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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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are scant.¹⁷⁻²¹ Here we report on the relation between birth defects and the intake of vitamin A from food and supplements in a prospectively studied population of more than 22,000 pregnant women.

METHODS

The study cohort was originally recruited to evaluate risk factors for neural-tube defects.²² Between October 1984 and June 1987, women from the practices of more than 100 participating obstetricians were identified when they either had a maternal serum alpha-fetoprotein measurement or underwent amniocentesis. The study protocol was reviewed and approved by the Boston University Medical Center's Institutional Review Board for Human Research.

Nearly all the women were enrolled between week 15 and week 20 of pregnancy. Nurse interviewers contacted the women by telephone to obtain information on diet, medications, and illnesses during the first trimester of pregnancy, as well as general information on their family and medical history and exposure to environmental and occupational agents. The interviewers called 24,559 women, of whom 23,491 gave their consent to participate. Of those interviewed, 29 women were excluded because their interviews were incomplete, 686 because they could not be located for follow-up, and 21 because information on the outcome of pregnancy was missing. These exclusions left 22,755 women with completed interviews and follow-up information.

Retinol Intake

The interviewers asked each woman detailed questions about her diet and her use of vitamin supplements. Women were asked, "In the three months prior to pregnancy, did you take a multivitamin?" Women who said yes were asked for the brand name of the vitamin and how many times it was taken each week. Each woman was then asked specifically whether she took supplements of vitamin A, vitamin C, vitamin E, nutritional yeast, folic acid, selenium, zinc, iron, or any other nutrient during the three months before she became pregnant. Then each woman was asked for similar information about the use of multivitamins and supplements during the first three months of her pregnancy, including the brand used, the week of pregnancy during which she began to take the vitamin, the frequency of use, and any changes in intake during this period. Information on the dosage of vitamin A was obtained from information on file about each multivitamin brand, or from the subject in the case of supplements of vitamin A alone. The timing of use during pregnancy was determined according to the reported date of the last menstrual period.

Some data on the multivitamin brand, the week vitamin use began, the frequency of intake, or the dosage of single-vitamin supplements were missing for 201 women. For these women, we substituted median values for the missing values. For example, if the week of first vitamin use was missing and the brand was a prenatal formulation, we used the median starting week for all users of prenatal vitamins. We also analyzed the data after excluding women for whom we had made such substitutions.

We estimated retinol intake during each of the 12 weeks since the last menstrual period for all the subjects for whom we had information on vitamin supplements, diet, and the outcome of pregnancy. For most analyses we classified retinol intake from food and supplements according to the mean amounts ingested during the four weeks of highest consumption during the first trimester.

The women were also asked about their consumption of 50 different foods, with this question: "How often, per day, per week, or per month, did you eat one serving of the following foods during the first eight weeks of your pregnancy?" Servings were defined by the interviewers for each food item (for example, one slice of cheese or half a grapefruit).

Our food-related analysis included only foods that are sources of retinol: milk, cheese, margarine, butter, eggs, mashed potatoes (which often contain butter and milk), chicken, chicken liver, beef, beef liver, processed meats, pizza, fish, and cold breakfast cereals. Since the women were asked to name up to three brands of breakfast cereal that they ate most often, we calculated an average retinol con-

tent for cereal based on the reported brands. We used the daily intake of retinol from each of the above foods to estimate the total daily intake of retinol from the diet.

For 106 women, information on some, but fewer than half, of the retinol-containing foods was missing. For these foods, we assigned values for retinol intake, using the median daily intake for all women in the study. We excluded from our analyses 6 women for whom information for half or more of the retinol-containing foods was missing and 1 woman for whom we lacked information on vitamin supplements; these additional exclusions left 22,748 women for whom we had completed interviews and usable data on retinol intake from both foods and vitamin supplements.

