CONTINUED MEDICAL EDUCATION

Folate supplementation as a strategy to reduce Neural Tube Defects

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Introduction

Folic acid is a vitamin known to prevent neural tube defects, megaloblastic anaemia, cardiovascular morbidity and mortality, etc. The main natural sources of folate are plant and vegetables e.g. green leafy vegetables, broccoli, asparagus, citrus fruits (orange, strawberry), beans, nuts, cauliflowers, beets, corn etc. and meat products like liver. The primary function of folate is its contribution in the synthesis and repair of the DNA. The bioavailability of food folate is approximately 50%. The bioavailability of folic acid taken with meal compared to with water on empty stomach is 85% and 100% respectively.(1) Hence, it is easier to achieve the recommended daily allowances with fortified food as compared to natural food due to higher stability and bioavailability of synthetic folate when compared to natural food.(2)

The Radioimmunoassay technique is currently the most widely used method for the estimation of folic acid level in serum and RBC. The normal serum folate level is 6 to 20 ng/ml whereas the normal RBC folate level as per WHO guidelines is more than 151 ng/ml.(3)

Indian Council of Medical Research - National Institute of Nutrition (ICMR-NIN) recommends 300 mcg of dietary folate for adult males and 220 mcg for adult females and an additional requirement of 300 mcg and 100 mcg, respectively, during pregnancy and lactation.(4) One of the most important functions of folic acid is to prevent neural tube defects (NTDs), when given during preconception period. Historically, folic acid was given during pregnancy to decrease the occurrence of megaloblastic anaemia.(5) Later on research on the effect of folic acid deficiency on fetal outcome was carried out and risk of neural tube defect was established.(6) Gradually, in the late 1980s periconceptional use of folic acid to reduce the risk of neural tube defects was advocated.(7) One of the first studies to see the effectiveness of folic acid supplementation in prevention of NTDs was carried out by the British Medical Research Council in 1991.(8) This RCT showed that women with previous history of NTD had 70% lesser chance of recurrent NTD in subsequent pregnancy by taking 4000 mcg of folic acid daily. This was followed by the RCT in Hungary which found 100% reduction in occurrence of NTD with 800 mcg of folic acid daily supplementation.(9) Following this, World Health Organization (WHO) made its first recommendation on the use of folic acid for prevention of NTD in 1993.(10)

Neural tube defects (NTDs) are severe birth defects of the central nervous system that originate during embryogenesis and result from failure of the morphogenetic process of neural tube closure.(11) The estimated prevalence of NTDs worldwide was 18.6 per 10,000 live births in 2015.(12) A systematic review of studies from 75 countries reported prevalence of NTDs by WHO regions: African (11.7 per 10,000 births), Eastern Mediterranean (21.9 per 10,000 births), European (9.0 per 10,000 births), Americas (11.5 per 10,000 births), South-East Asian (15.8 per 10,000 births), and Western Pacific (6.9 per 10,000 births). In India, the prevalence of NTDs was estimated as 41 per 10,000 live births.(13)

WHO currently recommends 400 mcg of folic acid from 12 weeks preconception to the end of first trimester (8–12 weeks) and upto 4 mg of folic acid in case of high risk of NTDs.(14) Most of the countries follow this recommendation. A review of folic acid supplementation policy of 36 countries was published by Gomes et al, including representation from developed and developing countries. It was observed that majority (69·4 %) of the

thirty six countries recommended folic acid supplement of 400 mcg/day. (15) The upper limit for the folic acid intake was capped at 1mg/day in some of these countries. Only three out of 36 countries recommended folic acid throughout the pregnancy.

Folate supplementation during pregnancy

The essential average requirement (EAR) in India during pregnancy is 60 mg of elemental iron with 500 mcg of folic acid.(16) However, there is no official recommendation for folic acid during second and third trimester. Hence, the advice given to pregnant women for folate supplementation often varies according to the treating physician.

