ALTERNATIVE THERAPIES IN WOMEN'S HEALTH

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Folic Acid and Neural Tube Defects

By Gerald T. Keegan, MD, FACS and Lynn Keegan, RN, PhD, HNC, FAAN

NEURAL TUBE DEFECTS (NTD) CONSTITUTE AN EXTENSIVE SPECtrum of disease processes—from relatively mild manifestations to those that have a devastating impact on the individual sufferer, the extended family, and society as a whole. Myelomenigocele is the most common defect reported. The incidence of NTDs varies by geographic region, genetic or racial origin, and economic and educational status. Diseases (such as diabetes), medication history (especially antiepileptic medications), and occupational status play significant roles. The chances of a U.S. couple with no prior history of NTDs having a child with an NTD are approximately 1/500 to 1/1,000. Having a child with any type of NTD increases the chances of producing another child with a similar problem by 1/30, or about 3%. When two siblings are affected, the risk rises to as high as 12%.[1] The incidence of the disease in the United States has declined over the years; part of this reduced incidence of NTDs may be related to intrauterine detection with subsequent elective termination of pregnancy.[2]

History of NTDs and Folic Acid

Epidemiological data incriminate environmental factors because the birth prevalence has varied over time and by geographical location; NTD epidemics appear to have taken place at different times and in different locations worldwide.[3] During the 1970s and 1980s, there was an ongoing debate as to whether supplemental vitamins decreased the disease prevalence. This controversy was resolved by two randomized, multicenter studies. The first study found a 72% reduction in the recurrence of NTDs among at-risk women who received a 4 mg/d supplement of folic acid (FA) in the periconceptual period.[4] The second study found that the risk of occurrence of first-time NTD was reduced by 60% through the use of periconceptual FA supplementation.[5]

Several additional randomized studies have demonstrated the critical role of FA supplementation in the prevention of NTDs. In 1992, the U.S. Public Health Service released its first recommendation of 0.4 mg/d FA consumption in all women of child-bearing age. Since that time, many national and international professional societies have released specific guidelines ranging from at least 0.4 mg/d for women of child-bearing age to 4 mg/d for women with a previous

infant with NTDs. Since 1998, mandatory folate fortification of certain foods has been associated with at least a 54% reduction in the incidence of open NTDs in Canada. However, throughout the United States, Canada, and Europe, and more so in third world countries, the rates of periconceptual FA use remain suboptimal, especially among minorities.[6]

Lack of awareness and education regarding the benefits of folate is the most common reason women give for not choosing to use FA supplements before pregnancy. Only 25% of Canadian women meet the recommendation for women capable of becoming pregnant[7] and educational programs have not resulted in increased supplement use.[8] In Norway, researchers found that most pregnant women do not use FA as recommended, and a dramatically low usage was seen in immigrant populations.[9] Despite educational programs in the Netherlands, a significant and persisting disparity in FA usage has been found in women of different socioeconomic status.[10] Despite its ability to reach many U.S. women of child-bearing age with multiple messages about regularly using multivitamins, the Kaiser Health Plan found only a temporary small increase in usage by women who received repeated messages via mail.[11] Health care providers must be alert to recognizing the more subtle NTD manifestations, such as hairy patches, dimples, fatty tumors of the lower back, and urinary tract symptoms.[12] The findings suggestive of minimal NTDs in children will lead to the recommendation of higher doses of FA in those women at risk during subsequent pregnancies.

Clinical Presentation, Risk Factors, and Diagnosis

There are numerous presentations of NTDs. The most severe cases present with anencephaly, where there is an absence of major portions of the brain, scalp, and skull, and which is incompatible with life. The least severe cases present as spina bifida occulta in which only a bony defect is present. The manifestations of severe spina bifida may include infectious complications, paraplegia, bladder and bowel incontinence, Arnold-Chiari malformations, hydrocephalus, and, as a complication of hydrocephalus, diminished intelligence.[13] Clinically, the most common problematic lesions include meningocoele with a meningeal sac but with intact neural elements; spina bifida cystica (myelomenigocele) with a skin-covered intact sac containing neural elements; and spina bifida aperta in which the sac is open.

