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Teratology Society Position Paper: Recommendations For Vitamin A Use During Pregnancy

RECOMMENDATIONS

It is well known that vitamin A is an essential nutrient for normal cellular function, including reproduction and development. Vitamin A deficiency is a worldwide problem of great magnitude. It should be noted that "vitamin A" is a term used often ambiguously. The total indicated vitamin A content of foods usually includes vitamin A derived from carotene,[1] a vitamin A precursor, as well as retinol. Carotene, e.g., beta-carotene, has not been associated with vitamin A toxic effects; accordingly the warning contained in this paper is intended for countries and their citizens that have high-potency vitamin A preparations (as retinol or retinyl esters) readily available. Supplements that contain 25,000 International Units (IU) or more of vitamin A per capsule are available as over-the-counter preparations in many areas. The risk of birth defects owing to synthetic vitamin A analogs has already been documented in humans, and recently the ingestion of excess vitamin A (25,000 IU or more) as retinol/retinyl esters during pregnancy has been associated with some birth defects in a small number of case reports, although it is not known that the relationship is causal. It is with this caution that the following recommendations concerning the use of vitamin A supplements as retinol/retinyl esters during pregnancy are presented to all interested individuals—parents, health care-providers, manufacturers, regulators, legislators, and scientists in our world community.

1. Women in their reproductive years should be informed that the excessive use of vitamin A shortly before and during pregnancy could be harmful to their babies. The National Research Council's recommended dietary allowance for vitamin A during pregnancy is 1,000 retinol equivalents (RE)/day, which is equivalent to 3,300 IU as retinol or 5,000 IU of vitamin A obtained from the typical American diet as a combination of retinol and carotenoids, e.g., beta-carotene. An average balanced diet contains approximately 7,000–8,000 IU of vitamin A derived from different sources. Therefore, women who are at risk for becoming pregnant should consider their dietary intake of vitamin A before taking supplements. The USRDA (recommended daily allowance) established by the Food and Drug Administration is 8,000 IU/day. Supplementation of 8,000 IU vitamin A (as retinol/retinyl esters) per day should be considered the recommended maximum prior to or during pregnancy until further evaluations can be performed in the human population. It is important to determine the type of vitamin A consumed, since beta-carotene has not been associated with vitamin A toxicity in animals or man.

2. Manufacturers of vitamin A (as retinol or retinyl esters) should lower the maximum amount of vitamin A per unit dosage to 5,000–8,000 IU (1,500-2,400 RE) and identify the source of the vitamin A. High dosages of vitamin A as retinol/retinyl esters (25,000 IU or more) are not recommended, since these dosages are not necessary as a nutrient supplement and may be teratogenic at some as yet undetermined dose. With over-the-counter preparations, a major concern is the use of multiple doses daily. The public perception of "one dose is good, two are better" must be addressed by the manufacturers concerning recommended daily intake of that particular preparation. It is suggested that beta-carotene be considered the primary source of these vitamins for women in their reproductive years to reduce risk even further.

3. Labeling of products containing vitamin A supplements (as retinol/retinyl esters) should indicate (a) that consumption of excessive amounts of vitamin A may be hazardous to the embryo/fetus when taken during pregnancy; and (b) that women of childbearing

[1]In its provitamin A form, e.g., beta-carotene, vitamin A is found in carrots, tomatoes, and many other 'red, yellow, and green" vegetables. As the retinol, vitamin A is found in oil of cod and other fish, egg yolks, cheese, liver, and butter.

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potential should consult with their physicians before consuming these products.

4. Studies of the reproductive and developmental toxicity of vitamin A are essential and should receive national and international priority. Well-controlled epidemiologic and pharmacologic studies in humans are essential. In addition, studies of dose-response relationships, metabolism/distribution, mechanisms of action for induction of birth defects, and postnatal dysfunction in animals are of critical importance.

INTRODUCTION

Vitamin A is important in maintaining normal growth, regulating proliferation and differentiation of epithelial tissues, and maintaining visual and reproductive functions (Goodman, '84). Vitamin A analogs (retinoids) are used in the clinical management of dermatologic diseases such as acne, psoriasis, icthyosis and in oncology. More than 1,500 retinoids have been synthesized in an attempt to separate side effects from clinically desirable therapeutic efficacy (Bollag and Matter, '81; Bollag, '83).

