Vitamin A in pregnancy: requirements and safety limits

Véronique Azaïs-Braesco and Gérard Pascal

ABSTRACT Most of the functions of vitamin A are mediated through the binding of retinoic acid to specific nuclear receptors that regulate genomic expression. Recent experimental work in transgenic mice showed clearly that normal embryonic development depends on the correct spatial and temporal expression of the receptors in the differentiating cells and on the binding of specific forms of retinoic acid. This implies that the parent compound, vitamin A, is available in adequate forms and quantities. Excessive dietary intake of vitamin A has been associated with teratogenicity in humans in <20 reported cases over 30 y. However, caution must be exercised to avoid unnecessary supplementation of women of childbearing age. Hypovitaminosis A affects millions of women and children worldwide. The main consequence of a poor vitamin A supply during pregnancy is a low vitamin A status at birth and in the next few months. Vitamin A deficiency is strongly associated with depressed immune function and higher morbidity and mortality due to infectious diseases such as diarrhea, measles, and respiratory infections. Vitamin A deficiency is often associated with an increased mother-to-child transmission of HIV-1. The initiation of vitamin A supplementation should be carefully examined in each case according to the risk-to-benefit ratio. The final decision should take into account the estimated vitamin A status of the woman, the availability of vitamin A–rich foods in her diet, and whether supplementation can be supervised. Am J Clin Nutr 2000;71(suppl):1325S–33S.

KEY WORDS Pregnancy, lactation, development, teratogenesis, immunity, supplementation, developing countries, women, vitamin A

INTRODUCTION Vitamin A is an essential micronutrient whose role in visual function has been known for thousands of years. The role vitamin A plays in other basic physiologic processes, such as growth, reproduction, immunity, and epithelial tissue maintenance, has been known for a long time but is only partially understood. Vitamin A is essential throughout the entire life span, yet its influence is particularly critical during periods when cells proliferate rapidly and differentiate, such as during pregnancy and early childhood. This review focuses on the metabolism and functions of vitamin A during the periconceptional period, pregnancy, and early childhood. The consequences on health of inadequate vitamin A status or supply are also discussed.

MECHANISMS OF VITAMIN A–DEPENDENT FUNCTIONS Vitamin A exerts its functions through oxidized metabolites of retinol. The first metabolite, retinaldehyde, constitutes the heme of the visual pigment, the rhodopsin, whose light-induced isomerization triggers a phototransduction cascade that ends with a signal transmission to neurons of the optical nerves (1). The second metabolite, retinoic acid, is a lipid-soluble hormone that controls gene transcription through receptor-mediated events.

The first human retinoic acid receptor (RARα) was isolated in 1987 (2, 3) and was subsequently shown to activate the transcription of target genes after binding to all-trans-retinoic acid. Other subtypes (RARβ and RARγ) that bind to the same ligand were isolated shortly after. A second class of receptors, retinoid X receptor (RXR)α, -β, and -γ, was characterized in 1990 (4); these receptors may bind all-trans-retinoic acid, yet their ligand was identified as 9-cis-retinoic acid. The preferred RAR and RXR subtypes have multiple isoforms that are expressed differently in various cell types and during the various stages of development. Moreover, RXRs can form heterodimers with a variety of receptors belonging to the same superfamily, including RARs. All these possible interactions may be related to the pleiotropic effects of retinoids, which regulate the expression of numerous genes involved in many physiologic events (5).

Although most vitamin A–dependent functions, except for vision, can be mediated by retinoic acid, direct involvement of retinoic acid in the immune system has not been definitely determined. A third oxidized metabolite of retinol, 14-hydroxy-4,14-retinoic acid, is suggested to be the active molecule in the immune system, but its mechanism of action is not known (6). The various modes of response of the immune system are affected by vitamin A, as discussed by Ross (7).

RETINOIC ACID AND EMBRYONIC DEVELOPMENT Over the past 10 y, considerable work has addressed the mechanisms whereby retinoic acid affects cell differentiation and, as a direct consequence, embryonic development. For obvi-
functional redundancy between the various subtypes and isoforms of the receptors in null mutant mice (18, 19). Such patterns of expression are also observed in the genes coding for the proteins involved in retinol metabolism.