Although most of these disorders are diagnosed at birth or in early childhood, an occasional abnormality, possibly mistaken for a skin or soft lesion indicating a minimal NTD, may be discovered on routine physical exam.[12] The risk factors of giving birth to a child with an NTD include FA deficiencies, genetic abnormalities of FA metabolism, and insulin-dependent diabetes.[14]

The risk of women with epilepsy bearing children with congenital malformations is approximately twice that of the general population. The mechanism suspect in the production of NTDs is the use of antiepileptic medications that reduce the availability of maternal FA already diminished by pregnancy. Use of a higher FA dose (4 mg/d or equivalent) is protective.[15] Valproate and carbamazine clearly have been incriminated in the development of NTDs and many of the newer anti-epileptic medications are suspect.[14] Valproate-induced NTDs in mouse embryos have been ameliorated by substantially elevated and maintained levels of FA and vitamin B_{12} throughout the period of organogenesis.[16] Studies demonstrating that phenytoin selectively inhibits neural tube closure also have shown that in early chick embryos FA decreased the phenytoin-induced NTD.[17] Additional factors, including occupational exposure to teratogens, medications such as cyclophosphamide,[18] excessive pregnancy weight, the use of oral contraceptives, and other nutrient deficiencies, can be contributory.[14]

Pathogenesis of NTDs

NTDs arise during the first few weeks after conception. The defect may begin developing in the unborn baby before the mother even knows she is pregnant. Many

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factors are involved in the proper closure of the neural tube. In human embryogenesis, the malformation generally is created by abnormal neural tube closure between the third and fourth weeks of gestational age. There is evidence, at least in other mammals, that the closure of the neural tube is intermittent at four discrete locations. Disruption of the process of fusion at any of these four sites may lead to an NTD, possibly arising through the mediation of site-specific genetic mechanisms. The genes responsible for this process include those of the folate metabolic pathway as well as those involved in folate transport.[19] Studies in FA-binding protein-deficient mice have shown that the deficiency of this factor impacted the expression of several downstream signaling molecules and contributed to failure of neural tube closure and the development of craniofacial defects.[20]

Another interesting ingredient in the pathogenesis of NTDs is the relationship with homocysteine. This amino acid is involved in several key metabolic pathways including methylation and sulphuration. Blood concentrations of this substance are moderated by various dietary factors, including FA and vitamin B_{12}, as well as by alterations in physiology, including renal impairment, and by variation in the activity of enzymes as a result of genetic polymorphism. In normal pregnancy, homocysteine levels should fall. Disturbances of this normal mechanism under atypical genetic control may produce metabolic abnormalities in both the mother and the fetus, resulting in elevated homocysteine levels associated with NTDs.[21]

In vitro studies of the behavior of neuroepithelial, cranial, and cardiac neural crest cells showed that the addition of FA increased neuroepithelial cell outgrowth and increased neural crest cell differentiation into nerve and smooth muscle cells. The addition of homocysteine to the cell culture increased the neural cell outgrowth but inhibited neural crest cell differentiation.[22] The authors concluded that NTDs caused by folate deficiency and hypercysteinemia developed secondary to increased neuroepithelial to neural crest transformation, leading to a shortage of neuroepithelial cells in the neural tube. The consistent findings that effective FA supplementation prevents the defect and that high homocysteine levels always are present in the mothers of children with NTDs have led to extensive studies of the genes involved in FA and homocysteine metabolism. A comprehensive list of genes known to be involved in folate and homocysteine metabolism has been identified.[23] Some of the more important studies have involved genes encoding the enzymes methylenetetrahydrofolate reductase or methylenetetrahydrofolate dehydrogenase (MTHFD) in FA metabolism. Genes encoding methionine synthase, its regulator methinine synthase reductase, and cystathionine synthase in homocysteine metabolism are also being studied.[23,24] Studies in Ireland (a country with an historically high rate of NTDs) have shown that genetic variation in the MTHFD1 gene is associated with an increase in the genetically determined risk that a woman will bear a child with NTDs. This gene also may be associated with decreased embryo survival.[25]

