

## Vitamin Under- and Over-Reactions

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### **Folic Acid Follies: When Will People Think About This Vitamin Rationally?**

See related articles in the November issue of The Nutrition Reporter.

Research linking the B-vitamin folic acid to the prevention of birth defects has been published in the medical literature since the 1960s. This vitamin is required in minuscule amounts during the first several months of pregnancy to ensure that the developing fetus' neural tube closes and protects the spine. When pregnant women are deficient in folic acid, the neural tube fails to close, and the infant faces a high risk of crippling and often deadly neural-tube defects, such as spina bifida.

The good news is that the relationship between folic acid and the prevention of birth defects is now well established. Even the March of Dimes has undertaken folic acid as its latest cause.

The bad news is that very little is being done to ensure that women actually receive sufficient folic acid. One problem is that many women do not realize they are pregnant at the time their fetuses require folic acid the most.

Federal officials have for at least two years debated whether common foods, such as bread, should be fortified with folic acid. Such fortification would provide a reliable source of the vitamin for most women. There are a number of arguments against such food fortification, some sound, some not so sound.

Adding folic acid to bread might increase the cost of a loaf by 1¢. That doesn't seem like much, but some people have questioned whether the effort and cost are really worth saving only a couple of thousand babies each year. Another problem is that folic acid is extremely sensitive to heat, and the baking of bread might destroy much of the vitamin.

On the other hand, the problem of spina bifida may be far greater than most people imagine. As with any condition, there is a range in severity. Sometimes, the spine is exposed at birth, and the prognosis for the infant is very poor.

At other times, neural tube defects may be more subtle. There are an unknown number of cases of "spina bifida occulta," in which the birth defect is mild and remains undiagnosed for years or even a lifetime. Such cases occur in mildly rather than severely deficient women. I have come to understand this situation through personal experience. Two years ago, at age 43, my wife was diagnosed with spina bifida occulta. She began developing numbness in her legs, and an x-ray revealed that her neural tube had not fully closed. How many people share her predicament? It's impossible to know — other than the fact that subclinical (marginal) deficiencies of many nutrients are common.

The issue of folic acid supplementation takes on greater significance with the recognition that 10 to 40 percent of all cases of coronary heart disease and stroke appear related to inadequate intake of folic acid

and other B vitamins. Instead of affecting 4,000 fetuses, folic acid deficiency could impact several hundred thousand Americans a year.

When consumption of folic acid or several other B vitamins is low and meat intake is high, the body cannot quench homocysteine, a byproduct of protein metabolism. Homocysteine attacks the walls of arteries and seems to set the stage for disease. It may even precede cholesterol as a causative factor.<sup>1</sup>

The role of homocysteine in cardiovascular disease was proposed by Kilmer S. McCully, MD, in 1969,<sup>2</sup> and it has taken almost a quarter-century for it to become medically acceptable. Recently, Shirley A. A. Beresford, PhD, of the University of Washington, analyzed 38 previous studies on homocysteine, folic acid, and cardiovascular disease. She reported in the *Journal of the American Medical Association* that high blood levels of homocysteine were clearly associated with cardiovascular diseases and that folic acid lowered its blood levels.<sup>3</sup>

Once again, public health authorities have responded with deadly silence instead of recommendations. The most common excuse is that excessive folic acid—one of the safest vitamins—might mask some of the symptoms of vitamin B12 deficiency. That is nothing more than a rationalization.

Years ago, vitamin B12 deficiency was typically diagnosed by looking at red-blood cell abnormalities under a microscope. Very high doses of folic acid can mask these blood abnormalities, allowing neurological damage from B12 deficiency to continue unnoticed. Today, a laboratory test for methylmalonic acid serves as a more sensitive and specific test for vitamin B12 deficiency.