Outcome of Pregnancy

Information on the outcome of pregnancy was obtained from a questionnaire mailed to the obstetrician around the expected time of delivery. If the physician did not respond, the same questionnaire was mailed to the mother. Information requested on the follow-up form included the presence of any birth defects as well as other information about complications and outcome of pregnancy. Physicians supplied the information for 76.5 percent of the pregnancies; the mothers supplied the information for the remainder.

Two coders reviewed the outcome forms, independently classifying reported birth defects according to the codes of the Centers for Disease Control and Prevention manual for birth-defect classification.²³ In cases of disagreement, a third coder examined the data and made a final decision about outcome codes. During the coding, all coders were unaware of the dietary information provided by the mothers. After coding, we classified each defect into one of the following categories: craniofacial defects (e.g., oral clefts and anomalies of the ears, eyes, and nose); central nervous system defects (e.g., reduction deformities of the brain, microcephaly, and hydrocephaly in the absence of spina bifida); anomalies of the thymus; heart defects; neural-tube defects (spina bifida, anencephaly, and encephalocele); musculoskeletal defects (limb-reduction deformities, clubfoot, syndactyly, polydactyly, and other bony defects of shoulder, forearm, wrist, and hand); urogenital defects (e.g., renal agenesis, congenital hydronephrosis, other defects of the kidneys, anomalies of the external genitalia, and hypospadias); defects of the digestive tract (e.g., tracheoesophageal fistula, congenital hypertrophic pyloric stenosis, and atresia or stenosis of intestines); and other defects (e.g., agenesis or hypoplasia of the lungs, single umbilical artery, anomalies of the spleen, and cystic hygroma).

In classifying babies with more than one birth defect, we counted each baby only once, using the following hierarchy, in descending order of priority: craniofacial, central nervous system, or thymic defects; heart defects; neural-tube defects; musculoskeletal defects; urogenital defects; defects of the digestive tract; and other defects. We did not code chromosomal defects or malformations stemming from genetic causes, such as Tay-Sachs disease or cystic fibrosis, nor did we include cerebral palsy, malabsorption syndrome, a limb defect reportedly caused by an amniotic band, or conditions that were listed as birth defects on the forms but were clearly not malformations.

Craniofacial, central nervous system, thymic, and heart defects arise, at least in part, from cranial-neural-crest cells. We grouped these defects as cranial-neural-crest outcomes. We considered neural-tube defects separately; we also considered musculoskeletal and urogenital defects separately, because in some reports they have been found to be related to retinoids.⁷ We grouped gastrointestinal and all other defects listed above into the fourth outcome category, "other defects."

Statistical Analysis

We analyzed the data first by obtaining contingency tables for the main study variables, from which we calculated the prevalence of birth defects according to the mothers' retinol-intake category, along with prevalence ratios and approximate 95 percent confidence intervals.²⁴ We then stratified the contingency tables according to each of several possible confounding variables, which included the age, education, and race of the mother and the maternal history or family history of birth defects. We also fitted a multiple logistic-regression model to the data that controlled for the above variables as well as

folate intake, alcohol consumption, genital herpes infection, treated maternal diabetes, fever (temperature, $\geq 38.3^{\circ}\text{C}$ [101°F]) during the first trimester of pregnancy, and the use of antiseizure medication, retinoids, or exogenous hormones.²⁴

High vitamin A intake from supplements can result from taking a multivitamin with a high vitamin A content (some contained as much as 25,000 IU), from taking more than one multivitamin pill per day with a smaller dose of vitamin A, from taking vitamin A supplements, or from some combination of these. For analyses of supplement use, we used an intake of more than 10,000 IU of retinol from supplements as the highest dose category, because many multivitamin supplements contained as much as 10,000 IU in a single pill, and only a few contained more than 10,000 IU. To obtain a clearer picture of the shape of the dose-prevalence relation, we used quadratic splines to smooth the dose-prevalence curve.²⁵

RESULTS

Among the 22,748 women in this analysis, 339 had babies with birth defects that met our study criteria. Of these, 121 were of cranial-neural-crest origin. The distribution of these birth defects according to major category is shown in Table 1.

