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Review Article

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Neural Tube Defects and Folic Acid

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Neural tube defects (NTD) are one of the most common structural congenital anomalies. The spectrum includes spina bifida, anencephaly (absence of brain calvaria, total or partial), encephalocele (herniation of brain and meninges through defect in calvaria), craniorachischisis (anencephaly associated with continuous bony defect of spine and exposure of neural tissue) and iniencephaly (dysraphism of occipital region accompanied by retroflexion of neck and trunk). Neural tube defects are usually associated with other congenital anomalies and dysfunction of organ systems. Many affected children would have lower body paralysis, bladder and bowel dysfunction, learning disabilities, hydrocephalus due to Arnold-chiari type 2 malformation and endocrinal abnormalities. All this leads to significant physical disability, psychosocial maladjustments and increased financial burden on the family(1). The quality of life does not only depend on the severity of lesion but also on availability of medical and surgical facilities.

Maternal malnutrition is an important risk factor for development of NTD. Studies till date have shown decreased maternal folate levels in NTD affected pregnancies(2-4). Periconceptional folic acid supplementation has shown to decrease both the occurrence and recurrence of NTD, though the exact mechanism for this protective effect remains unknown(5-7). The present review aims to study the intricacies of this important association in depth.

Burden of Disease

Each year 3- 4 lakh infants worldwide are born with spina bifida and anencephaly(8). The prevalence is approximately 1-5 per 1000 live births and the risk of recurrence is 2-3%(9). More than 95% of cases are contributed by the first affected pregnancies (10). The distribution of neural tube defects shows considerable geographical, temporal and ethnic variation.

In United States, the prevalence of NTD is 1/1000 live birth affecting 4000 pregnancies annually(11). Mexico, South Carolina and Central America are high-risk areas. Variation in rates as a function of ethnic background is complex. In United States, higher rates of NTD are found among white population than blacks(12). Females predominate among isolated NTD cases but sex distribution is equal among NTD cases associated with other congenital anomalies. In Canada and Denmark, the prevalence rates are 0.8/1000 and 1.4/1000 live births respectively(13,14). In China, 1 lakh infants are born annually with spina bifida or anencephaly. Northern China is identified as high-risk area for NTD with prevalence of 5-6/1000 live births. The occurrence of rare category of NTD, i.e., iniencephaly and craniorachischisis is considerably high as compared to other parts of world(15). In India the prevalence is 3.63/1000 live births, the highest reported from the northern states, namely Punjab, Haryana, Rajasthan and Bihar(16).

Folic acid: Known facts

Folic acid or pteroylmonoglutamic acid is a B group vitamin, first isolated from spinach leaf in 1941(17). It consists of related compounds containing pteridine ring, PABA and glutamic acid. Folic acid occurs naturally as folates, which are temperature and storage sensitive and cooking causes significant fall in their concentration. Sources rich in folates are liver, green leafy vegetables especially spinach and broccoli, nuts, egg, cereals, cheese, fruits, yeast, beans etc. Folic acid is required for synthesis of purine, pyrimidine, nucleoproteins and for methylation reactions that play an important role in cell division and development. Folic acid deficiency is associated with ulcers, glossitis and

impaired immunity. Its deficiency impairs DNA synthesis and most commonly affects rapidly dividing cells e.g., of intestines and bone marrow and hence diarrhea and megaloblastic anemia are earliest manifestations. Folate responsive megaloblastic anemia is reported to occur in 24% of unsupplemented pregnancies in certain parts of Asia, Central America and South America and 2.5-5% in developing world(18). Folic acid deficiency is also associated with increased thrombotic events which may be related to increased homocysteine levels. A recent meta-analysis showed that 500 -5000µg/d of folic acid intake reduces homocysteine levels by 25%(19). Folic acid seems to be protective against development of atherosclerosis and other vascular disease by virtue of its homocysteine lowering effect.

Folic acid in causation of NTD

The accumulating evidence has shown that maternal folate status is associated with increased incidence of NTD. The decreased levels could arise as a consequence of dietary deficiency, a genetic defect in the folate metabolism, or both.

Smithells et al.(20) showed that blood level of several micronutrients are reduced in women from lower social classes, especially if they had a child with NTD. Data from MRC Vitamin Study Research Group indicates lower levels of maternal red cell folate in affected pregnancies(7). Red cell folate is considered to be a more reliable index for assessing folic acid deficiency and better indicator of body folate stores, because it fluctuates less readily than serum folate in response to acute dietary changes(21). Daly, et al.(22) showed that there is an inverse linear relationship between the risk of NTD and plasma / red cell folate when folate is plotted on logarithmic scale. At value less than 150 µg/L, the risk of NTD is 6.6/1000 live births than when red cell folate levels are greater than 400 µg /L. Way back in 1965, a study in Liverpool(23) suggested the possible relationship between fetal malformation and defective folate metabolism in the mother. Positive formiminoglutamate (FIGLU) test in a NTD affected pregnancy suggested defective absorption or metabolism rather than deficient folate intake.

