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Correspondence

Awareness and use of folic acid among pregnant women in Taipei: Increase the periconceptional use of folic acid in Taiwan

I congratulate Dr Jou and colleagues [1] for drawing attention to the important issue of folate status. I completely agree that we should consider the importance of folic acid in pregnant Taiwanese, although it is a little late. Evaluation of the cost-effectiveness of a folic acid fortification policy and promotion of its supplementation are warranted in Taiwan. However, I think that the conclusion of the article that a public health policy or strategy "to increase the preconceptional use of folic acid is needed" in Taiwan is too strongly worded, because the paper did not give much evidence of this, even in the discussion section. "May be or probably is needed" would be the more appropriate words. Daily intake of food folate of is possibly inadequate in Taiwan. In the third paragraph of the discussion section, I could not find Taiwanese women had a higher rate of folic acid intake during the periconceptional period compared to other Asian areas with the original quad references 5, 9, and 12. Almost the same identical folate recommendations for the prevention of the first occurrence of neural tube defects (NTDs) have been set worldwide. Three options are suggested to achieve the extra 400 μg folic acid/day recommended by the official committees: increased intake of folate-rich foods, dietary folic acid supplementation, and folic acid fortification of food. A significant increase in foods naturally rich in folates was shown to be a relatively ineffective means of increasing red blood cell folate status in women compared with equivalent intakes of folic acid-fortified food, presumably because the synthetic form of the vitamin is more stable and more bioavailable. Although folic acid supplements are highly effective in optimizing folate status, supplementation is not an effective strategy for the primary prevention of NTDs because of poor compliance. Thus, food fortification is seen by many as the only option likely to succeed [2], and has been a great success in the USA [3], and also in Canada.

The recommended dietary allowance (RDA) for pregnant women is the average daily dietary intake sufficient to meet the requirements of 97% to 98% of pregnant women. The RDA is derived from the amount estimated to meet the requirement of 50% of healthy pregnant women, or the estimated average requirement (EAR). Maintenance of red cell folate was selected as the primary indicator of adequacy of folate status during pregnancy. The dietary folate equivalent (DFE) was used to interpret studies in which folate was provided as a combination of food folate and synthetic folic acid because folic acid is more bioavailable than is food folate that has mentioned previously. Many population-based studies confirmed that approximately 680 nmol (approximately 300 μg) folic acid/day consumed in conjunction with a low-folate diet prevented folate deficiency in pregnant women. Additional studies showed that 227 nmol (100 μg) folic acid/day was inadequate to maintain normal folate status in a significant percentage of the groups assessed. The EAR was derived by adding the DFE of this quantity [454 nmol (200 μg)/day] to the EAR for nonpregnant women [725 nmol (320 μg)/day] to provide an EAR of 1178 nmol (520 μg)/day. The RDA of 1362 nmol (600 μg) DFE/day was derived by multiplying the EAR by 1.2 to account for an estimated 10% coefficient of variation (CV). Data from the metabolic studies supported an RDA of 1362 nmol (600 μg) DFE/day on the basis of the maintenance of normal red cell folate concentrations and agreed with the findings from the population studies that 1362 nmol DFE/day was adequate to maintain normal folate status in pregnant women [4]. Now, do we know daily consumption of folate of Taiwanese adults? Is the RDA for Taiwanese the same as for westerners? And what should we recommend in Taiwan? A population study in Taiwan showed 58% male and 72% female adolescents had normal folate levels. People living on the east coast and Penghu islands had higher percentages of red blood cell folate deficiency [5]. A study showed that the average estimated folate intakes were 269 ± 9 μg/day in boys and 259 ± 9 μg/day in girls, and 42% of Taiwanese schoolchildren had a dietary folate intake below two-thirds of the RDA, indicating a poor dietary folate intake in this population [6]. Therefore, the folate status of Taiwanese schoolchildren was inadequate. Similarly, the average estimated folate intakes were 379 ± 18 μg/day in males and 351 ± 27 μg/day in females of Taiwanese elderly [7]. The study of folate status of pregnant Taiwanese women showed that 13.6% had marginal folate deficiency (plasma folate of 3–6 ng/mL) in early pregnancy [8].

