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Review Article

Prospective Guidelines for Folic Acid Supplementation in Periconception Care for the Prevention of Neural Tube Defects

Emmanuella Solomon[1,2] and Nicholas A Kerna[3]*

[1]*University of Health and Humanities, Tortola, BVI*

[2]*University of Science, Arts and Technology, Montserrat, BWI*

[3]*SMC–Medical Research, Thailand*

***Corresponding Author**: Nicholas A Kerna, POB47 Phatphong, Suriwongse Road, Bangkok, Thailand 10500. Contact: medpublab+drkerna@gmail.com

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Abstract

Neural tube defects (NTDs) are unwanted congenital expressions associated with a folic acid deficiency in pregnant mothers. In the United States, 1–2 per 1000 children are born each year with disruptive anomalies due to neural tube defects. Augmenting the diet with folic acid (vitamin B9) supplementation by the maternal parent before conception and during the first trimester of pregnancy reduces the risk of NTDs in children. Folic acid and folate cannot be synthesized in sufficient amounts by the body and must be obtained from the diet or supplementation. Many women have sub-optimal levels of folic acid, which is essential for nucleic acid synthesis. Folic acid supplementation in pregnancy dates to the 1930s and 1940s. Currently, folic acid is recommended and prescribed for pregnant women and during preconception. However, an excess amount of folic acid can have adverse effects on the mother and fetus. Thus, an optimal folic acid prescribed dosage should be further investigated. Some studies have demonstrated that the current standard of folic acid supplementation could be more than what an individual woman's body needs and can utilize, and excessive folic acid supplementation could prove harmful. A woman's existing folic acid levels are rarely evaluated before recommending the standard, "one-size-fits-all" recommendation. Thus, it would be more effective (and potentially less harmful) to determine a woman's folic acid level, and to prescribe an optimal dose customized for the individual. The following review provides 1) a historical backdrop to neural tube defects and folic acid, 2) describes the current folic acid supplementation protocol, and 3) suggests a more effective and potentially less harmful folic acid screening and supplementation regime. Continuing research and refining folic acid supplementation in periconception is worthwhile and fundamental as there are high financial and emotional costs associated with folic acid-related NTDs.

Keywords: *Anaemia; Birth Defects; Folate; Folic Acid; Neural Tube Defects; Periconception; Pregnancy*

Abbreviations

CDC: Centers for Disease Control and Prevention; CSF: Cerebrospinal Fluid; DHF: Dihydrofolate; DHFR: Dihydrofolate Reductase; MTHRF: Methylenetetrahydrofolate Reductase; NTD: Neural Tube Defect; RBC: Red Blood Cell; THF: Tetrahydrofolate

Introduction

Neural tube defects (NTDs) are severe congenital anomalies, such as spina bifida, anencephaly, and encephalocele (rarely). NTDs are due to a defect in the neurulation process in embryogenesis. This defective neurulation process causes incomplete closure of the neural tube, resulting in neural tissue deformity at the upper, middle, or lower portion of the spine during the third to the fourth week after conception—about day 26–28 post-conception [1]. This abnormality appears as an opening in the spine, spinal cord, or brain.

NTDs affect over 2500 infants born annually in the United States [2]; 1–2 per 1000 children are born each year with an NTD. Taking folic acid, also called vitamin B_9, by the maternal parent before conception and during the first trimester of pregnancy has been shown to reduce the risk of NTDs by 70 percent [3]. Folic acid is required for making red blood cells, the synthesis and repair of DNA and RNA, and the development of the brain and nervous system of the fetus.

Periconception care is a set of interventions that aim to identify and modify nutritional, biomedical, behavioral, and social risks to the mother's health or pregnancy outcome through prevention and management. Specific steps should be taken before conception or early in pregnancy to maximize health outcomes of the mother and child [2]. Hibbard (1964) noted that many women in their childbearing years did not take folic acid because they did not know about the importance of folic acid supplement, or the pregnancy was unexpected [4]. The signs and symptoms of folic acid deficiency are fatigue, weakness, sores around the mouth, irritable mood, loss of appetite, weight loss, and memory and cognition imparment. Folic acid deficiency has also been associated with macrocytic anaemia [5] and peripheral neuropathy in the mother; congenital abnormalities of the heart, face, limbs, and renal system, the manifestation of cleft palate, and cleft lip of the fetus have also been noted [6]. There is a need to emphasize the importance to women in supplementing their diet with folic acid in their reproductive years (12–45 years of age) and at least three months before pregnancy, during pregnancy, and after delivery [3].

