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ORIGINAL ARTICLE

Indian Perspective on Clinical Aspects, Usage, and Guidelines of Folic Acid

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Abstract Folic acid (pteroylmonoglutamic acid) is the stable, fully oxidized form of folate which is used in food fortification and supplements. Keen interest has been generated in folic acid due to its suggested role in prevention of various disorders. Strong evidence from clinical trials indicates preventive effect of folic acid on both occurrence and recurrence of neural tube defects. It also plays a significant role in mitigating the risk of cardiovascular disorders through homocysteine regulation. In addition, the beneficial effect of folic acid in various types of cancers, neurological disorders, conditions affecting pregnancy, and other clinical conditions has been reported in literature. Various guidelines reinforce the need for women to obtain adequate amount of folic acid either through food fortification or supplements. In India, national guidelines on the proper dose of folic acid to pregnant women are not available. Given its significant beneficial effects on health, awareness should be spread among communities on the usage and benefits of folic acid.

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Introduction

The attention of scientific community on folic acid has significantly increased in the recent times in comparison with other nutrients. The immense potential of this vitamin in the treatment of a range of important disorders has been recognized [1]. Folate describes a series of pteroylglutamic acid molecules with variable number of glutamic acid side chains. Folate is a generic term used to denote food folate, the naturally occurring folate in foods (food folate) and folic acid, the synthetic form of the vitamin. Folic acid is pteroylmonoglutamate which is more stable in food storage and preparation and is better absorbed when compared to naturally occurring form, folate. Thus, folic acid is used for supplements and food fortification [2]. The form of folate present in the systemic circulation is 5-methyl tetrahydrofolic acid. Dietary folates are converted in the intestinal mucosa to 5-MTHF. However, folic acid has to be reduced and methylated in the gut mucosa before it can be converted to 5-MTHF. Due to the limited capacity of the body to convert folic acid to 5-MTHF, biotransformation process is saturated at doses in the region of 400 μg folic acid and sometimes unmetabolised folic acid has been detected in the systemic circulation [1].

Clinical Relevance and Therapeutic Benefits of Folic Acid

The beneficial effect of folic acid and its involvement in mitigating the risk of various disorders had been widely discussed in literature. Folic acid was reported to prevent neural tube defects (NTDs) like spina bifida and suggested to have a positive influence in mitigating the risk of cardiovascular disease due to its ability to lower homocysteine. In addition to these clinical conditions, the useful role of folic acid has been discussed in various clinical conditions including other birth defects, several types of cancer, dementia, affective disorders, Down's syndrome, and serious conditions affecting pregnancy outcome. The involvement of folate in these conditions can be explained largely within the context of various metabolic pathways of folic acid. Folic acid, as a coenzyme, helps in several single carbon transfers involved in biosynthesis of nucleotide synthesis essential for DNA and RNA synthesis. Folate also regulates the function of various biological substances like DNA, proteins, phospholipids, and neurotransmitters by providing one-carbon unit for methylation. Another important factor is the genetic variability resulting from common polymorphisms of folate-dependent enzymes involved in the homocysteine remethylation cycle [3, 4].

Megaloblastic anemia, a distinct type of anemia characterized by macrocytic RBCs and typical morphological changes in RBC precursors, results from dietary deficiency of Vitamin B_{12} or folic acid. It has been reported that 5-mg daily dose of folic acid is not associated with adverse effects and is used as replacement therapy for treatment of megaloblastic anemia [5].

Available evidence supports an inverse relationship between folate intake, or blood folate levels, and risk of coronary heart diseases. The probable mechanism might be reduction of homocysteine concentrations by folic acid. It was hypothesized that increasing folic acid consumption will reduce the risk of heart attack and stroke by an amount related to the homocysteine reduction achieved [6]. Folic acid supplementation significantly reduced the risk of stroke in primary prevention [7]. Vitamin B supplementation (folic acid = vitamin B_9, vitamin B_6, and vitamin B_{12}) is an efficient and safe homocysteine (tHcy) lowering therapy, decreases tHcy by 30–50 % and has been shown to lower cardiovascular morbidity and mortality [8].

A growing body of evidence supports a role for folic acid in the prevention of disorders of CNS development, mood disorders, and dementias, including Alzheimer's disease and vascular dementia in elderly people [9]. Folate and vitamin B_{12} play a fundamental role in neurological disorders primarily due to their involvement in methionine-synthase mediated conversion of homocysteine to methionine, which is essential for nucleotide synthesis and genomic and non-genomic methylation. Recent findings suggest that risk of cognitive decline can be lowered by using combined folic acid + vitamin B_{12}. Thus, there exists a promising premise in using dietary supplements of folic acid and vitamin B_{12} to prevent cognitive decline [8]. The potential mechanism might be its role in the synthesis of S-adenosylmethionine used for adequate methylation of neurotransmitters, phospholipids or myelin in brain tissue [10].

NTDs, an important cause of mortality and morbidity globally, are congenital malformations of the brain and spinal cord and are caused by failure of the neural tube to close between 21 and 28 days following conception [11]. The neural tube (the embryonic structure that develops into the spinal cord and brain) defects are of two major categories: anencephaly (lack of closure in the region of the head) and spina bifida (lack of closure below the head), and the worldwide incidence of NTDs ranges from 1.0 to 10.0 per 1,000 births with almost equal frequencies between two major categories [12]. Spina bifida causes paralysis of the lower body and learning disabilities. Anencephaly affects the brain, and babies usually do not survive more than a few days after birth.