The folate intake among adult men and women was adequate in view of recommended daily intakes in The Netherlands. However, the folate intake among women did not meet the recommendation for those who want to become pregnant [9]. The bioavailability of folate in vitamin

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preparations is approximately double that of dietary folate. Most preparations contain 400 μg of folic acid and, if the woman took a multivitamin (400 μg of folate) in addition to her diet (230 μg of folate), she would not exceed 1000 μg (1 mg) daily, which is considered the upper limit of daily folate ingestion by dietary fortification and supplementation before the masking of vitamin B12 becomes a concern [10]. The comparison of folate inadequacy across eight countries in Europe revealed that about 25% of the adult female population had inadequate intakes when judged against the different recommendations used by the respective investigators, but nearly 75% had inadequate intakes when compared against the estimated average requirement cut-off point of 320 μg/day. The review showed that different methods were applied across Europe to estimate the adequacy of micronutrient intake, which led to different prevalence estimates of micronutrient inadequacy [11]. In Australia, response to health promotion was measured in three ways: (1) knowledge of the association between periconceptional folate and prevention of spina bifida (the 'correct message'); (2) use of periconceptional vitamin supplements of folic acid daily in the periconceptional period; and (3) daily folate intake from fortified foods in the 6 months before pregnancy. Folate promotion and voluntary fortification of certain foods with folic acid were associated with increased awareness of the role of periconceptional folic acid, increased folate consumption and a reduction in the prevalence of NTDs in South Australia by 40% (95% CI, 26–52%) from 1966 to 2007 [12]. All of the above evidence point to a geographic influence on folate intake.

The highest incidence rates of NTDs (myelomeningocele and anencephaly) were found in Ireland and Wales during the 1970s. What is the situation in oriental countries? In China, among the fetuses or infants of women who registered before their last menstrual period and who did not take any folic acid, the rates of neural-tube defects were 0.48% (pregnancies of at least 20 weeks' gestation) in the northern region and 0.1% in the southern region. Among the fetuses or infants of the women with periconceptional use of folic acid, the rates were 0.1% in the northern region and 0.06% in the southern region. The greatest reduction in risk occurred among the fetuses or infants of a subgroup of women in the northern region, with periconceptional use who took folic acid pills more than 80% of the time (reduction in risk, 85% as compared with the fetuses or infants of women who registered before their last menstrual period and who took no folic acid; 95% CI, 62–94%)]. In the southern region the reduction in risk among the fetuses or infants of women with periconceptional use of folic acid was also significant (reduction in risk, 41%; 95% CI, 3–64%) [13]. Northern China has the highest known rate of NTDs in the world. Birth defects are becoming the leading cause of infant mortality in the urban and developed areas in China. The results of studies conducted in the early 1990s and early 2000s showed significant geographic and seasonal variations of folate status among Chinese women of childbearing age, with lower serum and red blood cell folate levels in northern China [14]. They also found no evidence that daily consumption of folic acid before and during early pregnancy influenced the risk of miscarriage or twinning in China. The median dietary folate intake was 207.2 μg/day, the median serum folate level was 3.9 ng/ml. A normal serum folate level was significantly associated with increased dietary folate intake (odds ratio = 1.003, $p < 0.05$), use of folate supplements (odds ratio = 8.152, $p < 0.001$) in Japan [15]. The serum folate levels of the participants with high consumption of green tea or oolong tea was significantly lower than those of others ($p = 0.027$). A multiple regression analysis revealed the high consumption of green tea or oolong tea to be associated with a low serum folate level during pregnancy, after adjusting for confounding variables including dietary folate intake and use of folic acid supplements or multivitamins ($\beta = -0.131$, $p = 0.016$) [16]. In Thailand, a report of preliminary evidence showed that some pregnant Thai women may have sufficiently low serum folate levels to put their babies at risk. The authors recommended further study on a larger scale to confirm whether folate supplementation is needed for Thai women at child bearing age. In the interim, it may be wise for obstetricians to measure serum folate in pregnant women to determine whether folate supplementation is required [17]. Are not we in the same situation? Please be aware that the prenatal vitamins containing 1 mg of folic acid over the counter are easily available in Taiwan, and many pregnant women take them, although many clinicians advise to take them after 4 months of pregnancy.

