

## PROGNOSIS

# High vitamin A intake in early pregnancy was associated with birth defects

Rothman KJ, Moore LL, Singer MR, et al. *Teratogenicity of high vitamin A intake*. *N Engl J Med*. 1995 Nov 23;333:1369-73.

### Objective

To determine the relation between the intake of vitamin A in early pregnancy and birth defects.

### Design

Cohort of women assembled in early pregnancy and followed until delivery.

### Setting

Obstetrical practices in the northeastern United States.

### Patients

22 748 pregnant women who had had a maternal serum alpha-fetoprotein measurement or amniocentesis early in their pregnancy. Women were excluded if follow-up data were missing.

### Assessment of Prognostic Factors

Nurses interviewed women who were between 15 and 20 weeks of their pregnancy. The data collected included information on diet and dietary supplements; medications; illnesses during the first trimester;

family and medical history; exposure to environmental and occupational agents; vitamin intake (A, C, and E); and nutritional yeast, folic acid, selenium, zinc, iron, and other nutrients and supplements taken during the 3 months before conception and into the first trimester. Vitamin A intake was calculated from food and supplement information and was classified into 4 categories of daily intake (0 to 5000 IU, 5001 to 10 000 IU, 10 001 to 15 000 IU, or  $\geq 15 001$  IU).

### Main Outcome Measures

Obstetricians and mothers were contacted by mail to ascertain birth defects and other complications. Birth defects were classified using the Centers for Disease Control and Prevention birth defects classification scheme.

### Main Results

339 babies had birth defects; 121 defects were of cranial-neural-crest origin. Prevalence of total defects for each category of vitamin A intake in ascending order were 1.3%, 1.5%, 1.3%, and 3.0%. Prevalence of cranial-neural-crest defects for the respective categories of vitamin A were 0.51%, 0.47%, 0.63%, and 1.8%. When vitamin A

intake was from foods alone, the prevalence of cranial-neural-crest defects was 0.52% for 0 to 5000 IU/d, 0.62% for 5001 to 10 000 IU/d, and 1.06% for  $> 10 001$  IU/d; for vitamin A from supplements, the prevalence rate was higher (0.46% for 0 to 5000 IU/d, 0.51% for 5001 to 8000 IU/d, 1.18% for 8001 to 10 000 IU/d, and 2.21% for  $\geq 10 000$  IU/d). An unrestricted quadratic-spline logistic model with smoothed exposure-effect curves showed an approximate vitamin-A-supplement threshold value of 10 000 IU/d for birth defects.

### Conclusions

High consumption of vitamin A in early pregnancy, especially if taken in the form of nutritional supplements, was associated with cranial-neural-crest birth defects. 1 in 7 infants born to mothers who had received at least 10 000 IU/d of vitamin A had these birth defects.

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### Commentary

Vitamin A regulates cell differentiation and proliferation by binding nuclear receptors to retinoic acid to regulate gene expression.

Vitamin A can be consumed as preformed vitamin A (retinoids) in animal sources and vitamin supplements or provitamin A (carotenoids) in plant sources. Extensive experimental evidence points to the teratogenicity of retinoids in animals. In early pregnancy, placental transfer appears unrestricted until receptors and transport-binding proteins are synthesized in fetal tissue (1).

Little evidence exists on the teratogenic effects of vitamin A in humans. Therefore, the findings of this large cohort study with its good compliance rates are timely. We are likely to see increased consump-

tion of vitamin A by women of child-bearing age because of the increasing therapeutic uses of retinoids (e.g., acne) and the recommendation for preconceptional intake of folic acid that can be purchased in a multivitamin preparation. The prevalence, pattern, and timing of birth defects and the dose-response relation reported in the study by Rothman and colleagues provide convincing evidence that vitamin A is teratogenic in humans.

In Australia, the National Health and Medical Research Council has recommended a dietary intake for vitamin A of 1200 to 1800 IU/d with no additional allowance for pregnancy, but the average dietary intake is 5000 IU/d (60% from carotenoids). The teratogenic threshold of 10 000 IU/d in the first month of preg-

nancy can be quickly reached with vitamin supplements (up to 10 000 IU/tablet) or with regular consumption of liver (65 000 IU/100 g). Women of child-bearing age who are contemplating pregnancy should be advised to avoid medications and vitamin supplements that contain vitamin A and foods high in retinoids such as liver and fish liver oil. These products should be labeled appropriately to highlight the potential risks in pregnancy.

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### Reference

1. Pinnock CB, Alderman CP. The potential for teratogenicity of vitamin A and its congeners. *Med J Aust*. 1992;157:804-9.