Most women who took supplements containing vitamin A took multivitamins that contained retinol. There were 131 women, however, who took supplements of pure retinol, of whom 100 took multivitamin supplements as well. The distribution of total daily retinol consumption (from food and both types of supplements) for the entire cohort is shown in Table 2, along with the frequency of cranial-neural-crest and other birth defects in each of four categories of retinol consumption.

As Table 2 shows, the proportion of babies born with birth defects appeared to be relatively constant for the first three categories of total retinol intake, but the women who consumed more than 15,000 IU of retinol per day had a higher proportion of babies with birth defects. 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 per day to the prevalence among the babies born to women who consumed 5000 IU or less per day was 3.5 (95 percent confidence interval, 1.7 to 7.3). There was a less striking trend for musculoskeletal and urogenital defects, and no discernible trend for neural-tube defects or other birth defects. For all birth defects combined, the prevalence ratio was 2.2 (95 percent confidence interval, 1.3 to 3.8).

When we cross-classified retinol intake from food and intake from supplements, we found that the distribution of intake from food was nearly uncorrelated with the intake from supplements ($r = 0.005$). We therefore proceeded to examine retinol intake from supplements and from food separately (Table 3). Few women consumed large amounts of retinol from food alone. Among those who did, there was some indication of an increase in the prevalence of birth defects for those who consumed the highest amounts of retinol, but the small numbers make the estimate imprecise.

Table 1. Birth Defects According to Category.

TYPE OF DEFECT	No.
Cranial neural crest	
Craniofacial, central nervous system (except neural tube), and thymic	69
Heart	52
Total	121
Neural tube	48
Musculoskeletal and urogenital	
Musculoskeletal	58
Urogenital	42
Total	100
Other	
Gastrointestinal	24
Nongastrointestinal	46
Total	70
Total	339

The prevalence ratio for all birth defects among babies born to women who consumed more than 10,000 IU per day from food alone, as compared with the babies whose mothers consumed 5000 IU or less per day, was 1.8 (95 percent confidence interval, 0.8 to 4.3). For defects related to the cranial neural crest, the prevalence ratio was 2.0, but this ratio is statistically unstable, since it is based on only two cases of birth defects in babies born to women in the high retinol-intake category.

The effect of retinol from supplements was more striking. For all birth defects, the prevalence ratio for the babies born to women who consumed more than 10,000 IU per day as compared with the babies born to women who consumed 5000 IU or less per day was 2.4 (95 percent confidence interval, 1.3 to 4.4). For defects associated with cranial-neural-crest tissue, the corresponding prevalence ratio was 4.8 (95 percent confidence interval, 2.2 to 10.5). There was a progressive increase in the prevalence of cranial-neural-crest defects and in total birth defects from the lowest to the highest intake categories. We used the midpoints of the categories and, for the highest category, the mean intake (21,675 IU) to obtain the least-squares linear regression for the trend in cranial-neural-crest defects. From the regression we estimated that the prevalence of cranial-neural-crest defects increased by 0.00065 for each increase of 1000 IU in the daily intake of vitamin A from supplements (95 percent confidence interval, 0.00032 to 0.00097). The prevalence of cranial-neural-crest defects in the highest intake category was greater

Table 2. Pregnancies Resulting in Birth Defects, According to Daily Intake of Retinol from Food and Supplements Combined.

DAILY RETINOL INTAKE	TOTAL PREGNANCIES	CRANIAL-NEURAL-CREST DEFECTS	NEURAL-TUBE DEFECTS	MUSCULOSKELETAL OR UROGENITAL DEFECTS	OTHER DEFECTS	TOTAL DEFECTS
IU	no.	number (percent)				
0-5000	6,410	33 (0.51)	13 (0.20)	24 (0.37)	16 (0.25)	86 (1.3)
5001-10,000	12,688	59 (0.47)	29 (0.23)	62 (0.49)	46 (0.36)	196 (1.5)
10,001-15,000	3,150	20 (0.63)	5 (0.16)	10 (0.32)	7 (0.22)	42 (1.3)
$\geq 15,001$	500	9 (1.80)	1 (0.20)	4 (0.80)	1 (0.20)	15 (3.0)

Table 3. Pregnancies Resulting in Birth Defects, According to Category of Daily Retinol Intake and Source of Retinol.