Another recent study of five common functional polymorphisms in enzymes involved in homocysteine metabolism in young adults found that serum folate, red cell folate, vitamin B_{12}, and total plasma homocysteine concentration (tHcy) were influenced significantly by the variant genotype MTHFR 677C>T. A particularly strong interaction was observed between MTHFR 677TT genotype and FA, which led to a high tHcy phenotype that was more pronounced in males. The genetic contribution to the variance was estimated at only 9%, with approximately 35% being attributed to low folate and vitamin B_{12} levels. This study emphasizes that dietary factors were most important in the control of the tHcy levels in young adults with additional somewhat weaker genetic effects, and further stresses the importance of the implementation of folate/B-vitamin food fortification programs.[26] Many studies in laboratory animals have demonstrated that even in the presence of known genetic defects, FA can prevent the genetic expression of NTDs.[27]

FA Sources and Metabolism

FA is a B-vitamin obtained primarily from yeasts, leafy vegetables, and animal liver. (*See Table.*) The vitamin cannot be synthesized in animals and requires intake in the diet. Since 1998, the U.S. Food and Drug Administration has mandated that cereal products be fortified with 140 mcg of FA per 100 g. It is important to be able to adequately assay that content, and a microbiological trienzyme extraction procedure has been developed for that purpose. Use of these techniques has demonstrated differences in FA content in lentils and peas derived from different locations.[28] The protective effects of FA may be dose-related. Data on vitamin intake from more than 23,000 women from the northeastern United States were submitted to multiple logistic regression and restricted spline regression modeling with the finding that for each additional 500 dietary folate equivalents consumed per day, the prevalence of NTDs decreased by 0.78 cases. This study concluded that total folate dose, rather than supplemental folate alone, should be considered in formulating public health guidelines for NTD prevention.[29] When ingested or stored in the liver, FA exits as a polyglutamate form. By a process of removing some of the glutamate residues, the intestinal cell lysosomes make the charge of the folate more positive and capable of absorption through the basal membrane of the epithelial cells and into the blood stream. Within the liver, the FA is reduced to a

tetrahydrofolate (THF) through the action of dihydrofolate reductase, an NADPH-requiring enzyme. The function of THF is to carry and transfer various forms of one-carbon units during biosynthetic reactions. The role of vitamin B_{12} and the one carbon-THF's in the conversion of homocysteine to methionine can have a significant impact on the availability of the active form of FA to the cells.[30]

Table

Food Sources of Folic Acid

Food Source	Comments
Green leafy vegetables and beets	Cooking destroys varying amounts of the nutrient
Brussels sprouts, cauliflower, broccoli, and asparagus	The folic acid in brussels sprouts and asparagus survive cooking better due to their compactness
Brewer's yeast and wheat germ	Consider using powder in fruit drinks
Liver and other organ meats	Try eating liver with onions and bacon
Citrus fruits and juices	Fresher is better
Dried beans and peas	
Black-eyed peas	Better source than either liver or wheat germ
Nuts	
Milk	
Fortified grain products	All cereals are required to contain folic acid
Most uncooked foods	Cooking destroys varying amounts of the nutrient

Precautions in the Use of FA

FA is a water-soluble vitamin and it is unlikely that toxic levels could be reached under normal circumstances including standard vitamin and food supplementation. Doses in excess of 20 g/d for an extended period can produce renal damage. Concern has been raised as to whether excessive consumption of enriched cereal—in the face of significantly higher assayed levels of FA than listed on the food label—could lead to iron and FA toxicity, but considering the very high levels of FA needed for toxicity, this seems unlikely.[31] However, the potential exists that FA supplementation could disguise underlying B_{12} deficiency, which itself has the potential to produce NTDs.[32] Synthetic L-5-methyltetrahydrofolate has been proposed as being more appropriate as a fortificant because it is unlikely to mask the hematologic indicators of B_{12} deficiency.[33] Potential dangers exist that with supplementation of dietary staples, such as flour, with FA as opposed to the natural folate (N5CH3HFGlu1), the FA could enter the cell and the metabolic pathway by a cobalamin (B_{12})-independent pathway and exacerbate or perhaps even induce B_{12} deficiency.[34] In addition, there is a potential interaction between zinc plasma levels and FA metabolism as well as evidence suggesting a relationship between NTDs and lower levels of zinc as measured in the hair. For this reason all supplements should contain both zinc and folic acid.[35,36]