These studies clearly illustrate the fundamental role of retinoic acid and its receptors in embryonic development. To achieve harmonious tissue organization, a given quantity of retinoic acid, in its all-trans or 9-cis form, should bind specific receptors in due course. This implies that retinoic acid is available in the considered cell in an adequate amount and at the specific time. These spatial and temporal requirements imply a precise regulation of retinoic acid production, the mechanism of which is still largely unknown.

### VITAMIN A METABOLISM

Although retinoic acid circulates in the blood bound to albumin at concentrations close to 10 nmol/L (20), most retinoic acid is produced in the target cells. Vitamin A occurs in the human diet either preformed, as retinyl esters in animal products, or as provitamin carotenoids, mainly β-carotene, which are partly cleaved to produce vitamin A in the enterocyte. After intestinal absorption, vitamin A is packed into chylomicrons as retinyl esters. The chylomicron remnants are then taken up by hepatocytes, in which the retinyl esters are hydrolyzed into retinol (Figure 1). When vitamin A status is insufficient, ie, when extrahepatic organs urgently need vitamin A, the newly formed retinol is bound to retinol binding protein (RBP), a specific retinol carrier, and secreted into the blood. The overall process from ingestion to secretion takes ~5 h. When vitamin A status is satisfactory, the newly formed retinol is transferred in the form of retinyl esters to a specific cell type: the hepatic stellate cells (HSCs). These cells are also known as Ito cells or perisinusoidal liver cells and can store large quantities of vitamin A in characteristic lipid droplets. The lipid droplets are subsequently mobilized to maintain the homeostatic concentration of retinol at 2 μmol/L to meet the requirements of the organism (see reference 21 for a review).

RBP-bound retinol is taken up by cells via a mechanism thought to involve a membranous receptor specific for RBP. Such a receptor has been characterized in the retinal pigment epithelium (22) and in the placenta (23). Its existence is still controversial, however, and some investigators believe that the specificity of uptake would be ensured by a particular lipid composition of the cellular membrane (24, 25).

Vitamin A metabolism does not seem to be considerably affected during pregnancy. However, RBP is found in urine during normal pregnancies, whereas its excretion outside of pregnancy is considered to be a clinical symptom of renal failure (26). Vitamin A is transferred from the mother to the embryo across the placenta; vitamin A concentrations in fetal blood are approximately half of those in the mother. RBP is involved in this transfer from mother to embryo; nevertheless, its specific metabolism and the existence of other yet unknown binding proteins in maternal blood, the placenta, and fetal blood require further study (27–29).

After it is internalized, retinol is bound to a cellular RBP (CRBP) and is oxidized to retinal and then retinoic acid. This

### TABLE 1

Abnormalities described during fetal vitamin A deficiency reproduced in retinoic acid receptor (RAR) or retinoid X receptor (RXR) null mutant mice

<table>
<thead>
<tr>
<th>Knocked-out receptors in null mutant mice</th>
<th>Fetal abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>RARα1</td>
<td>None</td>
</tr>
<tr>
<td>RARα2</td>
<td>None</td>
</tr>
<tr>
<td>RARβ2</td>
<td>Retrolenticular eye membrane</td>
</tr>
<tr>
<td>RARα (all isoforms)</td>
<td>High neonatal mortality, growth retardation, male sterility</td>
</tr>
<tr>
<td>RARγ (all isoforms)</td>
<td>High neonatal mortality, growth retardation, male sterility</td>
</tr>
<tr>
<td>RARα, RARβ-RXRα, RARα</td>
<td>Lung hypoplasia</td>
</tr>
<tr>
<td>RARα, RARγ</td>
<td>Myocardial hypoplasia</td>
</tr>
<tr>
<td>RARβ, RARγ-RARα, RARβ</td>
<td>Anomalies of aortic arches</td>
</tr>
<tr>
<td>RARβ, RARγ-RXRα, RARα</td>
<td>Anomalies of aortic arches</td>
</tr>
<tr>
<td>RXRα, RXRβ-RXRα, RXRα</td>
<td>Renal hypoplasia</td>
</tr>
<tr>
<td>RXRα, RXRβ-RXRα, RXRγ</td>
<td>Uterine agenesia</td>
</tr>
<tr>
<td>RXRα, RARγ-RARβ, RARγ</td>
<td>Skeletal abnormalities (not occurring during fetal vitamin A deficiency)</td>
</tr>
<tr>
<td>RXRα, RARγ</td>
<td>Skeletal abnormalities (not occurring during fetal vitamin A deficiency)</td>
</tr>
</tbody>
</table>

