Review Article

Folic acid protection in congenital neural tube defects: A narrative review

ABSTRACT

Introduction. Neural tube defects, a congenital malformation of multifactorial source, affect more than 200,000 to 300,000 births a year, and are twice as common in developing countries. Food fortification with folic acid has been shown to be effective reducing this congenital malformation. The aim of this study was to look for evidence on the efficacy, interval and best dose of folic acid tobeadministered in the prophylaxis of neural tube defects.

Method. Narrative literature review, using the PubMed database, available at: https://pubmed.ncbi.nlm.nih.gov/, using the keywords "Folic Acid and Pregnancy and Neural Tube", and applying the filters "Systematic review" and "last five years". Two researchers independently selected articles on the effects of folic acid in preventing neural tube birth defects.After reading the titles and abstracts, 11 of the 21 articles selected were read in full and all were included in the review. Another nine articles obtained from the PUBMED database, using the same keywords and published in the year 2023, were included to discuss the synthesis of the data.

Synthesis of the data. Neural tube defects were associated with family history, previous stillbirth, unplanned pregnancy, stress during the periconceptional period, lack of prenatal care, use of alcohol, tobacco and exposure to medicines, pesticides, maternal age over 35, chronic maternal illness and low schooling. No evidence of side effects was found as to the supplementation with folic acid. Daily supplementation with 400-800µg, starting 1.5 months before conception and lasting 4 months, prevented the occurrence of neural tube defects and dietary supplementation with folic acid reduced the occurrence of the disease.

Conclusion: Current evidence indicates that folic acid supplementation for pregnant women, starting at 1.5 months before conception and lasting for 4 months, protects against congenital neural tube defects.

Keywords: Folic Acid, Pregnancy, Neural Tube

Introduction

Neural tube defects (NTDs) are the second most frequent group of congenital malformations[1,2,] resulting from the failure of the tube to close during embryogenesis, which occurs around the 21st to 28th day after fertilization[3,4,5].

The cause of this malformation is multifactorial and includes genetic and environmental factors and maternal age[2,3,4,6]. Insufficient folate levels during conception is the main preventable cause of NTDs[3,45]and can prevent 50-70% of cases[6].

The most common presentation is spina bifida, which is usually accompanied by neurological deficits, including the possibility of anencephaly[3], associated with variable morbidity and mortality in the neonatal and post-neonatal periods[4,5].

The worldwide prevalence of NTDs is two per 1,000, with double the occurrence in low-income countries, proving to be a major health problem in developing countries[3,4], generating substantial psychological and socio-economic costs[3,7,8].

Folic acid (Vitamin B9) supplementation, in synthetic form, before and during pregnancy, prevents the occurrence of NTDs[9,10], as well as protecting against low birth weight and maternal megaloblastic anemia[10]. The recommended daily dose for supplementation follows different protocols as established in Australia (400-500 mcg), USA (800mcg) and Canada 1000mcg[11].

Therefore, the aim of this review, based on systematic reviews published in the last five years, is to seek evidence on the effectiveness, interval and best dose to be administered in the prophylaxis of neural tube defects.

Method

Narrative review, with data search on December 20, 2023, where two researchers independently selected articles on the effects of folic acid in the prevention of neural tube birth defects. The search was carried out on the PubMed database, available at https://pubmed.ncbi.nlm.nih.gov/, using the keywords "Folic Acid and Pregnancy and Neural Tube", and applying the filters "Systematic review" and "the last five years' time span". The search resulted in 21 articles, which were submitted to an analysis of their titles and abstracts. Publications that did not directly address the topic and duplicates were excluded. Eleven articles remained, which were read in full and included in the

review. In addition, nine more articles published in the PUBMED database in 2023, using the same keywords and which did not include systematic reviews, served to support the discussion on data synthesis.

Data overview

A total of 11 systematic review studies were chosen for inclusion in this review, which included a total of 246 studies involving 14,307,439participants, as shown in Table 1.

Table 1 - Identification of the articles and the number of patients included in the 11 articles used in this descriptive review that evaluated the effects of folic acid on the prevention of congenital neural tube defects.