Historical context of folic acid in preconception care

Folic acid was named in 1941 after being isolated from spinach; folium is "leaf" in Latin. Folic acid supplementation in pregnancy dates to the 1930s and 1940s, when folic acid deficiencies were treated with liver and yeast extracts. Lucy Wills, an English hematologist, investigated macrocytic anaemia in pregnancy in India. Wills noted that the anaemia was most prevalent in more impoverished people with diets deficient in protein, fruits, and vegetables. Subsequently, Wills investigated the effect of dietary changes in rats with macrocytic anaemia [7]. In 1931, Wills discovered that yeast or yeast extract, called Marmite, prevented and corrected the macrocytic anaemia in the pregnant Bombay patients [8]. Wills treated several anemic women with Marmite, who showed remarkable improvement in their anaemic conditions.

Wills (1931) reported that patients with tropical macrocytic anaemia were cured by injections of crude liver extract, called Campolon, or by consuming autolyzed yeast extract; however, no response was noted using a purified liver extract called Anahaemin [8]. Wills and Evans (1938) reported that purified liver extracts do not correct nutritional, pregnancy-related, or macrocytic anaemia [9]. In New York in 1943, Bob Stokstad synthesized a pure crystalline form of folic acid [10]. Chanarin (1990) reported that folate deficiency is due to the increased metabolic demands in pregnancy and many bone marrow and other disorders [6]. Researcher Victor Herbert consumed a folate-deficient diet for four months while assaying folate in his blood. Herbert demonstrated that it took four months for megaloblastic anaemia to develop from a folate-deficient diet [11].

Rickes., *et al.* (1948) isolated vitamin B_{12} (cobalamin) from the liver and determined that B_{12} was needed for the treatment of anaemia and neuropathy in Addisonian anaemia (pernicious anaemia) [12]. Metz (2013) established that prophylactic folic acid reduced the incidence of prematurity in undernourished pregnant populations [13]. Furthermore, it was found that those receiving antifolate chemotherapy during pregnancy had an NTD-affected pregnancy outcome. Hibbard (1964) demonstrated an association between folate deficiency and megaloblastic anaemia, along with NTDs [4]. Smithells., *et al.* (1976) discovered that patients with megaloblastic anaemia

caused by pregnancy had a high incidence of NTDs [14]. Hibbard and Smithells (1965) ascertained that folate deficiency might lead to complications in pregnancy—other than megaloblastic anaemia in the mother [15]. These complications included abruptio placentae, antenatal hemorrhage prematurity, and NTDs (anencephaly, encephalocele, and spina bifida). Laurence., *et al.* (1981) performed a folate-intervention trial, which established that folic acid therapy (4 mg daily given during periconception) afforded about 75% protection to pregnant women—who had already given birth to an NTD-affected infant—from having a second child with the same defect [16]. Czeizel and Dudas (1992) in Hungary and Scott and Weir (1998) in Dublin reported the prevention of NTDs by giving folic acid during periconception [17,18]. Kirke., *et al.* (1993) showed that the addition of 400 µg of folic acid into the diet is needed to raise red cell folate levels to those levels associated with a reduction in NTD incidence in at-risk mothers [19}.

Discussion

Folic acid and folate cannot be synthesized by the body in sufficient amounts and must be obtained from the diet or supplementation. Folate is essential for nucleic acid synthesis and methylation reactions as a methyl donor in one-carbon metabolism [20,21]. Folate is a B vitamin found naturally in foods. Folic acid is the synthetic form of folate that can be added to food or used as an ingredient in vitamin supplements. The body absorbs folic acid more rapidly than folate. Neither folic acid or folate is metabolically active. Both forms must be reduced to participate in cellular metabolism [20,21].