Recommendation

Folic acid supplementation is highly recommended in all women of child-bearing age in a dosage of at least 0.4 mg/d. Women who are at risk because of diabetes, insulin-dependent diabetes, and having other children with even minimal NTDs should take at least 4 mg/d because of the clear protective effects both in the genetic and acquired forms of NTD. Compliance issues have been of concern and might be improved by weekly rather than daily usage. Studies in Mexico demonstrated that there was a 50% decrease in the incidence of NTDs using a single tablet of 5 mg FA weekly as an alternative to daily supplementation.[37] Investigators in New Zealand have shown a weekly dose of 2.8 mg FA was as effective as daily doses of 0.4 mg in lowering homocysteine levels in normal women of childbearing age.[38] Educational programs and physician counseling regarding the benefits of FA are essential. ❖

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Soy Supplements and Cognitive Function

By Mary L. Hardy, MD

THIS YEAR, AN ESTIMATED 1.35 MILLION U.S. WOMEN WILL become menopausal. The most common symptom experienced by these women besides cessation of menses is hot flashes.[1] Much less attention is paid to the cognitive symptoms of menopause, but for many women changes in memory and "ability to think straight" can be debilitating. More than half of mid-life women (62% in one study) report subjective changes in memory, which were worse in perimenopausal than postmenopausal women.[2] Although positive correlations were seen in the Seattle Midlife Women's Health Study between severity of cognitive complaints and stress/depressed mood, estrogen decline itself is thought to have a negative effect on cognitive function.

A number of studies have shown a protective effect of hormone replacement therapy (HRT) on cognitive decline and developing Alzheimer's disease.[3] Maki's systematic review of clinical and observational trials examining HRT's effect on the cognitive function of perimenopausal and menopausal women found the strongest data for protection against the development of Alzheimer's dementia (AD). No benefit was demonstrated for women already suffering from AD. The data in women without prior cognitive defects are more difficult to analyze due to variability in subjects and testing

methods, but many of the individual trials cited in this review are encouraging.

Experts recommend soy foods and products, especially those rich in isoflavones, for menopausal patients primarily for soy's effects on vasomotor symptoms. Isoflavones, also called phytoestrogens, are thought to have weak estrogenic activity.[4] Unfortunately, data to support soy's use for the relief of the cognitive symptoms of menopause were not considered strong enough for some experts to make a recommendation.[5] However, the observational data in women taking HRT suggest that there may be a possible mechanism for the isoflavones in soy to exert an estrogen-like protective effect on cognitive dysfunction, especially the development of AD. In fact, one primate model shows decreases in an abnormal brain protein, hyperphosphorylated protein tau, which is implicated in the development of AD.[6] Thus, the known activity of isoflavones, the epidemiologic data suggesting that estrogen can protect cognitive function in menopausal women, and animal data suggesting a biologic mechanism of action, all sustain interest in the use of soy products for support of cognitive function in mid-life women. Few studies have been conducted in this area. However, two recent articles, described below, were performed very carefully.

In the first study, Duffy et al tested a soy isoflavone supplement (60 mg/d isoflavones) in 33 postmenopausal women.[7] The study was blinded, randomized, and placebo-controlled—so the methodology was sound. Patients were tested not only for their cognitive function, but also for things that could confound cognitive performance such as mood, anxiety, or sleepiness. Groups had equivalent IQs and educational attainment. There were minor differences in the two groups at baseline based on assessment of their diets. The treatment group ate slightly more refined sugar, took more calcium, and drank less alcohol. The alcohol consumption in the placebo group also was quite low, and none of these differences were thought to be clinically significant. Both groups were asked to refrain from eating soy-containing foods during the trial.

Although the trial duration was short (12 weeks), significant improvements were seen in the active treatment groups. Treated subjects did better in tasks requiring sustained attention, recall of pictures, and planning a task. Learning new rules seemed to be equal in both groups, suggesting that new learning was less affected, but the manipulation of that new learning (learning rule reversals) was better in the treated group. This improvement was independent of any changes in menopausal symptoms, mood, or sleepiness as none of these parameters changed. The differences in the two groups were not always statistically significant and varied even within groups of related tests. It could be argued that the improvements noted were the result of "learning to take the test," but the treatment group in general tended to do better. The kinds of functions that demonstrated improvement included memory recall and task planning. So, even in a short intervention with a moderate dose of isoflavones, a difference can be demonstrated in postmenopausal women's cognitive function.