In our observational study conducted in Aurangabad, we have screened 430 pregnant women for a year (between February 2012 and January 2013). We have obtained the data in private clinic located in Aurangabad. Three patients were picked up on ultrasound as early as 12–13 weeks when these patients went for the nuchal translucency. These patients were not taking folic acid supplementation during antenatal period. We have concluded that Folic acid supplementation should be started as early as 3 months prior to conception. Simple measures to prevent bad obstetric outcome is to supplement Folic acid in periconceptional period, which is a very essential nutrient.

One of the significant scientific advances in recent years is the discovery that folic acid in early pregnancy reduces the risk of NTDs [13]. Both observational and intervention studies, including randomized, controlled trials, have demonstrated that adequate consumption of folic acid periconceptionally can prevent 50–70 % of NTDs [11]. It might also reduce the risk of other congenital malformations such as orofacial clefts. The mandatory folic acid fortification programmes in the USA and Canada have resulted in reduction in occurrence of NTD affected pregnancies [14, 15]. Studies have also shown that periconceptional use of supplements with folic acid alone, or multivitamins combined with folic acid, can lower the risk of NTDs by 40–80 % [16].

Reduced risk for cancers such as colorectal cancer, cervical cancer, and breast cancer was reported with adequate folate intake or status [17]. The potential mechanisms contributing to this beneficial effect could be

disruption of DNA integrity or repair systems or altered methylation [18].

Current Recommendations and Practice

According to the World Health Organization guideline, daily oral iron and folic acid supplementation is recommended as part of the antenatal care to reduce the risk of low birth weight, maternal anemia, and iron deficiency. Folic acid is recommended at the daily supplemental dose of 400 μg (0.4 mg) throughout pregnancy. Folic acid supplementation is recommended to begin as early as possible in all pregnant adolescents and adult women [19].

Indian Council of Medical Research recommends 200 μg as the intake of dietary folate for adult males and females taking the current level of intake and the prevalence of sub-clinical deficiency into consideration. An additional requirement of 300 and 100 μg, respectively, during pregnancy and lactation was decided to be added for meeting the factorial extra needs [20].

Available evidence indicates that 0.4 mg (400 μg)/day of folic acid will reduce the number of cases of NTDs. The U.S. Public Health Service in 1992 recommended 400 μg of folic acid daily for all women of childbearing age to prevent NTD. Subsequently, the Institute of Medicine (IOM) in 1998 stated that women capable of becoming pregnant should consume 400 μg of folic acid daily from fortified foods or supplements, or both, in addition to that obtained through a normal diet. The updated guidelines of the U.S. Preventive Services Task Force of United States Public Health Service published in 2009 reinforced these recommendations [2].

As per the joint SOGC-MOTHERISK Clinical Practice guidelines, folic acid in combination with multivitamin has been shown to reduce birth defects-NTD, heart defects, urinary tract anomalies, oral facial clefts, limb defects, and pyloric stenosis. Supplementation of diet with 5 mg folic acid along with additional daily supplementation of multivitamins should begin at least 3 months before conception and continue until 10–12 weeks post-conception. From 12 weeks post-conception and continuing throughout pregnancy and the postpartum period (4–6 weeks or as long as breastfeeding continues), supplementation should consist of a multivitamin with folic acid (0.4–1.0 mg). The folic acid dose of 5 mg is safe and has not been reported to have maternal or fetal risks [21].

Folic acid supplement pills and multivitamin preparations containing 0.4 mg of folic acid are now available. Supplements for pregnant women generally contain up to 0.8 mg of folic acid. Women should be made aware to obtain optimal intakes of 0.4 mg of folic acid given the number of alternative options available to them. As the closure of neural tube occurs by day 28 post-conception, the timing of usage of folic acid supplement is very important to prevent pregnancies affected by NTDs [22].

The National Anaemia Prophylaxis Programme in India mandates folic acid and iron (0.5 and 60 mg, respectively) supplementation to young girls and pregnant women. However, there is an urgent need to study current practices of vitamin supplementation of pregnant Indian women [23].

Folic Acid and Community Intervention

Each country should opt for policies which suit the local circumstances and should make certain that all women capable of becoming pregnant have an adequate periconceptional intake of folic acid [24]. Awareness on the use and benefits of folic acid should be spread among women by adequately funded national campaigns. An alternative approach is to add recommendation of folic acid supplementation to contraceptive packages (of intrauterine devices, pills, etc.) and recommending women to start folic acid supplementation after stopping their contraception.

Conclusion

Folic acid is of great clinical value and may give considerable protection against serious diseases such as birth defects, heart disease, and cancer. In our study, we have concluded that folic acid supplementation should be started as early as 3 months prior to conception. Further research should be focused on substantiating the indicated health benefits of folic acid especially cardiovascular disease and cancer. As the positive influence on health associated with maintaining an optimal folate status is clearly established, awareness should be created among people, particularly in women, on the proper usage and beneficial effects of folic acid.

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