The use of vitamin A and retinoids in the United States and other developed countries is increasing. Ingestion of excess nutrients, including "megadose" supplements, is being encouraged by popular writers such as Linus Pauling ('86), Adele Davis ('70), and others. The purpose of this paper is to express concern that indiscriminate use of vitamin A during pregnancy could lead to an increased risk of congenital anomalies. A large volume of literature documents the experimental use of these compounds as teratogens in animal models and as cellular modifiers in other biologic systems. Case reports of malformed children of mothers who have taken excess vitamin A are accumulating. Isotretinoin (13-cis-retinoic acid, Accutane®) has been established as a human teratogen; and etretinate (Tigason®), an aromatic retinoid, has also been implicated in such effects.

Vitamin A (retinol and retinyl esters) and its naturally occurring congeners, retinaldehyde and all-trans retinoic acid (tretinoin), are part of a large class of chemical compounds, the retinoids. Retinoids include both naturally occurring compounds with vitamin A activity and synthetic analogs of retinoic acid. Comprehensive reviews of the biology and function of vitamin A and retinoids have appeared recently (Bauernfeind, '83; Olsen et al., '83; Wolf, '84; Goodman, '84) including a two-volume treatise (Sporn et al., '84) and an issue of the New York Academy of Sciences (DeLuca and Shapiro, '81).

Chronic intake of vitamin A that greatly exceeds the recommended daily allowance leads to clinical manifestations of hypervitaminosis A with toxic effects to the central nervous system, liver, bone, and skin (Goodman, '84). The toxicity of retinoids has been reviewed (Underwood, '84; Howard and Willhite, '86).

Sources as retinol and beta-carotene are widely used as vitamin A supplements. To determine the source which provides the retinol, one must define the unit activity of each compound by its effectiveness. It is important to determine the type of vitamin A consumed, since beta-carotene is not metabolized or stored in the same way as vitamin A. Beta-carotene also has not been associated with vitamin A toxicity in animals or humans (Underwood, '84). Thus, such lack of vitamin A toxicity associated with beta-carotene suggests that beta-carotene is not a human teratogen, even though there are no data at the present time on which to confirm this conclusion.

To understand the biologic effectiveness of vitamin A, its synthetic analogs, and provitamin (carotenoids), a definition of unit activity must be appreciated. One international unit (IU) of vitamin A is equivalent to 0.3 μg of all-trans-retinol. A retinol equivalent (RE) is used to convert all sources of vitamin A and carotenoids in the diet to a single unit. Thus, 1 μg of all-trans-retinol equals 1 RE. For comparison by readers accustomed to international units, 25,000 IU of vitamin A is equivalent to 7.5 mg of all-trans-retinol. Generally, 1 μg of retinol is assumed to be biologically equivalent to 6 μg of beta-carotene or 12 μg of mixed dietary carotenoids. RE is becoming a more accepted term because it reflects the different activities of chemicals as noted for dietary cartenoids, e.g., beta-carotene. This position paper uses international units since it is the most common expression of daily dosage in the marketplace.

The metabolism of retinol and its derivatives/esters differ, especially transport and binding. Retinoic acid is absorbed through the portal system and transported in plasma, bound to serum albumin; it does not accumulate appreciably in liver and other tissues. Retinyl esters, on the other hand, are usually hydrolyzed in the intestinal lumen. The luminal retinol is absorbed into the mucosal cells where it is reesterified and absorbed into the lymphatic system. The retinyl esters in the form of chylomicron remnants are removed from the circulation and stored by the liver. Ingestion of high-retinol doses by humans yields high plasma retinyl ester concentrations without appreciably altering plasma retinol levels (Goodman et al., '83). Retinol is released from the liver bound to retinol-binding protein in the plasma and does not manifest its toxic effect unless the binding capacity is exceeded. Doses of retinol which yield high plasma retinyl ester concentrations are of principle concern.