Kritz-Silverstein and her colleagues tested a similar population but used a higher dose of isoflavones (110 mg/d) for a longer time (6 months).[8] Both groups were equivalent at baseline, as above. Mood was assessed, but neither sleepiness nor menopausal symptoms were assessed. Food patterns were checked, but most women did not consume significant amounts of soy foods during the trial. Compliance was checked carefully in this study and was very good. The trial was a randomized, double-blind, placebo-controlled trial, so again the methodology was sound. The memory tests used were not the same as the ones used previously, but similar types of functions were tested.

As demonstrated in the shorter study, treated subjects performed better both with respect to their own baseline and to the performance of the placebo patients. Specifically, statistically significant results were obtained in tests of verbal memory (category fluency), and non-statistically significant improvements were found for tests of visual motor tracking and attention. A cruder measure of cognitive function used in routine clinical practice, the Mini-Mental Status Examination (MMSE), did not change during the trial. This screening tool is designed to reveal the presence of dementia, not milder cognitive dysfunction. When the results were analyzed comparing the results of younger vs. older patients, the older patients showed a larger benefit. Again, some of the improvement observed in both groups could be attributed to learning effects (the fact that subjects perform better the second time they do a task than the first), but still differences that exceeded this learning effect were demonstrated between the groups.

In terms of applying these studies to our own patients, a few caveats. First, most of the women tested were fairly well-educated and in the second trial represented a very high socioeconomic status. These are the kind of patients who generally use supplements, but we don't know if the effects of the supplements will translate fully to different groups. Soy supplementation will not likely correct cognitive difficulties caused by depression, dementia, or other medical conditions, so these conditions should be ruled out before soy is tried. Also, all the women tested here were postmenopausal and there may be differences in the results for perimenopausal women.

The studies used pills that contained isolated isoflavones in moderate to fairly high ranges. These were obviously active and the isoflavones are more

likely to contribute to cognitive protection. However, it is always beneficial to try to use soy in a manner that also includes the protein component, as soy protein is a heart healthy food and has been shown to lower cholesterol. Some concern has been raised about using high doses of isolated isoflavones, but for the average patient, dosages in the ranges quoted here should be fine. More caution should be exercised in patients who are at high risk of adverse effects from increased exposure to the estrogenic effects of soy isoflavones. No risk has been directly proven, but this is another reason for the use of whole soy foods as opposed to isolated supplements.

Finally, it is important to make sure that our patients have accurate expectations for their soy intervention. Effects on menopausal symptoms are likely to be mild at best. Memory should improve, but the effects are subtle. Patients should be clear about having an endpoint to "test." Ask them to rate some activity they do regularly so that they can see the benefit over time. Remind them that these interventions work best in the context of a healthy lifestyle and take time to see maximal benefit. If the patient is eating soy as a food, then the additional beneficial effects on heart and bone health can accrue as well. In this context, it seems that the addition of isoflavone-rich supplements and/or foods could be a useful treatment for a nagging concern of women during menopausal transitions and should be discussed with women complaining of memory problems. ❖

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4. offer guidance to patients based on the latest science and clinical studies regarding alternative and complementary therapies.

CE/CME Instructions

Physicians and nurses participate in this continuing medical education/continuing education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. After completing this activity, you must complete the evaluation form provided and return it in the reply envelope provided at the end of the semester to receive a certificate of completion. When your evaluation is received, a certificate will be mailed to you.

CE / CME Questions

18. In 1992, the U.S. Public Health Service recommended that all women of child-bearing age take what amount of folic acid daily?

a. 0.04 mg
b. 0.4 mg
c. 4.0 mg

19. What risk factors warrant women of child-bearing age taking a higher dose of folic acid?

a. Diabetes (insulin-dependent or non insulin-dependent)
b. History of taking antiepileptic medications
c. Having a child with a neural tube defect
d. All of the above

20. Folic acid is a B-vitamin obtained primarily from yeasts, leafy vegetables, and animal liver.

a. True
b. False

21. Two recent studies indicate that postmenopausal women who take soy supplements may experienced subtle improvements in memory.

a. True
b. False

Answers: 18. b, 19. d, 20. a, 21. a.