NTDs are classified as examples of multifactorial inheritance from a genetic viewpoint. The development of NTDs is influenced by environment, diet, physiological abnormalities, teratogen exposure, family history, ethnic origins, fetal gender, nutrients, maternal diabetes, obesity, hyperthermia, certain antiseizure medications, and various genes [3]. The prevalence of NTD at birth declined to approximately five cases at birth per 10,000 births and seven to eight cases at birth or abortion per 10,000 births. This decline was independent of the amount of folic acid administered and apparently reveals a 'floor effect' for folic acid-preventable NTD. This clearly shows that not all cases of NTD are preventable by increasing the folate intake [18]. The relative decline depends on the initial NTD rate. Countries with NTD prevalence close to the observed floor may have much smaller reductions in NTD rates with folic acid fortification. We are in Taiwan, which is considered a low prevalence area. Additionally, potential adverse effects of fortification on other vulnerable population groups have to be seriously considered. For example, double use, defined as isolated folic acid preparations in addition to folate containing supplements (vitamins), was seen more frequently in women giving birth to children with positional plagiocephaly in The Netherlands; however, a potential empirical relationship requires attention in more extensive study, because the number of diseased children was too small [19]. In the USA and Canada, the additional intake of about 100 to 150 μg/day of folic acid through food fortification has been effective in reducing the prevalence of NTDs at birth and increasing blood folate concentrations in both countries. Most potential adverse effects associated with folic acid were associated with extra supplement use, and not with mandatory fortification [20]. The

daily intake of folic acid should not exceed 1 mg daily, which is considered the upper limit of daily folate ingestion worldwide. The maximal daily dietary folate intake is considered to be 250 mg with a bioavailability of 50% to 70%. Policy decisions concerning a national mandatory fortification program must take into account realistically projected benefits as well as the evidence of risks to all vulnerable groups. Do we know any baseline data about folate concentrations in women of childbearing age in Taiwan? Could we identify those (socially deprived) women in most need of folic acid? The national survey or epidemiologic investigations should be done urgently. By the way, therapeutic drug monitoring of red blood cells folate could be used to identify those pregnant women and to help them improve their folate status, thus reducing their risk for having a child with an NTD.

Finally, since the precise nature of the link between low folate status and NTDs is poorly understood, it remains unclear how folic acid prevents NTDs. However, risk of NTDs is determined by genetic and environmental factors, among which folate status appears to play a key role. An animal study on the effect of folate level on risk of NTDs in splotch mice, which carry a mutation in Pax3 showed that dietary folate restriction results in reduced maternal blood folate, elevated plasma homocysteine and reduced embryonic folate content. Folate deficiency did not cause NTDs in wild-type mice, but caused a significant increase in cranial NTDs among splotch embryos, demonstrating a gene-environment interaction. Folate deficiency in genetically predisposed splotch embryos, which exhibited developmental delay and growth retardation, therefore increased the risk of NTDs probably via embryonic growth retardation [21]. The effect of folate deficiency appeared more deleterious in female embryos than males, since defects were not prevented by exogenous folic acid. Another study that showed dietary folate deficiency caused an increase in the frequency of cranial NTDs in both curly tail (Grhl3 mutant) embryos and background-matched embryos that are wild type for Grhl3. Dietary folate deficiency could induce cranial NTDs in nonmutant mice with a permissive genetic background, a situation that probably parallels gene-nutrient interactions in human NTDs [22]. The authors also found that inositol supplementation might ameliorate NTDs resulting from insufficient dietary folate. So, suboptimal maternal folate status is considered really a risk factor for NTDs.

In conclusion, “adequate intake” of folic acid by women during very early pregnancy can markedly reduce risk of the development of preventable NTDs. A public health policy or strategy to increase the periconceptional use of folic acid is probably needed in Taiwan.

References

[1] Jou HJ, Hsu IP, Liu CY, Chung SH, Chen SM, Gau ML. Awareness and use of folic acid among pregnant women in Taipei. Taiwan J Obstet Gynecol 2010;49:306–10.

[2] McNulty H, Cuskelly GJ, Ward M. Response of red blood cell folate to intervention: implications for folate recommendations for the prevention of neural tube defects. Am J Clin Nutr 2000;71(5 Suppl.): 1308S–11S.

[3] Centers for Disease Control and Prevention (CDC). CDC grand rounds: additional opportunities to prevent neural tube defects with folic acid fortification. MMWR Morb Mortal Wkly Rep 2010;59:980–4.