*From reference 10, 11.*
biochemical pathway is similar to the oxidation of ethanol to acetaldehyde and acetic acid. Enzymes such as alcohol dehydrogenase and short-chain dehydrogenase or reductase can catalyze the first step, which is reversible, whereas aldehyde dehydrogenase and cytochrome P-450 can catalyze the irreversible oxidation of retinaldehyde to retinoic acid (30). This involvement of the enzymes belonging to the pathway of ethanol oxidation suggests that fetal alcohol syndrome, a teratogenic manifestation, may be due to the inhibition of aldehyde-catalyzed retinoic acid synthesis (31). Other authors characterized a pathway for retinol oxidation that seems to be more specific to retinol. Retinol can be dehydrogenated in the cytosol by 2 enzymes that differ by their cofactors or by a third enzyme localized in the microsomal fraction that accepts CRBP-bound retinol as its substrate. The second step, retinaldehyde oxidation, also seems to be mediated by several isozymes (32).

These studies concern primarily the biogenesis of all-trans-retinoic acid, although the 9-cis isomer of retinoic acid appears...
to be of at least equal importance. This isomer could be derived from a nonenzymatic isomerization of the all-trans form (33), or from a 2-step oxidation of 9-cis-retinol (34). Retinoic acid, in its all-trans or 9-cis form, can also be produced directly from β-carotene after cleavage into retinal via β-carotene dioxygenase (35). However, this seems to remain limited in vivo: in one study, feeding humans 120 mg β-carotene led to a small increase in circulating all-trans-retinoic acid from 5 to 7 nmol/L, whereas concentrations of 3-cis-retinoic acid were unchanged (36). However, circulating values do not necessarily reflect tissue concentrations.

Retinoic acid biogenesis is a complex process involving several biochemical pathways, the interactions and regulations of which are not yet completely understood. Two points should be stressed here, which will not be developed further. The first is related to the yet undetermined role of 2 specific intracellular binding proteins for retinoic acid: cellular retinoic acid binding proteins (CRABP) I and II. Although they have an apparently well regulated pattern of expression in the developing embryo (37) and determine the rate of retinoic acid metabolism in in vitro systems (38), the CRABPs have been shown to be dispensable. Mice in which the CRABP genes are disrupted have a normal phenotype (39). The second point concerns the large number of retinoic acid metabolites and isomers that have been detected in human blood. Some of these clearly have a function, such as 4-oxoretinoinic acid (40), or are considered to be a sink for active molecules, such as the glucuronidated derivatives of retinoic acid (41). Others are thought to be elimination metabolites, yet might have a physiologic role. For example, 13-cis-retinoic acid is usually considered as a degradation product; however, its administration in monkeys or humans leads to teratogenic events (42, 43).

