TERATOLOGY 55:132–133 (1997)

# Periconceptional Intake of Vitamin A Among Women and Risk of Neural Tube Defect-Affected Pregnancies

GARY M. SHAW,[1,*] ELLEN M. VELIE,[1] DONNA SCHAFFER,[2] AND EDWARD J. LAMMER[3]
[1]*California Birth Defects Monitoring Program, Emeryville, California 94608*
[2]*Kaiser Permanente, Oakland, California 94609*
[3]*Children's Hospital Oakland, Oakland, California 94609*

A WHO consultative group noted the need for more research regarding potential teratogenic risks of high or low intake of vitamin A during pregnancy (World Health Organization, '96). Recently, epidemiologic data suggested an increased risk of congenital anomalies of structures with a cranial neural crest cell contribution from maternal daily intake of vitamin A exceeding 10,000 IU (Rothman et al., '95). Because the neuroectoderm of the early embryo contributes cells that can become cranial neural crest cells or epithelium of the neural tube, we investigated the relation between neural tube defect (NTD)-affected pregnancies and maternal periconceptional intake of vitamin A, using population-based case-control study data of California pregnancies in 1989–1991, described in Shaw et al. ('95).

Eligible for this case-control study were singleton liveborn infants and fetuses (included those prenatally diagnosed and electively terminated between February 1989 and January 1991 with NTDs) among the cohort of 708,129 births (includes fetal deaths) between June 1989 and May 1991. Ascertained were 653 singleton infants/fetuses with an eligible NTD diagnosis. Controls were randomly selected from each area hospital in proportion to the hospital's estimated contribution to the total population of infants born alive in a given month from June 1989 to May 1991. Ascertained were 644 singleton infants who were born alive without a reportable congenital anomaly and whose mother was a California resident.

Women who only spoke languages other than English or Spanish or who had a previous NTD-affected pregnancy were excluded, leaving 613 cases and 611 controls. In-person interviews were completed with mothers of 538 (87.8%) cases and of 539 (88.2%) controls, an average of 4.9 months for cases and 4.6 months for controls after the actual or projected date of term delivery.

Women were asked about all multivitamin, single-vitamin, and food supplements they consumed in the periods 3 months before and after conception. Study women themselves also completed a 100-item food-frequency questionnaire (Block et al., '86) with interviewers present to assist. Each woman was instructed to estimate her usual frequency and portion size of the food items she consumed during the 3 months before conception, permitting estimation of daily intake of vitamin A from food (as retinol, without conversion from β-carotene). Of the 1077 women who completed an interviewer-administered questionnaire, 1,007 completed a food-frequency questionnaire; of these, 899 (448 case and 451 control mothers) revealed suitable data based on error checks built into the analytic software.

Vitamin A intake from supplements was estimated directly from the brand/product information or was imputed, assuming (1) prenatal and multivitamins: vitamin A was considered to be retinol of 4,000 IU unless otherwise specified (β-carotene was uncommon before 1991 in U.S. multivitamin supplements); and (2) single vitamin A supplements that did not specify β-carotene/retinol composition, contained at least 10,000 IU retinol.

For higher levels of intake, we estimated risk of NTD-affected pregnancies among women who consumed ≥10,000 IU (cutpoint approximated that used by Rothman et al., '95, who found increased anomaly risks among women consuming more than 10,000 IU vitamin A from supplements alone) of vitamin A preconceptionally from both food and supplements compared to those who consumed less. The numbers of women who consumed 10,000–14,999 IU or consumed ≥15,000 IU, and their associated NTD risks, are shown in Table 1. Twenty two of 448 case and 19 of 451 control mothers consumed ≥10,000 IU, resulting in an odds ratio (OR) of 1.2 (95% confidence interval [CI] 0.6–2.2). This result was not substantially changed by (1) excluding referent women (2 case and 4 control mothers) who began intake of ≥10,000 IU of vitamin A in the first trimester (OR = 1.2 [0.6–2.2]); (2) excluding referent women (56 case and 44 control mothers) who consumed less than 1,225 IU vitamin A, the lowest decile of intake among control women (OR = 1.2 [0.7–2.3]); or (3) single variable control for potential confounding influences of

*Correspondence to: Dr. Gary M. Shaw, California Birth Defects Monitoring Program, 1900 Powell St. Suite 1050, Emeryville, CA 94608.

Received 12 November 1996; accepted 30 January 1997

**TABLE 1. NTD risks (odds ratios) associated with maternal daily periconceptional intakes of vitamin A as retinol from both food and supplements**

| Daily vitamin A intake (IU) | Cases | Controls | Odds ratio | 95% Confidence interval |
|---|---|---|---|---|
| 0–9,999 | 426 | 432 | Reference | — |
| 10,000–14,999 | 16 | 12 | 1.4 | 0.6–2.8 |
| ≥15,000 | 6 | 7 | 0.9 | 0.3–2.5 |

maternal total (dietary and supplemental) folate intake, race/ethnicity, education, or body mass index.

Comparing women who consumed ≥10,000 IU from supplements alone (4 case and 6 control mothers) to those women who consumed less (525 case and 517 control mothers) revealed an OR of 0.7 (0.2–2.3). Comparing women who consumed ≥10,000 IU of vitamin A from supplements alone, to women who did not use any vitamin supplements periconceptionally revealed an OR of 0.5 (0.2–1.7).

These data do not indicate substantially increased risks among women for NTD-affected pregnancies associated with levels of periconceptional vitamin A intake ≥10,000 IU. Observed risk estimates, however, were imprecise owing to a relatively small number of women with intakes ≥10,000 IU. Nevertheless, this lack of an increased risk corroborates a recent study (Rothman et al., '95) that did not find a relation (prevalence ratio was approximately 1.0) between maternal daily intake of vitamin A >10,000 IU and risk of NTD-affected pregnancy.

## LITERATURE CITED

Block, G., A.M. Hartman, C.M. Dresser, M.D. Carroll, J. Gannon, and L. Gardner (1986) A data-based approach to diet questionnaire design and testing. Am. J. Epidemiol., *124:*453–469.

Rothman, K.J., L.L. Moore, M.R. Singer, U.S.D.T. Nguyen, S. Mannino, and A. Milunsky (1995) Teratogenicity of high vitamin A intake. N. Engl. J. Med., *333:*1369–1373.

Shaw, G.M., D. Schaffer, E.M. Velie, K. Morland, and J.A. Harris (1995) Periconceptional vitamin use, dietary folate, and the occurrence of neural tube defects. Epidemiology, *6:*219–226.

World Health Organization (1996) Safe Dosages of Vitamin A During Pregnancy and Post-partum. WHO, Geneva.