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High Vitamin A Intake in Early Pregnancy and Major Malformations: A Multicenter Prospective Controlled Study

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ABSTRACT The European Network of the Teratology Information Services (ENTIS) collected and evaluated data on 423 pregnancies exposed during the first 9 weeks of gestation to a "high" dose of vitamin A (10,000 IU per day or more). Data were collected prospectively; 394 women (93.1%) were followed by telephone interview up to the first few weeks after the expected date of delivery, using standardized procedures. The presence of major structural malformations, excluding chromosomal and genetic diseases, was evaluated in 311 infants exposed to a median daily dose of vitamin A of 50,000 IU per day (range, 10,000–300,000 IU per day; interquartile range, 25,000–60,000 IU per day). Three infants with a major malformation were reported: pulmonary stenosis, stenotic anus with fistula, and bilateral inguinal hernia. No congenital malformations were reported among 120 infants exposed to more than 50,000 IU per day of vitamin A. When the birth prevalence rate of major malformations in the study group was compared with two internal control groups of infants exposed to: 1) "high" vitamin A exposure later in pregnancy, and 2) nonteratogenic agent exposures, the rate ratio was, respectively, 0.28 (CI 95% interval, 0.06, 1.23) and 0.50 (CI 95% interval, 0.14, 1.76). The studied sample did not provide evidence for an increased risk of major malformations, associated with "high" vitamin A intake during the organogenetic period, higher than 2.76 above the control reference risk of 1.91% (power 80%, alpha 0.10). *Teratology 59:7–11, 1999.*

Vitamin A occurs naturally in two main forms: retinol and its analogues, i.e., a preformed vitamin A compound, and beta-carotene, a precursor of vitamin A found in certain vegetables, known also as "provitamin A." Vitamin A (retinol) in "high" doses is known to cause congenital malformations in animals (Cohlan, '54; Geelen, '79). Concern about possible teratogenic effects of "high" doses of vitamin A (retinol) in humans is based on the unequivocal demonstration of human teratogenicity of 13-cis-retinoic acid (Lammer et al., '85) and on the observed increase in serum levels of retinoic acid metabolites after ingestion of "high" doses of various vitamin A supplements (Eckhoff and Nau, '90; Eckhoff et al., '91).

The potential teratogenicity of "high" vitamin A (defined in this paper as 10,000 IU per day) in humans has been presented in case reports and analyzed in both cohort and case-control studies.

From reviewing the literature and their own case series, Rosa et al. ('86) reported 18 infants or fetuses with a congenital malformation exposed during pregnancy to "high" doses of vitamin A (25,000–500,000 IU per day). This series included 6 cases from the New York State Birth Defects Registry (Vallet et al., '85),

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selected because a retinoic acid-related anomaly was present (mainly an ear defect). Among the other 12 cases, 6 were published case reports and 6 were spontaneous reports to the US Food and Drug Administration. Including a recent report of an infant with microcephaly and dystonia exposed to large quantities of vitamin A during 4–5 weeks of pregnancy (Australian Drug Reaction Bulletin, '96), no pattern of anomalies is obvious among all these cases, although an excess of renal/urinary tract anomalies (3 cases) can be suspected among the six published case reports referred to by Rosa et al. ('86).