L-5-methyltetrahydrofolate (L-methylfolate) is the predominant micronutrient that circulates in the plasma and is involved in biologic processes. To become metabolically active, folic acid must first be converted to dihydrofolate (DHF) and then tetrahydrofolate (THF) by the enzyme dihydrofolate reductase (DHFR). After those processes, THF can be converted to biologically-active L-methylfolate by the enzyme methylenetetrahydrofolate reductase (MTHFR). This last step is necessary to provide L-methylfolate for the one-carbon transfer reactions; methyl donations are needed for purine and pyrimidine synthesis during DNA and RNA assembly and for DNA methylation [20–22]. MTHFR is the critical enzyme for nearly all biologic processes that involve the metabolism of folate and methionine. Periconceptional folate deficiency increases the risk of congenital malformations, especially NTDs [21,22].

NTDs can be classified as open or closed types based on embryological considerations and the presence or absence of exposed neural tissue. Open NTDs are a result of the failure of the neural tube to close properly along the dorsal midline. Neural tissue is wholly exposed or covered by a membrane with associated leaking cerebrospinal fluid (CSF). Open NTDs represent about 80% of all NTDs, the most common NTDs being meningocele or spina bifida, myelomeningocele, encephalocele, and anencephaly. Closed NTDs are localized and confined to the spine; the brain is rarely affected [14]. These irregular closures result from a defect in secondary neurulation. Neural tissue is not exposed, and the defect is fully covered by epithelium, although the skin covering the defect may be dysplastic with a tuft of hair, dimple, birthmark, or other superficial abnormality. Cranial manifestations include anencephaly, encephalocele (meningocele or meningomyelocele), craniorachischisis totalis, or congenital dermal sinus. The spinal presentation includes spina bifida occulta, spina bifida (with a dermoid cyst), spina bifida aperta (meningocele, myelomeningocele, meningomyelocele, or myeloschisis), split-cord malformations, diastematomyelia, diplomyelia, caudal agenesis, lipomatous malformations, or lipomyelomeningocele [20].

Current treatment regarding folic acid in periconception care

Most women do not take folic acid regularly. In one study, about 30% of women received folic acid pre-pregnancy. A majority of the women in the study (61%) reported they were not planning to get pregnant, while the remaining women did not know they needed folic acid [2]. Most women learn they are pregnant (after the missed first or second menstrual flow), then schedule an appointment with their physician or obstetrician. The physician routinely prescribes prenatal vitamins, which include the daily required folic acid. Thus, these women start supplementing folic acid after day 28 of gestation, at which point the neural tube has already closed and any neural tube defects are in place. During the early stage of pregnancy, there can be a lack of compliance in taking folic acid tablets, due to the

fear and discomfort of nausea and vomiting associated with morning sickness, characteristic in the first trimester of pregnancy. Some women avoid eating bread due to gluten sensitivity or want to reduce carbohydrate intake; therefore, they may lack dietary folic acid [22]. Generally, higher doses of folic acid may also be needed in sickle cell disease, liver disease, kidney disease (on dialysis), alcoholism, epilepsy (on medication), type 2 diabetes, lupus, psoriasis, rheumatoid arthritis, asthma or inflammatory bowel disease.

Pros and cons of the current treatment recommendations for folic acid supplementation during periconception

Neural tube defects in the United States have been associated with over $85 million in hospital cost per year [23]. It is beneficial to take folic acid during pregnancy to prevent or treat megaloblastic anaemia and peripheral neuropathy in the mother. An existing folate deficiency may affect the baby before a mother begins prescribed prenatal folic acid. Folic acid or folate is present in specific foods, such as brown rice, green leafy vegetables (broccoli and spinach), peas, beans, nuts, sunflower seeds, cereal, liver, citrus fruits, and many other fruits and vegetables. However, it is difficult to calculate the amount of folic acid or folate to ensure adequate intake. The United States has implemented the fortification of cereals with folic acid to ensure folate intake by the general population. The U.S. program adds 140 μg of folic acid per 100g of enriched cereal grain product, which has been estimated to provide 100–200 μg of folic acid per day for women of child-bearing age. For example, eating a bowl of cereal (394 μg) for breakfast, pretzels (172 μg) as a snack, a cup of cooked spaghetti (166 μg) for dinner, and a multivitamin will provide more than 1100 μg of folic acid. Currently, there is no reliable evidence that the 4 mg of folic acid given to high-risk women is more effective than 1 mg or less in preventing primary and recurrent NTDs. Higher than 1 mg of folic acid decreases the proportional absorption of folic acid. Recurrence risk for a fetus with an NTD is shared by the mother's and father's reproductive history; however, typically, only the mother is treated with the supplemental dose of preconception and first-trimester folic acid. A comprehensive Canadian analysis of neural tube reduction following flour fortification reported a 46% decrease in NTDs with a 53% reduction in spina bifida, a 38% reduction in anencephaly, and a 31% reduction in encephalocele [24].