Vitamin A deficiency is a worldwide problem of much greater magnitude than hypervitaminosis A; accordingly, the warning contained in this paper is intended for countries which have high-potency vitamin A preparations readily available to the public

EXPERIMENTAL STUDIES

The teratogenicity of excess vitamin A in laboratory animals was first reported more than 30 years ago by Cohlan ('53). He fed pregnant rats 35,000 IU vitamin A per day on days 2–16 of gestation and noticed a number of fetal anomalies such as exencephaly, cleft lip and/or palate, brachygnathia, and various eye defects. Subsequently, other animal species—including mice, guinea pigs, hamsters, and rabbits—were found to be similarily susceptible to hypervitaminosis A (Geelen, '79).

Experimental teratologists began studing synthetic retinoids in the mid' sixties (Kochhar, '67) because unlike natural vitamin A compounds, they accumulate minimally in body tissues, and more quantitative dosing could be achieved. Subsequently, these retinoids were found to affect almost every developing tissue and organ (Geelen, '79). Shenefelt ('72) documented almost 70 types of fetal anomalies after exposure of pregnant hamsters to all-trans-retinoic acid. The anomalies were developmentally stage-dependent; treatment during the immediate postimplantation period resulted in anomalies of the head, sensory organs, and the cardiovascular system, whereas exposure later in gestation resulted in limb and genitourinary defects (Kochhar, '73; Geelen, '79; Willhite and Balogh-Nair, '85; Webster et al., '86).

Most investigators have used a single high dose of retinoids given to pregnant animals on selected days of gestation to elicit stage-dependent developmental effects. The literature on the minimal teratogenic doses of retinoids is not extensive. Such information is important to estimate safe or no-effect levels in humans from animal data (Table 1). The doses of retinoids in this table are those commonly used in studies during organogenesis in which the animals are treated daily for about 10 days (e.g., days 6–15 of gestation in the rat). Single doses range between 25 and 100 mg/kg during organogenesis and affect virtually every exposed embryo.

TABLE 1. Lowest teratogenic dose (mg/kg/day) of vitamin A[1] and synthetic retinoids in animals and man

Species	Vitamin A[1]	Tretinoin	Etretinate	Isotretinoin
Human [2]	ND[7]	ND	0.2	0.4
Subhuman, [3,4] Primates	ND	7.5	5	5
Rat [3,5]	50	0.4–2	2	150
Mouse[3]	75	4	4	100[8]
Hamster [6]	15	12.5	2.8	25
Rabbit [3,5]	ND	2–10	2	10

[1]Retinol or retinyl esters.
[2]Rosa et al., '86.
[3]Kamm, '82; Kamm et al., '84.
[4]Kochhar and McBride, '86.
[5]Zbinden, '75a,
[6]Howard and Willhite, '86 (from single dose experiments).
[7]ND = not determined.
[8]Agnish, Roche, Inc. (personal communication).

The pattern of malformations induced by retinoid analogs is similar to that induced by naturally occurring forms of vitamin A if given during the same period of embryogenesis (Geelen, '79; Lammer et al., '85; Rosa et al., '86; Willhite et al., '86).

Several reports have documented functional and behavioral deficits in the offspring of animals exposed to maternal hypervitaminosis A. Cognitive and behavioral abnormalities were detected in rat offspring (Hutchings et al., '73; Vorhees et al., '78; Mooney et al., '81).

How does vitamin A or the retinoid molecule interfere with embryonic organ formation or cellular function? No definite answers are available. Early studies considered pathologic changes in the embryonic mesoderm (Marin-Padilla and Ferm, '65), but the combination of ear, thymus, great vessel, and brain abnormalities in isotretinoin-exposed human infants has raised speculation that a specific effect on cranial neural crest cells may be involved. Experimental studies on mouse and hamster embryos have strengthened this notion (Webster et al., '86; Goulding and Pratt., '86; Irving et al., '86). Thorogood et al. ('82) indicated that not only neural crest cells but also other migratory cells are susceptible to retinoic acid. Other experimental studies lend support to this hypothesis (Kwasigroch and Kochhar, '75; Morriss, '76).

