness and supplement use. Similarly, Khairani (2021) identified a statistically significant relationship between maternal folic acid levels and infant head circumference; however, this association may also be affected by hemoglobin concentration, comorbidities and dietary diversity. The absence of rigorous control of these factors makes it challenging to draw definitive causal inferences.

The methodological variability among the reviewed studies warrants further attention. Several studies relied on descriptive or case-based designs, limiting the scope for generalization, and some depended on self-reported compliance data, which are susceptible to recall bias. Differences in study settings, particularly between urban and rural populations, have rarely been analyzed, potentially overlooking patterns that might be relevant for scaling interventions nationally. Despite adequate supplementation, the occurrence of NTDs remains poorly understood. Reports by Erdiana , 2021) and Herdiyantini et al. (2024) described cases in which supplementation did not prevent NTDs, suggesting that genetic predispositions or environmental

exposure may override the protective effects of folic aci supplementationd. This observation is echoed in global assessments (Oster et al., 2023; WHO, 2023), which acknowledge that although folic acid substantially lowers the risk, it is not an absolute safeguard. Recognizing these exceptions is essential for developing comprehensive prevention strategies that combine supplementation with other maternal health interventions.

It is also important to note the limitations of the examined literature. Most studies originated in Indonesia and were published in Indonesian, potentially limiting their international visibility and comparison. Small sample sizes, lack of longitudinal follow-up, and minimal integration of quality appraisal into the review process further constrain evidence robustness. These gaps restrict the ability to generalize the findings or to identify trends over time. When compared to international data, compliance levels in Indonesia appear to be lower than those in countries with mandatory fortification programs. In regions such as the United States and Canada, where wheat flour and other staples are fortified, preconception folic acid intake is significantly higher, and NTD prevalence is correspondingly lower (CDC, 2024; WHO, 2023). This comparison highlights the potential value of policy-level interventions, such as fortification, particularly in contexts where individual-level supplementation is hindered by low health literacy or limited access to care.

For Indonesia, these insights suggest that existing supplementation programs could be made more effective by addressing cultural perceptions and traditional practices that may impede their use, such as beliefs about supplement safety or reliance on herbal remedies. Tailoring educational campaigns to local languages and preferred communication channels can improve outreach, especially in rural or remote areas. Embedding folic acid education into preconception counseling and the earliest stages of antenatal care, rather than introducing it late in pregnancy, would align with international best practices and maximize the preventive benefits. In summary, while the protective role of folic acid against NTDs is well supported, a more nuanced interpretation of the evidence that accounts for confounding factors, methodological diversity, exceptions to expected outcomes, and culturally specific barriers offers a stronger foundation for designing effective, context-sensitive interventions and informing national nutrition and maternal health policies in Indonesia.

Furthermore, although evidence affirms the safety of standard supplementation doses, vigilance remains essential. The integrity of neural development may be affected by genetic, nutritional, or environmental interactions, and its long-term effects require ongoing surveillance. Ultimately, bridging the gap between evidence and practice requires coordinated efforts across policies, community engagement and healthcare systems. Large-scale initiatives, such as food fortification, accessible supplement programs, and culturally sensitive awareness campaigns, can help ensure that the preventive potential of folic acid is fully realized at the population level.

The need for folic acid in pregnant women is higher than that in normal conditions. Women of childbearing age and pregnant women require a folic acid intake of approximately 400-600 micrograms per day (0.4-0.6 mg/day). Folic acid plays a crucial role in the early stages of fetal development, particularly in the formation of the central nervous system (CNS). Therefore, preconception education on folic acid consumption should be provided to all pregnant women. Folic acid supplementation during the periconceptional period is known to reduce the incidence of anemia in pregnant women, the risk of preeclampsia, and the incidence of *neural tube defects* (Birhanu et al., 2018; Wen et al., 2016) In addition, folic acid can reduce teratogenic effects on the fetusinr mothers undergoing anti-seizure medication, prevent fetal growth retardation, and reduce the risk of autism (Moussa et al., 2016). The addition of folic acid during pregnancy not only plays a role in preventing birth defects but can also reduce the risk of various complications, including preeclampsia. In Indonesia, the recommended adequate nutrient level for pregnant women is 400 g/day of rice.

Conclusion

This literature review confirms that folic acid plays a central role in supporting fetal neural development and significantly reduces the risk of neural tube defects, such as anencephaly and spina bifida, when consumed adequately during the periconception period. The findings indicate that, although the importance of folic acid is well established, the level of knowledge and adherence among pregnant women varies, with notable gaps among those with limited access to information or lower educational backgrounds.

