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Special Issue on Vitamin A Supplementation and the Control of Vitamin A Deficiency

Based on an informal WHO Technical Consultation on Vitamin A Supplementation held in Yverdon-les-Bains, Switzerland, 1–3 March 2000

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Food and Nutrition Bulletin, vol. 22, no. 3

United Nations University Press
The United Nations University
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E-mail: mbox@hq.unu.edu
ISSN 0379-5721
Design and Production by Desktop Publishing & Design Co., Newton, MA USA
Printed by Webcom Ltd., Toronto, ON Canada

Foreword

As well as being a major contributor to childhood morbidity and mortality, vitamin A deficiency is very likely to be a contributor to maternal mortality. Thus, it is a significant public health issue not only as the main cause of preventable blindness in children, but also as a threat to child and maternal survival. In recognition of this burden of illness, the elimination of vitamin A deficiency as a public health problem was set as a goal at the World Summit for Children in 1990 and reiterated by the World Health Assembly in 1991 and the International Conference in Nutrition in 1992. Although food fortification and dietary diversification approaches are fundamental to combating vitamin A deficiency, the administration of vitamin A supplements has proven to be a rapid and cost-effective complementary strategy that has received widespread support.

In 1997, a Task Force composed of the World Health Organization (WHO), UNICEF, and the International Vitamin A Consultative Group (IVACG) produced guidelines on the use of vitamin A supplements to prevent and treat vitamin A deficiency. Since then, knowledge has expanded and shed new light on vitamin A requirements in different age groups, especially in infants; the beneficial effects of vitamin A supplements in pregnant women and young children; and the interaction between vitamin A status and the course of HIV infection, especially with regard to the mother-to-child transmission of the virus and pregnancy outcomes. Moreover, it has been recognized that the vitamin A dosage schedule also needs to take into account the most effective channels currently used to deliver vitamin A supplements. For example, with the global effort to eradicate poliomyelitis, an increasing number of countries are organizing national immunization days and utilizing these events to administer vitamin A supplements with polio vaccines.

For these reasons, it was felt timely to revise the current WHO/UNICEF/IVACG recommendations on vitamin A supplementation. As a first step, WHO commissioned reviews of the scientific literature to examine the current state of knowledge concerning the use of vitamin A supplements to control vitamin A deficiency. Then it convened an Informal Technical Consultation on vitamin A supplements in Yverdon-les-Bains, Switzerland, March 1–3, 2000. In light of those reports, the consultation addressed the following topics: safety of vitamin A supplementation; vitamin A requirements in infants less than six months of age; vitamin A supplementation in various population groups living in vitamin A-deficient areas, pregnant and postpartum women, young infants, sick children, and populations where HIV infection is a public health problem. The objectives were to undertake a critical review of the safety and efficacy of vitamin A supplementation in order to provide WHO with guidance on the use of vitamin A supplementation as a public health measure to prevent and treat vitamin A deficiency.

This special issue of the *Food and Nutrition Bulletin* contains the proceedings of this consultation. The results from this meeting are expected to serve as input to a broader process of revising the current recommendations and guidelines on the use of vitamin A supplements.

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Acknowledgments

The World Health Organization gratefully acknowledges the financial support provided by the Micronutrient Initiative, which made it possible to commission the scientific literature reviews presented in this issue and to convene the Informal Consultation on Vitamin A Supplementation held in Yverdon-les-Bains, Switzerland, March 1–3, 2000.

Vitamin A requirements of infants under six months of age

Lindsay H. Allen and Marjorie Haskell

Abstract

Infants are born with negligible liver stores of vitamin A. To enable some storage of the vitamin, the infant needs to be predominantly breastfed with milk containing at least 30 μg/dl. Where vitamin A in breastmilk is low, maternal supplementation with a single postpartum high dose increases milk vitamin A for three to eight months. The current cutoff levels for serum retinol and the modified relative dose response (MRDR) ratio probably need to be revised for young infants. Kinetic analyses of infants' retention of vitamin A from breastmilk and supplements indicate that the doses of vitamin A given with immunizations in the World Health Organization (WHO) multicenter trial were inadequate to maintain adequate normal stores for more than a few months. The recommendation to double the doses currently given to mothers and infants in the Expanded Program in Immunization should prevent the depletion of liver vitamin A stores for most of the first year of life.

Scope of the review

This article reviews what is known about the vitamin A requirements of infants under six months of age and their vitamin A status in different situations. During this process, it was necessary to evaluate the validity of the markers and cutoffs used to evaluate vitamin A status at this age, and the prevalence of vitamin A deficiency based on different criteria. The review also considers factors that modify the risk of vitamin A deficiency in infancy, including maternal vitamin A status and the ability of the infant to meet vitamin A requirements through breastmilk. Finally, the review estimates the effect on vitamin A status of directly supplementing infants and/or their mothers with high doses of vitamin A.

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Current estimates of the vitamin A requirements of infants

During infancy, the recommended intake of most micronutrients is based on the amounts usually consumed by exclusively breastfed infants whose mothers are well nourished. Vitamin A is no exception.

Infants who are exclusively breastfed by well-nourished mothers for the first six months of life receive enough vitamin A to maintain health, permit normal growth, and build sufficient liver stores of the vitamin. The Food and Agriculture Organization/World Health Organization (FAO/WHO) estimates are that the intake by such infants is 350 μg RE (retinol equivalents)/day, assuming an average breastmilk intake of 700 ml/day and a vitamin A content of 50 μg/dl [1].

The FAO/WHO recommendations also state that, based on observations by Belvady and Gopalan in India [2], infants fed by vitamin A–deficient mothers whose breastmilk provides as little as 120 ± 15 μg RE/day grow normally and have no clinical signs of vitamin A deficiency. These infants meet their "basal requirement" for vitamin A, which is defined as the minimum daily intake that prevents the appearance of clinical signs of vitamin A deficiency (night-blindness and epithelial lesions of the conjunctiva and cornea of the eye) and permits growth. Thus, the basal requirement for infants is based on this value of 120 μg RE/day, increased to 180 μg RE/day to account for "variability in growth rates" [1].

The recommended "adequate intake" (AI) for infants in the United States and Canada is 400 μg/day during the first six postpartum months and 500 μg/day during the second six months [3]. The AI is based on observed mean intakes of a group of healthy (nondeficient) individuals, and is "expected to meet or exceed the amount needed to maintain a defined nutritional state or criterion of adequacy in essentially all members of a specific healthy population" [3]. The vitamin A recommendation for infants is based on reports that the milk of well-nourished women contains about 50

μg/dl (1.7 μmol/L) and an average breastmilk intake of 780 ml/day.

In the United Kingdom the recommended vitamin A intake for infants is 350 μg RE/day [4] and is based on the FAO/WHO recommendation [1]. The UK group then worked backwards, subtracting 2 standard deviations (40%) to obtain an estimated average requirement (EAR) of 250 μg/day, and another 2 standard deviations to obtain the value of 150 μg/day for a lower recommended nutrient intake (LRNI, defined as being 2 SDs below the EAR). This LRNI is not based on data, but it was pointed out that breastfed infants "do not show signs of vitamin A deficiency even on intakes little above 100 μg/day." This statement is again based on the Belvady and Gopalan report [2], as well as on data from lactating Navajo women and their infants in the United States [5].

There are few data on the minimum intake of vitamin A that will meet the basal requirements of infants. In 1947, Lewis et al. provided 100 μg RE of retinol daily in a low-fat milk diet to six infants aged one to two months. After two to four months, serum vitamin A concentrations had fallen (instead of undergoing the normal rise at this age), but growth and dark adaptation were normal [6]. In Guatemala, there was no difference in the serum retinol concentrations of infants suckling from mothers whose milk was low in vitamin A (18 μg/dl) versus those with a normal concentration (30 μg/dl, higher because they consumed vitamin A–fortified sugar) [7]. Intake by exclusively breastfed infants consuming the milk low in the vitamin would have been about 126 μg/day.

Taken together, these data suggest that an intake of 300 μg RE is normal for many exclusively breastfed infants in populations where vitamin A deficiency is virtually nonexistent in infants or children. An intake of about 125 μg/day will probably maintain serum retinol concentrations and prevent clinical symptoms of deficiency.

Methods for the assessment of vitamin A status

General approaches

At any age, the best estimate of vitamin A stores is the liver retinol concentration. The liver contains about 90% of the total body vitamin A [8]. For obvious reasons, this method is not suitable for the routine assessment of the vitamin A status of populations.

Serum retinol concentrations are the most commonly used indicator of vitamin A status. However, these only reflect vitamin A stores at the extremes of deficiency or toxicity, because they are homeostatically regulated [8]. In children, the recommended serum retinol cutoff for indicating vitamin A deficiency is <0.35 μmol/L, with <0.70 μmol/L indicating marginal vitamin A status [9]. This is based on an experiment conducted in Sheffield over 50 years ago, in which adult men underwent depletion and repletion of vitamin A [10]. These cutoffs are considered to be more useful for assessing the status of populations than that of individuals. When 20% or more of preschoolers have serum retinol concentrations less than 0.70 μmol/L, this is classified as a severe public health problem.

The relative dose response (RDR) and modified relative dose response (MRDR) tests are used as indicators of the adequacy of liver vitamin A stores. Dose-response tests are based on the concept that apo-retinol-binding protein accumulates in the liver of vitamin A–deficient individuals. When these individuals are challenged with a small oral dose of retinyl palmitate (3.5 μmol, 1.0 mg RE for infants) or vitamin A_2 (3,4-didehydroretinol acetate, 5.3 μmol, or 1.5 mg RE), the ingested vitamin A binds rapidly to the accumulated apo-RBP (retinol-binding protein) and is secreted into the blood, producing a transient increase in circulating levels of retinol or 3,4-didehydroretinol, depending on the form of vitamin A in the test dose. Two blood samples are required for the RDR test, at baseline and at five hours after the dose. The RDR is the percent change in serum concentrations of retinol in five hours. A RDR of 20% or more indicates inadequate hepatic vitamin A stores [11]. The modified relative dose response (MRDR) requires that only one blood sample be drawn four to seven hours after the dose, because 3,4-didehydroretinol concentrations at baseline are negligible. The MRDR is calculated as the serum molar ratio of 3,4-didehydroretinol to retinol, and a ratio ≥0.06 indicates inadequate liver retinol reserves [12].

Serum retinol as an indicator of vitamin A status in the first six months of life

A summary of reported concentrations of serum retinol in cord blood of infants in industrialized and developing countries is provided in tables 1 and 2. These concentrations are about 50% of maternal values and independent of sex [13].

Concentrations at birth are about 1.0 μmol/L in most reports from industrialized countries (table 1). Substantially lower values were found in Japan [22] and in Navajo Indians [24]. In Pakistan and India, values appear to be generally lower than in industrialized regions [25, 26] (table 2). In the few studies that presented the proportion of serum retinol concentrations less than 0.70 μmol/L, the mean percent of newborn values below this cutoff ranged from 0% to 29% in industrialized countries and 0% to 89% in the developing countries. Part of the explanation for the higher proportion of low values in developing regions may be the higher rates of preterm deliveries and

TABLE 1. Serum retinol concentrations of newborns' and mothers' health and status in industrialized countries

Country	*n*	Maternal health or status	Infant health	Birthweight (kg)	Newborn serum retinol (μmol/L)	% with serum retinol <0.70 (μmol/L)
Italy [14]	14	Middle class	No complications	NA	0.90 ± 0.27	29
Taiwan [15]	29	Healthy	Not specified	NA	1.6 ± 0.7	0
Sweden [16]	25	Healthy	Healthy full-term	NA	1.15 ± 0.33	NA
Canada [17]	123	No severe health problems	Not specified	NA	1.15 ± 0.39	15
Finland [18]	72	Not specified	Full-term	3.7 ± 4.3	0.83 ± 0.2	NA
Britain [19]	44	Not specified	Not specified	NA	0.96 ± 0.27	NA
Israel [20]	251	No chronic disease	Healthy full-term	3.3 ± 0.4	1.18 ± 0.95	29
Canada [21]	10	Healthy	Healthy	3.6 ± 0.3	0.79 ± 0.10	NA
Japan [22]	13	Not specified	Full-term	NA	0.38 ± 0.07	NA
USA [23]	51	Not specified	Healthy full-term	3.3 ± 0.06	0.78 ± 0.03	NA
USA [24]	28	Not specified	Birthweight >2.5 kg	3.4 ± 0.4	0.51 ± 0.15	NA

NA, Not available.

TABLE 2. Serum retinol concentrations of newborns and mothers in developing countries

Country	*n*	Maternal health or status	Infant health	Birthweight (kg)	Infant serum retinol (μmol/L)	% with serum retinol <0.70 μmol/L	Maternal serum retinol (μmol/L)
Pakistan [25]	20	Affluent	Healthy	NA	0.88 ± 0.04	NA	NA
India [26]	70	High SES	Full-term	3.0 ± 0.1	0.68 ± 0.03	NA	1.05 ± 0.04
	114	Low SES	Full-term	2.5 ± 0.1	0.46 ± 0.04	NA	0.76 ± 0.04
Nigeria [27]	100	Healthy, nonanemic	Full-term	3.05 ± 0.45	0.88 ± 0.15	0	2.34 ± 0.49
Namibia [28]	51–77 per age group	NA	90% with adequate anthropometry	NA	NA	6	NA
Indonesia [29]	666 total	NA	No clinical signs of vitamin A deficiency	NA	NA	58	NA
Bangladesh [30]	120	NA	No systemic infection	NA	NA	89	NA

SES, Socioeconomic status; NA, not available.

low birthweight. As will be discussed below, maternal transfer of retinol to the fetus is relatively protected, even when the mother is vitamin A deficient.

Serum retinol concentrations increase during the first year of life [25]. There are no longitudinal data from industrialized countries. This is unfortunate, because they could serve as a reference against which to judge the vitamin A status of infants in developing countries. In Canada, serum retinol concentrations at six months of age averaged about 2 μmol/L in Caucasian infants and about 1.3 μmol/L in Inuit and native Indian infants [17]. In an affluent Pakistani population, serum retinol increased with age and reached about 1.58 μmol/L towards the end of the first year of life [25] (table 3). This is close to the normal concentration in adults. Neither maternal vitamin A status nor feeding practices were described so whether the infants were truly well-nourished cannot be determined.

Reported values from less-developed countries are quite variable (table 3). In the WHO multicenter trial in Ghana, India, and Peru, the mean retinol concentration of unsupplemented infants at six weeks of age was 0.68 μmol/L, increasing to 0.80 μmol/L at six months,

TABLE 3. Serum retinol concentrations of infants in developing countries aged 1 to 24 months

Country	*n*	Infant health	Serum retinol concentration (μmol/L) according to age					% with serum retinol <0.70 μmol/L	Feeding practices
			1–3 mo	4–6 mo	7–9 mo	10–12 mo	1–2 yr		
Ghana, India, Peru [31]	~300	NA	0.68 ± 0.32	0.80 ± 0.27		0.83 ± 0.47		62 (1–3 mo) 37 (5–6 mo) 32 (12 mo)	94% breastfed
Bangladesh [32]	85	Healthy		0.60 ± 0.29 (2–7 mo)		0.87 ± 0.30 (7–12 mo)		67 (2–<5 mo) 60 (5–<7 mo) 33 (7–12 mo)	Breastfed, duration unspecified
Bangladesh [33]	192	Recent diarrheal illness	0.38 ± 0.23					90	>80% breast-fed, duration not stated
Nigeria [27]	100	NA	1.22 ± 0.24	1.29 ± 0.20	NA	1.50 ± 0.44	NA	0	Breastfed, duration not stated
Namibia [28]	51–77 per age group	90% adequate anthropometry, no signs of vitamin A deficiency	1.22 ± 0.63	1.26 ± 0.42	1.19 ± 0.31	1.26 ± 0.59	NA	6	50% of infants 1–2 mo and 30% 11–12 mo breastfed exclusively
Indonesia [29]	666	No signs of vitamin A deficiency, no chronic disease, afebrile	NA	NA	NA	0.59 ± 0.02 (6–12 mo)	0.66 ± 0.03 (12–24 mo)	58	Usual duration of breastfeeding 24 mo
Bangladesh [31]	120	No systemic infection	NA	0.42 ± 0.23 (~5 mo)	NA	NA	NA	89	NA
Pakistan [25]	20	No sign of infection or poor growth	1.10 ± 0.06	1.32 ± 0.08	NA	1.58 ± 0.08	1.63 ± 0.08	NA	NA

NA, Not available.

but showing no further increase at nine months [31]. At six weeks of age, about 62% of the infants had a serum retinol concentration ≤0.70 μmol/L, and in about 8%, the concentration was ≤0.35 μmol/L. In a concurrent vitamin A supplementation group, the mothers received a single high dose of vitamin A (200,000 IU) at six weeks, and the infants themselves were supplemented with 25,000 IU at 6, 10, and 14 weeks. This made no difference to the infants' mean serum retinol concentrations at six months, although there were significantly fewer low values in the vitamin A group (30 vs 37% below 0.70 μmol/L). These infants were breastfed, and 94% received at least some breastmilk after the age of nine months. It might be assumed that the infants who were receiving breastmilk from supplemented mothers, and who received three high-dose supplements, had adequate vitamin A status. However, the serum retinol concentrations of these infants at all ages were substantially less than the 1.1 to 1.6 μmol/L in infants from Nigeria and Namibia [27, 28] and the affluent group in Pakistan [25]. The method used for analyzing serum retinol was not stated in the Namibia article [28]. In Nigeria serum retinol was analyzed by the fluorometric method, which overestimates retinol concentrations due to contaminating sources of fluorescence.

The serum retinol concentrations in the multicenter trial were similar to those reported for infants in Bangladesh [34] and Indonesia [35], where mothers were given a single postpartum dose providing 60 mg RE (200,000 IU) and 90 mg RE (300,000 IU), respectively. At six months, there was no significant difference between the infant serum retinol concentrations as a result of vitamin A supplementation. Serum values were 0.84 and 0.77 μmol/L in the supplemented versus placebo groups in Bangladesh, and 0.67 versus 0.65 μmol/L in the supplemented versus placebo groups in Indonesia. In both locations, the mean serum retinol

concentrations at six months of age were similar to those in the multicenter trial. However, in the Indonesian study, even though maternal supplementation did not affect the mean serum retinol or the proportion of infants with a concentration less than 0.70 μmol/L, significantly fewer infants whose mothers received supplementation had a serum retinol concentration <0.52 μmol/L. All of the shift in serum retinol distribution resulting from vitamin A supplementation occurred below 0.70 μmol/L. The respective approximate percentages of infants with serum retinol less than 0.35, 0.35 to 0.52, and 0.52 to 0.70 μmol/L were 10, 26, and 47 in the placebo group and 2, 12, and 25 in the supplemented group. In the Bangladesh study, the data were not compared using these cutoffs, but it is possible that a similar pattern existed. There was no significant difference in serum retinol concentrations between the placebo and vitamin A groups, and no significant difference in the proportion of infants with a concentration less than 0.70 μmol/L. However, values fell below 0.70 μmol/L in 17% of infants in the vitamin A group, as compared with 24% in the placebo group.

The need to reexamine the serum retinol cutoff that denotes vitamin A deficiency in young infants is also supported by another study in Bangladesh. Vitamin A (50,000 IU) was administered to 120 infants aged 6 to 17 weeks (mean age about 75 days), with their first diphtheria-pertussis-tetanus/oral polio vaccine (DPT/OPV) immunizations [30]. After three months, mean serum retinol concentrations were 0.62 μmol/L in the placebo group and 0.74 μmol/L in the supplemented group. The percent prevalences of concentrations <0.35, 0.35 to 0.52, 0.53 to 0.69, and ≥0.70 μmol/L were 12, 9, 15, and 19 in the placebo group and 2, 8, 14, and 30 in the supplemented group. These results also support the usefulness of a cutoff less than 0.70 μmol/L to discriminate between supplemented and nonsupplemented infants.

To summarize, reported serum mean retinol concentrations vary across countries, with the highest values in Africa and the affluent Pakistani group. The reliability of the African values is unclear, however. There is a trend for serum retinol concentrations to increase during the first six months of life, but not in all locations. A very high proportion of infants in all locations had concentrations less than 0.70 μmol/L, except in Nigeria, even where breastmilk concentrations were higher as a result of maternal supplementation (as in Indonesia [35]). Neither maternal supplementation postpartum, nor, in the multicenter trial, infant supplementation, significantly increased the mean serum retinol concentrations of the infants. It appears that if intakes are not extremely low or high, the serum concentrations of infants can be homeostatically regulated in the range of about 0.7 to 0.8 μmol/L. The cutoff of less than 0.70 μmol/L may be too high to detect response to vitamin A supplementation in infants aged zero to six months. However, maternal supplementation did reduce the proportion of Indonesian infants aged six months with concentrations less than 0.52 μmol/L. In the multicenter trial, maternal and infant supplementation reduced the prevalence of infant values ≤0.70 μmol/L only at six months. These data are consistent with the need to lower the cutoff for low serum retinol concentrations in young infants, possibly to less than 0.52 μmol/L.

Relative dose-response tests for assessing liver vitamin A stores in the first six months of life

The MRDR and RDR tests have not been validated against direct measures of liver vitamin A concentration in infants. The RDR has been validated against liver vitamin A concentrations in a small number of children and adults who underwent abdominal surgery for medical reasons in France and the United States [36, 37]. An alternative approach to exploring the validity of the RDR tests in infants and young children is to see if they respond to supplementation in a plausible way.

Two studies suggest that the RDR is useful for measuring the change in liver stores of retinol in preschoolers. The test was used to compare the vitamin A status of Brazilian children aged 18 to 85 months, prior to supplementation, and at intervals after receiving a single high dose of vitamin A (209 μmol, 60 mg RE) [38]. Based on an RDR ≥20%, liver stores were inadequate in 26% of the children at baseline, 0% at 30 days, 1.5% after 120 days, and approximately 43% at six months postsupplementation. The RDR data are consistent with the repletion of liver stores for three months but not for six months. The results are expected to have been similar had the MRDR been used [12]. The MRDR was used to assess the change in vitamin A status after treatment of Indonesian children aged seven months to six years who were infested with *Ascaris lumbricoides* [39]. The MRDR test was administered before and after supplementation with 209 μmol of retinol (60 mg RE) and/or a dose of albendazole. At three to four weeks after supplementation, the mean MRDR ratio of vitamin A–supplemented children (0.033 ± 0.017) was significantly lower than that of unsupplemented children (0.055 ± 0.042), reflecting their improved vitamin A status. Before treatment, 31% to 40% of children had a MRDR ratio ≥0.06, as compared with only 2% to 13% after treatment. The data were not disaggregated by age of the children, so that it is not possible to calculate the proportion with a high MRDR ratio at six months of age. The MRDR also detected an effect of red palm oil consumption on the vitamin A status of children [40].

Taken together, these studies suggest that the relative dose-response tests do detect changes in vitamin A status of preschoolers in response to treatment with a single high dose of vitamin A or smaller daily doses of vitamin A or β-carotene.

Is the relative dose-response approach valid for assessing vitamin A status during the first six months of life? The ratio of ≥0.06 is based on data from older children in Indonesia [12]. MRDR values ≥0.06 are seen in about 76% to 85% of infants in some developing countries [34]. In children in the United States, MRDR values are much lower. The mean ratio for socioeconomically disadvantaged children zero to two years of age was 0.025 ± 0.012 [41], and two well-nourished children had ratios <0.023 at one and three years of age [42]. It is interesting that the MRDR ratio for children in the United States is set at ≥0.03, rather than ≥0.06 [43]. Of 24 children studied in the United States, only one had an MRDR ratio >0.03. This fell to 0.019 two weeks after treatment with 52.5 μmol of vitamin A [43]. In contrast, treatment of Indonesian children with MRDR ratios ≥0.06 with a high dose of vitamin A caused the ratios to fall below 0.06, but only occasionally below 0.03 [12]. The explanation for the different response of children in the two populations is not clear, but it could be related to a higher prevalence of micronutrient deficiencies that may have affected vitamin A metabolism in the Indonesian group (e.g., iron or zinc).

Alternatively, the higher cutoff for the MRDR in less developed countries may be related to the lower, but adequate, serum retinol concentrations of preschoolers in those countries (~0.87 μmol/L) compared with well-nourished children in the United States (~1.40 μmol/L); clearly a lower baseline retinol concentration will increase the response ratio. Likewise, MRDR ratios in infants may be high (≥0.06) because their serum retinol concentrations are normally lower at this age (~0.70 μmol/L). Rice et al. [34] proposed a cutoff of ≥0.12 for the MRDR ratio for Bangladeshi infants. In their study, there was no difference in the prevalence of low liver vitamin A stores across treatment groups using the conventional cutoff of ≥0.06, but with a ≥0.12 cutoff there was a significantly lower prevalence of inadequate stores in the vitamin A–supplemented infants (33%) compared with the placebo group (59%).

Prevalence of vitamin A deficiency in the first six months of life

Clinical symptoms of vitamin A deficiency rarely occur in breastfeeding infants during the first year of life, even in populations with endemic vitamin A deficiency [44]. For example, in rural Indonesia, 1.7% of children zero to five years of age had active xerophthalmia. Of these, only 0.6% were below one year of age, as compared with 3.4% at age one year, 16% at two years, and 26% at three years [45]. More than 90% of the children had been breastfed through at least the first 12 months of life. A survey of the prevalence and severity of xerophthalmia in Malawi revealed no cases of this condition in infants age 0 to 11 months, but it affected 37% in the two- to three-year-old group [46]. Close to 100% of the infants were breastfed through 12 months of age. In another Indonesian example, at one year of age 76% of children with Bitot's spots were not being breastfed, as compared with 29% of those who were consuming breastmilk [47]. In the second year of life, weaned children had an eightfold greater risk of developing Bitot's spots than those who were consuming some breastmilk. In Bangladesh, breastfed children aged 6 to 36 months had a 74% lower risk of clinical vitamin A deficiency compared with those who were not breastfed [48]. Overall, it is clear that breastmilk affords protection against vitamin A deficiency in predominantly breastfed infants, even where breastmilk vitamin A content is low. However, when the infants are weaned, clinical signs of deficiency develop relatively rapidly.

As discussed above and shown in table 3, unless intakes of vitamin A are very low or very high, the serum retinol concentrations at six months of age may be homeostatically regulated in the range of 0.70 to 0.80 μmol/L. Mean values in this range were seen in supplemented and unsupplemented infants in Indonesia, Bangladesh, Peru, Ghana, and India. Likewise, in another Bangladesh study, the mean serum retinol concentration was 0.66 ± 0.30 μmol/L for apparently healthy, breastfed infants 2 to 11 months of age [32] (table 3). Moreover 56% of the infants had a serum concentration <0.70 μmol/L, with most (67%) low concentrations occurring at 2.5 months of age.

Diarrhea can cause serum retinol levels to fall substantially below the 0.70 to 0.80 μmol/L range, probably because liver retinol stores are depleted. One week after the discharge of moderately malnourished Bangladeshi children for watery-type diarrhea, 64% of infants age 3 to 36 months (mean age, 17 months) had an RDR ratio >20% indicating low hepatic reserves of vitamin A [49]. In another study in Bangladesh, the mean serum retinol concentration was very low (0.38 ± 0.23 μmol/L) in infants aged 6 to 17 weeks who had recently recovered from diarrhea. Almost all of these infants (89%) had a serum retinol concentration <0.70 μmol/L, even though about 84% of them were breastfed [48]. As discussed above, interpretation of MRDR ratios in young infants is problematic. It is therefore difficult to use these ratios to estimate the prevalence of vitamin A deficiency in this group.

Factors affecting vitamin a status in the first six months of life

The vitamin A status of young infants is influenced by their liver retinol stores at birth, consumption of the vitamin from breastmilk and other foods, and loss due to infections and parasites. The mother's vitamin A status can affect her breastmilk vitamin A concentration and subsequently the status of her infant.