Five case-control studies assessing the association between congenital malformations and vitamin A exposure in pregnancy have been published (Martinez-Frias and Salvador, '90; Werler et al., '90; Shaw et al., '96; Khoury et al., '96; Mills et al., '97). Only two of these studies obtained information on the daily dose of vitamin A assumed during pregnancy, allowing conclusions on the "high" vitamin A dose teratogenicity. One study (Martinez-Frias and Salvador, '90) concluded that a teratogenic effect might exist for "high" exposures (range, 10,000–100,000 IU per day) of vitamin A (OR = 2.7; 95% CI, 0.8, 11.7). The effect seemed to be related to the organogenetic period, since the OR for exposures in months 1–2 of pregnancy was higher than in the following months. However, the OR for the early exposure was 4.0, with a wide CI (95% CI = 0.4, 195.2), and it was based on 4 cases: preauricular tag, cleft lip, epulis and craniotabes, and hip instability. Given the small number and the clinical and etio-pathogenetic variability of these defects, this study can be considered, at the least, inconclusive. The other study (Mills et al., '97) did not find an association between periconceptional (30 days before last menstrual period up to 45 days thereafter) vitamin A exposure from supplements and fortified cereals at doses ≥10,000 IU per day and the frequency of congenital malformations in general (OR, 0.73; 95% CI, 0.27, 1.96), cranial neural crest defects (OR, 1.09; 95% CI, 0.24, 4.98), or neural tube defects (OR, 0.92; 95% CI, 0.40, 2.11).

Three cohort studies on "high" exposure of vitamin A during pregnancy have also been published (Conway, '58; Zuber et al., '87; Rothman et al., '95). The first (Conway, '58) was a small nonrandomized trial to prevent recurrence of cleft lip and palate among women who had had one previous child with an orofacial cleft. A multivitamin supplement containing 12,500 IU of vitamin A was given in the periconceptional period up to 3 months of pregnancy. Among the 59 pregnancies so treated, no orofacial clefts or other defects were seen. The second cohort study was conducted by a Teratology Information Service in Pennsylvania and published only as an abstract, nonpeer-reviewed, and with incomplete follow-up data (Zuber et al., '87). Twenty-seven women were evaluated, all of whom had consumed vitamin A in doses between 25,000–150,000 IU per day from weeks 4–6 of gestation. Among the 21 pregnancies for which outcomes were available, there were 4 induced abortions, 3 spontaneous abortions, and 14 livebirths without any obvious malformations. The third cohort study (Rothman et al., '95) provided information on the pregnancy outcomes of 317 women who took more than 10,000 IU per day of vitamin A supplements during the first 12 weeks of gestation. There were 10 infants with congenital malformations, giving a rate ratio of 2.36 (95% CI, 1.26, 4.44) compared to women who consumed 5,000 IU per day or less. Of the 10 defects observed, seven were classified as anomalies of structures with a cranial neural crest cell contribution: ventricular septal defects (VSD), transposition of great vessels (TGV), unspecified multiple heart defects, cleft lip, hydrocephaly (two infants), and craniosynostosis. The rate ratio of these anomalies compared to the reference group was 4.8 (95% CI, 2.2, 10.5). The authors estimated that about one infant in 57 had a malformation attributable to the "high" vitamin A (10,000 IU per day or more) supplementation. This study raises some concerns because of some methodological problems: the broad definition of cranial-neural-crest defects used by the authors, which included all defects of organ systems that actually have only some structures derived from cranial-neural-crest cells; the lack of a detailed phenotypic description of the defects; the study's low overall rate of birth defects and the accuracy of ascertainment; and the possible misclassification of exposure, diagnosis, or both, for at least 4 of the 7 cases in the intake category of more than 10,000 UI of vitamin A (Brent et al., '96; Watkins et al., '96; Werler et al., '96).

The aim of the present study was to evaluate whether infants exposed during organogenesis to "high" doses of vitamin A have a higher risk of major malformations than the general population. We studied women counseled during pregnancy by 13 European Teratology Information Services. All of them are part of the European Network of Teratology Information Services (ENTIS). All studied women were exposed during the first 9 completed weeks of gestation to a daily dose of 10,000 IU of vitamin A or more.