Most of the pregnant women continue folic acid throughout pregnancy. The benefits of continuing the folic acid in later pregnancy is not well documented and varied evidence is available. Folate is critically required for fetal, placental, and maternal tissue growth during pregnancy. Studies have found that continued folic acid supplementation had no benefit in placental weight or gestational age of the pregnancy.(17,18) There is no consistent agreement on the need to maintain high folate level during entire period of pregnancy. A study from China concluded that folic acid supplementation in second and third trimester of pregnancy was associated with higher birth weight, length, head circumference, and chest circumference of the newborn.(19)

Approach to address folic acid deficiency

The main approaches to address the folic acid deficiency include food fortification and diet diversity. Chemically, the most stable form of folic acid is synthetic folic acid. Hence, its use in fortification of food is getting popular in developed countries.

After the discovery of association between folic acid deficiency and NTD, many developed and developing countries made folate fortification either voluntary or mandatory.(20) Most commonly fortified food items included breakfast cereals and bread products in developed countries. In Australia and New Zealand, due to the higher prevalence, NTD was declared as a public health threat and mandatary fortification of wheat flour was recommended from September 2009 with the aim of increasing folic acid intake by 100 mcg/day.(21) Currently 53 countries have mandatory fortification of wheat flour with folic acid.(22) The fortification level ranges from 140 mcg/100 gm to 220 mcg/100 gm of flour in various countries.(23) Recently, in India, rice fortification with iron, folic acid and vitamin B12 has been approved by the Food Safety and Standards Authority of India (FSSAI).(24) Various studies have shown that fortification of flour by folic acid has decreased the risk of NTDs by 19-32% in United states since its implementation in 1998.(25–27)

Fortification of food can come with its own challenges. Continuous monitoring of the blood folate level of the population is required to detect potential adverse effects.(20) Folic acid overuse may mask anaemia caused by vitamin B12 deficiency, hence delaying the diagnosis of B12 deficiency.(1) As folic acid helps in DNA methylation, some epigenetic changes may be seen that may promote occurrence and growth of various neoplasia.(28)

Folic acid recommendations in India

National Nutrition Anaemia Prophylaxis Program (NNAPP) was launched in 1970 during the fourth five-year plan with main objective to treat anaemia in pregnant women (less than 10 g/dl) and children (less than 8 g/dl). Anaemic adult women were prescribed 60 mg of elemental iron with 500 mcg folic acid and anaemic children (1-5 years) were given 20 mg of elemental iron and 100 mcg of folic acid for 100 days. Modifications were made to this program in 2007 and infants aged 6-12 months were also included in this program.(29) Now, as per the National Iron Plus Initiative, 2013, preventive iron and folic acid supplementation is offered from 6 months onwards with appropriate doses.(30)

The periconceptional use of folic acid for prevention of NTDs is based on strong evidence. The main challenge is the coverage of periconceptional use of folic acid. In India, only 70% of women have an antenatal check-up in first trimester of pregnancy, rest 30% come to the clinic directly in the second trimester.(31) Hence, it is difficult to achieve pre-conceptional coverage of folic acid. The focus in India should be on food fortification and diet diversity to supplement the required folate. A balanced diet may not only help in achieving the daily requirement of folic acid but also of other micronutrients. But, dietary practices are linked with cultural practices and are influenced by socio economic conditions. Hence, dietary modification is difficult to achieve. Food fortification may be a better option to achieve required folate levels.

It is very rare for folate deficiency to occur in isolation. Most of the times, it is associated with other vitamin and mineral deficiency like vitamin B12, Vitamin B6, vitamin A, Zinc, Selenium, Copper, etc. (32) Hence, the multiple micronutrient powder for adolescent by UNICEF also addresses anaemia and micronutrient deficiency.(33) However, its acceptability in pre-conceptional period is not well established.

There is dearth of available information on the doses of folic acid including the safe upper limit. Research agenda focusing on the longitudinal studies and randomised controlled trials are required to see the effectiveness of only iron versus iron plus folic acid in preventing anaemia during second and third trimester of pregnancy. This will help in generating evidence for continued use of folic acid during the entire period of pregnancy.

Conclusion & Recommendation

Folic acid provide primary prevention against many serious diseases including neural tube defects, heart disease, and cancer. Diet diversity, food fortification and multiple micronutrient powders are same of the ways to

overcome folic acid deficiency. Newly married women and women who are planning pregnancy within a year may be a priority group for intervention.

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