Liver stores of vitamin A at birth

Although the fetal liver accumulates vitamin A, it is clear that the concentration in livers of human fetuses, stillborn infants, and those who die within the first few months of life is much lower than that of older children and adults (table 4). Table 4 provides both mean and median concentrations, because liver vitamin A concentrations are not distributed normally.

Infants are born with low liver vitamin A stores, even when maternal vitamin A stores are abundant [13]. Few infants have more than 0.07 μmol/g liver stores at birth, which is the minimum acceptable level for adults. Approximately 70% to 90% of infants in the United States have a liver retinol concentration less than 0.07 μmol/g during the first three months of life, as compared with 25% from three to six months of age (table 4) [50]. Only in the Swedish study were stores higher, with 21% of infants below the 0.07 μmol/g cutoff [51]. The percentage of infants with stores less than 0.07 μmol/g in less affluent populations appears to be similar to that in the United States, dropping from approximately 70% for newborns to 25% at three months of age (table 4). It is clear that infants in both well-nourished and poorly nourished populations have limited hepatic vitamin A stores at birth.

Most investigators report that maternal vitamin A status in pregnancy does not have a major influence on the vitamin A stores of the newborn rat [57] or infant [19, 51]. Placental retinol concentrations and

TABLE 4. Hepatic retinol concentrations in human fetuses and infants

Country	Gestational age	Age	Hepatic retinol			
			Mean (μmol/g)	Range (μmol/g)	Median (μg/g)	% <0.07 μmol/g
USA [50]	Premature	≤30 days	0.06 ± 0.11	0–0.59	11 (0–6 days) 3 (7–30 days)	76
USA [50]	Full-term	≤30 days	0.08 ± 0.08	0–0.34	11 (0–6 days) 21 (7–30 days)	54
USA [50]	Full-term	1–2 mo	0.05 ± 0.03	0–0.11	14	80
USA [50]	Full-term	3–5 mo	0.15 ± 0.09	0.01–0.34	45	24
USA [50]	Full-term	6–11 mo	0.30 ± 0.21	0.08–0.58	103	0
USA [50]	Full-term	12–23 mo	0.27 ± 0.15	0.06–0.50	65	0
Sweden [51]	15–44 wk	Fetal	0.17 ± 0.15	0.01–0.83	37	21
Ethiopia [51]	20–44 wk	Fetal	0.11 ± 0.16	0–0.59	9.1	69
Brazil [52]	Full-term	≤41 days	0.10 ± 0.08	0–0.39		
Brazil [52]	Full-term	42 days – <3 mo	0.15 ± 0.16	0–0.45	18	
Brazil [52]	Full-term	3–5 mo	0.12 ± 0.18	0–0.54	11	
Brazil [52]	Full-term	6–11 mo	0.10 ± 0.14	0–0.41	10	
Brazil [52]	Full-term	12–23 mo	0.12 ± 0.10	0–0.33	28	
Brazil [38]	Full-term	≤28 days	0.13 ± 0.12	0–0.42	18.5	53
Brazil [38]	Full-term	1–11 mo	0.21 ± 0.17	0–0.77	47	18
Brazil [38]	Full-term	12–23 mo	0.42 ± 0.38	0.02–1.50	74.5	8
Brazil [53]	Full-term	<12 mo	0.21 ± 0.15	0.02–0.44	62	12
US [54]	NA	0–1 mo	0.07 ± 0.04	0.01–0.19	4	NA
US [54]	NA	2 mo	0.04 ± 0.01	0.02–0.05	11	NA
US [54]	NA	3 mo	0.19 ± 0.04	0.04–0.22	33	NA
US [54]	NA	4–8 mo	0.30 ± 0.12	0.18–0.58	82	NA
US [54]	NA	13–24 mo	0.30 ± 0.06	0.10–0.44	98	0
India [55]	28–40 wk	Fetal	0.08 ± 0.03	0.06–0.11		50 (<0.035 μmol/g)
Thailand [56]	37–40 wk	Fetal	0.06 ± 0.02	NA	16.4	58.7 (all ages)

transfer, and infant retinol concentrations, are normal even when maternal serum retinol is low [57, 58]. Indeed, the serum retinol concentrations of infants sometimes exceed those of their vitamin A–deficient mothers [59–61]. One exception was an Indian report, in which newborns of women with low socioeconomic status had lower serum retinol concentrations than those born to women with a higher status (0.46 ± 0.04 μmol/L vs 0.68 ± 0.03 μmol/L) [26]. This reflected similar differences in maternal retinol concentrations (0.76 ± 0.4 vs 1.05 ± 0.04 μmol/L).

Low-birthweight, small-for-gestational-age, and preterm births occur more commonly in developing countries and could be a cause of lower vitamin A stores at birth. There is no doubt that preterm infants have low liver retinol concentrations and content [62]. Cord blood and serum retinol and RBP concentrations are also lower in such infants [63].

The fetus may be protected against maternal vitamin A deficiency by the low activity of the placental RBP receptor. This enables efficient placental uptake of retinol-RBP, even when maternal serum concentrations of retinol are below normal [58, 64]. Little maternal RBP crosses the placenta, and vitamin A is transferred to the fetus as free retinol [65, 66]. This retinol from the maternal circulation is bound to RBP in the fetal amniochorionic membrane and secreted into the amniotic fluid [66, 67]. This fluid could be an important source of vitamin A for the fetus, which swallows up to 15 ml/day at 20 weeks and 450 ml/day at term, supplying 0.8 and 20 μg/day, respectively [67, 68].

Although the newborn infant's serum retinol concentration seems to be relatively unaffected by maternal deficiency, this might occur at the expense of fetal liver stores so that extrahepatic tissues can be supplied with vitamin A. Fetal liver stores may be built up only if there are high enough concentrations of the vitamin in maternal serum. Evidence to support this possibility comes from a Brazilian study in which there was a significant correlation between placental and serum retinol in newborns of mothers with serum retinol less than 0.70 μmol/L, but no correlation between these measures when mothers had a serum concentration ≥0.70 μmol/L [58]. The mean serum retinol concentrations of infants born to women with low or normal serum retinol levels were similar at birth. More direct evidence derives from a comparative investigation of affluent Swedish and poor Ethiopian infants [51]. The liver vitamin A of Swedish fetuses was 0.13 μmol/g (37 μg/g), significantly higher than in Ethiopia (0.01 μmol/g, 9.1 μg/g). However, the mean concentration of retinol-binding protein in cord blood was similar in both groups, about 20 mg/L.

Supplementation of well-nourished pregnant women with vitamin A does not affect cord blood retinol concentrations [6, 19, 69, 70]. In Finland, for example, after supplementation with 8.4 μmol vitamin A per day (2.4 mg RE/day) from 30 weeks of gestation to term, cord blood retinol concentrations were not statistically higher in newborns of supplemented mothers than in those born to unsupplemented mothers (1.04 ± 0.29 μmol/L supplemented vs 0.84 ± 0.23 μmol/L unsupplemented), even though the concentrations in maternal blood were significantly higher [18]. Daily supplementation of pregnant women in the United States with doses of 10.5 μmol/day (3 mg RE) from five months of gestation to term [6], 105 μmol (30 mg RE) during the ninth month of gestation, or up to 525 μmol RE during labor did not increase cord blood concentrations compared with controls [6, 13, 71, 72]. In contrast, supplementation of vitamin A–deficient pregnant women might increase cord retinol concentrations. In an Indian study in which mothers received supplements of 31.5 μmol/day (9 mg RE/day) during the last trimester, cord blood retinol was significantly higher among newborns in the supplemented group than in the unsupplemented group (0.88 ± 0.03 μmol/L vs 0.52 ± 0.07 μmol/L) [59].

Vitamin A requirements during infancy in relation to liver vitamin A stores at birth

At birth, liver stores of vitamin A are very small in relation to postnatal requirements for the vitamin. On the basis of the observed median liver vitamin A concentration of newborns in the United States (0.04 μmol/g, ~11.0 μg/g) [50] and an estimated liver weight of 158 g at birth (4.5% of body weight [56]), the total liver content of retinol would be 1.74 mg RE. This amount of vitamin A is sufficient to meet the WHO estimate of the basal requirement of infants (180 μg RE) for about the first 10 days of life. Under the best of circumstances, such as the 0.13 μmol/g (37.7 μg/g) concentrations reported for Swedish infants [51], total liver stores would be about 5.85 mg and sufficient to meet basal requirements for about 33 days. Infants must rely on an exogenous source of vitamin A to meet their requirements and build hepatic reserves during infancy.

It is possible to estimate how much dietary vitamin A would be required to enable the observed accumulation of liver retinol in well-nourished infants between birth and six months of age. Based on reported median liver vitamin A concentrations and estimates of liver weight (4.5% of body weight), stores in infants in the United States would be 6.1 μmol (1.74 mg) at birth, increasing to 44.4 μmol (12.7 mg) at six months of age [50]. This is an accumulation of about 38.5 μmol or 11 mg. Assuming that 50% of dietary vitamin A is retained [73, 74] and that the fractional catabolic rate during infancy is about 2.2% per day [75], about 484 μg per day would need to be consumed to accumulate this amount of retinol in six months. The fractional

catabolic rate ($=e^{-0.022(d)}$) of 2.2% per day was estimated in a population of rural Peruvian children, 12 to 24 months of age, and might be higher than that of infants with lower rates of infection [75]. The estimated fractional turnover rate of 0.5% for adults is likely to be too low for infants; their turnover is expected to be higher to support their rapid growth. However, if the adult rate of 0.5% per day is used, approximately 300 μg would need to be consumed daily to result in a liver store of 38.5 μmol. These estimates of the amount that would need to be consumed daily (~300 to 484 μg RE/day) to enable the observed liver accumulation are consistent with observed intakes of 350 μg per day.

Vitamin A intake from breastmilk

Because infants are born with low stores of vitamin A, they rely on vitamin A from human milk and other foods to meet their needs. The consumption of retinol in breastmilk is critical to the vitamin A status of the young infant.

Vitamin A content of breastmilk

Under normal dietary conditions, vitamin A is probably delivered to the mammary gland as retinol bound to retinol-binding protein (RBP); in the fasted state, about 95% of circulating retinol is bound to RBP. The retinol is transferred to the mammary gland by a receptor-mediated process, re-esterified in the breast tissue, and secreted into breastmilk as retinyl esters [76, 77]. When maternal dietary intake of retinol is high, however, as would be the case when the mother receives oral high-dose retinol supplements, it is probable that additional vitamin A enters the mammary gland as retinyl esters derived from maternal chylomicrons [78]. At least in rats, retinol uptake by the mammary gland increased in a linear proportion to the mass of circulating chylomicron vitamin A [57]. These data explain why breastmilk vitamin A increases in response to maternal supplementation and dietary intake.

Vitamin A in breastmilk is in the form of retinyl esters and provitamin A carotenoids. The relative proportion is dependent on the usual diet of the mother, so carotenoids account for a larger proportion of the vitamin A in breastmilk of women from developing countries [69]. Carotenoids can presumably be taken up by the mammary gland from chylomicrons or lipoproteins in maternal plasma. The extent to which the mammary gland can convert provitamin A carotenoids to retinol is not known, but it is probably limited, based on the higher carotenoid levels in breastmilk of women who consume more carotenoids [79].

In addition to maternal vitamin A intake and status, the concentration of vitamin A in breastmilk is influenced by its fat content and the stage of lactation. Colostrum in the first four to six days postpartum, and transitional milk from about days 7 to 21 of lactation, contain much higher concentrations of vitamin A than mature breastmilk [80] (table 5). After one month postpartum, the breastmilk vitamin A content remains fairly stable in industrialized countries. Because the vitamin A in breastmilk is strongly associated with the fat fraction, the retinol concentration is lowest early in a feeding episode, when breastmilk fat is low, and highest at the end when the fat content increases. Breastmilk fat and retinol contents both tend to be higher at midmorning but are also related to the number and spacing of feeding episodes during the day [81].

Effect of maternal vitamin A deficiency on the breastmilk content of vitamin A

The average breastmilk concentration of women in industrialized countries is 2.1 μmol/L (60 μg/dl),

TABLE 5. Retinol and carotene in term breastmilk of unsupplemented mothers in industrialized countries by time postpartum

Time postpartum	Retinol (μg/L)	Carotene (μg/L)	Retinol + carotene (μg/L)	Average milk intake (L/day)	Mean retinol intake (μg/day)	Mean retinol + carotene intake (μg/day)
1–6 days	1,524 (161)	130 (170)	1,654	0.43 (47)	655	711
7–21 days	1,023 (117)	25 (64)	1,048	0.61 (60)	624	639
1–2 mo	683 (284)	33 (82)	716	0.71 (59)	485	508
3–4 mo	640 (242)	54 (34)	694	0.72 (22)	461	500
5–6 mo	745 (151)	35 (12)	780	0.81 (34)	603	632
7–12 mo	NA	NA	NA	0.63 (74)	NA	NA

Numbers in parentheses are total numbers of samples for each time period.
NA, Not available.
Source: ref. 80.

as compared with 1.75 μmol/L (50 μg/dl) in poorer countries, where individual values are often less than 1.05 μmol/L (30 μg/dl) [80]. These differences parallel maternal vitamin A intake in the two situations, which averages 5.4 μmol per day (1543 μg RE/day) in wealthier countries and 2.3 μmol per day (660 μg RE/day) where the prevalence of vitamin A deficiency is higher [82]. Maternal serum and breastmilk retinol concentrations are usually similar, although the breastmilk concentration is less tightly controlled, possibly because of the transfer of the vitamin from maternal chylomicrons.

Because of the relatively large amount of vitamin A that is secreted into breastmilk, the liver retinol stores of marginally vitamin A–deficient lactating women may become progressively more depleted as lactation progresses. For example, breastmilk concentrations in unsupplemented women from rural Bangladesh remained fairly constant from one to nine months postpartum—0.83, 0.87, and 0.79 μmol/L at 3, 6, and 9 months, respectively [34]. The prevalence of abnormal maternal MRDR ratios (≥0.06) increased from 14% to 42% during the same period. Thus, breastmilk concentrations of the vitamin were maintained at the cost of maternal stores. However, at some point during lactation this might result in a lower concentration of retinol in breastmilk, so that the prevalence of vitamin A deficiency could gradually increase in exclusively breastfed infants.

Lactating mothers become vitamin A–depleted in many developing countries. For example, night-blindness among pregnant and lactating women in rural Nepal ranges from 8% to 16% in the Terai [83] and may reach 52% at higher elevations [84]. To address the problem of maternal vitamin A deficiency during lactation, WHO recommends that all breastfeeding women in vitamin A–deficient areas should be supplemented with a single dose of 209 μmol (60 mg RE) during the first two months postpartum. After that time, they should not be given more than 10.5 μmol (3 mg RE) per day or 87.4 μmol (25 mg RE) per week because of the possibility of a new pregnancy, when the high-dose supplement could cause fetal malformations [85].

The proportion of women with breastmilk retinol concentrations <1.05 μmol/L (<30 μg/dl) or ≤8 μg of fat per day, can be used as an indicator of the vitamin A status of groups of lactating women and their infants. Vitamin A deficiency is considered to be a mild public health problem when retinol in breastmilk samples from 10% or more of women falls below this value, a moderate problem when it affects ≥10% to ≤25%, and a severe problem at ≥25% [9]. The value of this indicator is that it predicts the vitamin A status of both mothers and infants and does not require blood samples.

Effect of maternal vitamin A supplementation on the breastmilk content of vitamin A

The vitamin A concentration in human milk can be increased by high-dose vitamin A supplements [35, 59, 86–88], fortification programs [89, 90], low-dose supplements [91], or vitamin A–rich foods [92].

The results of some maternal vitamin A supplementation trials are shown in table 6. Supplementation of Indonesian mothers with 312 μmol (90 mg RE, 300,000 IU) of vitamin A at one to three weeks postpartum increased breastmilk vitamin A concentrations significantly (by 0.48 to 1.18 μmol/L) during the period from one to eight months postpartum as compared with a placebo group [35]. Maternal serum retinol concentrations were also significantly higher at three months (1.39 ± 0.49 μmol/L vs 1.24 ± 0.43 μmol/L) and six months (1.23 ± 0.34 μmol/L vs 1.08 ± 0.37 μmol/L).

A trial in rural Bangladesh evaluated the effects of two doses of vitamin A delivered to women at different stages of lactation [34]. The women either received one dose of 209 μmol (60 mg RE) within the first one to three weeks postpartum followed by a daily placebo, or they were given daily doses of 14.6 μmol (as 7.8 mg β-carotene, 1.3 mg RE), or daily placebos until nine months postpartum. There were no differences in maternal serum retinol concentrations at baseline or at three, six, or nine months postpartum. At three months postpartum, women in the vitamin A group had significantly higher breastmilk retinol concentrations (1.20 ± 1.00 μmol/L vs 0.83 ± 0.43 μmol/L, 34.3 ± 28.6 vs 22.9 ± 11.4 μg/dl), and fewer of them had inadequate vitamin A stores (18% vs 54% in the placebo group, MRDR test). There were no differences in these measures between the groups at six or nine months.

A comparison of the Indonesia and Bangladesh trials suggests that the greater and longer-term impact of the single high dose among Indonesian women may have been related to their better baseline vitamin A status, and/or the higher dose (300,000 IU in Indonesia, 200,000 IU in Bangladesh).

There is relatively little information on the effects on breastmilk retinol when mothers are given smaller doses of vitamin A in pregnancy or lactation. Low-income Indian women supplemented with 31.5 μmol (9 mg RE) daily during the last trimester of pregnancy had a higher vitamin A concentration in colostrum (1.57 μmol/L vs 0.72 μmol/L in controls) and in breastmilk until 10 days postpartum [59].

Breastmilk retinol concentrations can improve as a result of vitamin A fortification programs. Vitamin A–fortified monosodium glutamate (2.8 μmol vitamin A/g, 810 μg/g, daily intake 324 μg) signifi-

TABLE 6. Controlled trials that assessed the impact of vitamin A supplementation on breastmilk vitamin A concentration and infant vitamin A status

Measurement	Bangladesh (rural) [34]	Bangladesh (urban) [88]	Indonesia [35]	Lebanon [93]	Indonesia [90]
Baseline maternal plasma retinol (μmol/L)					
Supplemented	1.79 ± 0.60	1.38 (95% CI, 1.22–1.55)	1.17 ± 0.45	1.37 ± 0.54	NA
Controls	1.56 ± 0.71 (NS)	1.18 (95% CI, 0.94–1.41)	1.31 ± 0.51 (NS)	1.60 ± 0.58 (NS)	NA
% of mothers with low liver stores					
Supplemented	18	NA	9.2	NA	NA
Controls	54 ($p < .01$)	NA	4.4 (NS)	NA	NA
Dose of vitamin A	209 μmol, 1 dose at 1–3 wk postpartum	209 μmol, 1 dose at 1–3 wk postpartum	312 μmol, 1 dose at 1–3 wk postpartum	629 μmol, 1 dose at 1–3 wk postpartum	324 μg RE/day ongoing, 11 mo
Milk vitamin A (μmol/L)					
Supplemented	1.2 ± 1.0 (3 mo)	1.34 (3 mo)	2.45 ± 1.23 (3 mo)	11.4 ± 4.7 (1 mo)	0.6 ± 0.3 (initial)
	0.85 ± 0.53 (6 mo)	1.06 (6 mo)	2.04 ± 1.19 (8 mo)	NA	0.67 ± 0.3 ($p < .05$)
Controls	0.8 ± 0.4 ($p < .05$)	1.12 ($p < .01$)	1.82 ± 1.28 ($p < .01$)	6.99 ± 3.85 ($p < .05$)	0.61 ± 0.45 (NS)
	0.87 ± 0.61 (NS)	0.73 ($p < .02$)	1.56 ± 0.99 ($p < .01$)	NA	0.58 ± 0.20
Infant plasma retinol (μmol/L)					
Supplemented	0.84 ± 0.22	NA	0.67 ± 0.19	NA	NA
Controls	0.77 ± 0.21 ($p < .06$)	NA	0.65 ± 0.26 (NS)	NA	NA
% of infants with low liver retinol					
Supplemented (6 mo)	87	NA	10	NA	NA
Controls (6 mo)	93 (NS)	NA	23 ($p < .03$)	NA	NA

NS, Not significant; NA, data not available.

cantly improved breastmilk retinol in rural Indonesian women, from 0.60 μmol/L (17.2 μg/dl) at baseline to 0.67 μmol/L (19.2 μg/dl) after 11 months. There was no change in the control communities [90]. After two years of vitamin A fortification of sugar in Guatemala, the proportion of breastmilk vitamin A concentrations less than 1.05 μmol/L (<30 μg/dl) dropped from 63% to 23%, although there was no control group [89]. When a vitamin A–fortified tea drink supplied 2.3 μmol (650 μg RE) daily to Gambian women, breastmilk concentrations of retinol increased substantially [91]. Concentrations averaged 2.5 μmol/L (71.5 μg/dl) in the control community and 3.0 μmol/L (85.8 μg/dl) in the supplemented village. These studies suggest that smaller, sustained doses of vitamin A can sustain an increase in breastmilk retinol concentration. Supplementation of well-nourished Hungarian women with pork liver (150 g liver supplying 57.7 μmol, 16.5 mg RE) doubled breastmilk retinol concentrations, but values had fallen to normal 48 hours later [92].

There has been relatively little research on the effect of maternal β-carotene supplementation on breastmilk β-carotene content or vitamin A concentration. Colostrum is rich in carotenoids. Among a small group of US women, total carotenoids in colostrum ranged from 0.63 to 14.1 μmol/L (34–757 μg/dl) [94]. The predominant carotenoids were the provitamin carotenoids, α–carotene, β-carotene, and β-cryptoxanthin, as well as non–provitamin A lycopene. The mature breastmilk of 42 women in the United States con-

tained 0.086 μmol/L (4.6 μg/dl) and did not vary substantially between two weeks and seven months postpartum [95].

Supplementing well-nourished Hungarian women with 100 to 200 g of carrots did not affect their breastmilk vitamin A but increased the carotenoid content of their breastmilk slightly [92]. In contrast, β-carotene supplementation (a single dose of 112 μmol, 60 mg) produced a 4.1-fold increase in breastmilk β-carotene within 24 hours, and a 2-fold increase up to 8 days [96]. Daily doses of 56 μmol (30 mg) β-carotene for 28 days resulted in a 6.4-fold increase in breastmilk concentrations of β-carotene. Neither the single nor the daily doses affected the concentration of retinol in the breastmilk [79, 96]. Although the provitamin A carotenoids accounted for more than half the total carotenoids in breastmilk, the concentration of β-carotene was 30-fold lower than that of retinol, and breastmilk carotenoid concentrations were one-tenth their respective concentrations in maternal plasma. It seems that the contribution of β-carotene to the vitamin A intake of infants would be minimal in these well-nourished women.

The few studies in developing countries also suggest that supplementation of lactating women with β-carotene has relatively little effect on breastmilk vitamin A content. Daily supplementation of lactating Indonesian women with 6.5 μmol (3.5 mg) of β-carotene from stir-fried leafy green vegetables for 12 weeks did not affect breastmilk retinol concentrations, suggesting poor bioavailability of provitamin A from the vegetables [97]. When the same amount of β-carotene was given as an enriched wafer, breastmilk retinol did increase [97]. Giving lactating Bangladeshi women 14.6 μmol (7.8 mg, 1.3 mg RE) of β-carotene per day starting early in lactation produced only a slight increase in breastmilk vitamin A after nine months (table 7). However, the β-carotene may have protected maternal retinol stores to some extent, since the percentage of women with low liver stores increased from 14% at baseline to 42% at nine months in the placebo group, as compared with 26% and 31% in the β-carotene group. Breastmilk carotenoid concentrations were not reported in these developing-country studies. A comparison of breastmilk carotenoid concentrations in Swedish and Ethiopian women showed that the Swedish mothers had lower concentrations than the Ethiopians (0.30 to 0.39 μmol/L vs 0.45 to 0.48 μmol/L). The breastmilk retinol concentration was higher in the Swedish mothers (1.40 to 1.86

TABLE 7. Controlled trials that assessed the impact of β-carotene supplementation on breastmilk vitamin A concentration and infant vitamin A status

Measurement	Bangladesh (rural) [34]	Indonesia [97]	Indonesia [35]
Baseline maternal plasma retinol (μmol/L)			
Supplemented	1.79 ± 0.60	0.84 ± 0.04	0.89 ± 0.04
Controls	1.56 ± 0.71 (NS)	0.81 ± 0.04 (NS)	0.81 ± 0.04 (NS)
% of mothers with low initial liver stores			
Supplemented	31	68% for all treatment groups at baseline	68% for all treatment groups at baseline
Controls	14 (NS)		
Dose of vitamin A	14.6 μmol/day for 8 mo	6.5 μmol/day for 3 mo, fortified wafer	6.5 μmol/day for 3 mo, vegetables
Milk vitamin A (μmol/L)			
Supplemented	1.0 ± 0 6 (9 mo)	+0.59 (95% CI, 0.35 to 0.84)(3 mo)	–0.04 (95% CI, –0.31 to 0.23)(3 mo)
Controls	0.8 ± 0.4 ($p < .05$)	+0.16 (95% CI, 0.02 to 0.30)(NS)	+0.16 (95% CI, 0.02 to 0.03)(NS)
Infant plasma retinol (μmol/L)			
Supplemented	0.79 ± 0.19	NA	NA
Controls	0.77 ± 0.21 (NS)	NA	NA
% of infants with low liver retinol			
Supplemented (6 mo)	84	NA	NA
Controls (6 mo)	94 (NS)	NA	NA

NS, Not significant; NA, data not available.

μmol/L vs 0.98 to 1.16 μmol/L). The molar ratio of retinol to β-carotene content was 4.8:1 in Sweden, and 2:1 in the Ethiopian women [51]. Thus, β-carotene may make an important contribution to breastmilk vitamin A among women who rely on plant sources of the vitamin. However, research is needed to determine whether human infants can absorb and convert provitamin A carotenoids in breastmilk to vitamin A.

The ability of infants to meet their vitamin A requirements from breastmilk

The extent to which infants can meet their vitamin A requirements from breastmilk has been estimated in table 8. The following assumptions were made in the creation of this table.

Usual intakes of breastmilk during the first six months were obtained from our review of reported intakes in developing countries [98]. The mean, mean –2 SD, and mean+ 2 SD of these volumes are used for the "low," "average," and "high" breastmilk intake categories, respectively. The "high" intake column best represents exclusive breastfeeding. Breastmilk vitamin A concentration was defined as "deficient" (<20 μg/dl), "low" (<30 μg/dl), or "adequate" (≥50 μg/dl).

Vitamin A intake (μg) is calculated by multiplying breastmilk volume by vitamin A concentration in each case. The percent of requirements met by this intake is calculated based on the assumption that a daily intake of 300 μg retinol is adequate to build stores (S) of the vitamin, and an intake of 125 μg per day is the basal requirement (B) to prevent clinical symptoms of deficiency. The value of 300 μg is slightly lower than current recommendations but will almost certainly allow stores to be built. An intake of 125 μg per day has been reported to prevent clinical symptoms of deficiency during the first six months and perhaps protect serum retinol concentrations.

Although the values in table 8 are approximate, these simple estimates of the contribution of breastmilk to infant vitamin A status provide some interesting information. The conclusions, similar across age groups, are as follows:

» The breastmilk intake of infants in the "high" milk intake group, which represents exclusive breastfeeding, is enough to allow vitamin A stores to accumulate if the breastmilk retinol concentration is low (<30 μg/dl) or adequate (≥50 μg/day), but not if it is deficient (<20 μg/dl).

» The amount of breastmilk consumed on average in developing countries is slightly less than that needed to supply enough vitamin A to build stores. If the breastmilk retinol concentration is 30 μg/dl, a content of 20 μg/dl will probably prevent the appearance of deficiency symptoms. Infants ingesting this average amount of breastmilk are presumably consuming some other foods, especially at ages six to eight months, the vitamin A content of which will be an important influence on the infant's vitamin A status.