In the 1980s, Carlton Fredericks, PhD, offered a simple safeguard for anyone contemplating folic acid supplements: take some vitamin B12 as well. Writing in *JAMA*, Beresford echoed this advice in suggesting that people take 1 mg of B12 with every 400 mcg tablet of folic acid. It's a simple solution.

Increasingly, homocysteine is being used as a marker of folic acid deficiency, and folic acid and other B vitamin deficiencies are common, particularly among the elderly.<sup>4,5,6</sup> The implications are profound. The more foot-dragging on folic acid, the more cardiovascular deaths and birth defects that will occur. It's simply time to act—and to supplement with multiple vitamins.

### **Vitamin A and Pregnancy: How Many People Will the Panic Injure?**

October's newspaper headlines on the dangers of vitamin A broke the custom of not disclosing data before its publication in a scientific journal. Some researchers complained because they would not be able to read details of the study for several weeks.

Lead investigator Kenneth J. Rothman, DrPH, of the Boston University School of Medicine, and the *New England Journal of*

*Medicine* (which planned to publish the study Nov 23, 1995) contended that they released the findings early because it was a matter of urgent public health.

It seemed more like an excuse for grandstanding and headline grabbing. The *NEJM* has not seen similar public health value in pre-releasing studies showing that folic acid and vitamin E reduce the risk of coronary heart disease, or that calcium supplements prevent osteoporosis. Such acts would help far more people than excess vitamin A would hurt.

Still, Rothman's findings are important. He reported that women consuming large amounts of vitamin A, either from food or supplements, had about a two- to four-time greater risk of delivering children with craniofacial defects than did women with lower vitamin A intake. The study was based on women's recollections of what they ate and the vitamins they took.

The period of greatest risk was around the time of conception or during the first several months of pregnancy. Taking vitamin A at these times did not mean that a baby would definitely suffer defects—only that there was a higher risk of defects. According to Rothman, 1 in 57 babies born to women taking high-dose vitamin A had birth defects. Another way to look at this is to say that 56 of the 57 infants born to the high vitamin A group were normal.

Richard Miller, PhD, director of the Prenatal Environmental and Drug Exposure Consultation Service at the University of Rochester, decried the post-press conference vitamin A panic. In written statements and a phone interview, he criticized Rothman's broad definition of craniofacial birth defects. He was also distressed that some pregnant women might stop taking all vitamins or might react to the news by aborting otherwise healthy fetuses.

Often overlooked in the vitamin A headlines and stories were a number of other important issues.

First, vitamin A is essential for normal cell differentiation, and there is evidence that vitamin A deficiency also leads to birth defects.<sup>7</sup> Yet Rothman concentrated on vitamin A excesses, not deficiencies. In his paper, he stated that 98.6 percent of the women consumed "safe" levels of vitamin A, but these were approximately RDA levels or below. When queried, Rothman said he did not analyze data as to how many women actually consumed less than the RDA for vitamin A.<sup>8</sup> If he had, he might have better demonstrated the effects of low vitamin A, as well as an optimal dose for pregnant women.

Second, the risk of vitamin A in pregnancy does not apply to beta-carotene, which is completely safe. The body converts beta-carotene to vitamin A only as needed. Even Rothman pointed this out in his paper and at his press conference.

Third, Rothman's study was based on women questioned from 1984 to 1987. Since that time, a large number of vitamin companies selling multiple vitamins have replaced vitamin A with beta-carotene. That means women today are now less likely to encounter high doses of vitamin A—and therefore the practical risk of vitamin A overdose is less than it was.

