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TERATOGENICITY OF HIGH VITAMIN A INTAKE

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Abstract *Background.* Studies in animals indicate that natural forms of vitamin A are teratogenic. Synthetic retinoids chemically similar to vitamin A cause birth defects in humans; as in animals, the defects appear to affect tissues derived from the cranial neural crest.

Methods. Between October 1984 and June 1987, we identified 22,748 pregnant women when they underwent screening either by measurement of maternal serum alpha-fetoprotein or by amniocentesis. Nurse interviewers obtained information on the women's diet, medications, and illnesses during the first trimester of pregnancy, as well as information on their family and medical history and exposure to environmental agents. We obtained information on the outcomes of pregnancy from the obstetricians who delivered the babies or from the women themselves. Of the 22,748 women, 339 had babies with birth defects; 121 of these babies had defects occurring in sites that originated in the cranial neural crest.

Results. For defects associated with cranial-neural-crest tissue, the ratio of the prevalence among the babies born to women who consumed more than 15,000 IU of preformed vitamin A per day from food and supplements to the prevalence among the babies whose mothers consumed 5000 IU or less per day was 3.5 (95 percent confidence interval, 1.7 to 7.3). For vitamin A from supplements alone, the ratio of the prevalence among the babies born to women who consumed more than 10,000 IU per day to that among the babies whose mothers consumed 5000 IU or less per day was 4.8 (95 percent confidence interval, 2.2 to 10.5). Using a smoothed regression curve, we found an apparent threshold near 10,000 IU per day of supplemental vitamin A. The increased frequency of defects was concentrated among the babies born to women who had consumed high levels of vitamin A before the seventh week of gestation.

Conclusions. High dietary intake of preformed vitamin A appears to be teratogenic. Among the babies born to women who took more than 10,000 IU of preformed vitamin A per day in the form of supplements, we estimate that about 1 infant in 57 had a malformation attributable to the supplement. (N Engl J Med 1995;333:1369-73.)

VITAMIN A is essential for embryogenesis, growth, and epithelial differentiation. By the term "vitamin A," we refer to retinoid compounds that have the biologic activity of retinol. Preformed vitamin A in the diet comes from animal sources, such as dairy products and liver, and from fortified foods and vitamin supplements. Beta carotene and other carotenoids are plant-synthesized precursors of vitamin A that are partially converted to retinol during or after absorption.[1] Currently, the Recommended Dietary Allowance for women is 800 retinol equivalents, which corresponds to about 2700 IU of vitamin A per day.[2] In the United States, about 25 percent of adults ingest supplements containing vitamin A and about 5 percent take supplements of vitamin A alone.[3]

Experiments in animals have shown that retinoids (but not carotenoids) can be teratogenic.[1,4-6] In humans, isotretinoin, a synthetic retinoid used in the treatment of severe acne, causes congenital fetal anomalies.[7,8] Lammer et al. estimated that, with fetal exposure to isotretinoin, the risk of a malformation was 25 times greater than normal.[8] As in the studies in animals, a specific group of malformations ("retinoic acid embryopathy"), including those of craniofacial, cardiac, thymic, and central nervous system structures, appears to be involved.

Thus, the available evidence is consistent with the existence of a common teratogenic mechanism by which natural and synthetic retinoids affect the development of cephalic neural-crest cells and their derivatives and perhaps interfere with the closure of the neural tube.[8-14] Recent evidence indicates that the teratogenic effect of retinoids may derive from an effect on the expression of the homeobox gene *Hoxb-1* that regulates axial patterning in the embryo.[15,16]

Data on the teratogenicity of vitamin A in humans

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