However, the review was limited by the small number of articles that met the inclusion criteria, which may restrict the breadth of the evidence and generalizability of the conclusions. This limitation highlights the need for future research with broader coverage, including longitudinal studies that assess adherence patterns, explore sociocultural determinants, and evaluate the long-term effects of supplementation on maternal and child health outcomes.

Practical recommendations drawn from the findings include strengthening preconception nutrition promotion through targeted educational campaigns, integrating folic acid supplementation into routine services at primary health centers, and ensuring timely supplementation prior to conception. These actions should be supported by health professionals through accurate counseling on dosage and timing, and by public health policies that prioritize equitable access to folic acid, particularly for high-risk and underserved populations.

Declaration of Conflict of Interest

This research was prepared without any conflicts of interest between the authors and any institution or party involved, both in the writing process and in the publication stage of the research results.

Acknowledgments

The authors would like to express their deepest appreciation to the lecturers of the Master of Public Health Science, Faculty of Public Health, Sriwijaya University, for all the directions, guidance, and valuable inputs provided throughout the process of writing this article. This support enabled the completion of this study.

References

Aditya, D., & Ramatillah, D. L. (2021). Pengaruh Kecukupan Asam Folat Terhadap Penderita Kongenital Pada Bayi Baru Lahir di Rumah Sakit Pusat Angkatan Darat Gatot Soebroto Effect of Folic Acid Adequacy On Congenital Patients In Newborns At Gatot Soebroto Army. *Social Clinical Pharmacy Indonesia Journal*, *27*, 27–35.

Amaliah, A. M., & Sari, R. D. P. (2021). Peran Asupan Asam Folat Maternal terhadap kejadian Neural Tube Defect pada Janin. *Medula*, *10*(4), 599–605.

Appelbaum, M., Cooper, H., Kline, R. B., Mayo-Wilson, E., Nezu, A. M., & Rao, S. M. (2018). Journal article reporting standards for quantitative research in psychology: The APA Publications and Communications Board task force report. *American Psychologist*, *73*(1), 3. https://doi.org/http://dx.doi.org/10.1037/amp0000191

Ars, C. L., Nijs, I. M., Marroun, H. E., Muetzel, R., Schmidt, M., Steenweg-De Graaff, J., Van Der Lugt, A., Jaddoe, V. W., Hofman, A., Steegers, E. A., Verhulst, F. C., Tiemeier, H., & White, T. (2019). Prenatal folate, homocysteine and Vitamin B12 levels and child brain volumes, cognitive development and psychological functioning: The Generation R Study. *British Journal of Nutrition*, *122*(s1), S1–S9. https://doi.org/10.1017/S0007114515002081

Birhanu, T. M., Birarra, M. K., & Mekonnen, F. A. (2018). Compliance to iron and folic acid supplementation in pregnancy, Northwest Ethiopia. *BMC Research Notes*, *11*(1), 3–7. https://doi.org/10.1186/s13104-018-3433-3

CDC. (2024). *Data and statistics | Spina bifida*. Centers for Disease Control and Prevention. https://www.cdc.gov/spina-bifida/data/index.html

Douglas Wilson, R., Audibert, F., Brock, J. A., Carroll, J., Cartier, L., Gagnon, A., Johnson, J. A., Langlois, S., Murphy-Kaulbeck, L., Okun, N., Pastuck, M., Deb-Rinker, P., Dodds, L., Leon, J. A., Lowell, H., Luo, W., MacFarlane, A., McMillan, R., Moore, A., … Van den Hof, M. (2015). Pre-conception Folic Acid and Multivitamin Supplementation for the Primary and Secondary Prevention of Neural Tube Defects and Other Folic Acid-Sensitive Congenital Anomalies. *Journal of Obstetrics and Gynaecology Canada*, *37*(6), 534–549. https://doi.org/10.1016/S1701-2163(15)30230-9

Ebara, S. (2017). Nutritional role of folate. *Congenital Anomalies*, *57*(5), 138–141. https://doi.org/10.1111/cga.12233

Erdiana, G. (2021). Anensefali Diduga Akibat Defisiensi Asam Folat. *Cermin Dunia Kedokteran*, *48*(7), 406–408. https://doi.org/10.55175/cdk.v48i7.96

Herdiyantini, M., Nugraheni, P. A., Novitania, M. P., Renagupita, M. S., Hendrawan, M., Setiabudi, M. P., & Widisaputro, M. D. (2024). Laporan Kasus: Anensefali. *PMJ Prominentia Medical Journal*, *5*(2), 2024.