Fourth, vitamin A is one of the most potent and worthwhile immune stimulants and is especially protective against respiratory infections.<sup>9</sup> It is essential for the formation of epithelial cells, which function as a physical barrier against infections, and it also stimulates the production of T cells, and antibody-producing B cells.<sup>10</sup> One recent study reported that occasional high doses of vitamin A improved the

well being of infants with HIV infections.<sup>11</sup>

Fifth, the bigger problem (from a public health standpoint) is not a small number of cases of vitamin A overdose, but widespread vitamin A deficiency. In the 1980s, Alfred Sommer, MD, of Johns Hopkins University documented that one or two very high doses of vitamin A (more than 100,000 IU) could prevent one-third of childhood deaths from measles in developing nations.<sup>12</sup> The World Health Organization (WHO) and UNICEF now routinely recommend occasional vitamin A supplements for children at risk of dying from measles, and the American Academy of Pediatrics has issued similar recommendations.<sup>13</sup>

Although the latest edition of the *Recommended Dietary Allowances*, published by the National Academy of Sciences, describes vitamin A deficiency as "rare" in the United States,<sup>14</sup> evidence suggests that the opposite is really true. According to one major survey, one-half of Americans consume 19 percent or less of the RDA for vitamin A, and one-fourth of the population consumes no more than 11 percent of the RDA.<sup>15</sup>

So, what conclusions should you draw from the vitamin A and pregnancy study?

There is a risk of vitamin A overdose, but the risk is generally overstated. Women likely to become pregnant should exercise caution taking high doses of vitamin A or eating liver (a 3-ounce serving provides 30,000 IU), but there is no need for worry with beta-carotene. If you're not likely to become pregnant—and this includes the male half of the population and older women—vitamin A toxicity is less of an issue.

Miller and others believe that high-dose vitamin A supplements should be banned or put on prescription. In my opinion, this is bad advice. A warning label, comparable to the one found on wine bottles, would be appropriate and sufficient, and such warning labels on vitamin A are currently required on vitamin A supplements in California.

It is also worthwhile being watchful of symptoms of vitamin A overdose, including chronic headache, vomiting, loss of hair, dryness of the mucous membranes, and liver damage. But according to the American Academy of Pediatrics, vitamin A toxicity generally doesn't occur unless someone consumes more than 1,000,000 IU in a two- to three-week period.<sup>16</sup>

Let's be sensible and remember that most vitamin problems are related to deficiencies, not overdoses.

<sup>1</sup> McCully KS, *Annals of Clinical & Laboratory Science*, Nov-Dec 1993;23:477-93.

<sup>2</sup> McCully KS, *American Journal of Pathology*, July 1969;56:111-28

<sup>3</sup> Beresford SAA, et al., *Journal of the American Medical Association*, Oct 4, 1995;274:1049-57.

<sup>4</sup> Ubbink JB, *American Journal of Clinical Nutrition*, Jan 1993;57: 47-53.

<sup>5</sup> Selhub J, et al., *JAMA*, Dec 8, 1993, 270:2693-2698.

<sup>6</sup> Naurath HJ, et al., *Lancet*, July 8, 1995;346:85-9.

<sup>7</sup> Bendich A and Langseth L, "Safety of vitamin A," *American Journal of Clinical Nutrition*, February 1989;49:358-71.

<sup>8</sup> E-mail communication, October 12, 1995.

<sup>9</sup> Neuzil KM, et al., *Journal of Pediatrics*, March 1994;124:433-6.

<sup>10</sup> Dennert G, in: Sporn MB, Roberts AB, and Goodman DS, eds. *The Retinoids*. Orlando: Academic Press, 1984;2:373-390.

<sup>11</sup> Coutsoudis A, et al, *American Journal of Public Health*, Aug 1995;85:1076-1081.

<sup>12</sup> Sommer A, *Journal of Infectious Diseases*, May 1993;167:1003-7.

<sup>13</sup> Committee on infectious diseases, American Academy of Pediatrics, *Pediatrics*, May 1993, 91:1014-1015.

<sup>14</sup> *Recommended Dietary Allowances*, National Academy Press, 1989.

<sup>15</sup> Block G, *Nutrition Reviews*, June 1992;50:207-213.

<sup>16</sup> Committee on infectious diseases, American Academy of Pediatrics, *Pediatrics*, May 1993, 91:1014-1015.