» Unless other sources of vitamin A (supplying about 200 μg RE) are added to their diet, infants who have low intakes of breastmilk (due to premature introduction of other foods) will not come close to meeting the recommended vitamin A intake that will build stores, even if the breastmilk concentration is normal (≥50 μg/dl). They will usually consume enough to prevent clinical symptoms of deficiency

TABLE 8. Estimated vitamin A intakes compared with requirements assuming different values for breastmilk volume and vitamin A concentration

Age (mo)	Breastmilk retinol[a]	Low breastmilk intake[b]			Average breastmilk intake[b]			High breastmilk intake[b]		
		Milk volume (ml)	Vitamin A intake (μg)	% of requirements[c]	Milk volume (ml)	Vitamin A intake (μg)	% of requirements[c]	Milk volume (ml)	Vitamin A intake (μg)	% of requirements[c]
0–2	Deficient	457	91	30 / 73	714	143	48 / 114	959	191	64 / 153
	Low		137	46 / 110		214	71 / 171		288	96 / 230
	Adequate		228	76 / 182		357	119 / 286		479	160 / 383
3–5	Deficient	515	103	34 / 82	784	157	52 / 126	1,022	204	68 / 163
	Low		154	51 / 123		235	78 / 188		307	102 / 246
	Adequate		257	86 / 206		392	131 / 314		511	170 / 409
6–8	Deficient	355	71	24 / 57	776	155	52 / 124	982	196	65 / 157
	Low		106	35 / 85		233	78 / 186		295	98 / 236
	Adequate		177	59 / 142		388	129 / 425		491	163 / 392

a. Deficient, <20 μg/dl; low, <30 μg/dl; adequate, ≥50 μg/dl.
b. Low intake, –2 SD below mean; average intake, mean intake in developing countries; high intake, +2SD above mean (from ref. 98).
c. Requirement to build stores (300 μg/day) / basal requirement (125 μg/day).

if breastmilk retinol is low (<30 μg/dl) or normal (≥50 μg/dl), but not if the concentration is less than 20 μg/dl.

What improvement in vitamin A status of the infant can be expected from providing a single high-dose vitamin A supplement to the mother at the beginning of lactation? At three months of lactation (i.e., the middle of the zero- to six-month period), maternal breastmilk concentrations averaged 70.1 μg/dl in Indonesia [35] and 34.3 μg/dl in Bangladesh [34], when the women received 300,000 and 200,000 IU, respectively. At a breastmilk concentration of 70 μg/dl, infants with low, average, and high intakes of breastmilk (table 8) would ingest 360, 549, and 715 μg per day, respectively, at three months of lactation. Even low breastmilk intakes would be sufficient to build liver retinol stores. This is consistent with the reduction in low retinol concentrations observed in the infants of vitamin A–supplemented Indonesian mothers. Taking the 34.3 μg/dl for supplemented women in Bangladesh, the infants in the three groups would be consuming 177, 269, and 350 μg RE per day, so that only the exclusively breastfed group would have an intake judged adequate to build stores. This is also consistent with the fact that almost all of the Bangladeshi infants had MRDR ratios ≥0.06, including those whose mothers had been supplemented.

When low-income Bangladeshi women were given a single dose of 209 μmol vitamin A (60 mg) 24 hours after delivery, there was a significant increase in maternal serum retinol through three months of lactation, as compared with controls [88]. Breastmilk retinol concentrations improved within 24 hours and were still significantly higher at six months postpartum. The concentrations were 38.3 μg/dl at three months, as compared with 32.0 μg/dl in controls. At three months of age, the intakes of infants of supplemented mothers would have been 197, 300, and 391 μg/day based on the low, average, and high breastmilk intakes in table 8. There was a significantly lower incidence of respiratory tract infections and fever in the infants of supplemented mothers, which is consistent with the breastmilk retinol being adequate to meet their requirements, but their actual vitamin A status was not assessed.

Other risk factors for vitamin A deficiency in infants

Poor absorption of vitamin A is a problem during diarrheal disease and febrile infections, during which there is also a higher rate of utilization and disposal of the vitamin. Logically, retinol from human milk may be better absorbed than other sources of the vitamin, because human milk contains a latent lipase that is activated by bile salts in the duodenum and may hydrolyze the retinyl esters in the milk [99]. Vitamin A metabolism is adversely affected by severe protein-energy malnutrition, in which synthesis of retinol-binding protein is impaired [82]. Zinc deficiency and iron deficiency also interfere with the transport and utilization of stored retinol [100–102]. Ascaris infection also reduces vitamin A absorption. These and other factors will all increase the risk of vitamin A deficiency in young infants, a fact that should be taken into consideration when evaluating the need for supplements in this group.

Predicted beneficial effects on vitamin A status of direct supplementation with vitamin A in the first six months of life

The health benefits of vitamin A supplementation for infants are described in more detail by Kirkwood [103]. Briefly, evidence is not entirely consistent whether supplementation prior to six months improves child survival in areas with a high prevalence of vitamin A deficiency. In Indonesia direct supplementation of infants with 52 μmol (15 mg RE) retinol at birth caused a 64% reduction in infant mortality during the first year of life. The greatest impact was on deaths between one and four months of age, when about 75% of the deaths in the control group occurred, but there was no difference in the first month of life [104]. Interestingly, this was a population group in which maternal serum retinol concentrations were generally adequate and the mothers were relatively privileged. It is not clear that the infants were vitamin A deficient, and the reduction in mortality caused by the supplement was greater among those with normal than among those with low birthweights, and greater among those with a higher ponderal index. In contrast, supplementation of Nepalese infants with 52 or 105 μmol (15 or 30 mg RE) between about two weeks and five months of age had no effect on mortality during the first year of life, although there was a suggestion that the 30 mg RE supplement was protective between four and five months [105]. The difference in results between the two trials could be explained by the fact that the dose in Indonesia was given very soon after birth, or that children who were supplemented at older ages in the Nepal trial already had significant exposure to dietary and environmental risk factors associated with childhood illness [105]. Serum retinol concentrations of infants were not assessed in either trial.

Data on the impact of administering vitamin A at immunization contacts are available from two studies in Bangladesh. In the first of these, 52 μmol (15 mg RE) or a placebo was administered to infants 6 to 17 weeks old, at the time of their first DPT/OPV (diphtheria-pertussis-tetanus/oral polio vaccine) immunization and again one and two months later with their second

and third doses of vaccine [33]. Prior to dosing, 89% of the infants had a serum retinol concentration less than 0.70 μmol/L, and 56% of the supplemented infants still had a low concentration after all three doses of vitamin A. Serum concentrations were similar at the end of the study: 0.70 ± 0.29 μmol/L and 0.63 ± 0.28 μmol/L in the supplemented and placebo groups, respectively. Likewise, a smaller dose (26 μmol, 7.5 mg) was given to Bangladeshi infants at 6 to 17 weeks of age at the time of their first DPT/OPV dose, and with their second vaccines one and two months later [106]. About 88% of the infants had low serum retinol levels at baseline, and 47% of the supplemented group still had low serum retinol levels after the three doses. Retinol concentrations after supplementation were not significantly different from those of unsupplemented infants (0.80 ± 0.30 μmol/L in the vitamin A group, and 0.70 ± 0.30 μmol/L in the placebo group).

These data suggest that administering three doses of 52 μmol (15 mg RE) or 26 μmol (7.5 mg RE) with vaccines in Bangladesh did not improve serum retinol concentrations significantly, even when the last measurement was taken only one month after the last dose. The data are consistent, however, with our premise that average serum retinol concentrations in this age group would tend to be maintained in the range of 0.70 to 0.80 μmol/L, obscuring the possibility that liver retinol concentrations may have been higher in the supplemented group. The fact that serum retinol concentrations were less than 0.70 μmol/L in 39% of the infants in the first study and 47% in the second may reflect the need for a lower serum retinol cutoff rather than a lack of benefit from the supplement.

The WHO/Child Health and Development (CHD) randomized, placebo-controlled, multicenter trial also examined the effect of maternal and infant vitamin A supplementation on measures of infant vitamin A status [31]. The research centers were in Ghana, India, and Peru. Mothers of infants in the vitamin A–supplemented group received 209 μmol of vitamin A (60 mg RE) within the first four to six weeks postpartum, and their infants received 26 μmol (7.5 mg RE) with each dose of DPT/OPV vaccine at 6, 10, and 14 weeks of age. Control infants received a placebo at these time points. At nine months of age, children in the vitamin A group received 26 μmol (7.5 mg RE) and those in the control group received 105 μmol (30 mg RE) with their measles vaccine. All infants were followed until 12 months of age. The intervention had no effect on mortality, morbidity, or anthropometry of the infants. Their vitamin status was assessed at baseline and at 3, 6, 9, and 12 months using serum retinol concentrations and the MRDR. At baseline, about 62% had low serum retinol (defined as <0.70 μmol/L), and about 7% had a concentration <0.35 μmol/L. At six months, significantly fewer supplemented infants had lower concentrations than those in the placebo group (29.9% vs 37.1%), and only about 4% in both groups had concentrations less than 0.35 μmol/L. However, at 9 and 12 months, there was no difference between the groups in the proportion of children (~32%–35%) with low values.

The MRDR data revealed a similar pattern. Initially, about 76% of children were judged to have low hepatic vitamin A, based on an MRDR cutoff of ≥0.06. At six months there was a small but statistically significant difference between the two groups (43.5% with low reserves in the vitamin A group as compared with 52.5% in the placebo group), but the prevalence of low stores in both groups was rather high. There was no difference at the later time points, and about 30% of the children in both groups had estimated low vitamin A reserves at the end of the study. The data suggest that the intervention had little effect on vitamin A status.

There are at least three possible explanations for the lack of detectable impact of the vitamin A supplements in this study. The first is that the cutoff value of <0.70 μmol/L for serum retinol is not appropriate in this age group. A cutoff of <0.52 μmol/L may have been more sensitive for detecting effects of the supplement. There was no difference between the groups in the percentage of children with a concentration <0.35 μmol/L, but few infants (about 8% at the beginning and end of the study) had a concentration this low. The mean serum retinol values were about 0.7 to 0.8 μmol/L, within the normal range for infants who do not have depleted liver retinol. The infants were almost all breastfed. Breastmilk retinol concentrations were measured but not described in the first publication on this study [31]. It would be useful to estimate the intakes of the vitamin based on the measured breastmilk retinol concentrations and the volumes presented in table 8, and to compare these with requirements.

Another possible explanation is that the cutoff of ≥0.06 for the MRDR may be too low in infants because they have low serum retinol concentrations. The ≥0.12 cutoff that discriminated between the supplemented and unsupplemented groups in Bangladesh [34] may have been more useful for detecting differences between the groups in the multicenter trial. The amount of vitamin A administered was insufficient to maintain increased liver vitamin A stores.

The third possible explanation is that, as suggested by the investigators, any effect of the vitamin A supplements on infant serum retinol may have disappeared by the time the serum was collected. The measurements at six months, when significantly fewer low concentrations were seen in the supplemented group, were taken only 10 weeks after the last of the three doses was given to the infants, and their mothers were supplemented. The nine-month measurement was taken four to five months after the last dose and eight months after the mothers had been supplemented. The 12-month

measurement was taken three months after the infants in the vitamin A group received their fourth 25,000-IU dose and the control group received the 100,000-IU dose. A similar equilibration of post-dose serum retinol was seen in other studies, in which there was no effect of a 100,000-IU or a 200,000-IU supplement on serum retinol four months after the dose [107].

What would be the expected change in liver vitamin A stores in response to the vitamin A supplements given in the multicenter trial? We assume that 50% of vitamin A consumed is retained in the liver and that 2.2% of total body vitamin A is catabolized daily by infants. Table 9 provides estimates of retention assuming that the breastmilk retinol concentration is 30, 40, or 50 μg/dl. Assuming the highest of these concentrations (50 μg/dl), and the average volume of breastmilk consumed by exclusively breastfed infants in developing countries (from table 8), about 8 mg would be retained from breastmilk at each period. Of the supplemental vitamin A given to the infants at 6, 10, and 14 weeks, about 3.7 mg is retained at three months, 1.1 mg at six months, and almost nothing at nine months. Of the 25,000-IU dose given at nine months, almost none remains at 12 months. Liver concentrations of vitamin A would have been adequate at 3 and 6 months, and very marginal (using a cutoff of <20 μg/g as low) at 9 and 12 months. In the control group, if breastmilk retinol concentration was 30 μg/dl, liver vitamin A would have been adequate at 3 months, and below 20 μg/g at 3, 6, and even 12 months. Based on these assumptions, it appears that the doses of vitamin A given in the Expanded Program on Immunizations (EPI) would be inadequate to maintain adequate stores of the vitamin at about 9 and 12 months in the vitamin A group and from closer to 3 months in the control group. These estimates should be repeated using the actual breastmilk retinol concentrations when they are reported.

TABLE 9. Estimated amount of vitamin A retained from breastmilk and vitamin A supplements, and estimated liver vitamin A concentration, of infants in the WHO/CHD multicenter trial according to age

	Age (mo)			
Group and measurement	3	6	9	12
Vitamin A group, assuming 40 μg/dl				
Breastmilk vitamin A (mg)	6.04	6.64	6.37	6.33
Supplemental vitamin A (mg)	3.72	1.13	0.16	0.48
Total vitamin A (mg)	9.76	7.77	6.53	6.81
Liver vitamin A concentration (μg/g)	54.2	28.8	19.3	16.8
Vitamin A group, assuming 50 μg/dl				
Breastmilk vitamin A (mg)	7.55	8.30	7.96	7.91
Supplemental vitamin A (mg)	3.72	1.13	0.16	0.48
Total vitamin A (mg)	11.27	9.43	8.12	8.39
Liver vitamin A concentration (μg/g)	62.6	34.9	24.0	20.7
Control group, assuming 20 μg/dl				
Breastmilk vitamin A (mg)	3.16	3.18	3.32	3.02
Supplemental vitamin A (mg)	—	—	—	1.86
Total vitamin A (mg)	3.16	3.18	3.32	4.88
Liver vitamin A concentration (μg/g)	17.6	11.8	9.8	12.2
Control group, assuming 30 μg/dl				
Breastmilk vitamin A (mg)	4.53	4.98	4.78	4.75
Supplemental vitamin A (mg)	—	—	—	1.86
Total vitamin A (mg)	4.53	4.98	4.78	6.61
Liver vitamin A concentration (μg/g)	25.2	4.78	14.1	16.3

Assumes that breastmilk consumed from birth contains 30 μg/dl (unlikely), 40 μg/dl, or 50 μg/dl, and that breastmilk volumes are the average reported for exclusively breastfed infants in developing countries (from table 8). In the vitamin A group, mothers received one 200,000-IU dose of vitamin A during the first 8 weeks postpartum, and supplemental vitamin A was administered directly to infants at 6, 10, and 14 weeks (25,000 IU at each time point) and at 9 months (100,000 IU). In the control group, vitamin A (100,000 IU) was only given to infants at 9 months. Liver weight was estimated as 4.5% body weight. Vitamin A retention was estimated as $0.5 \times \text{dose}\ (e^{-0.022 \times \text{days since dose}})$.

We also calculated vitamin A retention using the same assumptions as in table 9, but based on the new dosing recommendations from this consensus meeting (table 10). In this scenario, the mothers would receive two 200,000-IU doses of vitamin A during the first 8 weeks postpartum, and the infants would be given 50,000-IU supplements at 6, 10, and 14 weeks, followed by 100,000 IU at 9 months. In table 10 the calculations are shown for breastmilk retinol concentrations of 30, 40, and 50 μg/dl. (A value of 30 μg/dl would be surprisingly low, given that the mothers would be supplemented early in lactation). If the milk contains 50 μg/dl, it is estimated that the liver retinol concentrations of the infants will exceed 20 μg/dl at 6, 9, and 12 months. If breastmilk retinol is only 40 μg/dl, liver concentration of infants will be adequate at 6 and 9 months and borderline at 12 months.

Summary and conclusions

In the first six months of life, infants probably require about 300 μg of vitamin A per day to accumulate adequate liver stores and about 125 μg per day to prevent clinical symptoms of deficiency from developing.

Assessment of retinol status in the first six months of life is complicated by the generally lower serum concentrations of infants at this age. There is evidence that the serum retinol cutoff for deficiency may need to be lowered from 0.70 μmol/L, possibly to 0.52 μmol/L, and that the MRDR ratio cutoff should be raised from ≥0.06, possibly to ≥0.12. Further research is needed to determine the appropriate cutoffs for the indicators in this age group.

Liver stores at birth are sufficient to supply the infant's vitamin A requirements for only a few days, even when the mother is well nourished during pregnancy. Maternal vitamin A supplementation during pregnancy does not appreciably affect the vitamin A status of her newborn, except perhaps when she is severely deficient.

There is a very low prevalence of clinical symptoms of vitamin A deficiency in infants who are predominantly breastfed during the first year of life, even in regions where breastmilk concentrations of retinol are low. The concentration of vitamin A in breastmilk is maintained by maternal retinol stores and maternal dietary vitamin A intake. Lactation is a time when maternal vitamin A stores can become depleted. In general, breastmilk retinol concentrations are lower in developing countries. Maternal supplementation with a single high dose of retinol postpartum significantly increases the concentration of the vitamin in breastmilk for a period of three to eight months across

TABLE 10. Estimated amount of vitamin A retained from breastmilk and vitamin A supplements, and estimated liver vitamin A concentration, based on the new recommendations to increase vitamin A doses in the Expanded Program in Immunization, according to age

Group and measurement	Age (mo)		
	6	9	12
Vitamin A group, assuming 30 μg/dl			
Breastmilk vitamin A (mg)	4.98	4.78	4.75
Supplemental vitamin A (mg)	2.26	2.38	2.15
Total vitamin A (mg)	7.24	7.16	6.90
Liver vitamin A concentration (μg/g)	26.8	21.2	17.0
Vitamin A group, assuming 40 μg/dl			
Breastmilk vitamin A (mg)	6.64	6.37	6.33
Supplemental vitamin A (mg)	2.26	2.38	2.15
Total vitamin A (mg)	8.90	8.75	8.48
Liver vitamin A concentration (μg/g)	33.0	25.9	20.9
Control group, assuming 50 μg/dl			
Breastmilk vitamin A (mg)	8.30	7.96	7.91
Supplemental vitamin A (mg)	2.26	2.38	2.15
Total vitamin A (mg)	10.56	10.34	10.06
Liver vitamin A concentration (μg/g)	39.1	30.6	24.8

Assumes that breastmilk consumed from birth contains 40 or 50 μg/dl in the supplemented group, because mothers received 200,000 IU of vitamin A postpartum, and 20 or 30 μg/dl in the control group. Assumes breastmilk volumes are the average reported for exclusively breastfed infants in developing countries (from table 8). Infants in the vitamin A group received 50,000 IU at 6, 10, and 14 weeks and 100,000 IU at 9 months. Infants in the control group received 100,000 IU at 9 months. Liver weight was estimated as 4.5% body weight. Vitamin A retention was estimated as $0.5 \times \text{dose}\ (e^{-0.022 \times \text{days since dose}})$.

studies. Assessment of the impact on infant vitamin A status has been complicated by uncertainty about the appropriate cutoffs for this age group, but there are several indications that the infants do benefit from this practice—as well as their mothers. Vitamin A fortification programs can also increase breastmilk retinol.

The prevalence of vitamin A deficiency in infant populations will be determined primarily by the amount of breastmilk consumed. Estimates are presented for the percentage of infants' requirements that will be met from breastmilk, assuming different volumes of milk intake and different concentrations of retinol in milk.

Improvements in the vitamin A status of young infants in developing countries through direct high-dose supplementation at the time of DPT/OPV delivery have been difficult to demonstrate, perhaps partly because of the use of inappropriate cutoffs for vitamin A indicators in this age group, but most likely because relatively little of the supplement is retained at three and six months. The proposed recommendations should provide sufficient vitamin A stores through 12 months of age for exclusively breastfed infants consuming milk containing ≥40 μg/dl vitamin A. Because breastmilk will still provide most of these infants' retinol stores, the importance of continuing breastfeeding is clear.

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The relationship between vitamin A deficiency and HIV infection: Review of scientific studies

Anna Coutsoudis

Abstract

Review of the literature shows that in adults there are variations in the association of hyporetinemia with disease progression as well as variations in the response to supplementation. Populations that are likely to be deficient in vitamin A show the biggest responses. Additional vitamin A supplementation may not be necessary, and may even be harmful, in adults who already have a good dietary intake of vitamin A and who take many other vitamin supplements. Vitamin A supplementation does not appear to have any impact on mother-to-child transmission of HIV; nevertheless, vitamin A supplementation of pregnant women in the third trimester may be useful to reduce the incidence of low-birthweight and premature infants. The impact of vitamin A on mother-to-child transmission of HIV in preterm infants is awaiting further investigation. Vitamin A supplementation of HIV-infected children appears to be beneficial to reduce the incidence and severity of diarrhea in particular. Randomized, placebo-controlled trials in pregnant women and adults have shown that the association between vitamin A and HIV is probably an association of reverse causality.

Introduction

HIV/AIDS

The last two decades have seen a catastrophic increase in the prevalence of human immunodeficiency virus and acquired immune deficiency syndrome (HIV/AIDS), and in many of the poor countries where the epidemic is taking its toll, the historic gains of public health efforts are rapidly being canceled or reversed. Young people, especially women, bear the brunt of the epidemic, with an estimated 7,000 young men and women around the world being infected every day. An additional 1,600 children under the age of 15 are infected every day [1]. Children have a further burden to bear because of the HIV pandemic as they are left as orphans; worldwide more than eight million children have had to grow up without their mothers. Over 90% of those orphaned by AIDS live in sub-Saharan Africa [2]. The cruel irony of the HIV-1 pandemic is that antiretroviral drugs, which are the most effective measures for prevention and treatment of HIV-1 infections, have become available only in regions where the global proportions of the disease are the smallest.

However, in countries that bear the heaviest burdens [1], prophylaxis and care are scarcely affordable and mostly unavailable. There has therefore been a concerted effort to search for alternative strategies more relevant to poorer populations. One such alternative is vitamin A, which is cheap and easily provided through existing health services and which has been shown to be capable of reducing child mortality. Given the affordability of this intervention, even substantially lesser degrees of benefit for HIV than those achieved for child morbidity and mortality will be important for developing countries. The epidemiologies of HIV infection and vitamin A deficiency bear some similarity, inasmuch as they are both prevalent in situations of poor socioeconomic development.

Vitamin A

The term *vitamin A* refers to all retinoids having the biological activity of all-*trans*-retinol. Preformed vitamin A is found as retinyl esters in foods of animal origin. Retinol is derived from hydrolysis of retinyl esters and from provitamin A carotenoids. Although there are several hundred naturally occurring provitamin A carotenoids in dark-green and yellow-orange fruits and vegetables, not all have biological activity. The one that is most efficiently converted to retinol is β-carotene [3]. This review will focus on both retinol and β-carotene.

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Vitamin A and related retinoids play an important role in the regulation of immune function. They have been shown to influence many aspects of immunity, including mucin and keratin expression; hematopoiesis; apoptosis; growth, differentiation, and function of neutrophils, natural killer cells, monocytes, Langerhans cells, and T and B lymphocytes; immunoglobulin production; and expression of cytokines and adhesion molecules [4]. Vitamin A deficiency therefore results in major morbidity and mortality as a result of compromised immunity. Vitamin A is referred to as the "antiinfective vitamin," and in 1968 Scrimshaw et al. [5] made the observation that vitamin A deficiency, of all the micronutrient deficiencies, was most consistently associated with infectious disease. A metaanalysis of community- and hospital-based trials has shown that vitamin A supplementation reduces child mortality by about 30% [6].

The term *vitamin A deficiency* refers to a situation in which an individual has insufficient vitamin A stores to meet the biological requirements of the vitamin. Serum concentrations of at least 0.70 μmol/L (children) and 1.05 μmol/L (adults) are considered necessary to meet the biological requirements of the individual. Even in situations of low vitamin A stores, serum retinol is homeostatically controlled, and only in situations of extremely depleted vitamin A stores does the serum retinol concentration fall below the set point. Serum concentrations are, however, also affected by the acute-phase response to infection, and low levels at the time of infection do not necessarily imply low vitamin A stores or vitamin A deficiency. The term vitamin A deficiency should therefore, strictly speaking, be used only when there are clinical indicators of vitamin A deficiency (xerophthalmia). In cases where serum retinol levels are low but no information is available on other indicators, the term *hyporetinemia* should be used. Nevertheless, many of the articles reviewed for this report have used the term vitamin A deficiency to denote low serum retinol levels.

Methods

This report was specifically commissioned to review the relationship between vitamin A and HIV in pregnant women and children, and accordingly provides a comprehensive review of these relationships. However, in order to provide a context for this review, a cursory review has also been given of the relationship between vitamin A and HIV in adult men and nonpregnant women.

The studies included in the report were identified by searching the Medline database from 1990 to 1999 and by referring to the reference lists of those articles reporting on vitamin A and HIV. All relevant scientific studies published in peer-reviewed journals, as well as reports of international organizations such as the World Health Organization (WHO), the United Nations Children's Fund (UNICEF), or the United States Agency for International Development (USAID), were included. In addition, where relevant, data from presentations given at the following international conferences were included: International Vitamin A Consultative Group (IVACG) Meeting, International AIDS Conference, and Conference on Global Strategies to prevent Mother-to-Child Transmission of HIV.

Prevalence of low serum vitamin A concentrations associated with HIV infection

Adults

Low serum retinol concentrations are rare in individuals in developed countries. However, in several studies in the United States, HIV-positive individuals have been shown to have a relatively high prevalence of hyporetinemia: up to 29% in outpatients [7–10] and even higher (49%) in hospitalized AIDS patients [11]. In one of these studies, asymptomatic HIV-positive patients who had a higher daily average vitamin A intake than HIV-negative controls (25,000 vs 17,000 IU/day) nevertheless had lower serum retinol concentrations (1.50 vs 1.78 μmol/L) [8].

In a hospital-based study in Germany [12] comparing 116 HIV-infected patients with 33 controls, the serum carotene concentrations were significantly lower in the HIV-infected patients than in the controls (0.47 vs 1.37 μmol/L). The authors speculated that the low serum carotene concentration in a population whose daily intake of vitamin A exceeded the recommended daily allowance (RDA) was probably related to fat malabsorption. There was a strong correlation between serum carotene concentrations and CD4/CD8 cell ratios in the HIV-infected patients.

Pregnant women

Pregnant HIV-infected women, especially in developing countries, are at particular risk for vitamin A deficiency, presumably because of the increased nutritional demands of pregnancy. Night-blindness, which is one of the earliest clinical manifestations of vitamin A deficiency, has been associated with pregnant women in developing countries, e.g., Nepal and India. A case-control study among pregnant women in Nepal showed that women with night-blindness had significantly lower serum retinol levels and higher infectious disease morbidity than matched controls without night-blindness [13].

In Nairobi, 58% of HIV-infected pregnant women attending an antenatal clinic had serum retinol con-

centrations <1.05 μmol/L, and 17% had concentrations <0.70 μmol/L [14]. Similarly, 58% to 63% of HIV-infected pregnant women in Malawi had serum retinol levels <1.05 μmol/L [15, 16].

In Thailand, serum retinol and β-carotene levels were measured in 74 HIV-infected women in the first trimester of pregnancy and compared with those of 148 pregnant uninfected controls [17]. HIV-infected women with CD4 counts <200 cells/μl (n = 17) exhibited 37% lower serum retinol levels (0.820 vs 1.308 μmol/L, $p < .001$) and 37% lower mean serum β-carotene levels (1.487 vs 2.362 μmol/L, $p < .001$) than the controls. However, there were no differences in serum retinol and β-carotene levels between the two groups when CD4 counts were greater than 200 cells/μl. Serum retinol and β-carotene levels correlated significantly with CD4 counts and CD4/CD8 ratios.