News Briefs

NCCAM Announces Research Fellowship Program

The National Center for Complementary and Alternative Medicine (NCCAM), a component of the National Institutes of Health (NIH), has announced the creation of a new NCCAM Director's Fellowship in Complementary and Alternative Medicine (CAM) Research.

The new fellowship program will sponsor outstanding research fellows to work in NCCAM's Division of Intramural Research (DIR), based at the NIH in Bethesda, MD. A selection committee comprising leaders from the CAM and scientific communities will choose the recipient of the fellowship from a highly competitive international pool of applicants. Applicants must possess an MD, DO, PhD, DC, DMD, ND, DVM, or other equivalent degree, and have a record of excellence and promise in clinical and/or laboratory-based research—preferably related to CAM.

The primary goal of the training program is to prepare the fellow for a career as an independent CAM investigator. The fellowship includes full salary, benefits, professional travel, and research support for two to three years. The fellow will undertake clinical, translational, and/or laboratory research in NCCAM's DIR. The DIR provides state-of-the-art research facilities as well as access to the extensive clinical research infrastructure of the NIH Clinical Center.

For more information about the fellowship, applicants should contact: Christopher Baron, Human Resources Specialist, Office of Human Resources, NIH, 31 Center Drive, Room 2C12, Bethesda, MD 20892. His e-mail address is Baronch@mail.nih.gov. The deadline for receipt of applications is Nov. 24, 2003.

Herbal Remedy Might Raise Cholesterol

A study has found that an herbal remedy widely used in Asia to lower cholesterol actually might raise it instead. Guggul is the yellowish resin that is produced by the mukul myrrh (*Commiphora mukul*) tree, a small, thorny plant that grows throughout northern India. Since guggul is being used with increasing frequency as a cholesterol-lowering agent in the United States, researchers decided to look at the herbal remedy. They studied the short-term safety and efficacy of two doses of a standardized guggul extract in 103 healthy adults with hyperlipidemia who were eating a typical Western diet.

The study participants were given by mouth three daily doses of 1,000 mg of guggulipid, a standard dose; three higher daily doses of guggulipid at 2,000 mg; or placebo. The researchers then measured the percentage changes of low-density lipoprotein cholesterol (LDL-C) after eight weeks of therapy.

Compared to the participants taking the placebo, whose LDL-C levels decreased by 5%, the standard-dose guggulipid had raised LDL-C levels by 4%, and the high-dose raised the levels by 5% at eight weeks. In addition, six participants on the treatment developed a rash. The researchers concluded that guggulipid did not appear to improve levels of serum cholesterol over the short term in this population of study participants.

The study appeared in the Aug. 13 issue of the *Journal of the American Medical Association*.

FDA Seizes Bogus Dietary Supplement that Claims to Cure Cancer

At the request of the U.S. Food and Drug Administration (FDA), U.S. marshals have seized the dietary supplements, Forticel and Forticel Mix, from Jean's Greens in Norway, NY. After an investigation of this company and its marketing practices, FDA has determined that Jean's Greens is making unapproved medical claims for these herbal products. Specifically, the products claim to treat and cure various life-threatening and serious illnesses such as cancer, although there is no scientific evidence to support these claims.

The seizure included 385 bottles and 78 mix packages worth more than $4,000. Because the Forticel and Forticel Mix products make disease claims, the FDA considers these products to be unapproved new drugs. Before a new drug product is approved for marketing, it must be shown to be safe and effective. Furthermore, drug product labeling also must include adequate directions for their intended use, which the seized products' labeling did not provide.

After its investigation of the firm's marketing practices, the FDA advised the firm that its products were making disease claims and are subject to be regulated as drugs. Despite the FDA's warnings, the firm failed to comply. To date the FDA has received no reports of illnesses associated with taking the seized products. ❖

In Future Issues:

Current U.S. Regulations of Dietary Supplements

Alternative Therapies for Vaginitis

Exercise for Cardiovascular Disease