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Preventing Folate-Related Neural Tube Defects: Problem Solved, or Not?

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Are we preventing all the folate-related neural tube defects (NTDs)? Tinker et al. (in press) attempt to answer this important question using data from Irish (Daly et al., 1995) and Chinese (Berry et al., 1999; Crider et al., 2014) studies that estimated how high a woman's red cell folate concentration had to be to put her at low risk for having an affected child. They use these data to determine what proportion of U.S. women of childbearing age in NHANES fall below this protective concentration.

The authors chose a cut off of less than 9 NTDs per 10,000 live births as the target. By this standard, 22.8% of women had sub-optimal folate status. Not surprisingly, minority women, smokers, and low income women were at greater risk. This is predictable because smokers are less health-conscious and minority and low income women may have less access to supplements or be less well informed about the benefits of folic acid. The study findings suggest that those who may need additional folic acid could be a difficult population to reach.

The findings by Tinker et al. that approximately a quarter of the population is at risk stands in sharp contrast to two case control studies that asked whether fortification was preventing all folate-related NTDs. Both Ahrens et al. (2011) and Mosley et al. (2009) found that in the post fortification era, case mothers were no less likely to use folic acid supplements than normal control mothers. They concluded that fortified food provided sufficient folic acid to prevent folate-related NTDs.

How can this apparent contradiction be resolved? Ideally, we would be able to look at the proportion of NTDs that are folate preventable and the proportion of NTDs that have been prevented in the United States since fortification began. This is impossible for two reasons. First, estimates of the folate-preventable fraction vary from less than 50% to 70% or more. The 72% reduction found in the Medical Research Council recurrence trial (MRC, 1991) is often cited. It is rarely noted that the 95% confidence interval for that finding was 29 to 88%. Even when data from other trials are added, the confidence interval for the protective effect remains fairly large. Second, U.S. data on NTD rates suffer from the problem that terminated cases are not reported in all areas. Because a large proportion of NTDs are detected prenatally, using birth prevalence data is far from ideal. Therefore, we are in the

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unfortunate position of knowing neither the target level for prevention, nor what percentage we are actually preventing.

Then how can we explain the contradictory findings? It is possible that the two case control studies were underpowered, as Tinker et al. suggest. Alternatively, women at the low end of the folate spectrum, that is, those who had folate-related NTDs might not have participated. This seems unlikely, but cannot be ruled out. It is also possible that the standard populations used to define the high risk concentrations of red cell folate were not appropriate for the U.S. population. Both the genetic risk factors and the diet in Ireland in the 1980s were quite different from the United States. The Chinese study population was also quite different in diet and genetics; moreover, it consisted of women who were offered the opportunity to purchase folic acid before conception (Berry et al., 1999). Some accepted and some declined. Their subsequent folate status could have been a marker for health consciousness or other factors as well as supplement taking.

The Chilean experience may shed some light on the question. Chile elected to fortify at a much higher concentration—220 micrograms per 100 grams of grain— than the United States and Canada—140 and 150 micrograms per 100 grams of grain, respectively. They calculated that this delivered an average of 427 micrograms of folic acid per day to women of childbearing age (Hertrampf et al., 2004) compared with an estimated 128 micrograms per day from fortified foods delivered to U.S. women (Yang et al., 2007). Because the Chilean women received much more folic acid than the American or Canadian women, one would have expected a larger drop in NTD rates if the assumption that there were many women at high risk was correct. In fact the drop in NTD rates seen in Chile was comparable to the drop seen in other countries that used lower doses of folic acid, approximately 50% (Castillo-Lancellotti, 2012). While this is by no means the definitive analysis, it suggests that most folate-related NTDs are being prevented by the current program.

On the population level, Tinker et al. provide interesting data on high risk groups. They note that non-Hispanic blacks and Hispanics are significantly more likely to fall into the increased risk category than non-Hispanic whites. They also point out that, despite this, non-Hispanic blacks are not a high risk group. Thus, race and ethnicity are not sufficient to predict higher risk. Hispanics present a different picture. CDC researchers have pointed out (Hamner and Tinker, 2014) that corn masa flour is not fortified. Because this is an important cereal grain in the diet of many Hispanics, these researchers have suggested that finding a way to fortify corn masa flour could improve the folate status of the Hispanic population.

How can we deal with this uncertainty at the clinical level? On an individual basis, the USPHS (USPHS, 1992) recommends that all women of childbearing age capable of becoming pregnant should take 400 micrograms of folic acid per day. Neural tube closure occurs over a brief period ending on day 28 after conception. Chance events such as taking antifolate drugs or a change in diet that reduces folate intake during that period could adversely affect a woman's folate status. We do not know whether a woman who has good body stores of folate (as reflected in a high red cell folate concentration) is safe, or whether a good level of serum folate, which reflects current concentrations in the circulation, is critical to providing folate to the developing embryo. Thus, it is possible that a brief drop in intake

could adversely affect neural tube closure. Therefore, regular use of supplements is a good insurance policy. Women should be advised to follow the USPHS recommendation and take folic acid supplements routinely.

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References

- Ahrens K, Yazdy MM, Mitchell AA, Werler MM. 2011 Folic acid intake and spina bifida in the era of dietary folic acid fortification. *Epidemiology* 22:731–737. [PubMed: 21659881]
- Berry RJ, Li Z, Erickson JD, et al. 1999 Prevention of neural-tube defects with folic acid in China. China-U.S. collaborative project for neural tube defect prevention. *N Engl J Med* 341:1485–1490. [PubMed: 10559448]
- Castillo-Lancellotti C, Tur JA, Uauy R. 2013 Impact of folic acid fortification of flour on neural tube defects: a systematic review. *Public Health Nutr* 16:901–911. [PubMed: 22850218]
- Crider KS, Devine O, Hao L, et al. 2014 Population red blood cell folate concentrations for prevention of neural tube defects: Bayesian model. *BMJ* 349:g4554. [PubMed: 25073783]
- Daly LE, Kirke PN, Molloy A, et al. 1995 Folate levels and neural tube defects. Implications for prevention. *JAMA* 274:1698–702. [PubMed: 7474275]
- Hamner HC, Tinker SC. 2014 Fortification of corn masa flour with folic acid in the United States: an overview of the evidence. *Ann N Y Acad Sci* 1312:8–14. [PubMed: 24494975]
- Hertrampf E, Cortes F. 2004 Folic acid fortification of wheat flour: Chile. *Nutr Rev* 62:S44–S48. [PubMed: 15298448]
- Mosley BS, Cleves MA, Siega-Riz AM, et al. 2009 Neural tube defects and maternal folate intake among pregnancies conceived after folic acid fortification in the United States. *Am J Epidemiol* 169:9–17. [PubMed: 18953063]
- MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. MRC Vitamin Study Research Group. [No authors listed] *Lancet* 1991 338:131–137. [PubMed: 1677062]
- Tinker S, Hamner H, Qi YP, Crider K. U.S. women of childbearing age who are at possible increased risk of a neural tube defect-affected pregnancy due to suboptimal red cell folate concentrations, National Health and Nutrition Examination Survey 2007–2012. *Birth Defects Res A Clin Mol Teratol* (in press).
- United States Public Health Service. 1992 Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. [No authors listed] *MMWR Recomm Rep* 41(RR-14):1–7.
- Yang QH, Carter HK, Mulinare J, et al. 2007 Race-ethnicity differences in folic acid intake in women of childbearing age in the United States after folic acid fortification: findings from the National Health and Nutrition Examination Survey, 2001–2002. *Am J Clin Nutr* 85:1409–1416. [PubMed: 17490980]