Stage-dependent perturbation of cellular events, which is common to most developing organs, is a logical assumption for one possible mechanism of retinoid action. Cell death, interference with some aspect of cell multiplication pattern, cell differentiation, extracellular matrix synthesis, or an alteration in overall pattern formation are additional mechanisms that have been advanced. Changes in pattern formation have been observed by developmental biologists working on retinoid-treated chick and amphibian embryos (Maden and Summerbell, '86).

Diverse cell types, both normal and transformed, are responsive to retinoids, pointing to some fundamental molecular and cellular mechanisms of action (Sporn and Roberts, '83). Some evidence suggests that the retinoid enters the cell, binds to a specific cytoplasmic binding protein, and may be transported to the nucleus, where it may alter the pattern of gene action. Two cellular binding proteins, one specific for retinol and the other for retinoic acid—called cellular retinol binding protein (CRBP) and cellular retinoic acid binding protein (CRABP), respectively—are present in various tissues (Chytil and Ong, '84). The presence of CRABP has been detected in mouse and chick embryos (Kwarta et al., '85; Maden and Summerbell, '86). The role of these binding proteins or of changes in gene transcription which mediate the teratogenic action of vitamin A is not well defined.

HUMAN STUDIES

The recommended dietary allowance (RDA) of vitamin A during pregnancy is 1,000 RE, which is equal to 3,300 IU of retinol or retinyl esters or 5,000 IU in an average U.S. diet containing a mixture of retinol and carotenoids (Food and Nutrition Board, 1980) (Table 2). The RDA of vitamin A during pregnancy was established by extrapolating from that recommended for the nonpregnant adult (800 RE/day or 4,000 IU/day). The International Vitamin A Consultative Group (IVACG) recommended a daily intake of 9.3 RE/kg plus 100 RE during pregnancy (Underwood, '86); this is approximately 620 RE/day (1,800 IU/day) of vitamin A for a 55-kg woman. The World Health Organization (WHO) and IVACG state that a daily supplemental dose of 3,000 RE (10,000 IU) of vitamin A is appropriate in geographical areas or under conditions where vitamin A intake is known to be inadequate and when diet cannot be improved. The USRDA (U.S. recommended daily allowance) of 8,000 IU/day during pregnancy has been established by the U.S. Food and Drug Administration (FDA) as a standard for nutrition labeling, including the labeling of nutritional supplements. Most prenatal vitamin preparations contain 8,000 IU/capsule of vitamin A as a daily supplement. Dietary surveys in the U.S., however, have defined that the average unsupplemented adult diet contains 7,000–8,000 IU/day of vitamin A (Russell-Briefel et al., '85). Therefore, women who are at risk for pregnancy should consider their total dietary intake of vitamin A before taking supplements.

At least seven case reports of adverse pregnancy outcome associated with a daily intake of vitamin A of 25,000 IU or more have been published (Rosa et al., '86). These authors have also presented unpublished information from eleven Adverse Drug Reaction Reports associated with the use of vitamin A during pregnancy that were filed with the

FDA. Almost all of the FDA cases are brief, retrospective reports of malformed infants or fetuses exposed to supplements of 25,000 IU/day or more of vitamin A during pregnancy. The biases that contributed to the decision to report or publish these cases of malformed vitamin A-exposed infants are unknown but are probably substantial. Some of these infants have malformations similar to those found among isotretinoin-exposed infants; the malformations of the others were quite different. At best, it can be said that the malformations of some of the vitamin A-exposed infants fit the pattern of malformation seen among infants exposed to isotretinoin. There are no epidemiologic studies that provide the data necessary to quantitate the risk for major malformation following daily fetal exposure to supplements of any dose of vitamin A.