Genetic defects in folate metabolism have also been identified. Molloy, et al.(24) found that 5-15% of western population is homozygous for point mutation C677 ® T. This mutation is associated with an increase in the incidence of NTD, with mild hyper-homcysteinemia. The homozygotes have partial deficiency of key folate metabolizing enzyme, i.e., 5,10 methylene tetrahydrofolate reducatase and hence have low red cell folate concentration. Another study in Norway showed that people with C677 ® T homo-zygous genotype show a satisfactory homo-cysteine lowering response to modest daily folate supplements in the range of 100-200 µg/day, confirming the above observations(25).

Several studies have shown protective role of periconceptional intake of folic acid in reducing both the occurrence and recurrence of NTD. Goldenbergh, et al.(26) showed that folic acid improves the outcome of pregnancy by not only decreasing NTD but by decreasing growth retardation and increasing birth weight. Folic acid also prevents preterm delivery, placental abruptions and infarctions. Theunissen, et al.(27) demonstrated elevated folate level in amniotic fluid following oral supplementation. In 1980, Smithells, et al.(28). concluded that periconceptional intake of multivitamins containing folic acid reduces the risk of having NTD in previously affected pregnancy. These observations were strengthened by the 1992 Hungarian study which concluded that multivitamin supple-ment containing 400-800 µg of folic acid given on a daily basis decreased the incidence of NTD(5). Another trial sponsored by British Medical Research Council (1991) concluded that 4000 µg of dietary folate prevented 72% of recurrences of NTD(7).

Prevention of neural tube defects

Despite significant advances in medical technology for early detection and manage-ment of NTD affected fetuses and infants, prevention of NTD remains the foremost priority. Prevention of first occurrence is a more significant public health concern as it represents more than 95% of all NTD cases. It is not practically possible to modify genetic factors hence all efforts should be con-centrated in direction of improving maternal nutrition especially the folate status. Folic acid is highly recommended for preventing both occurrence and recurrence of NTD. It is however essential that all women should receive folic acid before or immediately after conception to have the desired effect. Unfortunately, during this period most of the females are unaware of their pregnancy. Also, most pregnancies are unplanned(29). The females realize their pregnancy after third week of conception, when folic acid supplements will be too late as neural tube closes by 27th day(30). Thus the difficulty in choice occurs, whether to ask all women at risk of getting pregnant to take supplements; or, to fortify the food supply to ensure that all women at risk receive additional folic acid.

Strategies for improving maternal folate status

The ultimate goal of achieving better folate status in women of reproductive age group may be achieved by increasing the folate rich food intake, supplementation or food fortification.

Dietary modifications

Dietary recommendations of consuming food high in folate content is beneficial in a way that it is a natural behavior and consistent with other dietary recommendations. However, this method is dependent on a proper diet consumption, which may not be practically possible in many cases or have financial restraints. On an average, women consume 200 µg of folic acid from natural food. To meet the current recommendations, women have to increase the levels by 2-3 times which requires major dietary modifications; an uphill task.

Vitamin supplementation

The second approach is daily folic acid supplementation to all women in the reproductive age group (18-44 years). The benefit of supplementation is that appropriate groups are targeted but the primary limitation is compliance. Also, many cases in need might not be reached.

Food fortification

Food fortification has the advantage that it is likely to reach all women before conception and also allow general population to enjoy the benefits. The major limitation is that non-targeted population will also receive additional folic acid.

An interventional study compared the relative effectiveness of the three suggested methods by monitoring changes in red cell folate levels in response to a 12-week trial in 3 groups (dietary modification, supple-mentation and fortification)(31). Results showed that increased folate intake was reflected as increased folate status only in women taking supplements or fortified food. The consumption of natural food folate resulted only in modest (non-significant) increase in red cell folate levels. The explanation for the difference in response is that synthetic form of vitamin is more bioavailable and stable form than natural food folates. Hence, supplementation and fortification seem to be more beneficial approaches.