Due to folic acid supplementation and fortification, high concentrations of folate and unmetabolized folic acid have been detected in most maternal and fetal circulations as well as in breast milk [17,19]. A report from the Framingham Heart Study showed that most Americans have some folic acid in their blood, and 20% have high folic acid levels. It was reported that high folic acid intake might mask a vitamin B_{12} deficiency [15,19,20,22]. This masking could allow a B_{12} deficiency to progress to a state of confusion, dementia, or severe and irreversible damage to the nervous system, especially in vegetarians. An excess of folic acid corresponded to an incidence of twin births [25], accelerated cancer progression [26], and suppressed thyroid function with a deficit in motivation and spatial memory, and might be associated with an increased risk of autism spectrum disorder, insulin resistance, and asthma [27]. Several studies have suggested that ingesting excessive amounts of folic acid might cause depression, cognitive impairment [28], and promote colorectal, breast, and prostate cancers by keeping folate out of the cells and inducing aberrant patterns of DNA methylation, leading to carcinogenesis. One trial showed that taking high doses of folic acid after angioplasty increased the chances of having a recurrence of artery-clogging—all of these being as mentioned above, possible adverse effects of unmetabolized synthetic folic acid. Thus, it has been suggested that L-methylfolate, rather than folic acid, may reduce the risks of developing these adverse effects [29].

Something new in periconceptional folic acid recommendations

It is recommended that women take 400 μg of folic acid daily for at least three months before conception to assure that they have adequate folate stores during pregnancy [30]. Once pregnant, it is advised that women should increase the amount of folic acid intake to 600 μg and maintain a daily intake of 500 μg while they are lactating [31]. The Centers for Disease Control and Prevention (CDC) recommends that every woman of reproductive age receive at least 400 μg of folic acid every day. Women who have had a prior NTD-affected pregnancy, a first degree relative with an NTD, or are themselves affected by an NTD, and women with diabetes, epilepsy, and malabsorption are at a higher risk of having a child with the same defect. Thus, they should seek genetic counseling regarding the risks, pregnancy management, and the appropriate dose of folic acid to take beginning three months before conception, or at least one month

before.

Currently, high-dose folic acid supplements—4000 µg (4 mg daily)—are being prescribed to all at-risk women without assessment of their folate status. This recommendation should change as there is no reliable evidence that a 4 mg-intake is more effective than 1000 µg (1.0 mg) in preventing primary or recurrent NTDs. The current recommendation is 400–800 µg per day for all patients, in conjunction with an assessment of maternal folate status. The normal range of folic acid in the blood is between 2.7 and 17.0 nanograms per milliliter. Higher levels may indicate vitamin B_{12} deficiency [26].

Suggestion regarding a safer folic acid supplemental protocol

It is suggested to educate healthcare providers and women of childbearing age regarding more appropriate and contemporary use and dosage of folic acid supplementation before and during pregnancy. Creating public awareness of the prevention of NTDs through optimal folic acid supplementation can make the difference between a healthy baby or one with a disability. For women at high risk of having an NTD-pregnancy outcome, measuring red blood cell (RBC)-folate concentrations as part of routine preconception care is vital. Clinicians should only prescribe the necessary level of folic acid supplementation (up to 1.0 mg)—according to a woman's individual needs—to achieve optimal folic acid concentration and avoid any consequences of taking an excessive amount [32]. Additional research is needed to assess health risk of folic acid supplementation when the current upper limit of 1mg for folic acid is exceeded.

Conclusion

The clinical application of the supplemental intake of folic acid and folate to prevent neural tube defects has been well established in the last 20–25 years. For parents, the cost of consuming folate-rich food and daily folic acid supplements is better than the financial burden and emotional pain of having children with neural tube defects and other congenital defects [23]. Supplementation with an adequate and appropriate dose of folic acid in periconception care is vital in preventing neural tube defects. However, the total daily folic acid intake should not be more than 1 mg, even for high-risk women.

Conflict of Interest

The authors declare that this paper was written in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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