After the initial report of three malformed infants (Roche Laboratories '83), epidemiologic evidence began to accumulate that isotretinoin is a human teratogen (Rosa, '83). Lammer et al. ('85) found that isotretinoin use during early pregnancy caused major malformations in almost 20% of exposed fetuses. The malformations involved craniofacial, central nervous system, cardiac, and thymic structures. Isotretinoin-exposed infants were 26 times more likely to have brain, cardiac, or ear malformations than unexposed infants. The brain malformations included hydrocephalus (several types), microcephaly, cerebellar micro- and macrodysgenesis, and other abnormalities which can be via neuronal migrational defects. Cardiac malformations included aorticopulmonary septation abnormalities or conotruncal developmental defects (Lammer and Opitz, '86). Craniofacial malformations included malformed external ears, stenotic/atretic external ear canals, micrognathia, facial asymmetry, and cleft palate. Most of the mothers of affected infants took daily doses of isotretinoin at levels of 0.5–1.5 mg/kg (Lammer et al., '85).

Can we extrapolate from the known teratogenic daily dose of isotretinoin to an equivalent intake of vitamin A? Probably not at this time. We know that the malformations in laboratory animals and humans after isotretinoin treatment are strikingly similar. Yet the pharmacologic differences between vitamin A and isotretinoin make it difficult to estimate the amount of each compound to which an embryo is exposed when comparable amounts have been taken orally. For example, the relative teratogenic concentrations for various retinoids could be deter-

TABLE 2. Vitamin A[1] and synthetic retinoids in humans

Substance	Retinol equivalents	IU/day	mg/day	mg/kg/day
Vitamin A				
Retinol and retinyl esters				
RDA for nonpregnant women[2]	800	2,640	0.8	0.015
RDA for pregnant women[2]	1,000	3,300	1.0	0.018
Reported adult[3] adverse levels	9,600–20,400	32,000–68,000	9.6–20.4	0.15–0.3
Lowest teratogenic level	ND	—	—	—
Synthetic Retinoids				
Isotretinoin				
Therapeutic Dose	—	—	20–80	1–2
Reported lowest Teratogenic level[4]	—	—	—	0.4
Etretinate				
Therapeutic dose	—	—	25	0.3–5.0
Reported lowest Teratogenic level[4]	—	—	—	0.2

[1]Retinol or retinyl esters.
[2]See Food and Nutrition Board: National Academy of Sciences, '80.
[3]Kamm, '82; Kamm et al., '84.
[4]Rosa et al., '86.

mined by using whole postimplatation rodent embryo cultures; however, there are no widely accepted procedures to extrapolate these data to the pregnant human. Finally, in a single case, regardless of vitamin A intake, one cannot impute the cause of birth defects to vitamin A based upon present knowledge.

CONCLUSIONS

In summary, the review of vitamin A has raised questions concerning its human teratogenicity. It is essential to evaluate these concerns in a systematic manner (Shepard '73 '86; Wilson '77; Brent '78, '86a, '86b; Stein et al., '84; Hemminki and Vineis '85).

1. Do human clinical studies or epidemiological studies consistently support the concept that high doses of vitamin A may be teratogenic and produce a recognizable group of malformations?

No human epidemiologic studies are available. Although not conclusive, the case reports suggest that high doses of vitamin A may be teratogenic, since some of the infants had malformations that fit the recognizable pattern that occurred following human exposure to isotretinoin.

2. Do secular trends of high-dose vitamin A exposure and the birth prevalence of malformations correlate?

There is sufficient information concerning trends in exposures to high-dose vitamin A and concerning knowledge of defects that may be induced by use of vitamin A.

3. Does vitamin A induce malformations in experimental animals following exposures to doses that are pharmacologically comparable to the maternal use (25,000 IU or more) of one or several unit doses per day of the vitamin A products that are available to the public?

Yes—in multiple species.

4. Is the frequency of malformations dose related and in the pharmacologic range of human toxic exposures?

Data are not available for the human.

Yes—for animal studies.

5. Is it biologically plausible that high doses of vitamin A may cause birth defects in the human?

Yes, isotretinoin is a known human teratogen. Since isotretinoin and vitamin A (retinol and retinyl esters) induce similar patterns of malformations in animals, it is probable that similar pathogenetic mechanisms are involved in inducing the malformations. Currently there is no evidence to suggest that vitamin A should act differently than isotretinoin in the human conceptus. Beta-carotene, a provitamin A, does not produce vitamin A toxicity nor does it produce teratogenicity in animals. All of these data are consistent with a specific vitamin A-related teratogenic response.

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