[4] Bailey LB. New standard for dietary folate intake in pregnant women. Am J Clin Nutr 2000;71(5 Suppl.):1304S–7S.

[5] Lin BF, Lin RF, Yeh WT, Pan WH. The folate status in Taiwanese population from the NAHSIT 1993–1996. Nutr Sci J 1999;24:99–117.

[6] Chen KJ, Shaw NS, Pan WH, Lin BF. Evaluation of folate status by serum and erythrocyte folate levels and dietary folate intake in Taiwanese schoolchildren. Asia Pac J Clin Nutr 2007;16(Suppl. 2):572–8.

[7] Chen KJ, Pan WH, Shaw NS, Huang RF, Lin BF. Association between dietary folate-rich food intake and folate status of elderly Taiwanese. Asia Pac J Clin Nutr 2005;14:244–9.

[8] Chen KJ, Shaw NS, Lin BF. The folate status of pre-natal follow up pregnant women at hospital in Taipei. Nutr Sci J 2006;31:8–16.

[9] Brussaard JH, Löwik MR, van den Berg H, Brants HA, Goldbohm RA. Folate intake and status among adults in the Netherlands. Eur J Clin Nutr 1997;51(Suppl. 3):S46–50.

[10] Berg MJ. The importance of folic acid. J Gend Specif Med 1999;2: 24–8.

[11] Tabacchi G, Wijnhoven TM, Branca F, Román-Viñas B, Ribas-Barba L, Ngo J, et al. How is the adequacy of micronutrient intake assessed across Europe? A systematic literature review. Br J Nutr 2009; 101(Suppl. 2):S29–36.

[12] Chan AC, van Essen P, Scott H, Haan EA, Sage L, Scott J, et al. Folate awareness and the prevalence of neural tube defects in South Australia, 1966–2007. Med J Aust 2008;189:566–9.

[13] Berry RJ, Li Z, Erickson JD, Moore CA, Wang H, Mulinare J, et al. Prevention of neural-tube defects with folic acid in China. China-U.S. Collaborative Project for Neural Tube Defect Prevention. N Engl J Med 1999;341:1485–90.

[14] Zhu L, Ling H. National Neural Tube Defects Prevention Program in China. Food Nutr Bull 2008;29(2 Suppl.):S196–204.

[15] Matsuzaki M, Haruna M, Ota E, Sasaki S, Nagai Y, Murashima S. Dietary folate intake, use of folate supplements, lifestyle factors, and serum folate levels among pregnant women in Tokyo, Japan. J Obstet Gynaecol Res 2008;34:971–9.

[16] Shiraishi M, Haruna M, Matsuzaki M, Ota E, Murayama R, Murashima S. Association between the serum folate levels and tea consumption during pregnancy. Biosci Trends 2010;4:225–30.

[17] Sirikulchayanonta C, Madjupa K, Chongsuwat R, Pandii W. Do Thai women of child bearing age need pre-conceptional supplementation of dietary folate? Asia Pac J Clin Nutr 2004;13:69–73.

[18] Heseker HB, Mason JB, Selhub J, Rosenberg IH, Jacques PF. Not all cases of neural-tube defect can be prevented by increasing the intake of folic acid. Br J Nutr 2009;102:173–80.

[19] Michels A, El Bakkali N, Bastiaenen CH, De Bie RA, Colla CG, Van der Hulst RR. Periconceptional folic acid use and the prevalence of positional plagiocephaly. J Craniofac Surg 2008;19:37–9.

[20] Berry RJ, Bailey L, Mulinare J, Bower C. Folic Acid Working Group. Fortification of flour with folic acid. Food Nutr Bull 2010;31(1 Suppl.): S22–35.

[21] Burren KA, Savery D, Massa V, Kok RM, Scott JM, Blom HJ, et al. Gene-environment interactions in the causation of neural tube defects: folate deficiency increases susceptibility conferred by loss of Pax3 function. Hum Mol Genet 2008;17:3675–85.

[22] Burren KA, Scott JM, Copp AJ, Greene ND. The genetic background of the curly tail strain confers susceptibility to folate-deficiency-induced exencephaly. Birth Defects Res A Clin Mol Teratol 2010;88:76–83.

Horng-Jyh Tsai
Kuang Tien General Hospital, 117, Shatien Road, Shalu, Taiwan
E-mail address: hjtsaics@yahoo.com.tw