A study in South Africa [18] reported that HIV-infected mothers postpartum (n = 25) had lower serum retinol levels than a suitably selected control group of 25 HIV-negative mothers (30.2 vs 47.4 μg/dl, $p = .007$). Forty percent of the HIV-infected women had serum retinol levels <0.70 μmol/L, as compared with 4% of the controls. However, there were no significant differences in serum retinol between HIV-infected and HIV-negative women during any stage of pregnancy.

In the United States, Greenberg et al. [19] found that 9% of HIV-infected pregnant women had low serum retinol concentrations (<0.70 μmol/L).

Children

Most of the studies of vitamin A status have been in adults. One study in France was designed specifically to look at vitamin A levels in HIV-infected children [20]. The study included 21 HIV-infected children and 21 suitably matched control subjects of similar age (2–9 years). Serum retinol levels in controls were nonsignificantly higher than those in non-AIDS HIV-infected children (n = 11)(1.40 vs 1.19 μmol/L) and significantly higher than those in HIV-infected children with AIDS-defining criteria (1.40 vs 1.08 μmol/L).

A South African study* showed that of 75 HIV-infected children, 50% had marginal vitamin A status (<0.70 μmol/L) and 12% were vitamin A deficient (<0.70 μmol/L).

Omene et al. [21] compared vitamin A and β-carotene levels in 15 symptomatic HIV-infected children (of African-American and Hispanic origin) with those of uninfected age- and sex-matched controls. There were no differences in serum retinol levels between the two groups, although the β-carotene levels were reduced 4.9-fold in the HIV-infected children as compared with the controls.

In the United States, of 28 HIV-infected children and 10 HIV-negative controls between the ages of two and nine years, unlike the French study but similar to the other US study discussed above, there were no differences in serum retinol between the HIV-infected and -uninfected children [22].

Causes of hyporetinemia in HIV-infected individuals

The causes of hyporetinemia in HIV-infected individuals are not well defined, but factors thought to contribute, include decreased intake of food, diarrhea and malabsorption, decreased mobilization of hepatic stores, and increased utilization and abnormal urinary losses of vitamin A [23]. Protein-energy malnutrition may also increase the risk of development of vitamin A deficiency, probably because vitamin A transport relies on a carrier-protein complex of retinol-binding protein (RBP) and transthyretin. Stephenson et al. [24] highlighted the fact that urinary losses of low-molecular-weight proteins such as RBP during episodes of fever may account for a daily loss of up to 50% of the RDA of retinol. There is also evidence that indicates that urinary losses of low-molecular-weight proteins in patients with early HIV infection (but with no other evidence of renal disease) may result in losses of RBP and retinol that are far greater than those in HIV-negative controls [25]. Serum retinol may also be depressed as part of the acute-phase response to infection, even in the presence of adequate liver stores [26, 27].

In the study mentioned earlier [8], despite a 50% higher daily average vitamin A intake, asymptomatic HIV-infected individuals had lower serum retinol concentrations than did HIV-negative controls. This could imply that HIV-infected individuals may require quantities of vitamin A several times higher than the RDA in order to maintain normal serum retinol levels. Alternatively, as discussed, it could be a marker of severity of disease and an acute-phase response to infection.

Association of vitamin A with disease progression and mother-to-child transmission of HIV

Association of serum retinol with disease progression

Adults

A study in Baltimore, Maryland, USA, among HIV-positive intravenous drug users found that subjects

*Hussey G, Hughes J, Potgieter S. Vitamin A status and supplementation and its effect on immunity in children with AIDS. In: Abstracts of the 17th International Vitamin A Consultative Group Meeting held in Guatemala in 1996.

with low serum retinol concentrations (<0.70 μmol/L) had a 6.3 times increased risk of mortality [28]. This finding was later confirmed by the results of a nested case-control study in which 50 HIV-infected intravenous drug users who died of AIDS during two years of follow-up were compared with 235 who survived [10]. Low serum retinol and low CD4 counts were found to be independent risk factors for mortality. Subjects with low serum retinol had a higher risk of death (odds ratio, 4.6).

Baum et al. [29] conducted a longitudinal study to evaluate the relationship between plasma retinol and CD4 counts in 108 HIV-infected homosexual men at baseline and over three six-month time periods. The results showed that the development of hyporetinemia (<1.05 μmol/L) was associated with a decline in CD4 cell count ($p = .03$), and normalization of vitamin A was associated with higher CD4 counts ($p = .049$).

In a study of 311 HIV-infected men who were part of the Multicenter AIDS Cohort Study (MACS) in the United States, there was no consistent association between lower serum retinol concentrations and increased progression of AIDS [30]. However, very few of the subjects had low serum retinol levels, with the median being 2.44 μmol/L.

In a 3.5-year follow-up study, low concentrations of vitamin A, vitamin $B_{12,}$ zinc, and selenium were significant predictors of mortality when assessed individually and when CD4 counts were controlled for [31]. However, in a multivariate model controlling for CD4 counts, vitamin A was no longer a significant predictor of mortality, and only serum selenium was a significant predictor of mortality.

Jolly et al. [32] conducted a case-control study in the United States comparing 11 HIV-infected adults who were hospitalized with acute illness and 15 HIV-infected adults who attended the outpatient clinic. Mean serum retinol was slightly lower in hospital patients than in outpatients (difference not significant). However, urinary retinol loss was significantly higher in hospital patients than in outpatients (0.09 vs 0.04 μmol/L, $p = .02$). Urinary loss of retinol was significantly predicted by decreased CD4 count ($p = .045$) in clinic patients but not in hospital patients.

High HIV-1 RNA levels in plasma are significantly correlated with the clinical stage of HIV disease [33], risk of disease progression [34], and increased risk of mother-to-child transmission of HIV [35].

A study of 284 HIV-infected intravenous drug users, of whom 29% had low serum retinol levels, showed that serum retinol levels were not significantly correlated with HIV viral load [36]. A study in Rwanda of 30 HIV-infected women, of whom 14 were rapid progressors with high viral load and 16 were slow progressors with lower viral load, showed that both groups of women had similar serum retinol levels at baseline [37]. In subsequent measurements (obtained at a median of 12 and 24 months past baseline), there was a trend toward decreasing serum retinol levels and increasing HIV-1 RNA/viral load.

Children

Vitamin A levels were measured in 207 children who were part of the National Institute for Child Health (NICH) intravenous immunoglobulin clinical trial. It was found that baseline serum retinol was not associated with CD4 counts or HIV viral load or mortality [38]. These North American children had relatively normal vitamin A levels (mean, 1.05 μmol/L).

Association of vitamin A intake with HIV disease progression

Measuring dietary intake of vitamin A may be more useful as an indicator of vitamin A status, since it circumvents the disadvantages already mentioned of using biochemical indicators (serum retinol concentrations), which are affected by the acute-phase response to infection. Among well-nourished HIV-infected men who participated in the San Francisco Men's Health Study, high energy-adjusted vitamin A intake at baseline was associated with higher CD4 cell count at baseline, as well as with lower risk of developing AIDS during the six years of follow-up [39].

The results of the MACS study also indicate that vitamin A intake appears to be an important determinant of progression of disease [40] and mortality [41]. The MACS study followed 281 heterosexual men for up to eight years and documented a U-shaped relationship between vitamin A intake and disease progression. The lowest and highest quartiles for vitamin A were associated with increased progression of the disease, whereas the middle two quartiles (9,000–20,000 IU/day) were associated with a reduction in its progression [40]. Other studies, however, have found no association between vitamin A intake and progression of HIV disease.*

Association of vitamin A status with mother-to-child transmission of HIV

Mother-to-child transmission of HIV may take place through three separate routes: *in utero*, during the delivery process as the infant passes through the birth canal (intrapartum), and during breastfeeding (postpartum). Prior to the routine use of antiretrovirals, the rates of mother-to-child transmission of HIV in developed countries ranged from 14% to 25%, whereas

* Dennoter DM, Strathdee SA, Craib KJ. The relationship of dietary micronutrient intake to disease progression in a cohort of HIV + gay men. In: Abstracts of the 11th International Conference on AIDS held in Vancouver, Canada in 1996.

the rates in developing countries were much higher [42]. A proportion of this difference is attributable to breastfeeding, but micronutrient deficiencies among women in developing countries, exacerbated by the higher requirements during pregnancy, may also play a role. Deficiencies of micronutrients, in particular of vitamin A, could result in impairment of immune functions in the mother, or they could influence the micronutrient status of the fetus or infant, thereby affecting immune functions and susceptibility of the fetus to infection.

Semba et al. [15] were the first to report an observation made in a cohort of 338 pregnant HIV-infected women in Malawi that mother-to-child transmission of HIV was associated with serum retinol concentrations; an increased transmission was associated with lower serum retinol levels. Mothers who transmitted HIV to their infants ($n = 74$) had lower serum retinol than those who did not (0.86 vs 1.07 μmol/L, $p < .0001$). The relative risk of transmission was 4.38 times higher (32.4%) in mothers with serum retinol concentrations <0.70 μmol/L than in mothers with serum retinol concentrations >1.33 μmol/L.

Greenberg et al. [19] found a similar relationship in the United States, where women with serum retinol concentrations <0.70 μmol/L had an increased risk of transmitting HIV to their infants. In this study of 133 HIV-infected women, 16% of the women who transmitted the virus to their infants had low serum retinol concentrations, as compared with only 6% of the nontransmitting mothers ($p = .05$). In both studies, the adverse relationship persisted even after adjustment for confounding factors, including CD4 lymphocyte counts. However, another study in the United States did not find an association between serum retinol concentrations and mother-to-child transmission of HIV [43]. This study differed from the previous studies in that a very low percentage of women had low serum retinol concentrations (<0.70 μmol).

A recent analysis from a multicenter study in the United States (WITS) also showed that there was no association between vitamin A level and mother-to-child transmission of HIV [44]. In a recent study in South Africa among black women of low socioeconomic status, infants born to women with low serum retinol levels (<0.70 μmol/L) had a higher probability of infection at three months of age than those with higher serum retinol levels (25% vs 15.6%)[45].

Association of vitamin A status with HIV in body fluids of HIV-infected pregnant and lactating women

In a study of 107 Kenyan women, severe vitamin A deficiency (serum retinol <0.70 μmol/L) was associated with a 20-fold increase in risk of HIV-1 DNA in breastmilk in women with low CD4 lymphocyte counts [14]. Another study among 281 HIV-infected Kenyan women showed that after adjustment for CD4 count, the risk of vaginal shedding of HIV DNA increased considerably with serum retinol levels <0.70 μmol/L (odds ratio, 12.9)[46]. In another study from Kenya [47], low serum retinol was a risk factor for identifying HIV DNA in vaginal, but not cervical, secretions among pregnant women in the third trimester (CD4 counts and vaginal discharge were controlled for). These three studies suggest that maternal vitamin A deficiency could lead to an increased exposure of the child to HIV as it passes through the birth canal and during breastfeeding.

Association of maternal vitamin A status and the health and survival of infants

The risk of mortality was almost doubled among infants of 146 HIV-infected Rwandan mothers with low serum retinol as compared with infants of mothers with normal vitamin A status.* In a longitudinal study in Malawi of 467 HIV-infected women and their children, Semba et al. [48] found that low serum retinol concentrations in mothers were related to linear and ponderal growth of children after adjustment for confounding factors. In another study in Malawi [16], the vitamin A status of mothers was inversely related to mortality of their infants during the first year of life. Mortality fell from 93% in infants of women with serum retinol concentrations <10 μg/dl to 14% in infants of mothers with normal serum retinol concentrations. Infant birthweight was also significantly lower among those born to vitamin A–deficient mothers, although the magnitude of the difference was quite small.

Supplementation studies

Vitamin A supplementation in adults and effects on health and immunity

In an open-label study of 60 mg/day of β-carotene supplements given for four months, an increased number of natural killer cells and activated lymphocytes was observed in the study subjects [49]. β-Carotene supplements (180 mg) given daily for four weeks to HIV-infected individuals in the United States resulted in small increases in CD4 cell count in one study [50], but not in a second, larger, study by the same investigators [51]. In a small open-label study in California, 21 well-nourished HIV-infected men received β-carotene supplements (180 mg/day) for four weeks [52]. There

*Dushimimana A, Graham NMH, Humphrey JH. Maternal vitamin A levels and HIV-related birth outcome in Rwanda. In: Abstracts of the 8th International Conference on AIDS held in Amsterdam, Netherlands, in 1992.

were no changes in HIV viral load concentrations or CD4 counts after four weeks of supplementation. There was also no correlation between pre- or post-supplementation vitamin A concentrations and pre- or post-supplementation CD4 counts or HIV viral load.

A placebo-controlled study in Zambia used vitamin A supplementation in conjunction with vitamins C and E and selenium and zinc for two weeks in HIV-infected adults with persistent diarrhea [53]. There was no effect of supplementation on diarrhea. However, the lack of efficacy may be related to the facts that the patients enrolled were already manifesting symptoms of AIDS and that the period of supplementation was only two weeks.

Vitamin A supplementation in adults and effects on HIV viral load

The active metabolite of vitamin A, all-*trans*-retinoic acid, regulates gene expression via nuclear receptors known as retinoic acid receptors (RAR). RAR bind to specific sequences on DNA that are known as retinoic acid response elements (RARE). Many human genes are known to contain RARE, and this regulation of gene expression may explain the effects of vitamin A on immunity and other biologic functions. The long terminal repeat of retroviruses also contains a RARE, and *in vitro* studies have suggested that all-*trans*-retinoic acid may either increase or decrease HIV replication, depending on the cell line and culture conditions [54, 55].

In a double-blind, placebo-controlled trial in the United States, 120 HIV-infected injecting drug users received a single dose of 200,000 IU of vitamin A or placebo, and the effect of the supplement on HIV load was tested [56]. Vitamin A supplementation had no significant impact on HIV load at two and four weeks after treatment.

A second double-blind trial in the United States randomly allocated 40 HIV-infected women of reproductive age to receive a single oral dose of 300,000 IU of vitamin A or placebo [57]. The quantity of plasma HIV-1 RNA was measured before supplementation and at various time points over an eight-week period after supplementation. The mean and median viral load concentrations at each time point and change in viral load from baseline to each follow-up point did not differ between the vitamin A–supplemented and placebo groups.

Vitamin A supplementation in pregnant women and effects on HIV viral load

In a small trial in South Africa [58], the effect of vitamin A supplementation on viral load was tested in 24 women enrolled in a double-blind, placebo-controlled trial. The 12 women in the vitamin A group received a daily dose of 5,000 IU of retinyl palmitate and 30 mg of β-carotene during the third trimester of pregnancy, as well as 200,000 IU of retinyl palmitate at delivery. HIV viral load was measured at baseline and one week after delivery. There was no significant difference in the mean change in viral load after treatment in the two groups (viral load, $\log_{10}$ was –0.02 vs 0.31 in the vitamin A and placebo groups, respectively, $p = .31$).

Vitamin A supplementation in pregnant women and effects on mother-to-child transmission of HIV

Three randomized, placebo-controlled vitamin A supplementation studies were set up in Africa (South Africa, Malawi, and Tanzania) to test the observation made by Semba et al. [15] that vitamin A deficiency results in increased mother-to-child transmission of HIV. The South African study was conducted in Durban at two hospital antenatal clinics and enrolled 728 HIV-infected women, who were all black women of lower socioeconomic status [45]. The vitamin A treatment consisted of a daily dose of 5,000 IU of retinyl palmitate and 30 mg of β-carotene during the third trimester of pregnancy and 200,000 IU of retinyl palmitate at delivery. There was no difference in mother-to-child transmission rates at three months between the two groups; on the basis of the Kaplan-Meier analysis at three months of age, the estimated transmission probability was 20.3% (95% CI, 15.7%–24.9%) among the vitamin A group and 22.3% (95% CI, 17.5%–27.1%) among the placebo group.

Although there was no effect in the group of infants as a whole, a reduction in the mother-to-child transmission rates was detected in the group of preterm babies in the vitamin A–treated group. Among 80 preterm deliveries, those assigned to vitamin A treatment had a lower probability of HIV infection by three months of age (17.9%; 95% CI, 3.5%–32.2%) than those on placebo (33.8%; 95% CI, 19.8%–47.8%). This is a 47% decrease in mother-to-child transmission, but the number of subjects is small and the confidence intervals are large. The difference in transmission rates between the vitamin A and placebo groups among preterm deliveries was more obvious at one month of age than at day one. This would imply that the reduction observed is due to a reduction in intrapartum and early postnatal transmission rates. Possible explanations for this observation are discussed below.

The mucosal surfaces and skin are thinner and more permeable in preterm babies than in term babies [59, 60]. Vitamin A supplementation during pregnancy may have improved the vitamin A status of infants in the treatment group, resulting in better integrity of epithelial tissues. In addition, vitamin A supplementation may improve the integrity of cervical and vaginal epithelium in the treated mothers, thus reducing the

risk that the vulnerable, preterm infant will come into contact with infectious material during delivery; vitamin A deficiency was associated with a higher risk of viral shedding in lower genital tract infections in two studies from Kenya [46, 47]. Another explanation could be a vitamin A–induced improvement in the fetal/neonatal immune response.

In the Tanzanian study involving 1,085 women, those in the vitamin A supplementation group received the same dose of vitamin A as those in the South African study. This study differed from the South African study in that the effects of multivitamins were also included, and a two-by-two factorial design was used. The women received a daily oral dose of one of four regimens from enrollment (12–27 weeks) until delivery: vitamin A alone, multivitamins excluding vitamin A, multivitamins including vitamin A, or placebo. Preliminary data on the infection rates at six weeks were recently reported [61, 62]. There was no effect of vitamin A supplementation or multivitamins on mother-to-child transmission at six weeks. The investigators also examined the effect of supplements on a composite endpoint of "HIV-infected or dead" at birth and found no effect of vitamin A or supplements.

The Malawian study set up to investigate the same effect used a slightly different dosage of vitamin A; a daily dose of 10,000 IU of retinyl palmitate was used, and no β-carotene was included in the supplement. Detailed results of the study have not yet been reported, although preliminary data suggest that the results are in concordance with the two other intervention studies, since no effect of vitamin A was found on mother-to-child transmission of HIV at six weeks; the transmission rates in both groups were about 27% [63].

The Tanzanian and Malawian studies have not yet reported the effect of vitamin A on mother-to-child transmission of HIV in the preterm infants, and it is intended that the principal investigators will pool the results of the three intervention trials in order to have a larger sample size to examine this effect.

The lack of a strong effect of vitamin A supplementation on reducing mother-to-child transmission of HIV in our clinical trial, despite the association of low serum retinol levels with increased risk of transmission, suggests that serum retinol concentrations may be markers of HIV-1 disease progression rather than being causally related to mother-to-child transmission of HIV. Serum retinol is known to be depressed by the acute-phase response to HIV infection, even in the presence of adequate liver stores [26]. It is unlikely that the lack of a strong effect was related to insufficient vitamin A supplementation, since two of the studies used a high dose of β-carotene as well as a relatively high dose of preformed vitamin A, which was considered the safest to use to avoid any possible teratogenicity [64].

Vitamin A supplementation in pregnant women and pregnancy outcome

In the South African vitamin A supplementation trial to reduce mother-to-child transmission of HIV, one of the primary outcomes being investigated was the effect on pregnancy outcome [45]. In this study, 728 pregnant HIV-infected women randomly received either a placebo or a daily dose of 5,000 IU of retinyl palmitate and 30 mg of β-carotene during the third trimester of pregnancy and 200,000 IU of retinyl palmitate at delivery. The results of this trial suggest that vitamin A given for a maximum of 12 weeks from around the 28th week of pregnancy may reduce preterm delivery among HIV-infected African women. The incidence of preterm deliveries was reduced from 17.4% in the mothers in the placebo group to 11.4% in the treated group ($p = .03$). Vitamin A appeared to counteract the adverse effects of anemia (Hb < 10 g/L) during gestation, which increases the risk of preterm deliveries. In the placebo group, women with anemia had, as expected, a larger incidence of prematurity (25%), as compared with that in nonanemic women (12%). On the other hand, there were similar rates of preterm delivery among anemic and nonanemic women in the vitamin A treatment group. Other mechanisms by which vitamin A supplementation may have mediated this effect are not clear, although alterations in morphology of the placenta may be involved. A study in rats showed that the placenta of vitamin A–deficient rats was unable to carry fetuses to term and that supplementation of the rats with retinyl esters reversed micro-morphologic changes in the placenta, allowing fetuses to be carried to term [65]. Preterm delivery has been shown to be strongly associated with intrapartum transmission (RR = 3.7; 95% CI, 2.2–6.1) [66], and therefore vitamin A may be very important to reduce the incidence among this group of infants, who would be more susceptible to HIV infection.

In Malawi, there was a reduction in the incidence of low-birthweight deliveries among HIV-infected women supplemented with vitamin A as compared with the incidence in a placebo group [36]. Women in the vitamin A group received a daily dose of 10,000 IU of retinyl palmitate in the third trimester of pregnancy.

In Tanzania, large positive effects of multivitamins on perinatal outcomes (fetal mortality, low birthweight, and severe preterm births) in HIV-infected women were found, although vitamin A supplementation alone had no effect [61]. A study from Nepal that supplemented all women (not only HIV-infected women) reported no effects of vitamin A on newborn characteristics but a major impact on maternal mortal-

ity (reduced by 43%) [67]. These differing results are not entirely unexpected. Indeed, in their diversity they resemble some of the variability of outcomes in the field studies of vitamin A supplementation in preschool children in developing countries [6]. It should be borne in mind that because multiple micronutrient deficiencies usually coexist and often interact, design of intervention studies, data interpretation, and generalization of the results are difficult. For example, zinc is required for mobilization of vitamin A from liver stores, and therefore the effects of vitamin A supplementation cannot necessarily be generalized to populations with different zinc intakes.

A recent study has shown that antiretroviral drug therapy appears to increase the risk of preterm deliveries [68], and therefore vitamin A may even be useful in industrial countries to counter the effects of such therapy.

Vitamin A supplementation in pregnant women and effects on health and immunity

In the Tanzanian study discussed above, multivitamins (but not vitamin A alone) resulted in increased levels of T-cell subsets [61]; however, the long-term clinical relevance of this finding is yet to be determined.

A placebo-controlled study in South Africa among 312 HIV-infected pregnant women who received vitamin A supplements during the third trimester of pregnancy and 200,000 IU of vitamin A at delivery showed an effect of vitamin A on postnatal maternal weight gain [69]. Vitamin A supplementation as compared with placebo was associated with greater body mass index (BMI) retention three months after delivery ($p = .02$). This improvement in BMI retention remained statistically significant, even after control for baseline CD4 lymphocyte count. In subgroups with baseline CD4 counts <200 cells/μl and serum retinol <20 μg/dl, BMI at three months postpartum was significantly greater in the vitamin A–supplemented group ($p = .01$ and .03, respectively). Clearly this finding may not be relevant in countries where antiretroviral drug therapy is readily available. However, in poorer countries vitamin A may be a relatively inexpensive treatment that could help ameliorate some of the weight loss common during HIV infection.

Vitamin A supplementation in infants and children born to HIV-infected women

The first study to test the premise that HIV infection is associated with vitamin A deficiency in children and that supplementation with vitamin A could improve outcome was a randomized, controlled trial in South Africa [70]. This placebo-controlled trial involved 118 infants born to HIV-infected women. Those assigned to the vitamin A treatment group received 50,000 IU of vitamin A at 1 and 3 months of age, 100,000 IU at 6 and 9 months, and 200,000 IU at 12 and 15 months. Among all children, the supplemented group had lower overall morbidity than the placebo group (OR = 0.69; 95% CI, 0.48–0.99). However, when the frequency and severity of diarrhea and pneumonia episodes were considered, there was an effect only on diarrheal morbidity, and only in the HIV-infected infants who were supplemented was there a significant reduction in diarrheal morbidity (OR = 0.51; 95% CI, 0.27–0.99). No effect on diarrhea was observed in the uninfected children.

In another South African study, HIV-infected children were randomly assigned to receive either a placebo or a daily dose of 200,000 IU of retinol for two days.* Supplementation was associated with a significant increase in the total lymphocyte and CD4 count after four weeks. No details on clinical endpoints were available.

A third randomized trial of vitamin A supplementation was conducted in Tanzania [62]. It involved 687 children aged six months to five years who were hospitalized with pneumonia. The children received 400,000 IU of vitamin A (or half for infants) on admission to the hospital and then received further doses of the same regimen four and eight months after discharge. They were followed up for an average of 24 months. Of the 648 children for whom HIV status was ascertained, 9% were HIV-infected. As expected, compared with uninfected children, all-cause mortality was higher among HIV-infected children, as was mortality caused by pneumonia or diarrhea ($p < .001$ for each).

Among all children, vitamin A supplementation resulted in a 49% reduction in mortality (RR = 0.51; 95% CI, 0.29–0.90; $p = .02$). In the HIV-infected children only, vitamin A supplementation caused a far greater (63%) reduction in all-cause mortality (RR = 0.37; 95% CI, 0.14–0.95; $p = .04$). As in the previous study, vitamin A supplementation appeared to reduce the incidence and severity of diarrhea but not of pneumonia; vitamin A supplementation had an effect only on diarrhea-related mortality and not on pneumonia mortality. Vitamin A supplementation could have its effect by improving cellular and humoral immunity [4]. Additionally, vitamin A supplementation may affect mucosal immunity; Chandra et al. [71], showed that vitamin A deficiency was associated with reduced replication of gastrointestinal epithelial cells, resulting in a breach of the physical integrity of the epithelium, reduced mucosal secretions, and impairment of the mucosal immune system, including

* Hussey G, Hughes J, Potgieter S. Vitamin A status and supplementation and its effect on immunity in children with AIDS. In: Abstracts of the 17th International Vitamin A Consultative Group Meeting held in Guatemala in 1996.

reduced concentration of mucosal immunoglobulins. These mucosal changes weaken local defense against invading microorganisms and could therefore explain the increase in severity of gastrointestinal infections.

In a recent substudy nested within the vitamin A intervention trial to reduce mother-to-child transmission of HIV in South Africa, Rollins et al. [72] conducted lactulose/mannitol dual sugar intestinal permeability tests, which are indirect tests of the integrity of the gut epithelium. These tests were conducted on 238 infants at 1, 6, and 14 weeks of age. HIV-infected infants born to mothers who had been supplemented with vitamin A during the last trimester of pregnancy and at delivery had significantly better gut integrity than the HIV-infected group of infants whose mothers had received a placebo. No effect of vitamin A supplementation was found in those infants who were not HIV infected. This study has similar findings to the Tanzanian and South African studies discussed earlier, in that the effect of vitamin A supplementation is more marked in infants who are HIV infected and presumably use up vitamin A faster than they take it in.

Vitamin A supplementation in conjunction with immunization in HIV-infected children

Because the delivery system of vitamin A to children often makes use of the Expanded Program on Immunizations (EPI) contact points, concern has been raised about the consequences of giving vitamin A in conjunction with immunization to HIV-infected children. Hanekom et al. [73] conducted a double-blind, randomized trial of vitamin A or placebo before influenza vaccination to HIV-infected children. Vitamin A relative to placebo had no effect on vaccine serological responses, but it did dampen the increase in the HIV viral load 14 days after immunization.

Conclusions

Review of the literature on HIV and vitamin A in adults has shown that there are variations in the association of hyporetinemia with disease progression, as well as variations in the effects of supplementation on disease progression. Most of the negative results come from studies of well-nourished individuals in the United States. Populations that are likely to be deficient in vitamin A showed the biggest responses. The MACS study [41] is important, because it provides evidence that in well-nourished populations, although vitamin A is important, too much may actually be harmful and care needs to be exercised in individuals who are not at risk for poor vitamin A status.