Little information is available about the biogenesis of retinoic acid in pregnancy or in the embryo. During organogenesis, the retinoic acid concentration in the rat placenta is 0.06 nmol/g. The concentration increases to 2 nmol/g in the fetus during organogenesis and then decreases to 0.01 nmol/g after organogenesis (44). In the rat conceptus, the latter of the 2 pathways of retinol oxidation described above seems to occur preferentially; the role of aldehyde dehydrogenase is unclear, however, and there seems to be no involvement of cytochrome P-450 (45). Studies in humans are scarce; nevertheless, some authors have shown an increase in circulating concentrations of retinoic acid and of 4-oxoretinoic acid (in their all-trans and 13-cis form) after the intake of vitamin A (46–49). The results of these experiments are difficult to compare, however, because the experimental designs varied. Furthermore, the half-life of the compounds measured is usually very short (50) and thus serum concentrations may not reflect cellular concentrations, as shown in animal models (51). Moreover, the teratogenic threshold of circulating retinoic acid is not known, nor is the nature of the specific teratogenic metabolite in humans. Uncertainty also remains concerning the extent of transplacental transfer of vitamin A, retinoic acid, and their derivatives, as well as concerning the embryonic or fetal metabolism of these compounds in humans. For example, the main compound found in the human placenta and embryo 72 h after 13-cis-retinoic acid exposure is all-trans-retinoic acid, whereas maternal serum concentrations of both isomers remain low (52).

A better understanding of retinoic acid metabolism in human tissue is a prerequisite for estimating potentially teratogenic doses of vitamin A during human pregnancy.

**CONSEQUENCES OF EXCESSIVE VITAMIN A INTAKE DURING PREGNANCY AND EARLY CHILDHOOD**

**Acute hypervitaminosis A**

Acute hypervitaminosis A occurs after the administration of very high amounts of the vitamin, usually in a single dose. The prescription of supplemental vitamin A has been reported to induce intracranial hypertension (53). A bulging fontanelle is often reported in infants and young children (54), yet such an outcome remains limited and should not prevent the administration of doses ≤50 000 IU [15 000 retinol equivalents (RE)] to neonates when vitamin A status is critically low at birth or later (55). The situation is different when the need for vitamin A is not clearly established. In this case, the prescription of supplemental vitamin A to young children should be considered with extreme caution. Other symptoms related to chronic hypervitaminosis A are observed after supplementation with low to moderate doses of vitamin A on a regular basis over a long period of time. This may induce severe, yet usually reversible liver damage (56).

**Teratogenesis**

Teratogenesis of high vitamin A intakes has been reported in several animal species, as reviewed by Hathcock et al (57). The pattern of birth defects sometimes called retinoic acid syndrome includes central nervous system, craniofacial, cardiovascular, and thymus malformations. Similar abnormalities were observed in humans when pregnancies occurred during therapeutic treatment with retinoic acid, especially 13-cis-retinoic acid (43).

Up to 20 case reports of the relation between a high vitamin A intake and an adverse pregnancy outcome in humans were published in the past 30 y (58). These reports are of limited use for establishing a quantitative link between vitamin A intake and teratogenic events, however. Furthermore, the pattern of the observed malformations is not always consistent with the retinoic acid syndrome, thus calling into question the origin of these malformations.

Five case-control studies have been published since 1990 in which the intake of vitamin A was estimated retrospectively in both control subjects and mothers of malformed babies (59–63). These data are summarized in Table 2. The design of these studies varied, especially regarding the classification of the observed malformations, the statistical power, and the data on vitamin A consumption. In most cases, no association was found between moderate doses of vitamin A (≈10 000 IU, or 3000 RE) and fetal malformations. However, in all of these studies, the number of women consuming high amounts of vitamin A was too limited to reach statistical significance and the information available is insufficient for assessing the potential teratogenic effect of such high doses.

Only one prospective study has been conducted to date (64) and the results of this study are clearly inconsistent with those of the retrospective studies. The prospective study showed that an intake exceeding 10 000 IU (3000 RE) vitamin A significantly increased the risk of malformations (prevalence ratio: 4.8; 95% CI: 2.2, 10.5). This paper has been largely criticized (65), particularly in relation to a suspected misclassification of the malformations, yet its conclusion should not be ignored. A clinical trial was carried out in Hungary in which a supplement of 6000 IU (1800 RE) vitamin A did not increase the incidence of fetal malformations. However, only limited conclusions can be drawn from this study regarding the incidence of neural tube defects because folic acid was administered simultaneously with vitamin A (66).
Thus, the teratogenicity of high vitamin A intakes during pregnancy remains unclear and it is unlikely that new findings will shed light on this issue over the next few years. Human clinical trials are not ethically possible, so we must rely on those already performed, on forthcoming epidemiologic trials, and on our knowledge of vitamin A metabolism and functions, which is largely derived from animal studies. This information clearly shows that the teratogenicity of vitamin A is biologically and physiologically possible, yet its real occurrence in humans seems limited. One drawback in all human studies is that the specific effects of vitamin A intake cannot be determined. Most of the information comes from the use of supplements or, at best, supplemented foods, that are taken on a regular basis and in moderate doses. However, data from animal studies clearly show that one single, high dose of vitamin A can be teratogenic, provided it is given at a critical period of embryonic development. Such information is not available today in humans; thus, any attempt to establish a safe threshold of vitamin A consumption during the early period of human pregnancy would be hazardous.