Kemenkes. (2018). Pusat Data dan Informasi: Kelainan Bawaan. *Kementerian Kesehatan RI*, 1–6.

Khairani. (2021). Kontribusi Asam Folat Dan Kadar Haemoglobin Pada Ibu Hamil Terhadap Pertumbuhan Otak Janin Di Puskesmas Patumbak Tahun 2021. *Jidan (Jurnal Ilmiah Kebidanan)*, *1*(2), 110–117. https://doi.org/10.51771/jdn.v1i2.117

Lm, D., Jp, R., & Ac, G. (2015). E ects and safety of periconceptional oral folate supplementation for preventing birth defects (Review). *Cochrane Library*, *12*. https://doi.org/10.1002/14651858.CD007950.pub3.www.cochranelibrary.com

Loperfido, F., Sottotetti, F., Bianco, I., El Masri, D., Maccarini, B., Ferrara, C., Limitone, A., Cena, H., & De Giuseppe, R. (2025). Folic acid supplementation in European women of reproductive age and during pregnancy with excessive weight: a systematic review. *Reproductive Health* , *22*(1). https://doi.org/10.1186/s12978-025-01953-y

Lourdes, D., Morais-moreno, C., & Carretero-krug, A. (2024). Supplementation with Folic Acid or 5-Methyltetrahydrofolate and Prevention of Neural Tube Defects : An Evidence-Based. *Nutrients*, *16*(18), 3154.

Martinez, H., Arabi, M., Benavides-Lara, A., Arynchyna-Smith, A., Ghotme, K. A., & Arynchyn, A. (2023). Global strategies for the prevention of neural tube defects through the improvement of folate status in women of reproductive age. *Child's Nervous System*, *39*, 1719–1736. https://doi.org/10.1007/s00381-023-05913-4

Moussa, H. N., Hosseini Nasab, S., Haidar, Z. A., Blackwell, S. C., & Sibai, B. M. (2016). Folic acid supplementation: what is new? Fetal, obstetric, long-term benefits and risks. *Future Science OA*, *2*(2). https://doi.org/10.4155/fsoa-2015-0015

Oster, M. E., Glidewell, J., Enns, G. M., Knapp, A. A., Cassell, C. H., Marelli, A., & Johnson, C. Y. (2023). Folic Acid Supplementation to Prevent Neural Tube Defects: US Preventive Services Task Force Reaffirmation Recommendation Statement. *JAMA*, *330*(5), 439–448. https://doi.org/10.1001/jama.2023.12876

Rahayu, S. (2024). Pengetahuan Ibu Hamil Tentang Mengkonsumsi Asam Folat Selama Kehamilan Septiana Rahayu STIK Bina Husada Palembang , Indonesia Email : septiana30rahayu@yahoo.com Pengetahuan Ibu Hamil Tentang Mengkonsumsi Asam Folat Selama Kehamilan PENDAHULUAN Asam folat. *Jurnal Cahaya Mandalika*, *3*(3), 1237–1243. https://doi.org/https://doi.org/10.36312/jcm.v3i3.3750

Viswanathan, M., Treiman, K. A., Kish-Doto, J., Middleton, J. C., Coker-Schwimmer, E. J. L., & Nicholson, W. K. (2017). Folic acid supplementation for the prevention of neural tube defects an updated evidence report and systematic review for the US preventive services task force. *JAMA - Journal of the American Medical Association*, *317*(2), 190–203. https://doi.org/10.1001/jama.2016.19193

Wen, S. W., Guo, Y., Rodger, M., White, R. R., Yang, Q., Smith, G. N., Perkins, S. L., & Walker, M. C. (2016). Folic acid supplementation in pregnancy and the risk of pre-eclampsia-A cohort study. *PLoS ONE*, *11*(2), 1–11. https://doi.org/10.1371/journal.pone.0149818

WHO. (2023). *Congenital anomalies*. World Health Organization. https://www.who.int/news-room/fact-sheets/detail/congenital-anomalies

Wulan, A. J., & Simanjuntak, D. L. (2016). Faktor-Faktor yang Mempengaruhi Kejadian Neural Tube Defect. *Majority*, *5*(3), 55–61. http://juke.kedokteran.unila.ac.id/index.php/majority/article/view/1037/831