Folate awareness among laity and experts

Various studies have shown lack of folate awareness among women in reproductive age group regarding its role in preventing birth defects. A telephone survey in 1995 in US reported 52% of women had heard about folate but only 5% knew that folate helps in preventing birth defects and only 2% knew it should be taken before pregnancy(32). Similar survey in 1996 among women attending genetic clinics in Ottawa Pediatric Hospital showed 81% awareness of pregnant women, 78% took supplements but only 27% began supplementation early enough to reduce birth defects(33). Survey in 1998 by March of Dimes Birth Defect Foundation found only that 68% of women had heard of folate(34). The awareness was least in women of age group (18-24) years and in low education status. Only 13% knew it reduces birth defects and 7% knew it should be taken before pregnancy. Similar study among Irish women in 2000 yielded the following results: 92% had heard of folic acid, 67% knew it could prevent NTD, 30% were advised to take it but only 18% did so(35). Similar study from India reported only 20% women had heard about folic acid but none of them knew that it should be taken before pregnancy or it prevents birth defects(36).

Folate knowledge is not directly related to folate intake. Study in Vancouver, Canada concluded 95% of women had heard of folate but only 25% knew that it could prevent birth defect, 25% of women had good knowledge of folate rich foods(37). Though 86% of women met the average requirements (320 dietary folate equivalents (DFE)/d) but only 26% met the recommendation (400 DFE/d). Lack of awareness of folate was most common reason for not using folic acid supplements. Intense media campaigns have successfully increased the awareness e.g., in Netherlands optimal folic acid supplementation increased from less than 1% in 1994 to 52% in 1998(38). Further in 2001, two years after National Folic Acid Awareness Campaign in US, 79% of the women knew about folate and 19% knew its role in preventing birth defects(34).

Folate unawareness not only exists among general population but also among nurses, pharmacists and health professionals. A survey conducted among student pharmacists concluded that 94% knew folic acid supplements prevent birth defects, 74% knew supplementation should begin before pregnancy but only 55% knew the recommended levels or good folate sources (50%)(39). A telephone survey among obstetricians in Delhi, India reported that though all of them were aware of folic acid, only 63% knew that it prevents birth defects and 30% knew that it should be given before

pregnancy(36). None of them prescribed periconceptional folic acid or folate rich diet through child-bearing age. Interestingly, 80% of those surveyed were not aware of the preventive dose of folic acid.

Current Practices

After considerable evidence that folic acid decreases NTD, most countries brought in policies for improving the folate status of women in reproductive age group. The recommendations either promoted the use of supplements or food fortification. In 1992, the US Public Health Services recommended that all women capable of being pregnant should consume 400 µg of folic acid through childbearing age to reduce the risk of having pregnancy affected with NTD(40). Similar guidelines were proposed in other countries like UK, Australia, Netherlands and Germany. Society of Obstetrics and Gynecology of Canada Expert Advisory Group on Folic Acid in prevention of NTD recommended that all women of child bearing age should consume 400 µg of folic acid to prevent the first occurrence starting before conception and continued till the end of 12th week of gestation(41). A daily intake of 4000 µg of folic acid was recommended in previously affected pregnancies starting from one month before to 3 month after conception.

Poor compliance of supplement intake resulted in promotion of strategies for food fortification. US Food and Drug Administration authorized addition of folic acid to bread and grain products in March 1996 with compliance mandatory by January 1998(42). Grain products with fortified folate at level of 140 µg /100 g were marketed so to provide additional 100 µg /day of folic acid in population (based on dietary modeling and equal bioavailability)(43). Similar policies were implemented in other countries. In 1998, Canada implemented food fortification providing 150 µg /100g grain available in market(44). However, due to certain controversies for the food fortification in 1998, the Institute of Medicine (IOM) recommended that all women consume 400 µg of synthetic folic acid from fortified food or supplements in addition to food folate from normal diet(45).

Current fortification: Is it appropriate?

The lowest amount of folic acid required to prevent NTD is a critical question. Though 400 µg of folic acid is recommended to prevent NTD, the current fortification programs provide only 100 µg/d of additional folic acid. Such an increase although safe may be ineffective but a trial to assess its efficacy will be unethical. A randomized control trial compared groups with 100, 200 and 400 µg of folic acid supplementation to find out how much of folate supplementation is effective in prevention of NTD in women with red cell folate between 150-400 µg/L(46). The increment in red cell folate levels before and after supplementation were 0.67 µg/375 µg, 130 µg/475 µg and 200 µg/575 µg in the 3 groups respectively. The decline in the NTD rate was by 20%, 42% and 47% in corresponding groups. Thus, 400 µg of supplementation proved to be the most effective but posed safety concerns. Daily 200 µg of supplementation of folic acid appears to be effective and safe and 100 µg of dose taken continually also decreases NTD significantly. Because the supplements were taken in addition to dietary intake (not mentioned in study), the same results apply to food fortification with folate also. Mills, et al.(47) recommended against increasing fortification levels but in year 2000 U.K Committee on Medical aspects of Food and Nutrition Policy recommended universal folic acid fortification of flour at level of 240 µg/100 g, almost double the levels in USA(48).