SUBJECTS AND METHODS

This study was based on a cohort of women exposed to vitamin A doses of 10,000 IU or more during the first 9 weeks of pregnancy (69 completed days from the first day of last menstrual period), who directly, or through their doctors, contacted one of 13 European Teratology Information Services (TIS). Although each TIS has its own specific working procedures, in the past several years some common methodologies have been set up within the European Network of Teratology Information Services. The characteristics of some of these services have been described elsewhere (Basile et al., '92; Eléfant et al., '92; Garbis et al., '90; Kasilo et al., '88; Mastroiacovo et al., '93; Ornoy and Amon, '93). Briefly, the TIS staff doctor, when asked for the risk evaluation associated with a drug, either by the women or their doctors, conducts an interview that includes questions on demographic characteristics, previous and current

obstetrical history, family history of congenital malformations, and maternal chronic diseases. The interview also includes a detailed history of prescription and nonprescription drug use, which includes information on the commercial preparation, dosage, indication, and time during pregnancy when the drug was taken. Gestational age is calculated as the best estimate from available source by prenatal sonography and/or the first day of last menstrual period. Shortly after the expected date of delivery (usually 3–6 weeks), all women eligible for the follow-up, and/or their doctors, are contacted by the TIS staff by mail or telephone. The information obtained includes: outcome of pregnancy, type of delivery, birth weight, head circumference, length, perinatal complications, and the presence and type of any congenital anomaly. When the mother is the source of information, she is also asked to refer to her infant's "hospital discharge summary." If the mother reports any congenital anomaly, neonatal problem, or prolonged hospital stay, the staff doctor requests additional information from the attending pediatrician.

For this study we included all infants exposed to 10,000 IU per day or more (or 50,000 IU per week or more when the intake was not daily) of preformed vitamin A supplements for at least 1 week during the organogenetic period, i.e., the first 9 weeks of pregnancy (69 completed days from first day of last menstrual period).

The outcome of interest of this study was the presence or absence of "major" malformations. A major malformation was defined as a structural abnormality that has an adverse effect on either the functional or the social acceptability of the individual (Marden et al., '64), and which called for medical or surgical treatment.

The prevalence rate of major malformations found in the study group was compared to the birth prevalence of major malformations observed in two different control groups whose mothers consulted a TIS in the same period of study subjects: 1) all of the infants exposed to "high" vitamin A doses after 9 weeks of gestation (late exposure control group); and 2) all of the infants exposed to a documented nonteratogenic agent (nonteratogen exposure control group). A nonteratogenic agent was defined as a disease, or a medical or environmental agent, that has been proven not to increase the baseline risk for major malformations (Stevenson, '93).

In this study, chromosomal or genetic diseases, as well as deformations (e.g., clubfoot), minor anomalies (e.g., preauricular tag), birth marks (e.g., nevus or angiomas), functional problems (e.g., pyloric stenosis, gastroesophageal reflux), and mild findings (e.g., hydronephrosis identified by prenatal sonography and not demanding treatment during the neonatal period), were excluded from the analysis, both in the study group and in the control groups, due to the inherent limitations of a mail or telephone interview in determining the frequency of defects which are not always serious enough to be documented.

Ascertainment of major malformations was conducted as part of the ongoing TIS follow-up activity, without the interviewer being aware whether the women were part of a study on vitamin A or controls. In other words, the status of exposed case or unexposed control was not known before the study design.

TABLE 1. Description of major malformations in 3 infants exposed to high doses of vitamin A (≥10,000 IU/day) during the first 9 weeks of pregnancy

Case	Exposure period (weeks)	Vitamin A, daily (IU)	Major malformation
1	9–22	25,000	Pulmonary stenosis
2	1–4	30,000	Inguinal hernia, bilateral*
3	0–25	50,000	Anterior and stenotic anus with perineal fistula

*Diagnosed at birth, surgically treated at 4 weeks.

Birth prevalence mid-p 95% CI of major malformations, rate ratios (RR) and their mid-p 95% CI, and power calculation were computed with Epitable software of the Epi Info 6, version 6.02 (EPI6) (Division of Surveillance and Epidemiology, Center for Disease Control, and WHO, '94).

RESULTS

The 13 TIS provided data on 423 women who met the criteria of "high" vitamin A (≥10,000 IU) exposure during the first 9 weeks of gestation. Of the 423 exposed women collected, 154 (36.4%) were recruited from Telefono Rosso (Catholic University, Rome); 109 (25.8%) from the Saint-Antoine Hospital TIS (Paris). The remaining 160 exposed women (37.8%) were referred from the other 11 TIS centers.