### CONSEQUENCES OF A DEFICIENT VITAMIN A STATUS DURING PREGNANCY AND EARLY CHILDHOOD

Liver vitamin A stores are usually sufficiently high to withstand low or no vitamin A supply for a limited period, provided that usual intake is adequate. Therefore, more emphasis should be placed on vitamin A status than on vitamin A intake, yet this is difficult to do because of the lack of a satisfactory biomarker for assessing the vitamin A status of individuals or population except in the case of extreme hypovitaminosis A (67). Unfortunately, extreme hypovitaminosis A is sufficiently frequent to be ascertained in wide areas of the world. At the last International Nutrition Conference, it was stated that not only are ~250 million children under 5 y of age at risk, but 2.8 million are currently vitamin A deficient and have reached the xerophthalmia stage (68).

### Low vitamin A status and embryonic development

Up until the 1950s, a relatively large number of studies showed that laboratory animals (pigs, rabbits, chickens, rats, and mice) fed vitamin A–deficient diets gave birth to malformed offspring, mostly affected by microphthalmia and anophthalmia associated with abnormalities of the cardiac, lung, and urogenital systems (12). Because of the lack of appropriate analytic techniques at that time, maternal vitamin A concentrations were not recorded. More recent studies in RAR and RXR null mutant mice clearly confirm the role of vitamin A in embryonic development. Interestingly, a study in rats showed that retinol is required during midgestation for neonatal survival. In the absence of retinol, the pups exhibited a lethal failure in lung development (69). This seems similar to the respiratory distress syndrome observed in premature infants whose vitamin A status is often deficient. Severe vitamin A deficiency is also responsible for abnormal spermatogenesis in animals (70). Zootechnicians have found a positive association between *β*-carotene intake and fertility of cattle, but no similar relation for vitamin A intake (71).

In light of these findings, a higher incidence of malformed babies would be expected in areas of endemic vitamin A deficiency, but this is not the case. Although this apparent discrepancy may arise from the failure to report birth defects in these countries, the number of reported cases remains surprisingly low. The few cases reported occurred in India. One study reported 15 cases of microphthalmia or anophthalmia over a 10-y period, which is not considerably excessive (72).

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**Table 2:** Epidemiologic case-control studies of the association between vitamin A intake and fetal malformations in humans