The studies presented in this report indicate that low serum retinol concentrations are very common in HIV infection, and that they appear in many instances to be associated with increased viral load, increased progression to disease, and mortality, as well as increased mother-to-child transmission of HIV. However, increased viral load and progression to disease and mother-to-child transmission of HIV are not necessarily causally related to vitamin A deficiency, since very few trials of vitamin A supplementation have been effective in reversing the conditions associated with low serum retinol levels. Low serum retinol levels in adults appear to be a marker of severity of disease, which would explain the association between low serum retinol levels and increases in progression to disease, mortality, mother-to-child transmission, and viral load.

In a Malawian study of 58 HIV-infected women and 113 HIV-negative women, in addition to measuring serum retinol six weeks postpartum, Stallings et al. [74] also measured alpha-1 acid glycoprotein (AGP), an acute-phase protein. Among HIV-infected women, those with AGP levels above a standard cutpoint of 1.00 g/L had significantly lower mean serum retinol levels than those with AGP levels below the cutpoint. This study suggests quite strongly that the low serum retinol levels observed in HIV-positive women (and possibly men) may largely reflect the response of retinol as an acute-phase reactant, rather than actual lowered body stores of retinol.

In populations very likely to have less than adequate vitamin A intake, there are associations (in pregnant and lactating women) between low serum retinol and virus shedding in vaginal secretions and breastmilk and mother-to-child transmission of HIV. Nevertheless, the results of the intervention trials of vitamin A supplementation to reduce mother-to-child transmission of HIV would suggest that these associations are not in fact causal relationships and may be due to the residual confounding effect of advanced HIV disease. An alternative explanation could be the fact that since vitamin A deficiency often coexists with other micronutrient deficiencies, low serum retinol could merely be a marker, and the association might be due to the confounding effect of another micronutrient deficiency affecting progression and transmission.

Mention should be made of the fact that in interpreting the data from the observational biochemical and dietary intake prospective studies, one needs to be aware of a few limitations. First, as already mentioned, reverse causality may provide an explanation for the positive association between poor vitamin A status and disease progression. HIV infection could lead to reduced appetite, with subsequent reduction in food intake; additionally, absorption or metabolism of nutrients may be impaired as part of the disease process. Second, data from cohorts of individuals who are already infected at baseline (as was the case in all

the studies reviewed here) may be biased if vitamin users have different durations of infection at baseline or different drug treatment, diet, or other behavior during follow-up. A third limitation is that many of the studies used CD4 counts as surrogate markers of stage of HIV infection, and yet this was also the marker used to assess progression of HIV disease. Given these limitations, obviously the strongest studies will be those employing a randomized, placebo-controlled trial design. The randomized, placebo-controlled trials in pregnant women and adults have therefore shown that the association between vitamin A and HIV is most probably an association of reverse causality.

However, the situation in infants and children seems to be very different from that in adults. Infants and young children are unlikely to have large vitamin A stores, and the increased utilization of vitamin A during the infectious process will very likely leave infants and young children in negative balance for vitamin A. Therefore, unlike the situation we have observed in pregnant women and other adults, vitamin A supplementation appears to be effective in improving outcome in HIV-infected children.

In summary, additional vitamin A supplementation may not be necessary, and may even be harmful, in adults in the developed world who already have a good dietary intake of vitamin A and who take many other vitamin supplements.

Vitamin A supplementation does not appear to have any impact on mother-to-child transmission of HIV; nevertheless, vitamin A supplementation to pregnant women in the third trimester of pregnancy may be useful to reduce the incidence of low-birthweight and premature infants. The impact of vitamin A on mother-to-child transmission of HIV in preterm infants is awaiting further investigation. Vitamin A supplementation in HIV-infected children appears to be beneficial to reduce the incidence and

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Safety and toxicity of vitamin A supplements in pregnancy

Michael J. Dibley and David A. Jeacocke

Abstract

Vitamin A plays an essential role during fetal development; however, if consumed at high doses it can produce teratogenic effects. Synthetic retinoids are potent teratogens and are contraindicated during pregnancy. β-Carotene is free of toxic effects. Intakes of vitamin A less than 10,000 IU per day during pregnancy have not been associated with birth defects. However, there are conflicting results for intakes of 10,000 IU to 30,000 IU per day. Intakes of vitamin A greater than 10,000 IU per day are not recommended for well-nourished pregnant women. Intakes of 30,000 IU per day of vitamin A in nonpregnant women produce only minor increases in the primary teratogen of vitamin A embryopathy. In vitamin A–deficient populations, doses of vitamin A less than 10,000 IU per day or 25,000 IU per week are considered beneficial to pregnant women without risk to the fetus. In these populations, the risks of teratogenicity from high vitamin A intake may need to be balanced against those from a deficiency.

Introduction

Safety concerns relating to the use of vitamin A supplementation in pregnancy are twofold. First, there exists the risk to the mother of toxicity from sudden excessive intakes or continued high intakes of vitamin A over prolonged periods. Second, there is the potential for teratogenic abnormalities in the fetus at doses below those required to produce toxicity. The nature and clinical features of vitamin A toxicity are discussed, and a detailed account of the biological basis and evidence relating to birth defects arising from vitamin A exposure is presented.

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Types of toxicity

Retinol may result in toxicity when consumed in excessive quantities in both pregnant and nonpregnant women. Both acute and chronic forms of toxicity have been documented in the medical literature. The dietary intakes and characteristic features are described for each form of toxicity.

Acute toxicity

Acute toxicity may arise from ingestion of large quantities of retinol over short periods. Dosages in the order of 100 times the recommended daily allowance (RDA) are required to produce toxicity in adults, and for this reason acute toxicity is quite uncommon [1]. Symptoms of acute toxicity include gastrointestinal upset and neurological symptoms of headaches, blurred vision, vertigo, and muscular incoordination. In more extreme cases, further progression of these symptoms may occur to include drowsiness, malaise, inactivity, itching, skin exfoliation, and worsening vomiting approximately one week later. Lethal doses result in death from respiratory failure or convulsions [1].

Chronic toxicity

Chronic toxicity usually arises from doses less than 10 times the RDA consumed over extended periods, in some cases years, and is usually reversible following cessation of supplement use with complete recovery from toxic effects [1]. The most serious effects of chronic toxicity are on the liver, bone, and vision, where in some cases permanent damage may occur [1]. Hepatic damage from chronic vitamin A ingestion results in histological findings resembling cirrhosis caused by chronic alcoholism [2]. Chronic muscular and skeletal pain may arise [1], as may

psychiatric side effects, including severe depression and schizophrenia [2].

Teratogenic effects of vitamin A in pregnancy

The question about the safety of vitamin A use in pregnancy remains a complex and unresolved issue, even though it is recognized that vitamin A plays an important role in normal embryonic growth and development. The task of defining safe levels of vitamin A intake during pregnancy has received much attention since the discovery that the pharmaceutical agents etretinate and isotretinoin, both of which are vitamin A analogues, are potent teratogens in humans. Animal studies have shown that vitamin A intake may also result in birth defects similar to those produced by vitamin A analogues in humans. These findings have prompted considerable reassessment of the safety of vitamin A consumption in humans during pregnancy. In this section, an overview of the human and animal evidence for teratogenesis from synthetic retinoids, retinol, and research supporting the safety of the use of β-carotene in pregnancy is presented.

Summary of vitamin A metabolism and pharmacokinetics

Recent understanding of the involvement of retinoic acid in genetic regulatory control mechanisms in embryonic tissues suggests that retinoic acid, rather than retinol and retinol esters, may be responsible for the teratogenic effects of vitamin A [3]. The major teratogenic metabolite of retinol is all-*trans*-retinoic acid [4]. Other teratogenic metabolites include all-*trans*-4-oxo-retinoic acid, 13-*cis*-retinoic acid, and 13-*cis*-4-oxo-retinoic acid. It is believed that the teratogenicity of 13-*cis*-retinoic acid arises because of interconversion to all-*trans*-retinoic acid [4]. The rate of this interconversion may vary among women [5]. The metabolite all-*trans*-4-oxo-retinoic acid is thought to have a similar teratogenic potential to all-*trans*-retinoic acid [4].

Other pharmacokinetic properties also affect the serum levels of vitamin A metabolites, including their volumes of distribution and differing half-lives of elimination [6]. Miller et al. [6] reported on the preliminary results of a multicenter study conducted in six countries in which the serum levels of various teratogenic metabolites were analyzed in 85 pregnant women during the first trimester, providing reference values for safe concentrations. The highest plasma concentrations were found for 13-*cis*-4-oxo-retinoic acid. This metabolite is known to have a longer half-life than retinoic acid, which has a relatively short half-life [6]. The pooled effect of a number of teratogenic metabolites, rather than just the intake of retinoic acid, may be important in determining the potential for the development of birth defects. In considering the effects of the teratogenic metabolites on the fetus, it is also unclear which are important: peak concentrations of metabolites or the total cumulative exposure (area under the plasma concentration–time curve) [4].

Buss et al. [4] examined the serum levels of potentially teratogenic metabolites of vitamin A in 10 nonpregnant women, when consumed as dietary retinyl palmitate, both in the form of liver and as a supplement. Dietary retinol in the form of liver produced a smaller and delayed rise in serum retinol levels than vitamin A consumed as retinyl esters. This suggests that the latter form of vitamin A may have a more marked effect in producing teratogenic metabolites. Therefore, not only must pharmacokinetic properties of vitamin A metabolites be considered, but also the dietary form in which vitamin A is consumed.

In healthy nonpregnant female volunteers, dietary intakes of 10,000 IU of vitamin A resulted in serum retinoic acid and 13-*cis*-retinoic acid levels similar to the physiological range of these metabolites observed in pregnant women [3, 6]. Even at dosages of 30,000 IU, minimal differences in physiological levels were detected with mean serum levels at the upper limit of the physiological range [3]. These findings suggest that, on physiological grounds, the dosages required to produce teratogenic effects might be expected to exceed 30,000 IU.

Physiological basis of vitamin A teratogenicity

A further consideration in determining the potential for teratogenicity is the extent to which changes in maternal serum levels of these vitamin A metabolites result in changes in fetal exposure. The ability of retinol to be transferred across the placenta into the fetal circulation has been discussed previously. Importantly, it has been found that the placenta can transfer teratogenic compounds and continue to produce teratogens through ongoing oxidative metabolism and isomerization [7]. Therefore, in considering the potential teratogenic effects of vitamin A, the placental contribution to production of teratogens needs to be considered, as well as the contribution from maternal serum levels.

Evidence suggests that vitamin A transfer is regulated to maintain steady fetal levels of retinol [8]. The transfer of retinol across the placenta is also thought to be a saturable process at high doses [9, 10]. It is believed that maternal retinoic acid acts as the predominant teratogen in humans [3]. In one study, doses of 30,000 IU retinol did not result in serum

levels of vitamin A metabolites exceeding the usual range observed in women during the first trimester of pregnancy [5].

Transfer of vitamin A to the fetus

Little is known about the mechanisms by which the fetus and placenta regulate the transfer of retinol from mother to fetus. One study in mice has shown that during the embryogenic period there is a sudden reduction in maternal retinol levels corresponding to a steady increase in fetal retinol levels [11]. This depletion in maternal serum levels was followed by a subsequent rise in maternal retinol levels from hepatic stores. Little change was observed in the levels of retinyl esters and retinoic acid. Although it has been observed that maternal serum retinol levels drop during human pregnancies, especially in the third trimester (see earlier section), in vitamin A–replete populations this is due mainly to hemodilution. The mean retinol level in fetal liver is low (<20 μg/g); however the retinol concentration does increase as pregnancy progresses, especially in the third trimester [8]. It is important to note that fetal retinol levels do not increase significantly following maternal supplementation [1].

Both retinol and complexes of retinol and retinol-binding protein (RBP) are taken up by the placenta, and retinol is secreted into the fetal circulation [9]. Retinol is more rapidly transferred across the placenta when it is not in a complex with RBP because of its high lipid solubility in the unbound state [7]. Similarly, free retinoic acid can be taken into the placenta. Maternal β-carotene is also thought to be an important source of retinol precursor for the placenta. Retinol-deficient women are thought to have higher interconversion of β-carotene to retinol in order to maintain adequate vitamin A transfer to the fetus [9]. Maternal β-carotene, which is significantly correlated with cord retinol levels for women with serum retinol levels below 15 μg/dl, may therefore be an important source of retinol in vitamin A–deficient women [12].

Fetal RBP is synthesized initially by the amniochorionic membrane and later in gestation by the fetal liver, but it does not appear to be transferred from the maternal to the fetal circulation [9]. It is thought that retinol binds to RBP secreted into the amniotic fluid. This may provide an important source of retinol to the fetus, which is known to swallow 15 ml of amniotic fluid per day by 20 weeks of gestation [9].

Wallingford and Underwood [10] stated that the ratio of maternal to fetal serum retinol levels is approximately 2:1 in healthy women with adequate vitamin A intakes. In cases of deficiency, these researchers commented that it is possible for fetal levels to exceed maternal levels. This transfer process therefore appears to be homeostatically regulated to ensure adequate fetal vitamin A levels [9, 10]. In a study comparing serum retinol levels in postmortems of fetuses from Swedish women to levels in fetuses from Ethiopian women with low vitamin A reserves, similar although slightly lower serum RBP levels were found in cord blood of Ethiopian fetuses [8]. An exponential increase in fetal hepatic retinol reserves that was detected in fetuses of Swedish women in the second and third trimesters was not observed in the fetuses of similar gestation from the vitamin A–deficient Ethiopian women. This study suggested that the fetus can maintain relatively constant serum retinol levels by ensuring that vitamin A is retained in the fetal circulation in preference to storage in the liver [8]. Other studies have also suggested that the fetus attempts to maintain a steady serum retinol level in this way [12].

Synthetic retinoids

Animal studies

The teratogenic effects of isotretinoin have been examined in a number of species, including the mouse, the rat, and the rabbit [13, 14]. Exposure to synthetic retinoids has been shown to affect almost all organ systems [15]. In rhesus monkeys exposed to tretinoin and etretinate, the resulting abnormalities included microtia and craniofacial defects, nervous system abnormalities, eye abnormalities, and thymic abnormalities [14]. Cranial defects, vertebral defects, and limb reduction defects have been observed in monkeys, although they are not prominent findings in human case studies [14]. Animal studies have shown that the type of birth defect is dependent on the stage of pregnancy at which exposure occurs; abnormalities of the head, sensory organs, and cardiovascular system result from exposure shortly after conception, and limb and urogenital abnormalities result from exposure at a later stage [13].

Despite similarities in the patterns of abnormalities observed, differences across species in the degree of teratogenicity of isotretinoin have been reported [14]. The minimum teratogenic dose on a milligram per kilogram basis over a number of exposures is considerably lower in human than in animal studies. In contrast to other primates, where teratogenic dosages have been reported to range from 7.5 to 40 mg/kg/day [13, 14], the teratogenic dose for humans appears to be much lower (0.4 to 1.5 mg/kg/day). The minimum teratogenic dosage of etretinate in humans is 0.2 mg/kg/day, which is also much lower than that in other primates, rats, mice, hamsters, and rabbits (range, 2 to 5 mg/kg/day) [13].

Human studies

The drugs isotretinoin or 13-*cis*-retinoic acid (Accutane, Roaccutane) and etretinate have been shown to be highly teratogenic in humans [16]. These medications are used for the treatment of severe recalcitrant cystic acne and for psoriasis, respectively [17], both disorders that affect young women. Recently, a newer synthetic retinoid, acetretin (Neotigason), has been released to replace etretinate. Acetretin is an active metabolite of etretinate and, like isotretinoin and etretinate, has been classified as having a high risk of causing birth defects [18].

Birth defects arising from isotretinoin produce a well-described phenotype known as retinoic acid embryopathy [19]. Distinctive features include malformations of the ear (microtia, anotia) associated with heart defects (conotruncal and aortic arch abnormalities); brain defects. including hydrocephalus, microcephaly, and cerebellar abnormalities (absence or hypoplasia of the vermis); facial abnormalities (small mandible, cleft palate); and thymic abnormalities [20]. This combination of findings is suggestive that the impaired migration of cranial neural crest cells may be the underlying cause of these abnormalities [17]. These characteristics are similar to the pattern of fetal abnormalities resulting from exposure of pregnant animals to synthetic retinoids [14].

Lammer et al. [19] reported on 21 malformed infants exposed to isotretinoin whose abnormalities included central nervous system malformations (86%), craniofacial malformations (81%), cardiac defects (57%), and thymic malformations (33%) [21]. Infants exposed to isotretinoin in early pregnancy were 26 times more likely to develop abnormalities of the central nervous system, cardiac system, or ear. In addition to these abnormalities, a 22% miscarriage rate was reported [19].

Similar findings were described in 75 pregnant women who were exposed to the agent etretinate or etretin [22]. Following 14 pregnancy terminations, classic features of retinoic acid embryopathy were present in five cases. Typical malformations were detected in six infants of another 29 women who progressed to delivery. The range of dosages giving rise to malformed infants or fetuses varied from 25 to 75 mg [22]. Defects observed in humans have included craniofacial defects (microtia, micrognathia, and low-set ears), central nervous system abnormalities (meningomyelocele, anophthalmia, and brain defects), and skeletal defects (syndactyly, shortened or absent digits, club foot, and multiple synostoses) [18]. Developmental deficits have been observed in over half the children with exposure *in utero* to this agent [18].

An important consideration in potentially fertile women who have been prescribed synthetic retinoid agents is the safe period for conception. The synthetic retinoids isotretinoin, etretinate, and acetretin have half-lives of 20 hours, 120 days, and 50 hours, respectively. These long half-lives require that women delay conception following the cessation of these drugs. The newer agent acitretin has been released to replace etretinate due to its shorter half-life; however, in some women acetretin is converted to etretinate during therapy [18]. A two-year contraception period has been set for etretinate, representing approximately seven elimination half-lives, which is required for elimination of 99% of the drug from the body [22]. A similar time frame has been set for acetretin because of the potential for interconversion to etretinate [18]. A contraception period of at least one full menstrual period (one month) is required for isotretinoin [17].

The fetus of a 22-year-old woman who underwent a pregnancy termination four months after cessation of etretinate for treatment for Darier's disease displayed abnormalities including aplasia of the tibia and fibula and hypoplasia of the left femur [22]. Chan et al. [18] provided data from a prospective study of 45 subjects in whom pregnancy occurred within two years of cessation, resulting in an abnormality in one case or 2% of subjects examined (95% CI, 0%–12%). The pharmaceutical manufacturer Roche prospectively examined a group of 32 women exposed to Acetretin who became pregnant within two years of cessation; no episodes of abnormalities were recorded [18]. In another prospective case study of 48 women becoming pregnant within one month of completing treatment with isotretinoin, two birth defects were reported (4% of subjects; 95% CI, 1%–14%). These case studies confirm the importance of contraception periods for women of reproductive age undergoing treatment with synthetic retinoids.

In some countries, such as Australia, the prescription of synthetic retinoids has been restricted to specialist dermatologists [18]. Guidelines for the prescription of these agents have been recommended by Roche [18] and include the following:

» The possibility of pregnancy must be ruled out by a pregnancy test two weeks before commencing treatment.
» Treatment should be commenced on the second or third day of the next normal menstrual period.
» An effective form of contraception should be used for at least one month before treatment, during treatment, and for at least one month after cessation of treatment with isotretinoin and for two years after treatment with etretinate and acetretin.
» Women should be effectively counseled about the risks to a fetus, and if pregnancy does occur, they should immediately stop taking the drug and seek medical advice.
» To increase understanding of the implications of treatment, a specially designed consent form

should be signed by the patient before commencing treatment.

» Women should not breastfeed while taking oral retinoids. The drugs should not be given to others and should be kept out of reach of children.

Various methods have been attempted to improve compliance with these guidelines by patients and practitioners. Examples include check lists for practitioners, patient education information including pictures of birth defects, "avoid pregnancy" stickers on medication packets, periodic communications with prescribers and pharmacists, partially reimbursed contraception programs by manufacturers, and the use of two forms of contraception simultaneously [18].

Retinol

Animal studies

Rosa et al. [14] cite Geelen [23], who showed that defects similar to those arising from synthetic retinoids also occur because of excessive retinol consumption during pregnancy. In animal studies, naturally occurring vitamin A given at the same stages of embryogenesis produced similar deformities to those arising from synthetic retinoids. Based on animal studies, the dosage of retinol required to produce birth defects is much higher than those of etretinate and isotretinoin [13].

Defects observed in animals closely parallel abnormalities seen in humans from exposure to high doses of vitamin A. Abnormalities common to both animals and humans have been observed in the following organ systems: central nervous system (anencephaly, spina bifida, hydrocephalus); face (cleft lip and palate, micrognathia); ocular system (microphthalmia); abnormalities of the ear, teeth, salivary glands, and aortic arch; heart defects (ventricular septal defects, conotruncal abnormalities); gastrointestinal system (imperforate anus, omphalocele); liver and gallbladder abnormalities; genitourinary malformations (renal agenesis, polycystic kidney, hydronephrosis, genital malformations); endocrine abnormalities (pituitary, thymus, and thyroid abnormalities); skeletal abnormalities (affecting the skull, vertebrae, ribs, and extremities); and situs inversus [15].

When considering the results of animal studies to determine the teratogenic dose of retinol, it should be remembered that the teratogenic dose might differ across species, with primates possibly being less susceptible to vitamin A in forms other than isotretinoin or etretinate [14]. Geelen, who conducted an overview of the animal studies of hypervitaminosis A, commented that the intakes of retinol required to cause teratogenesis in animals are much higher than likely human exposures [23].

In addition to causing birth defects at high doses in animals, deficiency of vitamin A can result in incomplete pregnancies and birth defects [24]. A spectrum of birth defects has been observed similar to those found from excessive vitamin A consumption in a number of species, including the pig, rat, rabbit, cattle, and sheep [24]. These findings suggest that there may be an optimum level of maternal retinol consumption above and below which abnormalities may occur. A comparison of birth defects observed from excessive vitamin A consumption and vitamin A deficiency is shown in table 1.

Human studies

It is noteworthy that in spite of the widespread use of vitamin A supplements [15], relatively few cases of birth defects due to vitamin A teratogenicity have been documented in the medical literature [16]. Consequently, no minimum teratogenic dose for retinol has yet been established.

One possible explanation for the low rates of reporting of vitamin A teratogenicity is failure to recognize excessive retinol exposure. In spite of the low numbers of reports of vitamin A teratogenicity, one study has suggested that as many as 1 in 57 pregnancies exposed to usual vitamin A intakes greater than 10,000 IU per day may result in birth defects [26]. These results have not been confirmed by other studies, which failed to detect a significant association between vitamin A intake at this level and an increased risk of birth defects. A discussion of the evidence supporting vitamin A teratogenicity in humans arising from case studies and epidemiological studies is presented.

Case studies

A summary of reported cases of birth defects arising from high doses of vitamin A in pregnancy is provided in table 2. Vitamin A intakes reported by mothers of affected infants ranged from 25,000 to 500,000 IU and have been described for both a large single dose and long-term consumption throughout the pregnancy. Prior to 1986, the Food and Drug Administration (FDA) had received only two reports of birth defects associated with vitamin A [14]. These two cases were associated with daily vitamin A dosages of 40,000 IU and 60,000 IU during pregnancy, and both reported the congenital defect of microtia, a feature later found to be characteristic of synthetic retinoid embryopathy [14]. Although there are case reports of vitamin A supplementation possibly associated with birth defects, to date no birth defects have been reported from high intakes of vitamin A from food sources [14].

Epidemiological studies

Two case-control studies [16, 32] and one cohort study [26] have provided some evidence of teratogenicity

TABLE 1. Comparison of birth defects caused by vitamin A excess and deficiency

	Vitamin A excess		Vitamin A deficiency	
Defect	Human	Rat	Human	Rat
Absorption (resorption)		↑		↑
Growth Prenatal Postnatal			↓ ↓	↓ ↓
Craniofacial	Sloping forehead Narrow forehead Micrognathia Mandibular/maxillary hypoplasia	Oculofacial syndrome Mandibular hypoplasia Cleft lip/palate		Cleft palate
Eye	Microphthalmia	Anophthalmia/ microphthalmia	Anophthalmia Ocular deformity	Anophthalmia/ microphthalmia Postlenticular fibroplasia Coloboma
Ear	Tiny/stenotic ear canals Microtia/anotia	Malformations		
Central nervous system	Microcephaly	Microcephaly	Microcephaly	
Cranium		Exencephaly		
Brain		Neural tube defects Hydrocephalus	Mental retardation Neural tube defects	Hydrocephalus Neural tube failure in quail
Heart	Ventricular septal defects Auricular septal defects Conotruncal anomalies	Ventricular septal defects Single midline heart tube in chick embryo	Ventricular septal defects Auricular septal defects	Ventricular septal defects Aorticopulmonary septal defect (conotruncal) Branchial arch anomalies

Source: adapted from ref. 25.

from retinol supplementation in humans. The cohort study, conducted by Rothman et al. [26] suggested that daily retinol intakes as low as 10,000 IU may be teratogenic. Since this report, a number of investigators have attempted to further evaluate the safety of this vitamin A intake threshold and have failed to support the findings of Rothman et al. [33–37].

More recently, it has been accepted that folic acid supplementation is protective against birth defects. Many of the studies supporting this discovery have involved multivitamin supplements, including vitamin A at low doses. A small amount of evidence also suggests that low-dose vitamin A consumption may be protective against birth defects in women with inadequate vitamin A intake [25, 33, 38]. The association between vitamin A intake and risk of birth defects in humans is examined in more detail in the following section. The results of studies examining vitamin A intakes greater than 10,000 IU daily are compared with those of studies examining intakes below 10,000 IU.

Risk of birth defects from retinol consumption greater than 10,000 IU/day during pregnancy

All studies examining the relationship between vitamin A consumption and birth deformities have been observational studies. Five case-control studies and five cohort studies have been described in the scientific literature examining the relationship between retinol consumption and birth defects. Birth defects exam-

TABLE 2. Reported case studies of birth defects arising from excessive vitamin A consumption in humans

Study	Dose	Face and head	Cardiac	Genitourinary	Central nervous system	Musculo-skeletal and other
Pilotti and Scorta 1965 (cited in Rosa et al. 1986) [14]	40,000 IU			Bilateral hydroureter		
Morris and Thomson 1974 [27]	Not stated	Cleft palate	Heart defect			
Mounoud et al. 1975 [28]	Single 500,000-IU dose in 2nd month of gestation	Facial palsy, hemifacial atopy, atresia of ear canals, epibulbar dermoid, micrognathia, bilateral oculomotor palsy, left preauricular appendices				
Stange et al. 1978 [29]	150,000 IU days 19–40	Microcephaly		Hypoplastic kidney and adrenals	Microhydro-cephalus	
Bernhardt and Dorsey 1979 [30]	25,000 IU wk 0–13; 50,000 IU wk 14 to term			Unilateral ureteral duplication with one ureter ending in the vagina, hydroneph-rosis, bilateral hydroureter		
Von Lennep et al. 1985 [31]	150,000 IU days 1–24	Low ears, dys-morphic face, pterygium colli		Absence of external genitalia and urethral openings, polycystic kidneys		Partial sirenomelia, lumbar spine dysmorphism, imperforate anus/distend-ed abdomen
Physician report to FDA[a]	40,000 IU preconception to term	Tiny ear canals, facial dys-morphy, high arched palate				
Physician report to FDA[a]	60,000 IU preconception to term	Absent right ear, cleft palate/lip				
Physician report to FDA[a]	50,000 IU wk 3–9	Bilateral cleft lip				

continued

TABLE 2. Reported case studies of birth defects arising from excessive vitamin A consumption in humans *(continued)*

Study	Dose	Face and head	Cardiac	Genitourinary	Central nervous system	Musculo-skeletal and other
NY State BDR[a]	≤25,000 IU preconception to term	Absent right ear and canal				
NY State BDR[a]	≥25,000 IU preconception to term	Absent left auditory canal, Vater's syndrome				
NY State BDR[a]	≤25,000 IU to term	Hypoplastic left ear				
NY State BDR[a]	≥18,000 IU to term	Low deformed ears, micro-gnathia, micro-phthalmia				
NY State BDR[a]	≥33,000 IU to term		Transposition			
Danish National Health Service	50,000 IU	Cleft lip, palate, cheek, jaw, left eye absent				
Roche[b] (4 cases)	Not specified				Spina bifida Hydrocephalus	Club foot Turner's syndrome

a. Cited by Rosa et al. [14].
b. Based on research by Roche (cited by Rosa et al. [14]).
BDR, Birth defect registry; FDA, US Food and Drug Administration. Source: adapted from refs. 6, 14, 15.

ined mostly included cranial neural crest cell deformities, neural tube defects, and all major abnormalities. Selected controls have included mothers of babies without birth deformities and mothers of babies with other forms of abnormalities. Assessment of vitamin A status also varied across these studies. Only two cohort studies and one case-control study [35] assessed the contribution of dietary retinol to total retinol intake from supplements. All studies were capable of providing an estimate of the effects of daily vitamin A intakes from supplements of greater than 10,000 IU relative to intakes of retinol below this level. An overview of the results of these studies is presented below, and the main findings are summarized in table 3.