Three-hundred ninety-four (93.1%) of the 423 pregnancies eligible for the study had a complete follow-up. Of these, 35 (8.9%) had a spontaneous abortion and 47 (11.9%) an induced abortion. All the induced abortions were done for social reasons, except for one because of prenatal diagnosis of trisomy 13. Three-hundred and two pregnancies had a livebirth (none had a stillbirth): one of them was a 45,X (Turner syndrome), which was excluded from the analysis. Therefore, 311 births where included in the study group. The exposures in these infants ranged from 10,000–300,000 IU per day, with a median of 50,000 (interquartile range, 25,000–60,000 IU per day). One hundred and twenty women were exposed to more than 50,000 IU per day and 32 women to more than 100,000 IU. Considering the total dose in the first 9 weeks of gestation, the range was 70,000–8,400,000 IU with a median of 700,000 IU (interquartile range, 350,000–1,400,000 IU). Sixty-seven women were exposed to a total dose of more than 1,500,000 IU. The main reasons for high exposures were various dermatologic conditions and breast fibrocystic disease.

Among the 311 exposed births, only 3 infants with major malformations were reported (Table 1): pulmonary stenosis, identified at birth; anterior and stenotic anus with perineal fistula, identified at birth; and

TABLE 2. Number of infants with a major malformation by daily dose of vitamin A exposure*

Daily vitamin A intake (IU)	During 9 weeks of pregnancy: Births	Infants with a major malformation	Rate % (95% CI)
10,000	26	0	
10,001–20,000	28	0	
20,001–30,000	86	2 [1, 2]	2.33 (0.39, 7.47)
30,001–40,000	12	0	
40,001–50,000	39	1 [3]	2.56 (0.06, 13.48)
50,001–100,000	88	0	
100,001+	32	0	
Subtotal −40,000	152	2	1.32 (0.22, 4.28)
Subtotal 40,001+	159	1	0.63 (0.02, 3.50)
Total	311	3	0.96 (0.25, 2.60)

*Case reference numbers used in Table 1 are given in brackets.

bilateral inguinal hernia observed at birth and surgically treated at 4 weeks.

Considering the vitamin A daily dose exposure (Table 2) and the 3 infants with a major malformation, there were 2 infants out of 152 exposed to 40,000 IU per day of vitamin A or less and only 1, with a stenotic anus with perineal fistula, among 159 infants exposed to more than 40,000 IU per day of vitamin A. No major malformations were reported among 120 infants exposed to more than 50,000 IU per day of vitamin A. Considering the vitamin A total dose exposure, results did not change.

Therefore, no evidence of an increasing prevalence rate with increasing dose was seen.

When the birth prevalence rate of major malformations in the study group was compared with that found in the two control groups (Table 3), the rate ratio for the study group vs. the late exposure control group was 0.28 (95% CI, 0.06–1.23), and the rate ratio for the study group vs. the nonteratogenic exposed group was 0.50 (95% CI, 0.14–1.76).

The four major malformations reported in the late exposure group were: hypospadias with clubfoot, esophageal atresia, hypospadias, and horseshoe kidney. The 13 major malformations reported in the nonteratogenic exposed group were: anencephaly, encephalocele, hydrocephaly, congenital cataract, cleft lip and palate, Pierre Robin anomaly, VSDs (2 cases), biliary atresia, anal atresia, diaphragmatic hernia, unilateral absence of kidney, and double ureter.

DISCUSSION

In this study we did not find any evidence of an association between major structural malformations and a "high" intake defined as 10,000 IU per day or more of preformed vitamin A supplements during the first 9 weeks of gestation.

"High" vitamin A intake in early pregnancy has been postulated to be associated with an increased risk for malformations, especially for anomalies of structures with a cranial neural crest cell contribution (Werler et al., '90; Rothman et al., '95). This is not supported by our data.