<table>
<thead>
<tr>
<th>Population</th>
<th>Number of cases</th>
<th>Number of controls</th>
<th>Characteristics of exposure to vitamin A</th>
<th>Odds ratio (95% CI)</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10000 IU/d</td>
<td>11193</td>
<td>11293</td>
<td>&gt;10000 IU/d</td>
<td>1.1 (0.5, 2.5)</td>
<td>Only 11 cases, 4 controls at high exposure level</td>
<td>(58)</td>
</tr>
<tr>
<td>&gt;40000 IU/d</td>
<td></td>
<td></td>
<td>2.7 (0.8, 11.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2658</td>
<td>2609</td>
<td></td>
<td>During the 1st month</td>
<td>2.5 (1.0, 6.2)</td>
<td>No information on the vitamin A doses; well-characterized neural crest–derived malformations</td>
<td>(59)</td>
</tr>
<tr>
<td>3rd month</td>
<td></td>
<td></td>
<td>2.3 (0.9, 5.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>158</td>
<td>3026</td>
<td></td>
<td>Use of multivitamin supplement</td>
<td>1.6 (0.6, 4.5)</td>
<td>Focus on conotruncal defects only</td>
<td>(60)</td>
</tr>
<tr>
<td>548 (NTDs)</td>
<td>573</td>
<td></td>
<td>&gt;8000 IU/d from supplements</td>
<td>0.57 (0.33, 1.00)</td>
<td>Consumption of liver did not increase risk</td>
<td>(61)</td>
</tr>
<tr>
<td>387(other defects)</td>
<td></td>
<td></td>
<td>&gt;10000 IU/d from food and supplements</td>
<td>Other defects: 1.05 (0.51, 2.18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>426</td>
<td>432</td>
<td></td>
<td>0–9999 IU/d</td>
<td>1.0 (reference)</td>
<td>NTDs only; vitamin A from food and supplements</td>
<td>(62)</td>
</tr>
<tr>
<td>16</td>
<td>12</td>
<td></td>
<td>10000–14999 IU/d</td>
<td>1.4 (0.6, 2.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td></td>
<td>&gt;15000 IU/d</td>
<td>0.9 (0.3, 2.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 NTD, neural tube defect. To convert from IU to retinol equivalents, multiply by 0.3.
Pregnancy outcomes in women with low vitamin A status

These have been more extensively studied although no link has been established between vitamin A–deficient status and partial molar pregnancy (73), premature rupture of membranes (74), or eclampsia (75). One study reported lower vitamin A concentrations in placental abruption pregnancies than in normal pregnancies, but no cause-and-effect relation was established (76). It is possible that the requirements of the embryo are met first, as suggested by a 1962 study in which serum vitamin A values in the mother were deficient, whereas cord blood values were within the normal range (77). Such studies should be carried out again with use of better analytic techniques.

Low vitamin A status does not seem to be related to a higher incidence of intrauterine growth retardation (78–80), although one British study reported a significant correlation between birth weight and anthropometric indexes in a low-income area of London (81). More worrying is the link consistently established between low vitamin A status and high mother-to-child transmission of HIV. Several clinical trials are under way in Africa that should definitively establish whether a causal link exists (82).

Circulating retinol values in mature newborns are always 50% lower than those in the mother, and concentrations of ≈1 μmol/L are frequent and should not be considered indicative of a deficient status at this stage (83, 84). The situation is more critical for premature deliveries, because both serum and hepatic vitamin A concentrations can be very low and may pose a direct threat to the child’s health. Although vitamin A supplementation can be used, its ability to prevent and reduce lung injury such as bronchopulmonary dysplasia is still controversial (85, 86).

The fetus starts to accumulate vitamin A during the third trimester of pregnancy, and needs several months of sufficient intake after birth to build up an adequate hepatic store. In many countries, babies are breast-fed, in which case the vitamin A content of the breast milk is of primary importance. The composition of breast milk is influenced by the vitamin A status and serum concentrations of the mother during the last trimester of pregnancy (87). Colostrum and early milk are extremely rich in vitamin A, and even the milk of a mildly undernourished woman may meet the physiologic needs of the newborn during the first weeks (88–91).

After this time, however, a rapidly-growing infant may exhibit negative vitamin A balance, with severe consequences for health.

Young children who are vitamin A deficient are at greater risk of morbidity and mortality than vitamin A–sufficient children (89). Diarrhea, respiratory infections, and measles are the diseases most frequently associated with a deficient vitamin A status (90, 91). There are still some discrepancies in the results observed in various community trials: vitamin A supplementation does not always result in the expected decrease in morbidity, although mortality is usually reduced (92, 93). Infants born to HIV-infected mothers are more vulnerable to disease, possibly, at least partly, because of the impairment of their immune system.

PRACTICAL RECOMMENDATIONS: HOW CAN ADEQUATE VITAMIN A STATUS DURING PREGNANCY AND EARLY CHILDHOOD BE REACHED?