Case-control studies

Werler et al. [32] examined exposure to one week or more of vitamin A supplementation (estimated >10,000 IU) during the first three months of pregnancy among mothers of 2,658 children with abnormalities of structures derived at least in part from cranial neural crest cells, relative to mothers of 2,609 infants born with other malformations. Mothers of children with birth defects derived in part from neural crest cells were 3.3 (95% CI, 0.8–14.6) and 3.8 (95% CI, 0.9–16.0) times more likely to have consumed both vitamin A supplements and multivitamins in the first and second lunar months, respectively. By the third trimester, the odds ratio for birth defects among children of women consuming vitamin A–containing supplements had declined to 1.9 (95% CI, 0.5–7.4). Similarly, Martinez Frias and Salvador [16], who examined the risk of birth defects among 11,293 pregnant women relative to 11,193 normal pregnancies, observed a nonsignificant 2.7-fold increase in the odds ratio (95% CI, 0.8–11.7) for women consuming greater than 40,000 IU of retinol daily relative to women consuming less than 40,000 IU. Daily intakes of between 20,000 and 40,000 IU in this study were associated with a nonsignificant reduction in the odds ratio of birth defects to 0.5 (95% CI, 0.01–9.5).

Three case-control studies showed no association between retinol consumption and birth defects. Khoury et al. [33] used data from a population-based case-control study of 4,918 major birth defects conducted by the Centers for Disease Control in the 1980s and assessed vitamin supplement intake of three days or more per week in the first month preconception to the end of the first trimester.

TABLE 3. Studies examining associations between vitamin A exposure during pregnancy and the risk of birth defects

Study	Study design	Sample population	Region	Assessment of vitamin A status	Assessment of abnormalities	Results: PR/OR (95% CI) cases vs controls
Mastroiacovo et al. 1999 [37]	Prospective cohort	423 pregnancies (3 major abnormalities)	Europe (13 regions)	Patients ingesting ≥10,000 IU during wk 1–9 of pregnancy	European Network of the Teratology Information Services	Controls = exposure>wk9: 0.28 (0.06–1.23) Controls = unexposed: 0.50 (0.14–1.76)
Major et al. 1998 [36]	Case-control	11 CDH cases 11 healthy controls 7 matched newborn-mother pairs	Quebec, Canada	Cord blood samples from neonates (11) Maternal blood samples at term (7)	CDH cases and controls clinically diagnosed	Mean cord retinol (CDH vs controls) All 11 newborn: (lower $p < .0002$) 7 newborn-mother pairs: Newborn (lower $p = .003$) Mother (higher $p = .041$)
Mills et al. 1997 [35]	Case-control (population-based)	935 major abnormalities 573 normal controls	California and Illinois, USA 1985–87	Questionnaire recording periconceptional vitamin A intake (diet and supplements) (blind assessment at 1–5 mo antenatal)	Mandatory reporting registries, hospital records, "crippled children's" services, perinatal networks and support groups	Supplement only: <5,000 IU vs >8,000 IU All: 1.05(0.51–2.18); CNC: 1.06 (0.31–3.68) Supplement and cereals: <5,000 IU vs >10,000 IU All: 0.73 (0.27–1.96); CNC: 1.09 (0.24–4.98) Organ meat consumption All: 0.82(0.55–1.23)
Shaw et al. 1995, 1996 [34, 39]	Case-control	552,601 deliveries OFC: 731 cases, 734 normal controls CTH: 207 cases, 481 normal controls	California, USA 1986–89 (population-based)	Recall of supplement intake (average 3.5 yr after delivery)	California Birth Defects Monitoring Program	OFC: 0.55(0.21–1.15) CTH: 0 (0–2.2)
Khoury et al. 1996 [33]	Case-control	4,918 all defects 1,623 CNC 3,295 other 3,029 controls	Atlanta, Ga, USA (1980s)	Multivitamin/vitamin A supplement consumption 3 or more times/wk between 1 mo preconception and 3 mo antenatal	Centers for Disease Control population-based case-control study	MV alone All defects: 0.94 (0.86–1.03) CNC: 0.86 (0.76–0.97) VA alone All defects: 0.85 (0.41–1.78) CNC: 1.36 (0.57–3.19) Both MV and VA All defects: 0.60 (0.28–1.29) CNC: 0.69(0.24–1.91)

Rothman et al. 1995 [26]	Prospective cohort	22,748 pregnancies 339 birth defects (genetic defects excluded)	USA	Intake of dietary supplement assessed at wk 15–20 of pregnancy Mean dietary intake during 4 wk of highest consumption of retinol during trimester 1	Women attending 1 of 100 obstetricians for prenatal screening. Mailed questionnaire to obstetrician/mother	Fitted dose-response curve: apparent threshold for rise in CNC defects near 10,000 IU >10,000 IU vs <5,000 IU (food + supplement): CNC: 4.8 (2.2–10.5) All: 2.4 (1.3–4.4)
Czeizel 1993 [38]	Randomized, controlled trial	4,704 pregnancies Vitamin supplement vs trace element supplement each day for 1 mo preconception	Hungary	Folic acid 0.8 mg Retinol 6,000 IU 1989 4,000 IU 1990–91 + other vitamins and minerals	Deliveries and terminations in Hungarian obstetric outpatient units (validated)	Overall: lower in supplemented group ($\chi^2 = 6.68$ $p = .01$) Excluding NTDs: lower in supplement group ($\chi^2 = 4.69$ $p = 0.03$) RR 1.85 (1.02–3.38)
Mills et al. 1992 [40]	Case-control (population-based)	89 NTD cases 178 other pregnancies	Finland	Serum retinol levels determined at time of antenatal screen Questionnaire reporting supplement use in relation to period of neural tube closure (25–27 days of pregnancy)	Finnish Registry of Congenital Malformations (1983–89)	Mean retinol (NS) OR (adj) 0.99 (0.88–1.10) Differences in maternal vitamin use: Overall: ($\chi 2_{(2)}$ $p = .14$) Before neural tube closure: ($p = 0.62$)
Sandford et al. 1992 [41]	Case-control (population-based)	NTD 44 Normal infants 88 (matched)	South Louisiana, USA	Food-frequency questionnaire	Retrospective screening of obstetric records (17 hospitals) (validated)	β-Carotene fruit/vegetable intake (>1/wk): Overall: protective effect ($\chi^2 = 8.07$, $p = .004$) Spina bifida case-control pairs only: protective effect ($\chi^2 = 9.31$, $p = .002$) RR = 0.25
Martinez-Frias and Salvador 1990 [16]	Case-control (hospital based)	11,293 cases 11,193 controls (chromosomal defects excluded)	Spain	Open-ended question about drug use during pregnancy	Hospital surveillance data. Cases detected by local specialists days 1–3 antenatally	<20,000 IU: 0.5 (0.1–1.9) 20,000–39, 999 IU: 0.5 (0.01–9.5) 40,000 IU: 2.7 (0.8–11.7) Reduced risk if exposed later in pregnancy ($p < .05$)

continued

TABLE 3. Studies examining associations between vitamin A exposure during pregnancy and the risk of birth defects *(continued)*

Study	Study design	Sample population	Region	Assessment of vitamin A status	Assessment of abnormalities	Results: PR/OR (95% CI) cases vs controls
Werler et al. 1990 [32]	Case-control	2,658 CNC cases (84% response rate) (chromosomal/Mendelian disorders excluded) Controls: 2,609 other defects (82% response rate)	Boston, Philadelphia, and Iowa, USA; Toronto, Canada	Vitamin A supplement use (daily users for 1 wk vs nonusers in first trimester) Interviewed within 6 mo of birth	Contact with newborn nurseries from birth hospitals and routine review of discharge diagnoses from hospitals and specialty clinics	Any vitamin A supplementation: Lunar month 1: 2.5 (1.0–6.2) Lunar month 2: 2.3 (0.9–5.8) Lunar month 3: 1.6 (0.6–4.5) Vitamin A supplement + multivitamin: Lunar month 1: 3.3 (NS) Lunar month 2: 3.8 (NS) Lunar month 3: 1.9 (NS)
Smithells et al. 1976 [42]	Case-control	3 NTD cases 971 normal controls	Leeds, England	Serum retinol levels determined during 1st trimester	Not stated	Mean serum retinol: higher in cases ($p < .05$) Affected by high retinol intake in 1 case

CDH, Congenital diaphragmatic hernia; CI, confidence interval; CNC, cranial neural crest defect; CTH, conotruncal heart defect; MS/UG, musculoskeletal/urogenital defect; MV, multivitamin; NS, not significant; NTD, neural tube defect; OFC, orofacial cleft defect; OR, odds ratio; PR, prevalence ratio; RBP, retinol-binding protein; VA, vitamin A.

The odds ratio for cranial neural crest deformities was significantly reduced for subjects exposed to intakes of multivitamin supplements typically containing less than 10,000 IU retinol [33] (OR = 0.86; 95% CI, 0.76–0.97) relative to normal controls matched for period of birth, race, and hospital of birth. However, no significant protective associations were observed for subjects consuming supplements containing only vitamin A with higher retinol concentrations of up to 25,000 IU [43] (retinol and multivitamin supplements: OR = 0.69 and 95% CI, 0.24–1.91; retinol only: OR = 1.36 and 95% CI, 0.57–3.19). A similar population-based birth defect registry study by Shaw et al. [34, 39] showed a reduction in conotruncal heart defects (207 cases) and orofacial defects (731 cases) for women exposed to multivitamins containing folic acid and vitamin A during the periconceptional period relative to mothers with normal births over the same time period (orofacial defects: OR = 0.55 and 95% CI, 0.21–1.5; conotruncal defects: OR = 0 and 95% CI, 0–2.2). All birth defects identified were validated based on diagnostic imaging findings, surgery, or autopsy reports and were classified by a medical geneticist.

A third study by Mills et al. examined the intakes of vitamin supplements by mothers of 548 infants born with neural tube defects, 387 infants born with other major (not purely cosmetic) defects, and 573 normal controls [35]. Cases were identified through mandatory reporting registries, hospital records, services for crippled children, perinatal networks, and parent support groups. Mothers were interviewed about the nature of any birth defects that affected their children and later by an interviewer blinded to the existence of birth defects in offspring. Birth defects were validated by ultrasonographic and amniocentesis records, with 89 subjects meeting set criteria consistent with cranial neural crest defects [44–46]. Only 4 of the 1,508 mothers examined had intakes of above 25,000 IU, one of whom belonged to the group of 573 mothers with normal infants. No increased risk of either cranial neural crest defects (OR = 1.09; 95% CI, 0.24–4.98) or overall defects (OR = 0.73; 95% CI, 0.27–1.96) was observed when subjects with combined dietary and supplement intakes below 5,000 IU were compared with subjects with intakes over 10,000 IU. Organ meat consumption was also not associated with an increased risk of defects overall (OR = 0.82; 95% CI, 0.55–1.23).

Cohort studies

Conway [47] conducted a small, nonrandomized intervention in which mothers of infants with cleft lip, palate, or both were supplemented daily with 12,500 USP units of vitamin A plus other vitamins, including 0.5 mg of folic acid during a subsequent pregnancy. Among 48 mothers who received no vitamin sup-

plementation during pregnancy, there were five cases of congenital abnormalities, four of which included repeat cases of cleft lip, palate, or both. No cases of cleft lip or palate were observed in 39 women given supplementation during their subsequent pregnancy. Following this study, Smithells et al. [42] examined a cohort of 900 women to investigate the relationship between micronutrient consumption at 13 weeks of gestation and neural tube defects. A higher mean serum retinol concentration was observed in mothers of babies with neural tube defects (mean, 75.7 μg/dl; 95% CI, 58.5–92.9) than in mothers of unaffected babies (mean, 68.2 μg/dl; 95% CI, 43–108). However, this conclusion was based on a single high retinol level.

Subsequently, Zuber et al. [48] found no visible fetal malformations in 21 of 27 pregnant women for whom pregnancy outcomes were known and who had been exposed to high intakes of vitamin A during pregnancy. Vitamin A intakes varied from 100,000 IU per week to 250,000 IU in one week during pregnancy, with 18 subjects taking 25,000 IU per day.

Rothman et al. [26] conducted the first substantial cohort study on the teratogenic effects of vitamin A using a sample of 22,748 women undergoing screening for maternal serum alpha-fetoprotein or amniocentesis. Unlike earlier researchers, they evaluated retinol consumption taking into consideration dietary retinol consumption as well as that from supplements. Diet was assessed from telephone interviews by study nurses. Dietary retinol intake was calculated as the mean of the highest four weeks of intake during the first trimester. Birth defects were classified into cranial neural crest defects, neural tube defects, musculoskeletal or urogenital defects, and other defects.

A prevalence ratio of 4.8 (95% CI, 2.2–10.5) was observed for women consuming 10,000 IU or more of vitamin A relative to women with intakes of 5,000 IU or less. A total prevalence of cranial neural crest defects for women consuming greater than 10,000 IU of 3.2% was observed [43]. These researchers smoothed the dose-prevalence curve, which was fitted through individual data points by using quadratic splines [26, 43]. A rise in the prevalence of cranial neural crest defects was observed among women consuming more than 10,000 IU, although the curve for total retinol from diet and supplements rose more gradually. Rothman et al. [26] predicted that 1 in 57 babies born to mothers usually consuming more than 10,000 IU would have an abnormality attributable to this exposure.

Mastroiacovo et al. [37] prospectively evaluated the pregnancy outcomes of 423 women accessing the European Network of Teratology Information Service following exposures to vitamin A in excess of 10,000 IU daily or 50,000 IU weekly during pregnancy. Two groups of control subjects were followed: women with high vitamin A exposure later in pregnancy and women with reported exposures to nonteratogenic agents. Cases of chromosomal abnormalities and minor congenital deformities (e.g., preauricular tag) or problems were excluded from the analysis. A researcher blinded to the knowledge of the research hypothesis performed the identification of abnormalities in the women studied through telephone interviews with doctors or mothers.

The median dosage of retinol among cases was 50,000 IU per day (interquartile range, 25,000–60,000 IU per day). The prevalence rate in the cases relative to the control group exposed to retinol later than the first trimester was 0.28 (95% CI, 0.06–1.23). A prevalence rate of 0.5 (95% CI, 0.14–1.76) was also observed when women exposed to nonteratogenic agents were used as controls. These findings suggest no apparent relationship between total retinol dosage during the first trimester and birth defects. In this study of 120 infants exposed to more than 50,000 IU during embryogenesis, no abnormalities were observed. The results of this study do not support the teratogenicity of doses of retinol supplements of 10,000 IU or greater and contrast with the findings of Rothman et al. [26].

Discussion

Estimation of retinol consumption

Few studies have estimated overall retinol consumption in addition to supplement consumption. Only the prospective cohort study by Rothman et al. [26] and the case-control studies by the research teams headed by Mills [35, 40] and Smithells [42] provided estimates of total retinol consumption, either through assessment of dietary intake or serum retinol levels. It is likely, however, that intakes from regular vitamin A–containing supplements in many cases might far exceed intake from routine dietary sources for most participants. Therefore, although misclassification may have arisen for some participants, subjects consuming both vitamin A supplements and multivitamins containing vitamin A would mostly be correctly classified as having intakes exceeding 10,000 IU. Similarly, the study by Mastroiacovo et al. [37], in which exposure to vitamin A supplements was prospectively recorded, should provide fairly accurate records of high-dose vitamin A exposure.

All except one of the case-control studies examined suffered from potential recall bias, with retinol consumption being measured following births [35]. This bias is likely to be of particular importance for the study by Shaw et al. [34], in which the time delays between estimating nutrient consumption and the periconceptional period averaged 3.5 years. These

findings may have caused some misclassification of exposure status, resulting in the possible attenuation of significant results.

Relationship between timing of exposure and birth defects

The studies by Martinez Frias and Salvador [16] and Werler et al. [32], identified a higher risk of birth defects for exposure within the first two months of pregnancy. Martinez Frias and Salvador showed a decreasing risk of birth defects for women consuming doses higher than 40,000 IU from the first and second months of pregnancy to the fifth month and later. Similarly, Werler et al. showed a higher risk of overall deformities (OR = 2.5; 95% CI, 1.0–6.2) and cranial neural crest abnormalities (OR = 2.6; 95% CI, 1.0–6.9) for women exposed to high vitamin A intake in the first trimester.

The classification of vitamin A exposure into intake categories of 20,000 to 40,000 IU and more than 40,000 IU by Martinez Frias and Salvador showed a nonsignificant reduced risk of birth defects (OR = 0.5; 95% CI, 0.01–9.5) [16]. This is contrary to what might have been expected from the findings of Rothman et al. that 1 in 57 pregnant women with intakes beyond this level would be likely to have a child with a birth defect, although a wide confidence interval exists around this estimate [26]. This study has been criticized because of the possibility of recall bias in assessing vitamin A consumption, heterogeneity in the deformities observed, and the relatively low numbers of abnormalities identified in relation to the number of exposures in early pregnancy [37].

Association between vitamin A exposure and various forms of birth defects

Neural crest cell defects

The results of the study by Rothman et al. have been the source of much debate [37, 49]. It has been suggested that the classification used for cranial neural crest cells may have resulted in the inclusion of some birth defects from structures not derived from this cellular origin. An important criticism relates to the low number of cranial neural crest defects that were observed for subjects with dietary intakes exceeding 10,000 IU, of which at least four of the seven cases observed may have been misclassified [37, 50]. Khoury et al. [33] adopted a classification scheme for cranial neural crest defects similar to that used by Rothman et al. Possible misclassification in case definition may therefore have also arisen in this study, which might have been expected to attenuate the significant protective association that was observed for cranial neural crest defects (OR = 0.86; 95% CI, 0.76–0.97) arising from multivitamin consumption. Martinez Frias and Salvador observed higher relative risks of birth defects for subjects with intakes in excess of 40,000 IU, with reduced relative risks being observed for those with intakes below this level [16].

Variation has also existed between studies in the method of determining retinol consumption. The study by Rothman et al. [43] was unusual in that the four weeks of highest retinol intake were examined rather than the mean intake [6]. In addition, when the date of commencement of periconceptional multivitamins was unknown, the median date of commencement of multivitamins by the women examined was used [6]. However, if women with cranial neural crest defects, women with other abnormalities, and unaffected women were randomly misclassified with respect to retinol consumption, this would only be expected to increase the strength of the associations observed. These researchers have also been criticized for having an open-ended final category of retinol consumption (≥15,000 IU), although the analyses performed by these researchers were through individual data points [43]. Further analysis of the data into two groups according to daily intake of vitamin A–10,001 to 20,000 IU and 20,000 IU or greater—also showed a 4.6-fold higher prevalence ratio in the latter category [43]. These findings suggest that the inexactness of dietary assessment alone is unlikely to account for the findings observed in this study.

Shaw et al. [34] observed no evidence of an increased risk of cranial neural crest defects. Multivitamin intake was assessed by telephone interviews performed on average 3.5 years after delivery, with interviewers blinded until the end of the interview as to the birth outcome. Recall bias may have arisen if mothers of infants with birth defects recorded their exposure to vitamin A–containing supplements to a greater extent than mothers of normal infants. The existence of such bias would only be expected to reduce the relative risk estimates towards a protective effect still further. Similarly, the study by Mills et al. [35] failed to show a significantly increased risk of cranial neural crest defects from vitamin A and multivitamin consumption within six months of birth.

The findings of these studies relating to cranial neural crest defects contradict those of two studies showing increased risks of defects and other studies showing no increased risk of defects. Nevertheless, intakes of vitamin A above 10,000 IU daily should not be routinely recommended.

Neural tube defects

Smithells et al. [42] found that the mothers of babies with neural tube defects had higher mean serum retinol levels in the first trimester than mothers with normal births. An important weakness of this study was that a single high retinol level influenced these results. Mills et al. [35] did not confirm these findings

in a much larger study of 89 mothers of babies with neural tube defects. They observed no suggestion of a relationship between increased serum retinol and risk of neural tube defects, irrespective of the timing of the exposure in relation to neural tube closure. Sandford et al. [41] showed a significant protective effect of regular β-carotene and vegetable intake on neural tube defects; however, this is likely to have been influenced by folic acid consumption.

Congenital diaphragmatic hernia

A small case-control study by Major et al. [36] compared the retinol status of 11 newborns with congenital diaphragmatic hernia and 11 neonates without abnormalities. Controls were matched for gestational age, and no significant differences were observed in either birthweight or gestational age. Cord blood retinol levels and retinol-binding protein levels were significantly lower in cases than controls ($p < .0002$ and $p = .004$, respectively). In contrast, for seven case-control pairs for which maternal blood was collected, maternal serum retinol and retinol-binding protein levels were higher in cases than controls ($p = .41$ and $p = .004$). These authors suggested that rather than the low levels of retinol arising from low maternal levels, they may reflect a deficiency in the synthesis of retinol-binding protein in the fetal liver in the third trimester or a deficiency of a placental receptor.

Birth defects overall

Only the studies by Rothman et al. [26] and by Martinez-Frias and Salvador [16] suggested possible adverse effects from high levels of vitamin A consumption when birth defects were considered overall. Other studies did not confirm these findings and observed relative risks for birth defects near or below unity in all cases [33, 35, 37]. Rothman et al. [26] showed a significant increase in the risk of birth defects overall for women exposed to vitamin A above 10,000 IU relative to women with intakes below 5,000 IU; however, this increase was less marked than that for cranial neural crest defects. Therefore, concerns are still raised by this study about the safety of vitamin A exposure during pregnancy, even allowing for criticisms relating to possible misclassification of cranial neural crest cell-derived birth defects.

Rothman et al. [26] estimated that 1 in 57 babies would be born with a birth defect to women with intakes above 10,000 IU, a proportion that might be expected to increase with increasing dose based on their findings. The absence of birth defects among children of 120 women consuming greater than 50,000 IU [37] is a noteworthy observation, although the lack of cases may have arisen because of chance. The patient population examined by Rothman et al. [26] was unusual because of the relatively low rate of birth defects overall (1.5% total defects) [37] and because it consisted of women visiting a specialist for antenatal screening tests. The latter factor could introduce a specialist referral bias affecting reporting of outcome, exposure, or both [6]. Further birth defect registry studies may be of value in addressing this question.

Risk of birth defects from inadequate retinol consumption during pregnancy

Another concern is that inadequate dietary retinol intake may also result in birth defects. To date most studies on the effects of vitamin A intake on pregnancy have not been conducted in regions where vitamin A deficiency is endemic, so that limited evidence exists to address this question. Smithells et al. [42] commented that an inverse association between socioeconomic status and birth defects has been observed in a number of population-based studies. These researchers also showed that subjects with lower socioeconomic status have lower serum retinol levels. More recently, the finding that periconceptional multivitamin use in developed countries has resulted in reduced rates of fetal abnormalities also raises questions as to whether lower doses of vitamin A may have a protective effect during pregnancy, since many of these multivitamins contained doses of vitamin A below 10,000 IU [38].

Case-control studies

Evidence of a possible protective effect of low-dose vitamin A has been suggested by Khoury et al. [33], who observed a significant protective effect against cranial neural crest defects following consumption of multivitamins containing vitamin A during early pregnancy. It is unclear, however, whether this effect may have been attributable to other micronutrients within these multivitamin preparations, such as folic acid. The details of this study have been discussed previously.

More recently, a Hungarian population-based case-control study showed that the risk of birth defects may be reduced in women consuming vitamin A supplements during pregnancy [51]. This study examined 20,830 mothers of babies with isolated and unidentifiable multiple congenital malformations between 1980 and 1994, excluding congenital dislocation of the hip, congenital inguinal hernia, hemangiomas, and abnormalities of known origin. A total of 35,727 controls drawn from the national birth registry were matched by sex, birth week, and district of parents' residence. The supplement used was determined by questionnaires sent to all participants and through prenatal care logbooks completed by general practitioners.

Overall, a significantly greater number of controls (9.5%) than cases (7.9%, $p < .0001$) were exposed to vitamin A–containing supplements during pregnancy, this being medically validated in 57.4% of cases and 56.0% of controls. No statistically significant differ-

ences were observed in the proportions of cases and controls using vitamin A–containing supplements for each month of gestation. The odds ratio for a congenital malformation arising from exposure to vitamin A in the first trimester was significantly lower for polydactyly or syndactyly (OR = 0.52; 95% CI, 0.3–0.9), clubfoot (OR = 0.55; 95% CI, 0.4–0.9), and total congenital malformations (OR = 0.79; 95% CI, 0.7–0.8). For exposure at any time throughout the pregnancy, reductions in risk were observed for ear abnormalities (OR = 0.52; 95% CI, 0.3–0.9), cleft palate (OR = 0.53; 95% CI, 0.3–0.9), cardiovascular abnormalities (OR = 0.73; 95% CI, 0.6–0.9), undescended testis (OR = 0.72; 95% CI, 0.6–0.9), club foot (OR = 0.72; 95% CI, 0.6–0.9), and total malformations (OR = 0.79; 95% CI, 0.7–0.9).

Randomized, controlled trials

Results from the Nepal Nutrition Intervention Project (NNIP-2) have recently been evaluated. Unpublished data* from this randomized, controlled trial show a nonsignificant reduced risk of all birth defects (RR = 0.76, $p = .38$) for the group in this population treated with vitamin A or β-carotene relative to the placebo group. Reductions in relative risk were observed for cleft lip and palate (RR = 0.46, $p = .20$) and eye defects (RR = 0.21, $p = .05$). A nonsignificant higher risk of other craniofacial defects (RR = 1.86, $p = .37$) and ear or preauricular tags (RR = 1.19, $p = .72$) was observed.

Discussion

The study by Czeizel and Rockenbauer [51] is one of the largest case-control studies on this research question and therefore provides considerable power to examine the association between supplement consumption and birth defects. The weaknesses of this study were the failure to analyze the data according to dosage of vitamin A, the potential for recall bias, the possibility of a confounding effect due to folic acid consumption, and the low response rate among controls. Although dosage was not examined in the analyses, nearly all daily intakes of retinol for exposed subjects in the first trimester were in the range between 5,000 and 10,000 IU. No differences were seen in the proportion of cases and controls consuming vitamin supplements containing folic acid. The findings described could be explained if mothers who offered to act as controls had been more likely to consume supplements during pregnancy than potential controls who did not respond. No attempts were made to compare responders and nonresponders in terms of vitamin A consumption. Recall bias might also explain these findings, although the opposite finding of overreporting of vitamin A intake in cases relative to controls might be considered a more likely outcome to arise from this form of bias.

Despite the differences between the Hungarian population [51] and the Nepalese population [38] in terms of adequacy of maternal vitamin A intake, some similarities may exist in terms of the impact of low-dose vitamin A supplements on birth defects. Both studies showed lower overall rates of abnormalities and a reduced risk of cleft palate deformities. Czeizel and Rockenbauer [51] also reported a reduced risk of eye abnormalities, although this was not statistically significant (OR = 0.50; 95% CI, 0.1–2.0).

