Prevention of Fetal Neural Tube Defect with Folic Acid Supplementation

Neural tube defects (NTDs), such as spinal cord and brain defects, are due to abnormal embryonic development of the neural tube and associated with increased fetal and infant mortality, morbidity, lifelong disability, and high economic costs. Globally, more than 260,000 pregnancies are estimated to be affected by NTDs, and 75% of the NTD live births result in under-5 deaths.[1] Majority of NTDs are folic acid-sensitive; with much of the NTD burden preventable through consumption of folic acid before and during early pregnancy (periconception). An association between low folate status of women of reproductive age (WRA) and risk of NTD-affected pregnancy was first proposed in 1965 by Hibbard et al.[2] and was subsequently substantiated in several randomized controlled trials which demonstrated the effectiveness of folic acid supplementation during periconception in preventing the first occurrence of NTDs.[3] These findings resulted in a recommendation in 1992 by the U.S. Public Health Service that WTA consume 400 μg of folic acid daily to prevent occurrence of an NTD-affected pregnancy.[4] This recommendation together with other large-scale, global intervention studies demonstrated the efficacy of a daily periconceptional supplement of 400 μg in preventing a large percentage of NTDs.[5]

Folic acid is a synthetic, oxidized form of folate that acts as a coenzyme in the biosynthesis of DNA and RNA. With 4 mg folic acid daily, it may take 20 weeks to reach red-blood-cell folate levels between 1050 and 1340 nmol/L, which is optimal for reduction of the neural tube defect risk. Therefore, folic acid supplementation should be started 5–6 months before conception. The residual risk with optimal red-blood-cell folate levels is reportedly 4.5 per 10,000 total births whereas the residual risk in pooled data from countries with mandatory folic acid fortification is 7.5 per 10,000 pregnancies, regardless of pre-fortification rates.[6] In one study, the optimal RBC folate level was achieved in 80.4% of women who started FA 400 μg 4–8 weeks before their last menstrual period (LMP) compared to only 53.6% in women who started 4–8 weeks after their LMP ($P < 0.001$).[7] A worldwide survey of folic acid supplementation in WRA showed inadequate compliance to folic acid intake.[8] A systematic review and meta-analysis of pooled prevalence estimates of folic acid compliance showed 32–51% in North America, 9–78% in Europe, 21–46% in Asia, 4–34% in the Middle East, 32–39% in Australia/New Zealand, and 0% in Africa. Poor compliance was secondary to many factors. In the United States, the recommendation of 400 μg supplemental intake of folic acid daily has limitations as many pregnancies, including up to 50% of all pregnancies are unplanned.[9] In many countries, particularly among low- and middle-income countries, many barriers exist for the access of WRA to folic acid supplements, such as procurement of the micronutrients in a relatively costly prepackaged form and ineffective distribution system. An evaluation of NTD trends in multiple countries indicated that, regardless of form, timing, or intended target, issuing recommendations on folic acid use alone, in the absence of fortification, had no detectable impact on NTD incidence. Thus, food fortification with folic acid has been a component of national public health strategies; in particular, where folate status is insufficient and a fortifiable food vehicle, processed by a centralized industry is consumed regularly by WRA.[10,11] Other factors associated with poor compliance in folic acid intake include low income, smoking during pregnancy, alcohol consumption, multiple pregnancy, geographic location, and religious beliefs. On the other hand, preconception counselling, previous infertility therapy, multivitamin intake before pregnancy, older age planned pregnancy, previous infertility therapy, and multivitamin intake before pregnancy increased compliance.[12-16] Women who also believed that they had good general and obstetric health (e.g., no history of illness or miscarriage) had attitudes of not being susceptible to the health consequences of not taking folic acid supplements and were the low users of folic acid supplement.[17]

In the Philippines, although WRA are advised to consume 320 ug dietary folate equivalent per day,[18] about 0.9 % (around 1 in 5) are folate-deficient based on red cell folate count, while 38.7% (around 2 in 5) are folate-deficient based on serum folate.[19] Congenital malformations including NTDs remain in the top ten leading causes of infant mortality from 1960 to 2005.[20] In the index paper of Bernardo[21] a cross-sectional, cluster sampling survey of 184 healthy, pregnant women, of age 15–49 years was conducted in the Batangas province from May to July 2017 to assess the level of knowledge, attitude, and perceived practice among the subjects on the importance of folate periconceptionally. A pretested interview questionnaire was used. The mean scores were 77% (moderate level) for knowledge, 82% for positive attitude, and 71% for positive perceived practice. The scores in the survey were related to patient's age, civil status and to some extent, education. The study suggested that while respondents knew about folate (70%), they had low knowledge of the effect of its deficiency especially as it can lead to infant death. Knowledge had significant and positive moderate correlation with attitude ($r = 0.7$) and perceived practice ($r = 0.5$), but there was a weak positive correlation between attitude and perceived practice ($r = 0.4$). This likely indicates failure

to emphasize the translation of knowledge and awareness properly and sufficiently into actual practice. As recommended by the author, education is the principal means to achieve the desired outcome. However, it is not clear in the study whether some amount of educational intervention besides determination of prevalence was included. As in any prevalence study, the golden opportunity to improve health outcomes is to accompany the survey with educational intervention, which in many instances, is required by the institutional board review. Some regression analysis of the data may also have been useful to determine which factors contributed most to the outcome measures.

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