Impact of current programs

Different trials conducted to see the impact of supplementation and fortification programs have documented a declining trend of NTD. A trial conducted 6 months after the Department of Health recommendations showed that no woman took supplements as well as increased dietary consumption of folate(49). Only 2% women modified diet and 3% took folate tablets. Though 67% were aware of recom-mendations only 37% received information before conception. Similar studies in South America (1996) and Netherlands (1998) showed low rate of supplements usage ranging from 0 to 52% respectively(50,39). MRC Vitamin Study Group could demonstrate a 72% reduction in NTD in women in previous affected infant after supplementation(7). Post fortification analysis in US showed a decline of 19% from 37.8/lakh to 30.5 /lakh of NTD cases(51). After fortification in Ontario, (Canada) the prevalence of NTD has decreased from 1.13/1000 live births to 0.58 /1000 live birth(52). Similar declining trends in Nova Scotia were seen and after fortification 50% decline occurred with annual rate falling from 2.58 to 1.17 per 1000 live births(53). In China, vitamin supplementation has resulted in significant decline in NTD both in high risk area of Northern China (4.8 to 1.0 per 1000 live births) and in low risk area of Southern China (1.0 to 0.6 per 1000 live births)(15) The total annual incidence has decreased by 54% from 2.58 to 1.17 per 1000 live births after fortification programs. Trends in serum folate levels after fortification have shown that from 1994 to 1998 median rise in serum folate values have occurred from 12.6 to 18.7 µg/L (54) and continued to increase further, to more than 20 µg/L in 1999. Food fortification with folic acid is the likely explanation for increase in median values after 1997. The beneficial response of folate fortification is evident not only by the increased folate levels

and declining NTD but also by observing the effect of elimination of fortified diet among habitual consumers. A 12 week trial of elimination of fortified diet among regular consumers showed a decrease in folate intake by 78 µg/d. This was also reflected as a reduction in red cell folate concentration levels by 49 µg/L over a 12 week period, thus increasing the risk of NTD considerably (55).

Elimination of NTD

Folic acid and NTD contribute substantially to infant mortality and child disability. Approximately 75% of spina bifida and anencephaly are folic acid preventable and it is biologically possible to prevent nearly all Folic Acid Dependent Neural Tube Defects (FADNTDs). This magnitude of global burden and remarkable prevention impact suggests the possibility of elimination of FADNTDs. Together with other micronutrient deficiencies, FADNTD was also identified as a candidate for elimination by the Workshop on Non Infectious Diseases in London. Global efforts and coordination were suggested for achieving the same (56). The success of supplementation and fortification program proposed recommendations to eliminate FADNTD by 2005. Till date, efforts have reduced the NTD rates remarkably but certain questions regarding mechanisms of protective effect of folic acid and underlying biology of NTD are still unanswered. Further research in these areas may suggest new strategies for prevention and treatment of NTD and thus a step closer toward the goal of elimination.

Suggested strategy for India to prevent NTD

A targeted approach consisting of vitamin supplementation to married women in child-bearing age is suggested, to have early short term gains. To begin with, the exercise may be initiated in pockets with high incidence. Food fortification is a massive exercise and requires intersectoral co-operation. Financial burden, logistic barriers, and lack of centrally processed and distributed food to serve as fortification vehicle are major obstacles in adopting this approach for a large country like India.

Long-term sustained benefits are achievable through dietary modification. Innovative methods of educating women, health care providers, pharmacists, policy makers and general public need to be developed. Effective public awareness by use of media needs to be promoted.

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Key Message

• Each year 3- 4 lakh infants worldwide are born with neural tube defects (NTD).

• More than 95% of cases with NTD are contributed by the first affected pregnancies.

• Low folate status in the mother is associated with increased incidence of NTD in her fetus.

• Periconceptional intake of 400 µg of folic acid per day by the pregnant women (starting from 1 month prior to 3 months after conception) can prevent 75% of all neural tube defects. Intake of 4 mg /d is recommended to prevent recurrences.

• General population as well as nurses, pharmacists and other health professionals are not well aware of beneficial effects of periconceptional folic acid intake.

• Suggested strategies to prevent folic acid associated NTD include food fortification, vitamin supplementation and dietary modifications.

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