The major strengths of this study are the prospective information obtained about timing and dose of vitamin A intake. Since the women studied were enrolled in a TIS, where a specific question on the reproductive risk evaluation was asked, we believe that dose and timing information are very accurate.

The potential limitations of the study should be assessed. The ascertainment of major malformations was not obtained by the investigators. Mail or telephone interviews from doctors or mothers were the information source.

Underascertainment could affect the results. However we do not have any evidence of this, since mothers and/or their doctors are quite sensitive about reporting serious defects after a counseling session where the probability of a problem was minimized. Moreover, statistically speaking, the 95% CI of the rate of major malformations, excluding deformations, functional problems, and minor anomalies, either in the study group (0.96%; 95% CI, 0.25, 2.60%) or in the two control groups (3.45%; 95% CI, 1.11, 8.11%; and 1.91%; 95% CI, 1.07, 3.17%, respectively), included the rate of 2.0–2.5% found with other methods (Kallen, '88; Czeizel, '97). Moreover, in our study, chromosomal and genetic diseases were excluded.

Differential ascertainment in cases and controls is unlikely, since neither the TIS physicians nor the interviewed mothers or doctors were aware of the present study, and then of the case or control status of the infants. Any possible bias should have been present in the same direction in the early exposed cohort and in the two control cohorts.

Since the women contacting a TIS are usually a selected sample of the population, we minimized the selection bias, comparing the major malformations' prevalence rate in the study group with two internal control groups: infants exposed to "high" vitamin A after 9 weeks of gestation, and infants exposed to trivial agents usually not considered teratogenic. These comparison groups would have minimized major possible confounding variables, although we could not control for confounding factors such as diet and maternal characteristics.

The major recognized limitation of a study such as the present one is the sample size and the statistical power to detect a small increased risk. The sample size used in this study had 80% power to detect an increased risk higher than 2.76 (with alpha 0.10) using a 1 to 2 ratio for cases and controls, and a control prevalence rate of 1.91%. Moreover, this collaborative material appears to be the largest series prospectively collected of infants exposed early in pregnancy to supplements with "high" doses of vitamin A. For example, in Rothman et al. ('95), 129 infants were exposed to more than 20,000 IU per day, while in the present study 258 were available to be analyzed. Almost half of them (n = 120) were exposed to more than 50,000 IU per day, and no infant with a major malformation was found.

The results of this study suggest that a daily intake of preformed vitamin A supplements of 10,000 IU per day

TABLE 3. Birth prevalence of major malformations in infants exposed to high vitamin A during the first 9 weeks of gestation compared to that found in infants exposed to high vitamin A dose after 9 weeks of gestation, or nonteratogenic agents*

	Infants with major malformations	Total infants	Birth prevalence (%) (95% CI)
Study group, exposed to vitamin A (≥10,000 IU/day) during the first 9 weeks of gestation	3	311	0.96 (0.25, 2.60)
First control group, exposed to vitamin A (≥10,000 IU/day) after 9 weeks of gestation	4	116	3.45 (1.11, 8.11)
Second control group, exposed to nonteratogenic agents	13	679	1.91 (1.07, 3.17)

*Deformations, minor and functional defects, and chromosomal and genetic diseases are excluded. Rate ratio for study group vs. first control group, 0.28 (95% CI, 0.06, 1.23). Rate ratio for study group vs. second control group, 0.50 (95% CI, 0.14, 1.76).

or more does not seem to increase the risk of major malformations, nor the risk of serious anomalies of structures with a cranial neural crest cell contribution. The results, obviously, cannot be used as evidence that the "high" intake of vitamin A is safe. Therefore, these results do not change the current view that in developed countries there appears to be little or no scientific basis for supplementing women with vitamin A (Lammer, '90), nor does it change the recommendation to avoid intake of vitamin A higher than the daily allowance (Teratology Society, '87). We have, however, provided evidence that most infants born after a "high" vitamin A exposure are normal and without major malformations. This finding may be useful during the risk-evaluation counseling of an exposed pregnant woman.

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