DAILY RETINOL INTAKE	TOTAL PREGNANCIES	CRANIAL-NEURAL-CREST DEFECTS	NEURAL-TUBE DEFECTS	MUSCULOSKELETAL OR UROGENITAL DEFECTS	OTHER DEFECTS	TOTAL DEFECTS	
<i>IU</i>	<i>no.</i>	<i>number (percent)</i>					
From food							
0-5000	21,755	114 (0.52)	44 (0.20)	95 (0.44)	67 (0.31)	320 (1.5)	
5001-10,000	805	5 (0.62)	3 (0.37)	3 (0.37)	3 (0.37)	14 (1.7)	
≥10,001	188	2 (1.06)	1 (0.53)	2 (1.06)	0	5 (2.7)	
From supplements							
0-5000	11,083	51 (0.46)	21 (0.19)	44 (0.40)	32 (0.29)	148 (1.3)	
5001-8000	10,585	54 (0.51)	26 (0.25)	52 (0.49)	36 (0.34)	168 (1.6)	
8001-10,000	763	9 (1.18)	1 (0.13)	2 (0.26)	1 (0.13)	13 (1.7)	
≥10,001	317	7 (2.21)	0	2 (0.63)	1 (0.32)	10 (3.2)	

than the prevalence in the lowest intake category by 1.7 percent of births, or 1 baby in 57.

We then evaluated the effects of a high intake of vitamin A from food and supplements after stratifying the data according to potential confounding factors. We found little confounding by any single factor. We also constructed several multiple logistic-regression models incorporating vitamin A intake from food and supplements, with additional terms for the age, education, and race of the mother, the family history of birth defects, use of folate supplements during early pregnancy, treated maternal diabetes, alcohol consumption, genital herpes infection, fever (temperature, $\geq 38.3^{\circ}\text{C}$ during the first trimester), and use of antiseizure medication, retinoids, or exogenous hormones. The estimates of the effects of vitamin A from both food and supplements were similar to the corresponding estimates from Table 3, even when both factors were in the same model. Thus, there was little aggregate confounding from the factors mentioned.

To improve our estimate of the shape of the dose-response curve relating the intake of supplements to the occurrence of cranial-neural-crest defects, we fitted an unrestricted quadratic-spline logistic model, using the same four intake categories and the same terms for all the potential confounding variables cited above. The smoothed exposure-effect curve, shown in Figure 1, indicates an apparent threshold near 10,000 IU of vitamin A per day from supplements. The figure also shows the curve for total retinol, which rises more slowly.

To evaluate how the timing of vitamin A intake affected the risk of cranial-neural-crest defects, we examined the prevalence of defects among the babies born to women whose average daily vitamin A intake exceeded 10,000 IU during three mutually exclusive time periods before conception and during early gestation (Table 4). These findings indicate a high prevalence of birth defects related to the cranial neural crest in association with high levels of exposure before or during organ formation, but not after.

The seven babies with cranial-neural-crest defects who were born to mothers in the highest category of supplemental retinol intake (Table 3) had the following defects: cleft lip, ventricular septal defect, transposition of the great vessels, hydrocephaly (two babies),

multiple heart defects, and craniosynostosis. All seven mothers took high doses of vitamin A from supplements in the two weeks before conception or during the first month of pregnancy.