Fetal behavioral deficits from excessive vitamin A during pregnancy

Animal studies have shown behavioral deficits in the offspring of animals exposed to high dosages of vitamin A in early pregnancy, including delays in learning time [52]. These deficits have been shown to occur at doses in animals below levels required to produce gross teratogenic effects [15]. Hutchings et al. [53] found that the behavioral deficits did not correlate with brain size. It is possible that damage in hippocampal and cerebellar regions of the brain may be responsible for the behavioral defects [52].

β-Carotene

Absence of toxic effects

Excessive intakes of β-carotene are known to be nontoxic [1]. Dosages equivalent to 30 mg of β-carotene daily or greater result in hypercarotenemia and carotenodermia, which produces a characteristic yellowing of the palms and soles [1, 54]. These clinical features are reversible upon cessation of high β-carotene intake [54].

Evidence supporting safety in pregnancy

Animal studies. To date there have been no studies implicating β-carotene as a teratogen. Animal studies have shown that doses up to 1,000 mg/kg are not carcinogenic [17]. Polifka et al. [55] described one study in which 1 to 3 ml of red palm oil, a rich source of β-carotene and other carotenoids, was administered to pregnant rats that subsequently showed an increased frequency of fetal death, growth retardation, and malformations (anencephaly, ocular abnormalities). They stated that other studies have failed to confirm these findings in rats and rabbits. It was therefore concluded that some component other than β-carotene in the

* West KP. Effects of vitamin A supplementation of women during pregnancy on teratogenicity: a review of current literature and response to the National Technical Review (Bangladesh) 1999 (unpublished).

palm oil might have been responsible for the birth defects described in this animal study.

Human studies. Hathcock et al. [15] reported that infants born with carotenemia to mothers with high β-carotene intakes have been found to be normal. It is believed that the failure of large doses of β-carotene to increase serum levels of retinol may be responsible for the absence of a toxic effect [17]. Bendich and Langseth [52] described a study in which despite high dosages of supplemental β-carotene, sufficient to triple serum carotene levels, no increase in serum retinol was observed. β-Carotene has also been used in humans to treat protoporphyria at doses up to 180 mg per day without any increase in serum retinol levels [15].

Conclusions and recommendations

A number of policy statements have provided recommendations regarding safe levels of consumption and administration of vitamin A during pregnancy in relation to fetal development [3, 13, 56–59]. Recently, the World Health Organization (WHO) conducted a consultation to review this question [3]. In addition, the American College of Obstetricians and Gynecologists (ACOG) released a recent policy statement on vitamin A supplementation during pregnancy [58]. The recommendations from these policy statements are evaluated below in light of the evidence presented.

To whom is it safe to give vitamin A during pregnancy?

Existing recommendation (ACOG [58]):

> Dietary intake of vitamin A in the United States appears adequate to meet the needs of most pregnant women throughout gestation. Therefore, routine supplementation during pregnancy is not recommended.

Vitamin A and its derivatives are known to play an important role during morphogenesis [24]. Evidence in animals suggests that during pregnancy there is a reduction in serum retinol levels during the embryogenic period, which is met by an increase in serum retinol from maternal hepatic retinol stores. This suggests that vitamin A supplementation of pregnant women in areas where vitamin A deficiency is endemic and in whom hepatic stores may be inadequate could be beneficial.

Although many women in the fertile age range have suboptimal vitamin A intake, routine supplementation is not recommended in areas where vitamin A deficiency is not endemic [1, 60]. Given that the RDA is designed to provide a dosage of vitamin A that would conservatively ensure adequate hepatic vitamin A levels for three months across a population, allowing for groups with lower dietary intakes, it is likely that in industrialized countries there is little need for supplementation. This assumes, however, that groups with marginal deficiency do not fall substantially below the RDA. For women meeting the RDA, it is unlikely that any benefit would be obtained from additional vitamin A supplementation during pregnancy.

Further research would provide a clearer picture of the need for supplementation in high-risk population groups in developed countries and in subjects with potentially lower retinol consumption, including strict vegetarians [58], migrants from areas where vitamin A deficiency is endemic [61], and women not consuming liver [60]. The data from Czeizel [38], which suggested that low doses of vitamin A supplementation during pregnancy might be protective against birth defects in developed countries, warrant further examination and confirmation.

What is a safe dosage of vitamin A during pregnancy?

Existing WHO recommendations [3]:

> …independent of vitamin A status, 10,000 IU (3,000 μg retinol equivalents) per day is the maximum daily supplement to be recommended at any time during pregnancy.
>
> **Where vitamin A deficiency is endemic** among children under school age and maternal diets are low in vitamin A, health benefits are expected for the mother and her developing fetus with little risk of detriment to either from either a **daily supplement** not exceeding 10,000 IU of vitamin A (3,000 μg retinol equivalents), or a **weekly supplement** not exceeding 25,000 IU of vitamin A (8,500 μg) at any time during pregnancy.
>
> In this regard a single dose >25,000 IU is not advisable, particularly between day 15 and day 60 following conception (day 0); beyond 60 days after conception, the advisability of providing a single dose of >25,000 IU is uncertain; any risk of non-teratogenic developmental toxicity is likely to diminish as pregnancy advances. In the case of pregnant women who may be reached only once during pregnancy, health workers should balance possible benefits from improved vitamin A status against potential risk of adverse consequences from receiving a supplement.
>
> **Where habitual vitamin A levels exceed at least three times the RDA** (about 8,000 IU or 2,400 μg retinol equivalents) there is no demonstrated benefit from taking a supplement. On the contrary, the potential risk of adverse events increases with higher intakes—above about 10,000 IU—if supplements are routinely ingested.

None of the human studies examined has shown

a significantly greater risk of birth defects from consumption of vitamin A supplements of less than 10,000 IU per day. However, as discussed previously, there is likely to be no additional benefit to pregnant women who consume the RDA of vitamin A from taking additional dietary supplements of vitamin A. Based on one experimental study, dosages of vitamin A below 30,000 IU did not appear to be associated with levels of teratogenic metabolites higher than typically experienced in pregnant women. This again supports the safety of the maximum recommended dosage of 10,000 IU daily during pregnancy. Given the known potential teratogenic nature of vitamin A, its supplementation for women of childbearing age in well-nourished populations is not recommended at this point. At a population level, further studies would be necessary to determine whether benefits may exist from low-dose supplements in industrialized countries. Dosages of vitamin A below 10,000 IU should be adequate to meet the supplementary needs of women with inadequate intakes in industrialized countries and probably in developing countries.

At what period during pregnancy is it safe to provide vitamin A?

The recommendations discussed have provided safe ranges of vitamin A intake at all stages of pregnancy. Animal studies and human epidemiological studies suggested that the first trimester, during which organ development occurs, is the most critical period, particularly the first two months [14, 32]. Animal studies showing behavioral deficits from vitamin A exposure in later pregnancy suggest that it is not advisable to exceed the recommended intakes discussed at any stage throughout the pregnancy, although this risk might be expected to decrease as pregnancy progresses [3].

What form of vitamin A is safe? Dietary sources or supplements?

Buss et al. [4] have shown that dietary retinol produces less marked increases in serum levels of teratogenic metabolites than retinol consumed in the form of dietary supplements. Following consumption of 50 mg of dietary retinol, both the peak levels of retinol and the area under the plasma–concentration time curve showed negligible differences from endogenous levels [6]. In addition, only minimal increases above physiological levels of retinoic acid and 13-*cis*-retinoic acid have been observed following doses of vitamin A supplements as high as 30,000 IU. These findings suggest that both dietary and supplemental forms of retinol are safe at the levels stated in the existing WHO recommendations.

Because liver varies in vitamin A content, and frequent liver consumption could result in intakes above the recommended limit of 10,000 IU, van den Berg et al. [60] suggested restricting liver consumption to no more than one serving per day. They suggested that intakes resulting from consumption at this level would be unlikely to cause problems, although consumption regularly throughout pregnancy might be best avoided.

Given the findings that many women who do not consume liver may have vitamin A intakes below the RDA, these researchers cautioned against campaigns aiming at the avoidance of vitamin A–rich products. Some evidence exists that low-dose supplementation may be protective during pregnancy, particularly in populations with vitamin A deficiency; however, further confirmation of these findings is required.

The preferred form of vitamin A supplementation during pregnancy is as β-carotene. β-Carotene does not produce teratogenic effects during pregnancy in humans or animals. The fact that β-carotene plays an important role as a source of placental vitamin A provides further evidence that, when supplementation is necessary, vitamin A supplementation of pregnant women should be in this form.

Consideration should be given to the development of dietary interventions using food sources rich in β-carotene to provide additional vitamin A when needed rather than vitamin A supplements. This approach may allow pregnant women to achieve other nutritional requirements as well as their vitamin A requirements. In support of this approach is a report from rural Gambia in which vitamin A was increased by the use of sun-dried mangoes [3]. Strategies of this type warrant further evaluation.

Dangers of synthetic retinoids

Extreme caution should be taken to prevent pregnancy from occurring in women of childbearing age requiring synthetic retinoids for medical indications. These agents are known to be potent teratogens and produce a well-described phenotypic pattern of abnormalities. Detailed guidelines that have been proposed to prevent pregnancy have been discussed previously in this document. These pharmaceutical agents should only be prescribed by appropriately qualified medical personnel and with clear counseling about measures to prevent pregnancy, the teratogenic risks of these agents, and the need for a safe contraception period following their cessation.

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Vitamin A in pregnancy: Impact on maternal and neonatal health

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Abstract

Vitamin A is an essential nutrient, for which there is a slightly increased requirement during the third trimester of pregnancy, with even greater requirements for lactating women. Serum retinol levels decline during pregnancy, especially during the third trimester, followed by a rapid increase postpartum. Hemodilution and inadequate nutritional status contribute to this pattern. Night-blindness is more common in the third trimester of pregnancy, and night-blind pregnant women have lower mean serum retinol concentrations. Increased morbidity is associated with night-blindness in women, especially during pregnancy. Vitamin A supplementation during pregnancy in deficient populations reduces night-blindness, low serum retinol levels, and nutritional anemia during pregnancy and substantially reduces maternal postpartum infections. A substantial reduction in maternal mortality has been observed in malnourished vitamin A–deficient women following vitamin A or β-carotene supplementation. Infant cord blood retinol and birthweight appear to be resistant to maternal supplementation with vitamin A during pregnancy. No studies have reported an impact of maternal vitamin A supplementation on neonatal morbidity or mortality.

Introduction

Vitamin A is an essential nutrient because of its important roles in vision, cellular differentiation, embryonic development, reproduction, growth, and the immune system [1]. The need for vitamin A is particularly critical during periods of rapid growth and tissue development, such as occur in pregnancy and early childhood; however, it is known that excessive doses of vitamin A, particularly in some forms, may be harmful. This report examines the evidence relating to the health benefits of vitamin A supplementation in pregnancy for both the mother and the newborn infant.

The report is divided into two main sections. In the first section, the biochemical forms of vitamin A and their physiological importance in pregnancy, lactation, and fetal development are examined. In the second, studies of the effects of vitamin A supplementation in pregnancy on maternal and newborn outcomes are examined. The recommendations identify opportunities for program development as well as areas for future research.

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Metabolism of vitamin A in pregnancy and lactation

Vitamin A is a broad term used to describe a family of compounds, the parent of which is all-*trans*-retinol [1]. In addition to molecules derived from all-*trans*-retinol, provitamin A carotenoids, including β-carotene, that can be converted into all-*trans*-retinol are included in view of their biological activity [1]. Important derivates of all-*trans*-retinol include its aldehyde form (retinal), its acid form (retinoic acid), its storage form (retinyl palmitate), and its water-soluble form (β-glucuronide) [1]. Synthetic derivates of all-*trans*-retinol will also be discussed later in this report.

Absorption, transportation, and storage of vitamin A

Vitamin A in the form of retinyl esters and provitamin A carotenoids is absorbed from the small intestine during digestion following its release from food by proteolytic enzymes [1]. Bile and pancreatic enzymes hydrolyze these compounds, which are transported from micelles into the epithelia of the intestinal villi [1]. Cleavage of provitamin A carotenoids occurs within the intestinal villi to produce the retinal form

of vitamin A [1, 2]. Retinal within the intestinal villi is bound to a cellular retinol-binding protein (CRBP-II), which can be reduced to bound retinol [1]. This retinyl ester, along with some unesterified retinol, is released into the lymph system within chylomicrons [1].

The chylomicron remnants that result following hydrolysis within the plasma contain carotenoids and vitamin A, which are then taken up predominantly by liver parenchymal cells [1]. Within the liver, vitamin A is stored within the parenchymal cells, mostly as retinyl ester, but also in small quantities as retinol [1]. The other major cell type within the liver responsible for vitamin A storage is the stellate cell [1]. The parenchymal cell can transfer retinol to the stellate cell, which is the main storage site for vitamin A in the liver [1]. Vitamin A stored within the liver as retinyl ester is hydrolyzed to retinol and can then be released into the circulation when needed [1]. Upon release into the circulation, retinol is delivered to the tissues predominantly bound to retinol-binding protein (RBP) [2]. Little is known about the regulation of the release of retinol from the liver, although it is believed that homeostatic mechanisms control this process [1].

Within cells, retinol is bound by cellular retinol-binding protein (CRPB), one exception being within the intestine, where it is bound to CRBP-II [1]. Similarly, retinoic acid is bound to cellular retinoic acid-binding protein (CRABP) or cellular retinal-binding protein (CRALBP) in the case of the eye [1]. Recently two sets of nuclear retinoic acid receptors have been discovered in tissues [1]. These receptors have provided new evidence on the role of vitamin A in cellular differentiation.

Units for measuring vitamin A intake

In this article, vitamin A is usually reported in either international units (IU) or retinol equivalents (RE). To convert international units derived from retinol to retinol equivalents, the value must be multiplied by 3.33 [3]. Because each system of measuring vitamin A makes different assumptions about the efficiency of metabolism of provitamin A sources to equivalent retinol intake, conversion cannot always be obtained exactly on the basis of a simple multiplication [2]. Occasionally vitamin A intake may also be expressed in micrograms (μg) or micromoles (μmol). Table 1 provides details of interconversions between each of these units.

Required and observed intakes of vitamin A

There is an increased need for vitamin A during pregnancy, although the additional amount is small and is limited to the third trimester. The level of vitamin A stored in the fetal liver is low and does not increase greatly if additional vitamin A supplements are given to the mother [4]. The 1988 recommended dietary intakes (RDI) of the Food and Agriculture Organization and the World Health Organization (FAO/WHO) defined two levels of intake, basal and safe levels, both of which assume an adequate total body reserve of vitamin A. The basal requirement is defined as the "average daily amount needed to prevent clinically demonstrable impairment of function," and the higher safe intake is sufficient for those few individuals with particularly high needs [5]. The recommended dietary intake levels have been formulated to ensure sufficient hepatic stores for three months in a 62-kg woman to allow for suboptimal intake and stress. An additional amount of 100 μg RE/day has been recommended as sufficient in pregnancy to meet the extra needs of the fetus without depleting maternal stores [5]. The total vitamin A needs of the fetus in the third trimester of pregnancy are estimated to be about 9% of total mean maternal stores of vitamin A [4]. For women who have adequate vitamin A stores and average long-term intakes of vitamin A above the safe level, no additional vitamin A intake is required during pregnancy.

The estimated vitamin A requirements of lactating women are higher than those of pregnant women. During the first six months of lactation, from 25% to 50% of a woman's total reserve of vitamin A (estimated as 206 mg) would be secreted in breastmilk [4]. To maintain maternal hepatic stores of vitamin A during lactation, an additional amount of 500 μg RE/day has been recommended during the first six months of lactation [5] and a slightly lesser amount for women lactating for longer than six months (+400 μg RE/day). Inadequate maternal stores of vitamin A will impair the transfer of vitamin A to the newborn through breastmilk.

Table 2 compares the recommended dietary intakes of vitamin A in adult women and pregnant or lactating

TABLE 1. Conversion of different units of vitamin A

Unit	Equivalent unit
1 retinol equivalent (RE)	1.0 μg all-*trans*-retinol
	6.0 μg all-*trans*-β–carotene
	3.33 IU vitamin A activity from retinol
	10.0 IU vitamin A activity from β-carotene
1 international unit (IU)	0.30 μg all-*trans*-retinol
	0.60 μg all-*trans*-β–carotene
1 μg retinol	1.0 μg RE
	0.0035 μmol
1 μg β–carotene	0.167 μg RE
	0.0019 μmol
1 μmol retinol	286.44 μg retinol
1 μmol β–carotene	536.85 μg β–carotene

Source: adapted from ref. 3

TABLE 2. Recommended dietary intakes of vitamin A in retinol equivalents for adult women, and additional intakes for pregnancy and lactation (mg RE/day)

Group	RDI (FAO/WHO)[5]		RDA (USA)[6]	DRV (UK)[7]		
				Reference nutrient intake		
	Basal	Safe		Lower	Average	Upper
Women 10–70 yr	270	500	800	250	400	600
Pregnant women	+100	+100	0			+100
Lactating women 0–6 mo	+180	+350	+500			+350

Source: adapted from ref. 1.
RDI, Recommended dietary intake; RDA, recommended dietary allowance; DRV, dietary reference values.

women from three different sources: FAO/WHO [5], the United States [6], and the United Kingdom [7]. The safe intake of FAO/WHO, the recommended dietary allowance (RDA) in the USA, and the upper reference nutrient intake in the UK all have similar definitions. These recommended intakes vary from 600 μg RE/day to 800 μg RE/day. Different definitions, and different assumptions about reference weights for adult women, may account for the variation between the lower levels for the FAO/WHO and the UK recommendations [1].

These recommended levels of nutrient intakes have been established for healthy individuals, but the need for vitamin A would be substantially increased in the presence of illness, especially febrile infectious illnesses, and conditions causing lipid malabsorption [1]. These conditions are often met in populations from developing countries, where infectious diseases in women and children, such as diarrhea, respiratory tract infections, malaria, and intestinal parasites, are all more prevalent than in industrialized countries and can contribute to increased vitamin A needs in these populations.

Studies of observed intakes of vitamin A from food in adult women have reported a median intake of 686 μg RE/day in the UK but higher intakes of 880 μg RE/day in the USA [8]. The mean observed intake of vitamin A in pregnant women in the USA has been reported as 1,200 μg RE/day [9]. In developing countries, seasonal variation in intakes of vitamin A can be considerable because of fluctuations in the availability of foods with high levels of bioavailable provitamin A carotenoids, such as fruits and vegetables. In industrialized countries, these fluctuations in vitamin A intake are less marked, because a higher proportion of vitamin A is derived from preformed vitamin A. Furthermore, the well-developed food market systems that make available preserved and processed foods that are often fortified with vitamin A provide access to a variety of vitamin A–rich foods throughout the year. Nonetheless, even in highly industrialized countries, some disadvantaged groups may exist with low levels of vitamin A intake [1].

Changes in serum retinol during pregnancy

A large number of studies from both industrialized and developing countries have reported a pattern of declining serum retinol levels during pregnancy, especially in the third trimester, followed by a rapid increase postpartum [10–30]. Only three studies have failed to report a similar pattern [31–33]. The findings from most of these studies are summarized in table 3. It should be noted that no attempt has been made to adjust the results based on the method used to assay vitamin A.

In the largest study [16], there was a 9% drop in the average serum retinol values between the first and third trimesters, whereas in the longitudinal studies [12, 21, 29, 30], there was an average decline of 14% in the serum retinol levels between the first and third trimesters. Five percent or less of women early in pregnancy have been reported to have serum retinol levels below 20 μg/dl [11, 36], but this proportion increases up to 30% in the third trimester [11, 37]. Two main factors contribute to this pattern of declining serum retinol during pregnancy: hemodilution and nutritional status. As pregnancy progresses, hemodilution from an expanding blood volume contributes to the lowering of serum retinol levels, and the sudden reversal of this process following delivery leads to a rapid increase of serum retinol levels. Supporting this view is the observation that serum retinol does not change with gestation after adjustment with the corresponding hematocrit values [20]. In addition, the decline in serum retinol levels in the third trimester of pregnancy is of similar magnitude to the decline in serum albumin [23] and serum retinol-binding protein [38]. In contrast to retinol, serum β-carotene levels and other fat-soluble nutrients increase during the third trimester of pregnancy [16, 18–20, 23, 24].

In some populations, poor nutritional status and low dietary intake of vitamin A are also likely to contribute to the decline in serum retinol during pregnancy. As can be seen from table 3, the largest percentage declines in serum retinol between the first and third trimester,

TABLE 3. Plasma vitamin A concentrations in pregnant and postpartum women

Trimester 1	Trimester 2	Trimester 3	Postpartum (0–6 wk)	Design	Reference
Vitamin A (μg/dl)(no. of subjects)					
32 (35)	32 (35)	27 (62)	—	Cross-sectional	Bodansky et al. 1943 [11][a]
—	34 (12)	26 (12)	—	Longitudinal	Bodansky et al. 1943 [11][a]
25 (43)	26 (65)	23 (75)	31 (62)	Longitudinal	Lund & Kimble 1943 [12][a]
29 (30)	28 (44)	26 (27	32 (51)	Cross-sectional	Anderson et al. 1946 [13][a]
32 (16)	37 (19)	31 (26)	33 (16)	Semilongitudinal	Cayer et al. 1947 [14][a]
30 (5)	31 (42)	29 (19)	38[b] (37)	Cross-sectional and partly longitudinal	Hoch & Marrack 1948 [15][a]
33 (343)	34(1,376)	30(1,974)	42(1,553)	Longitudinal	McGanity et al. 1954 [16][a]
—	—	22[c] (35)	31 (96)	Cross-sectional and longitudinal	Pulliam et al. 1962 [18]
31 (10)	27 (10)	20 (33)	25[d] (35)	Cross-sectional	Venkatachalam et al. 1962 [19]
50 (29)	42 (39)	43 (55)	45 (55)	Cross-sectional	Kelner et al. 1969 [21]
46 (19)	36 (19)	33 (19)	38 (19)	Longitudinal	Kelner et al. 1969 [21]
45 (7)	47 (69)	44 (168)	—	Cross-sectional	Dawson et al. 1969 [20]
30 (10)	24 (24)	23 (56)	20 (10)	Cross-sectional	Basu & Arulanantham 1973 [23]
34 (?)	41 (?)	43 (?)	—	Cross-sectional and longitudinal	Gal & Parkinson 1974 [33]
51 (57)	48 (262)	49 (263)	66[e] (184)	Cross-sectional	Morse et al. 1974 [24]
—	45 (23)	49 (23)	—	Longitudinal	Howells et al. 1986 (Asians) [29][f]
—	55 (21)	39 (21)	—	Longitudinal	Howells et al. 1986 (others) [29][f]
—	34 (285)	29 (285)	—	Longitudinal	Tamura et al. 1997 [34]
38 (195)	34 (177)	36 (144)	45 (156)	Longitudinal	Dibley & Hakimi 1999 [35]

a. Calculated from original IU or USP units by multiplying by 3.
b. Value is for up to 63 days postpartum.
c. Value is for pregnant women (of varying stages of gestation).
d. Value is for nursing mothers (period postpartum not specified).
e. Value is for up to 58 days postpartum.
f. Calculated from original mmol/L by multiplying by 28.57.

and among the lowest mean serum retinol levels in the third trimester, were reported in women from low socioeconomic communities in India [23, 38]. In a malnourished rural population in Indonesia, 23% of pregnant women had serum retinol levels below 10 μg/dl [26]. In a US population of low-income pregnant women who were not taking vitamin supplements, 33% had serum retinol below 20 μg/dl [37]. Several other studies have shown an association between low socioeconomic status and low serum retinol levels in pregnancy [39–44].

Vitamin A in pregnancy: impact on maternal and newborn outcomes

Until recently, little attention was paid to vitamin A status in women during pregnancy. Initially the focus was on improving maternal vitamin A status as a means of improving vitamin A status in infancy and early childhood [8]. However, the recently reported finding of a substantial reduction in maternal mortality of a cohort of women in Nepal following supplementation with vitamin A or β-carotene [45] has led to a renewed interest in the role of vitamin A in the health of women during pregnancy and the postpartum period. These findings have raised a number of questions: Is there evidence of vitamin A deficiency in women during pregnancy? What are the health consequences of such deficiency? What is the evidence for important health benefits from vitamin A supplementation during pregnancy for the women and the newborn? Should vitamin A supplementation during pregnancy be recommended on a routine basis in populations with evidence of maternal vitamin A deficiency? Do we know enough about the extent of maternal vitamin A deficiency in different populations around the world to plan such interventions?

Maternal nutrition and health

Maternal vitamin A status: Serum retinol

Serum retinol declines during pregnancy to reach a nadir in the third trimester, followed by a rapid increase postpartum. Contributing to this decline are both hemodilution from an expanding blood volume as pregnancy progresses and inadequate intake of vitamin A. The frequency and extent of the decline are greater in women of low socioeconomic status;

however, the functional significance of this decline in serum retinol during pregnancy is unclear. A modest reduction in serum retinol levels during pregnancy that is not associated with symptoms of vitamin A deficiency does not necessarily indicate reduced vitamin A stores and may be of no significance for the health of the woman and her infant [27]. However, as will be noted in the following sections, night-blindness is more common in the third trimester of pregnancy [46], corresponding with the period when serum retinol concentrations are lowest. Furthermore, the decline in serum retinol levels during pregnancy can be reduced or stopped by treatment with vitamin A.

Maternal night-blindness

Night-blindness is the inability of individuals who have normal vision during daylight to see as the sunlight recedes in the evening. This poor adaptation to darkness occurs when there is a decreased production of rhodopsin, a vitamin A–dependent photosensitive pigment in the rod cells of the retina. Normally the rod cells are stimulated by dim light, allowing individuals to adapt to darkness and develop scotopic or night vision. In vitamin A deficiency, the reduced rhodopsin level results in a delayed visual adaptation to darkness, or even an inability to see at night if the deficiency is sufficiently severe [47].

The condition has been well recognized in children in developing countries, where it has been associated with an increased risk of childhood morbidity and mortality [48, 49]. In children night-blindness is an early indicator of vitamin A deficiency, and a history of night-blindness has been demonstrated to be a specific and sensitive indicator of low serum retinol levels [50]. In contrast, little attention has been paid to night-blindness in women of reproductive age [51, 52].

There are several clinic-based reports of night-blindness or impaired dark adaptation in pregnant women who were likely to have an inadequate dietary intake of vitamin A. Birnbacher in 1927 (cited in Oomen [53]) described an epidemic of night-blindness in postwar Vienna from 1920 to 1924. He observed that "pregnant women become night blind by preference towards the end of their term; in no case (of 30) was xerosis present; their nutritional state was satisfactory generally." There was a further report of night-blindness in pregnant women in Newfoundland and Labrador, Canada, in 1930 [54]. The condition appeared late in pregnancy and disappeared spontaneously after delivery. The investigator also noted that "three large tablespoon doses of cod oil" relieved the symptoms in one case within three days. In 1936, Edmund and Clemmesen [55] observed that 25 of 50 pregnant Danish women had dark dysadaptation that improved following an intramuscular injection of 40,000 IU of vitamin A. Ricketts in Ohio, USA, in 1939 reported two cases of vitamin A deficiency in pregnancy with night-blindness [56]. In 1940, Williams et al. [57] reported that 62% of 123 pregnant women examined in Philadelphia, USA, had vitamin A intakes below the recommended levels and that 35% had abnormal dark-adaptation times. The dark-adaptation time decreased in 21 of 28 women, who initially had abnormal dark-adaptation times, following 20,000 IU of vitamin A daily for one week. The review of vitamin A requirements of humans by Rodriguez and Irwin [58] provides more details of these early clinical studies. What is clear from these reports is that night-blindness in pregnancy was observed in Europe and the United States in the 1930s and 1940s but had apparently disappeared by the 1950s.