An adequate vitamin A status, one that is neither too low nor too high, is needed for harmonious fetal and child development. In practice, practical recommendations vary greatly according to the endemicity of inadequate vitamin A status, vitamin A availability, and the socioeconomic constraints of the country being considered. This is illustrated by the relatively wide range of recommended daily allowances for vitamin A (Table 3). Useful specific guidelines were published recently by the World Health Organization (94).

In industrialized countries, there is no endemicity of low vitamin A status, and consequently no need for vitamin A supplementation of pregnant women or women of childbearing age. Such a measure could even be harmful because of the potential risk of teratogenesis with high doses of vitamin A. For the same reasons, over-the-counter supplements should contain low amounts of vitamin A (less than one times the recommended daily amount) and caution should be taken regarding vitamin A–rich foods. Certain authorities, such as the World Health Organization, have taken an official stance. The World Health Organization recommends that a daily vitamin A supplement taking during any part of the fertile period be limited to 10000 IU (3000 RE) (94). The Teratology Society of the...
United States recommends that vitamin A supplements or total intake not exceed 8000 IU/d (2400 RE/d) (99). These recommendations should be taken into account by both individuals and practitioners. In France, the vitamin A content of a supplement for the general population cannot exceed 3000 IU (900 RE) (100), but a practitioner may prescribe higher doses in medically designed preparations.

Most countries recommend that vitamin A supplementation be avoided without medical advice. Physicians and gynecologists should be aware of all aspects of the vitamin A–pregnancy issue. They can then prescribe either a well-balanced diet rich in β-carotene–containing vegetables or vitamin A supplementation to women with suspected low vitamin A status. Such status is particularly difficult to assess. Indicators of low vitamin A status include a low serum retinol concentration (<0.7 μmol/L) and poor dietary habits.

In areas of endemic vitamin A deficiency, the problem and its solutions are quite different. The benefit that pregnant women or women of childbearing age and their children may derive from vitamin A supplementation outweighs the potential risk. However, extra caution should be taken to minimize this risk, especially for practical reasons supplementation is administered at high doses. The recommendations of the World Health Organization can be summarized as follows:

1) During pregnancy, a daily supplement should not exceed 10000 IU (3000 RE) and a weekly supplement should not exceed 25000 IU (7500 RE).

2) During the first 6 mo postpartum, supplementation is safer if the mother is breast-feeding, which reduces fertility. Otherwise, the supplement given after 6 wk postpartum should not exceed 10000 IU (3000 RE).

3) During the first 6 mo of age, the infant can receive a direct supplement of 50000 IU (15000 RE) or, preferably, 2 doses of 25000 IU (7500 RE) or more if he or she is not breast-fed.

Today, vitamin A supplementation is the most efficient way of correcting vitamin A deficiency. Its only drawback is the potential risk of teratogenesis. Interesting attempts have been made to replace vitamin A with the provitamin β-carotene, which has never been associated with any teratogenic risk. When β-carotene was provided as a synthetic supplement, it was as efficient as vitamin A in reversing abnormal eye cytology, a clinical marker of vitamin A deficiency (101). Other authors found that the β-carotene of orange fruit (S de Pee, CE West, D Permaesih, S Maruti, Muhilal, JGAJ Hautvast, unpublished observations, 1997) was a more efficient source of vitamin A than dark-green leafy vegetables (102), probably because of the lower bioavailability of β-carotene in the latter. Fostering the local production and utilization of sources of vitamin A is promising, yet the problem lies not only in the availability of vitamin A sources, but also in the economic status of the population.

Such a distinction between areas where vitamin A deficiency is endemic (ie, some low-income countries) and those where it is not (ie, industrialized countries) is convenient, but may not reflect the real situation. It is quite possible, and in our opinion rather likely, that a significant portion of the low-income population in some of the most industrialized countries suffers from undiagnosed low vitamin A status (103). Women in these populations, who often do not undergo prenatal examinations, would benefit from a safely designed vitamin A supplementation protocol. However, to our knowledge, there has been no attempt to identify these women or to correct their nutritional deficiencies.

REFERENCES