Some pregnancies included in our denominator ended in early fetal death. If these early terminations of pregnancy were unequally distributed among the categories of retinol intake, it could have biased our findings. To evaluate this possibility, we reanalyzed the data after excluding these pregnancies. The results were nearly identical to the results with-

out these exclusions. We also reanalyzed the data with all early terminations considered as adverse events and found a similar pattern of effects. When we omitted women for whom data substitutions were used to determine vitamin A intake, the results changed very little.

DISCUSSION

Our findings indicate that vitamin A is potentially teratogenic, but these findings relate solely to preformed vitamin A and not to beta carotene, a vitamin A precursor. We did not study beta carotene specifically, but studies in animals indicate that a high intake of beta carotene is neither toxic nor teratogenic.^{1,3-6}

A relation between high vitamin A consumption during early pregnancy and the occurrence of birth defects is consistent with the results of studies of retinol in animals^{4,5} and of the effects of isotretinoin in humans^{7,8} and with two earlier case-control studies.^{20,21} The strong

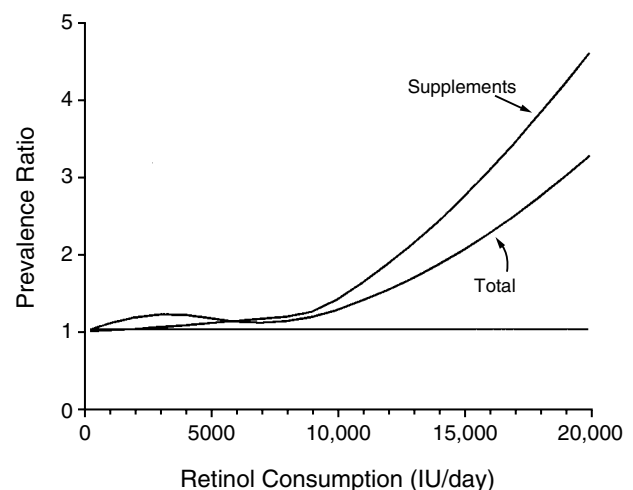


Figure 1. Estimated Prevalence Ratio for Birth Defects Related to the Cranial Neural Crest, According to Retinol Intake during the First Trimester of Pregnancy.

The smoothed curves were fitted with unrestricted quadratic splines. The prevalence ratio is the ratio of the prevalence of defects among the babies born to women who consumed a given amount of vitamin A (from food and supplements [total] or from supplements alone) to the prevalence among the babies of women with a hypothetical intake of zero.

Table 4. Cranial-Neural-Crest Defects among Babies Born to Women Taking More Than 10,000 IU of Vitamin A per Day from Supplements, According to the Timing of High Intake.*

VARIABLE	HIGH INTAKE ONLY DURING 2 WEEKS BEFORE CONCEPTION	HIGH INTAKE ONLY BEFORE WEEK 7 OF PREGNANCY	HIGH INTAKE ONLY AFTER WEEK 6 OF PREGNANCY
Cranial-neural-crest defects (no.)	2	3	0
Pregnancies (no.)	42	80	70
Prevalence (%)	4.8	3.8	0

*The three periods are mutually exclusive.

effect of high levels of retinol intake from supplements in our study is not easily ascribed to confounding or information bias. The stronger relation seen for vitamin A taken before or during organ formation than for vitamin A taken later is also consistent with a causal effect, but not with any plausible reporting bias. The apparently weaker relation between birth defects and retinol from food, as compared with supplements, may reflect greater error in measuring vitamin A levels in food or lower bioavailability of retinol consumed during meals.

These data appear to indicate a teratogenic effect of vitamin A at levels not far above those currently recommended. In our study population, about 1.4 percent of women averaged more than 10,000 IU of vitamin A per day from supplements. Since these data were collected, some manufacturers have decreased the retinol content of multivitamins, often substituting beta carotene. These changes may have lessened the teratogenic effects of vitamin A in the population as a whole. Among women who take more than 10,000 IU of preformed vitamin A per day from supplements, we estimate that 1 of every 57 babies is born with a birth defect attributable to the high vitamin A intake of the mother.

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