Reference	Articles included	Individuals included
1. Ssentongo, Paddy, et al. 2022	20	752,936
2. Tesfay, Neamin, et al.	42	611,064
3. Bitew, Zebenay Workneh, et al. 2020	15	540,980
4. Atlaw, Daniel, et al 2021	37	6,136,980
5. Viswanathan, Meera, et al. 2023	12	Not provided
6. Wang, Meng, et al. 2023	6	3,056
7. Rodrigues, et al. 2021	13	Not provided
8. Oumer, et al. 2021	43	6,086,384
9. Cheng, Zhengpei, et al. 2022	21	106,920
10. Rubin, Gal, et al. 2023	1	225
11. Ledowsky, Carolyn, et al. 2022	36	68,894
Total	**246**	**14,307,439**

In nine (81.8%) studies, the use of folic acid during pregnancy was described as a protective factor for NTDs[1-7,9,10].

Three (27.3%) reviews studied the adverse effects of folic acid supplementation, and found no evidence of a causal relationship for multiple gestation, autism, maternal cancer[5], ankyloglossia[10] and decreased risk of congenital heart disease[9].

Five (45.5%) reviews evaluated the determinants and risk factors for the development of neural tube defects, finding positive family history[2,3], unplanned pregnancy[3], stressful events for women in the periconceptional period[6], not having prenatal care, use of alcohol and tobacco during pregnancy, chewing the khat plant*(Catha edulis*), a

hallucinogenic plant, exposure to pesticides, maternal age ≥35 years, previous maternal chronic diseases such as diabetes and chronic hypertension and low maternalschooling[2].

In Africa, previous history of stillbirth, exposure to pesticides and X-rays in the first trimester of pregnancy were found to be predisposing factors for NTDs[4]. A systematic review and meta-analysis found no significantly relevant statistics for the risk factors evaluated, such as the use of folic acid, consanguineous marriage and substance abuse during pregnancy[8].

One study (9.1%)[7] evaluated the cost-effectiveness of mandatory fortification of foods with folic acid in the prevention of NTDs, observing that most folate dosages were cost-effective and offered positive health gains. Another review[11] evaluated whether the dosages of supplementation or fortification were adequate, but did not assess their relationship with the reduction of neural tube defects, noting that most fortifications do not reach adequate levels of folic acid while most supplementations exceed the upper limit of 1000µg.

Discussion

The strength and importance of this narrative review, built on systematic reviews, lies in the fact that it included almost 250 articles that passed strict inclusion criteria, involving more than 14,300,000 participants, in the search for the best evidence on dosage, the start and duration of treatment, side effects and the protective role of folic acid in preventing neural tube defects.

One of the limitations of this review is that no evidence was found on the best dose and the ideal interval for administering supplementation. However, this limitation was met by the studies used to discuss the synthesis of the data.

The disease has multiple risk factors and an approximate rate of 214,000 to 322,000 pregnancies worldwide every year, with an occurrence almost double that in developing countries[12], justifying every investment in its prevention.

The high morbidity and mortality from the neonatal period and during childhood resulting from this malformation[3,5], strengthen the need for prevention, considering that

observational studies affirm the benefit of folic acid supplementation in preventing these diseases[5].

Current guidelines recommend that all women who are planning to or may become pregnant take a daily supplement containing 400-800µg of folic acid[12,13]. Supplementation should begin 1.5 months before conception and last for 4 months[14.] Adjusting the supply period is important in order to safely achieve optimum levels of prevention and maximum benefits[15]and attention should be paid to pregnant women's adherence to supplementation[16.]

Non-evidence-based communications report risks about drug supplementation during prenatal care, considering the possibility of drug overdose in parallel with the offer of foods enriched with folic acid,[17,18]but current evidence reinforces that the benefits of supplementation far outweigh the possible risks[10,19]. The controversy is based on the fact that food fortification policies with folic acid have been implemented in manycountries[12], however, a drastic reduction in NTDs has been observed in countries that have implemented food fortification with folic acid[20].

Conclusion:

Current evidence indicates that folic acid supplementation for pregnant women, started at 1.5 months before conception and lasting for 4 months, protects against congenital malformations of the neural tube, without causing significant adverse effects. There is a need for new systematic reviews on the optimal dose and interval for folate supplementation in pregnant women.

References

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