Further reports of night-blindness in pregnancy did not appear in the literature until 1966, when Dixit observed that 77 of 203 pregnant women examined in a clinic in Maharashtra, India, reported night-blindness during their current or previous pregnancies, mainly in the third trimester [46]. The condition spontaneously resolved soon after delivery, corresponding to a time when serum retinol rises rapidly (see table 3). Furthermore, the symptoms were temporarily relieved by an intramuscular injection of vitamin A. In 1969, Mandal et al. observed that 4.6% of women admitted to obstetric wards in West Bengal, India, reported being night blind [59].

There are few reports of population-based surveys to assess the extent of night-blindness in pregnant and lactating women in developing countries. A survey of currently pregnant women from five districts in Sri Lanka [41] reported a prevalence of night-blindness at some time during pregnancy ranging from 0.6% to 2.8%. In contrast, a very high prevalence of any night-blindness (52%) during their previous pregnancy was reported by women in Jumla, Nepal, a remote community with a documented very high prevalence of vitamin A deficiency in children and a very high infant mortality rate (Starbuck 1993, cited in Katz et al.[51]). In the rural Terai region of Nepal, a cross-sectional study of pregnant and lactating women found that 8.1% of pregnant women were night blind at the time of interview, although 16.2% of the lactating women reported being night blind at some time during their preceding pregnancy [51]. Night-blindness has also been reported recently from Central Java, Indonesia, where 4.8% of the women in the placebo group of a trial of vitamin A and zinc supplements in pregnancy reported night-blindness during the seond or third trimester of pregnancy [30].

In cross-sectional surveys in three provinces in southern Vietnam in 1999, the prevalence of night-blindness among women aged 15 to 49 years during their most recent pregnancy within three years of the interview was 1.5% in Ben Tre Province, 5.6% in Long An Province, and 10% in Quang Ngai Province [60].

However, a lower prevalence of night-blindness (1.0%) in pregnant women was reported in a 1995 national vitamin A survey in Vietnam [61]. These different estimates of prevalence might relate to the way in which the information was collected in the two surveys.

In the three-province survey in Vietnam in 1999, women were asked for a detailed history of their most recent pregnancy, including whether they had ever experienced night-blindness, using local terms for the condition depending on the ethnic group being interviewed. In the national survey in 1995, all women with a preschool-aged child were questioned, and the estimate of night-blindness during pregnancy was based on those women who self-reported that they were currently pregnant at the time of interview. In addition, it was unclear whether local terms for night-blindness were used in these interviews. Since night-blindness is more frequent during the third trimester, it is likely that latter approach would record a lower prevalence than asking women if they had ever experienced night-blindness during their last pregnancy.

In a supplementation trial in Nepal, a trained village fieldworker, using a local term, asked women if they were night-blind. Reports of night-blindness were verified within a week by specially trained interviewers who asked more detailed questions about the symptoms and their effects on the women's activity. Seventy-nine percent of the histories of current night-blindness were verified by this method. Thus, it is likely that some of the variation in estimates of the prevalence of night-blindness between studies is related to the method used to collect the information. Finally, night-blindness will only be a useful indicator of maternal vitamin A deficiency if the condition is recognized in the community and there are locally meaningful terms to describe the symptoms.

A number of factors have been reported to be associated with night-blindness in women during pregnancy. Women of lower socioeconomic status are more likely to report night-blindness in pregnancy [51, 62]. Lower intakes of vitamin A–rich foods, either preformed vitamin A or provitamin A carotenoids, were also associated with night-blindness in pregnancy [61, 62], although this effect was modified by season in Nepal, possibly related to variations in the availability of these vitamin A–rich foods in some seasons [62]. In the 1995 National Vitamin A Deficiency Survey in Vietnam, the prevalence of night-blindness was higher in women of reproductive age who had less education and was slightly higher in older women [61]. In addition, recent morbidity, such as abdominal pain, dysentery, diarrhea, or nausea, was associated with an increased risk of night-blindness in women from Nepal [62].

Lower levels of serum retinol have been reported in women with night-blindness during pregnancy. In a case-control study of night-blindness in Nepal, the mean serum retinol in the women with night-blindness was 20.6 μg/dl, as compared with 29.4 μg/dl in the control subjects, and this difference was statistically significant ($p < .001$) [62]. Similarly, in a trial of vitamin A and zinc supplementation in Indonesia, 2.5% of the women reported they were night blind early in their second trimester. The mean serum retinol of the night-blind women was 20.2 μg/dl, as compared with 40.1 μg/dl in the women without night-blindness, and this difference was statistically significant ($p < .001$) [30].

Night-blindness during pregnancy is associated with poor health and nutritional status and an increased risk of pregnancy complications. In Indonesia, a cross-sectional study of pregnant women reported a significant positive association between hemoglobin levels, hematocrit, serum iron levels, and serum retinol levels [44]. In a multivariate analysis of these survey data, after confounding factors were controlled for, each 1 μg/dl increase in serum retinol predicted a 1.5 g/L increase in hemoglobin and a 0.48 L/L increase in hematocrit.

Given this association, it is not surprising that pregnant women who are night blind or xerophthalmic are more likely to be anaemic than are non-night-blind women. In India, xerophthalmic pregnant women had mean hemoglobin levels of 8.3 ± 0.3 g/dl, which was significantly lower ($p < .001$) than the mean hemoglobin of 10.8 ± 0.4 g/dl for non-xerophthalmic pregnant women [63]. In Nepal, pregnant women who reported being night blind had a significantly lower ($p < .004$) mean hemoglobin (8.9 g/dl) than women who were not night blind (9.6 g/dl) [62]. This association may be indirect because of the overall poorer nutritional status of night-blind women; however, the evidence of a response of hemoglobin levels to vitamin A supplementation in vitamin A–deficient pregnant women suggests an independent effect of vitamin A on utilization of iron [64].

One study from Nepal reported that pregnant women who were night blind had significantly lower body weight, body mass index (BMI), arm circumference, and skinfold thickness than control women [62]. An earlier, small clinic-based study from Nigeria found that clinically malnourished pregnant women had lower BMI, arm circumference, and serum retinol levels than clinically normal pregnant women; however, the investigators did not report whether the malnourished women had experienced night-blindness. Other studies have found an association between low serum retinol and indicators of protein-energy malnutrition in pregnant women [26, 65]. More research in different populations is needed to confirm this relationship between maternal vitamin A deficiency, including night-blindness, and maternal protein-energy malnutrition.

Recent maternal morbidity is associated with night-

blindness of women of reproductive age, especially during pregnancy. In women of reproductive age in Vietnam, there was a fourfold increase in the odds of maternal diarrhea during the two weeks prior to the interview in the night-blind women in comparison with the non-night-blind women [61]. Similarly in a case-control study of risk factors for night-blindness in Nepal, women who were night blind were two to three times more likely to report diarrhea or symptoms of urinary or reproductive tract infections during the week prior to the interview than controls [62]. This association persisted when morbidity was included in a multivariable logistic regression model that controlled for the effects of intake of vitamin A–rich foods and socioeconomic status of the women.

There is only limited information about the functional significance of vitamin A deficiency and in particular night-blindness in pregnancy and whether or not it is associated with an increased risk of maternal morbidity and mortality. There are no reports of cohort studies that have examined the relationship between maternal night-blindness during pregnancy and subsequent risk of pregnancy-related or other morbidities. The incidence of night-blindness was assessed by history in 9,932 women in Nepal who participated in the Nepal Nutrition Intervention Project–Sarlahi (NNIPS-2) trial of low-dose vitamin A and β-carotene supplementation before and during pregnancy. Among the women in this trial reporting night-blindness, the death rate was 25.6/1,000, as compared with 3.4/1,000 in non-night-blind women, a 7.5-times higher risk of maternal death (95% CI, 3.06–18.27) [66]. However, from this very brief report, it is not clear whether this comparison is restricted to the placebo group and whether the effect is independent of other health and nutrition risk factors for maternal deaths present in the study population.

Impact of supplementation on maternal vitamin A status

There are several early reports of an impact of vitamin A supplementation on serum retinol levels in pregnancy. A semilongitudinal observational study in 1943 in London of serum retinol levels during pregnancy noted that women taking vitamin A supplements had higher levels of serum retinol throughout pregnancy than women not taking supplements [15]. Nonetheless, the usual pattern of a decline in serum retinol as the pregnancy progressed was observed in both groups of women.

In 1947 in New York, a controlled trial examined the impact on serum retinol levels of daily supplements, starting in the middle of the second trimester, with 10,000 IU of vitamin A ($n = 122$) or the equivalent dose of β-carotene ($n = 123$), versus no treatment ($n = 93$). Supplementation resulted in significantly ($p < .001$) higher levels of serum retinol by the ninth month of pregnancy in both the vitamin A and the β-carotene treatment groups (36.8 μg/dl), in contrast to the control group (27.9 μg/dl) [67]. This intervention did not affect the level of serum retinol in infant cord blood, which remained lower than the maternal serum retinol levels in all treatment groups. Briefly, the serum retinol was 21.9 μg/dl in the control group, 19.8 μg/dl in the vitamin A–treated group, and 21.0 μg/dl in the β-carotene-treated group [67].

A small controlled trial of vitamin A supplementation in 29 pregnant Asian women in London revealed a significant ($p < .05$) increase in maternal serum retinol at delivery and a nonsignificant increase in infant cord serum retinol in the vitamin A–supplemented group [29]. The women selected for this trial had a serum retinol level <35.4 μg/dl at 28 weeks of gestation. The supplementation with 8,000 IU of vitamin A started at 30 weeks of gestation and continued until delivery. The serum retinol in the vitamin A–treated group ($n = 14$) was 37.7 μg/dl, in comparison with 28.6 μg/dl in the control group ($n = 15$) [29].

In India, a controlled trial of daily supplements with 6,000 IU (1,800 RE) of vitamin A, administered to 202 pregnant women at different stages of pregnancy and for different durations, revealed that supplementation for more than 12 weeks was needed to prevent the decline in serum retinol levels at 34 to 38 weeks of gestation [68]. Serum retinol was 29.5 μg/dl in the control group at 34 to 38 weeks ($n = 39$), 30.1 μg/dl in women supplemented for 8 to 10 weeks ($n = 5$), and 36.1 μg/dl in women supplemented for more than 12 weeks ($n = 29$). This finding might reflect the severity of the maternal vitamin A deficiency in this population, which required more than 12 weeks of vitamin A supplements for correction. However, the weak design of this trial leaves chance also as a possible explanation for these variations in serum retinol following different durations of supplementation.

A further analysis of data from 30 women in the trial who had four serial blood measurements during pregnancy suggested that only women with a plasma retinol less than 30 μg/dl before 20 weeks of gestation showed a significant increase in plasma retinol during pregnancy when supplemented with vitamin A [69]. In this trial, the infant cord serum retinol levels were higher in the vitamin A–supplemented group (19.5 μg/dl for 8 to 12 weeks of supplementation, and 23.2 μg/dl for more than 12 weeks of supplementation) than in the control group (13.5 μg/dl). However, this difference was only significant in those women who were supplemented for more than 12 weeks [68]. This response of infant cord serum retinol to supplementation with vitamin A might also reflect the severity of maternal vitamin A deficiency in this population. Night-blindness was not assessed in the pregnant women who participated in this trial.

In Indonesia in 1992, a double-blind, placebo-controlled trial, using a factorial design, examined the impact of vitamin A and iron supplementation, starting at 19 weeks of gestation and continuing for 8 weeks, on serum retinol and indicators of iron status [64]. The baseline serum retinol for all treatment groups in this study was 30.9 μg/dl. During the 8 weeks of treatment, there was an increase in serum retinol (after adjustment for change in the placebo group) of 5.7 μg/dl in the women treated with vitamin A alone, and of 7.14 μg/dl in the group treated with vitamin A and iron. Symptoms of night-blindness in the women participating in the trial were not monitored.

A further trial in Indonesia conducted from 1995 through 1997 examined the impact of vitamin A and zinc supplementation on maternal sepsis and vitamin A status, using a double-blind, placebo-controlled, 2 × 2 factorial design [30]. The trial included 2,173 pregnant women with an average gestation of 12.5 weeks at enrolment. Women were individually randomized to one of four treatment groups: a daily dose of 2,400 RE of vitamin A, a daily dose of 20 mg of zinc, the same daily dose of both zinc and vitamin A, or a placebo with no vitamin A or zinc. A prospective monthly surveillance system was used to detect night-blindness in the pregnant women participating in the trial. Compliance with the daily supplements was high in this trial, with an average of 81% of distributed capsules being consumed by trial participants. At baseline before treatment, when the women were in their second trimester of pregnancy, 2.1% (23/1,089) of the women in the vitamin A–treated group and 2.9% (31/1,084) of those in the non-vitamin A –treated group reported experiencing night-blindness. The women reporting night-blindness had a significantly lower mean serum retinol (20.2 ± 13.97 [SD] μg/dl) than the non-night-blind women (40.1 ± 13.92 [SD] μg/dl).

Vitamin A significantly reduced the percentage of women reporting night-blindness during the second and third trimesters of pregnancy from 6.3% (68/1,084) in the women not treated with vitamin A to 0.8% (9/1,089), an 87% reduction in the risk of night-blindness (RR = 0.13; 95% CI, 0.07–0.26) [30]. In this trial, a subgroup of 846 women had consented to have serial blood samples collected in each trimester and six weeks postpartum. There were no significant differences in the baseline serum retinol levels of these women between treatment groups, and the mean serum retinol for all groups combined was 38.2 ± 13.55 (SD) μg/dl.

At baseline the percentage of women with serum retinol less than 30 μg/dl was higher in the vitamin A–treated group (31.5%) than in the non-vitamin A–treated group (26.1%). However, in the third trimester the percentage of women with serum retinol less than 30 μg/dl was lower in the group treated with vitamin A (25.1%) than in the group not treated with vitamin A (34.5%). In contrast, the percentage of women with serum retinol less than 30 μg/dl was only slightly lower in the group treated with zinc (28.7%) than in the group not treated with zinc (30.7%). Furthermore, the mean serum retinol was higher in the group treated with vitamin A (40.5 μg/dl) than in the group not treated with vitamin A (37.0 μg/dl) [30].

The impact of vitamin A and β-carotene supplements on maternal night-blindness was examined in a large, community-based, group-randomized, placebo-controlled trial conducted in Nepal between 1994 and 1997 [70]. In this trial, 29,000 women of childbearing age from 171 wards were randomized to one of three treatment groups receiving weekly supplementation with 7,000 μg retinol equivalents (23,000 IU) of vitamin A, or β-carotene, or a placebo with no vitamin A. Night-blindness was assessed by prospective weekly surveillance during pregnancy and by recall at three and six months postpartum. The supplementation was continued over a period of three years, during which 9,932 woman who were pregnant for the first time were recruited into the trial.

Vitamin A significantly reduced the percentage of women reporting night-blindness during pregnancy from 10.7% in the control group to 6.7%, a reduction of 38% in the risk of night-blindness (RR = 0.62; 95% CI, 0.45–0.85). In contrast, β-carotene had less impact, with a nonsignificant 17% reduction in the risk of night-blindness (RR = 0.83; 95% CI, 0.45–1.11). When the analysis was restricted to women who took more than 95% of the supplements starting one month before conception until the end of pregnancy, vitamin A reduced the incidence proportion of verified night-blindness by 67% (RR = 0.33; 95% CI, 0.18–0.59); however, there was little impact of treatment with β-carotene.

There was no impact of vitamin A on night-blindness when compliance was 65% or less of the weekly supplements. Vitamin A, but not β-carotene, significantly reduced the incidence proportion of night-blindness at three and six months postpartum. For example, at three months postpartum, the incidence proportion of night-blindness was 11.3% in the control group, 4.3% in the vitamin A–treated group, and 8.7% in the β-carotene–treated group. This represents a 62% reduction in night-blindness with vitamin A treatment (RR = 0.38; 95% CI, 0.26–0.55) and a 23% reduction with β-carotene treatment (RR = 0.77; 95% CI, 0.57–1.04).

A possible explanation for the lower impact of vitamin A supplementation on night-blindness in the trial conducted in Nepal, in comparison with the trial in Indonesia, might be due to the severity of the vitamin A deficiency in the women in Nepal. The incidence of night-blindness in the women in the control group

in Nepal was much higher (10.7%) [70] than in the placebo group in the trial in Indonesia (4.8%) [71]. In addition, the dose of vitamin A was higher in the Indonesian trial (16,800 μg RE of vitamin A) than in the Nepal trial (7,000 μg RE of vitamin A per week) and was delivered more frequently (daily versus weekly supplementation). Further studies are needed to determine the optimal dose, duration, and frequency of supplementation with vitamin A during pregnancy to reduce night-blindness and the steep decline in serum retinol during the third trimester of pregnancy.

Vitamin A and maternal anemia

Evidence has accumulated over several decades from studies in both adults and children of a relationship between vitamin A deficiency and iron-deficiency anemia [30, 72]. Hodges et al. [73] in 1971 conducted a small trial in which they observed moderate anemia in volunteers who had very low intakes of vitamin A for about one to two years. Furthermore, this anemia did not respond to treatment with iron but did respond to treatment with vitamin A. This stimulated them to perform a reanalysis of nutrition surveys conducted by the Interdepartmental Committee on National Defense (ICNND) in the 1960s.

Using an ecological study approach, they examined the relationship between vitamin A status and hemoglobin in nonpregnant and nonlactating women from eight developing countries where dietary vitamin A intake was low. They observed a linear relationship between mean plasma vitamin A and mean hemoglobin levels ($r = 0.78$, $p < .05$), but no relationship between iron intake and hemoglobin. In another observational study at the Institute of Nutrition of Central America and Panama (INCAP) in Guatemala, Mejia et al. [73] reanalyzed cross-sectional nutrition surveys and found a significant positive correlation between hemoglobin and plasma retinol in older children (5 to 12 years) but not in younger children (1 to 4 years). In all age groups, there was a positive correlation between plasma retinal and iron. A significant positive correlation between plasma retinal and iron was observed in children with an adequate dietary intake of iron, but this correlation was not found if the iron intake was inadequate.

These observational studies prompted a series of trials to evaluate the impact of vitamin A supplementation on iron status or iron-deficiency anemia in children [52, 74–79]. Two of these trials delivered the vitamin A through fortification [52, 76], two used daily low doses of vitamin A [77, 79] for two weeks to two months, and the other two trials used single high doses of vitamin A [74, 78]. All the trials reported either a reduction in anemia or improved iron status following treatment with vitamin A, although the impact appeared to be greater following fortification or daily low doses of vitamin A in comparison with the single high dose of vitamin A.

In contrast, there have been few trials of the impact of vitamin A supplementation on iron status or anemia in pregnant women. Panth and associates [68] from India reported a trial of supplementation of pregnant women with 1,800 RE of vitamin A daily for six weeks or longer. There was a significant increase in hemoglobin restricted to women from 26 to 28 weeks of gestation. However, this trial is difficult to interpret. The description of the methods leaves uncertainty as to whether or not the interventions were blinded, and the design was complex, with recruitment of women into the trial at different stages of pregnancy, which clouds the interpretation of the results. In Indonesia, Suharno and colleagues [44] in a cross-sectional study observed that, after adjustment for confounders in a multivariable linear regression model, serum retinal concentration was significantly positively associated ($p < .01$) with hemoglobin, hematocrit, and serum iron levels in pregnant women.

Following these observations, Suharno et al. [64] conducted a randomized, double-blind, placebo-controlled trial of vitamin A and iron supplementation of pregnant women to assess the impact on nutritional anemia. The women were supplemented from 19 weeks of gestation for 8 weeks with daily doses of 2,400 RE of vitamin A, 60 mg of elemental iron, both vitamin A and iron, or a placebo. The largest response in hemoglobin was in the women receiving both vitamin A and iron supplements (12.78 g/L; 95% CI, 10.68–14.70); one-third of this response was attributable to vitamin A (3.68 g/L; 95% CI, 2.03–5.33) and two-thirds to iron (7.71 g/L; 95% CI, 5.97–9.45). At the end of the supplementation period, 84% of the placebo-treated women were anemic (hemoglobin ≤110 g/L), 65% of the vitamin A–treated women were anemic, 32% of the iron-treated women were anemic, but only 3% of the women treated with both supplements were anemic. Because there was no follow-up of the women in the trial, at or after delivery, it is not known how long the benefits of supplementation lasted.

A similar beneficial effect of vitamin A and β-carotene supplements on iron-deficiency anemia in pregnant women and their newborns has been briefly reported from Nepal [79]. In this double-blind, controlled trial, women of childbearing age were group-randomized to one of three treatment groups receiving weekly supplements of 7,000 μg RE (23,000 IU) of vitamin A, β-carotene, or a placebo with no vitamin A. Clinical studies were completed on approximately 10% of the pregnant women participating in the trial between September 1994 and June 1996. The analyses reported were from 978 pregnant women, 766 postpartum women, and 728 newborn infants. The results are summarized in table 4. There appears

TABLE 4. Impact of vitamin A and β-carotene supplements on indicators of iron status in Nepalese women and infants

Value	Placebo	Vitamin A	β-Carotene
A. Indicators of iron status in pregnant Nepalese women according to treatment group			
Mean Hb (g/dl) ± SD	9.9 ± 1.1	10.2 ± 1.5	10.1 ± 1.6
% <11 g/dl Hb	76.0	68.4	68.7
% <9 g/dl Hb	20.7	19.8	20.2
EPP[a] (μmol/mol) ± SD	97 ± 65	94 ± 61	101 ± 65
Ferritin (μg/L) ± SD	11.3 ± 11.6	13.3 ± 12.8	13.1 ± 15.9
% IDA[b]	62.7	52.3	58.0
B. Indicators of iron status in Nepalese women three months postpartum according to treatment group			
Mean Hb (g/dl) ± SD	10.6	10.7	10.6
% <11 g/dl Hb	82.9	75.2	77.8
% <9 g/dl Hb	13.3	13.4	16.3
EPP[a] (μmol/mol) ± SD	12.6 ± 11	17.4 ± 17.2	14.8 ± 14.9
Ferritin (μg/L) ± SD	11.2 ± 7.8	11.7 ± 8.4	11.4 ± 7.2
% IDA[b]	68.2	63.4	55.7
C. Effect of treatment on hemoglobin values of Nepalese infants			
Mean Hb (g/dl) ± SD	10.7 ± 1.1	10.9 ± 1.3	10.7 ± 1.2
% <12 g/dl Hb	89.9	80.1	87.6
% <11 g/dl Hb	61.4	55.2	55.9

a. EPP, Erythrocyte protoporphyrin.
b. IDA, Iron-deficiency anemia: Hb <11 g/dl, EPP >90 μmol/mol, ferritin <12 μg/L.
Source: adapted from ref. 79.

to be a reduction in iron-deficiency anemia in vitamin A– and β-carotene–treated pregnant women and a smaller reduction in postpartum women. The proportion of infants with hemoglobin less than 11 g/dl was also lower in the vitamin A– or β-carotene–treated groups.

The effects of treatment with vitamin A and β-carotene on iron-deficiency anemia were modified by hookworm (*Ancylostoma duodenale*) infection. All three groups had a high prevalence of hookworm (77%). In the women without hookworm, iron-deficiency anemia was 46% and 27% lower in the vitamin A and β-carotene treatment groups, respectively, in comparison with the placebo group. There were only small differences in iron-deficiency anemia between treatment groups in those women infected with hookworm.

These preliminary results suggest that vitamin A reduced anemia during and after pregnancy, but the effect was mainly on mild rather than severe anemia. There was also a slight reduction in the percentage of infants with low hemoglobin (<11 g/dl). Serum ferritin was increased by treatment with vitamin A and β-carotene. The effects were modified by hookworm infection. A limitation of the study in terms of applying the results for programs is the prolonged supplementation prior to pregnancy and uncertainty as to the extent of the benefits from more restricted supplementation during pregnancy linked to antenatal care programs.

Overall, the evidence from these studies indicates important benefits for malnourished women from supplementation with vitamin A during pregnancy in terms of reduced nutritional anemia.

Vitamin A supplementation and maternal sepsis

Relatively few studies have examined the relationship between vitamin A status and the risk of puerperal fever and sepsis, or assessed the impact of vitamin A in preventing these conditions. A series of studies conducted during the period from 1920 to 1940 examined the role of vitamin A as an "antiinfective" therapy for specific diseases, including puerperal fever [80]. Much of the research during this period was pioneered by Edward Mellanby, a Professor of Pharmacology from the University of Sheffield, and Harry N. Green, a physician also from Sheffield.

Based on a series of animal experiments in which they observed increased rates of infection in vitamin A–deficient animals, they theorized that "vitamin A plays a significant part in raising the bodily resistance to infection" [80]. In 1929, they conducted a small preliminary trial of cod liver oil in the treatment of puerperal fever. A much lower case fatality rate of 28% (5/18) was observed in women with puerperal sepsis

due to hemolytic streptococcal septicemia who were treated with cod liver oil, in contrast to a case fatality rate of 92% in a historical control group of untreated women [81]. This study prompted them to conduct a trial of cod liver oil as a prophylactic agent against puerperal sepsis [82].

In this study, 550 pregnant women attending antenatal care were alternatively assigned to either treatment with 1 ounce of cod liver oil daily during the final month of pregnancy or no treatment. Puerperal sepsis was defined by a body temperature higher than 100° F (38°C) on two occasions between the end of the first day and the end of the eighth day postpartum. Treatment with cod liver oil reduced the incidence proportion of puerperal sepsis from 4.7% (13/275) in the control group to 1.1% (3/275). There was also a significant reduction in the incidence of puerperal pyrexia (temperature >99° F on one or more days after the first day until discharge) from 30.9% (85/275) in the control group to 19.2% (53/275) in the cod liver oil–treated group [82]. Similar findings of a 60% reduction in the incidence of puerperal sepsis were also reported from Edinburgh in 1931 [83]. The advent of the sulfa antibiotics may have reduced interest in the effect of vitamin A as an antiinfective treatment. In 1936, a trial of sulfanilamide [80] reduced mortality from puerperal fever from 22% to 8%.

The relationship between vitamin A and puerperal sepsis was not examined again until a cohort study conducted in Tennessee, USA, in 1954 reported an increased risk of puerperal fever and sepsis in women with low serum retinol levels in the second and third trimesters of pregnancy [16]. The role of micronutrient supplements in preventing puerperal sepsis was examined in a community-based trial [84] conducted in Indonesia from 1995 through 1997.

As previously mentioned, the impact of zinc and vitamin A on puerperal sepsis was examined in a community-based, individually randomized, placebo-controlled trial using a factorial design with four daily treatments of either vitamin A (2,400 RE), 20 mg of zinc sulfate, the same dose of vitamin A and zinc, or a placebo. All treatments were in identical opaque gelatin capsules, prepacked with study number, and sequentially assigned following consent of the women participating in the trial. Newly pregnant women from a district in Central Java, Indonesia, were identified through a surveillance system involving monthly visits to 28,000 households. Women were enrolled if their pregnancy was identified within 120 days of their last menstrual period and a urine-sample pregnancy test was positive.

Trained fieldworkers who recorded body temperature and collected symptoms daily for two weeks postpartum detected maternal postpartum infections. Puerperal sepsis was defined as a body temperature 38°C or higher on at least one day between the end of the first day and the fourteenth day postpartum. The initial 680 women enrolled in the trial had their maternal postpartum sepsis outcomes recorded. Baseline characteristics for these women were similar between all treatment groups. There was a high level of compliance, and the trial participants consumed an average of 81% of the distributed capsules. Postpartum feverishness (defined as two reports between day 1 and day 14 postpartum) was reported by 12.0% (17/142) of the placebo-treated women, and 11.3% (16/142) had an elevated body temperature (38^0 C or higher) on at least one postpartum day.

Treatment with vitamin A reduced the incidence proportion of episodes of elevated body temperature 38° C or higher on at least one postpartum day, from 9.3% (25/268) to 2.8% (7/251) in the control group. This represents a 70% reduction in puerperal sepsis in the vitamin A-versus non-vitamin A–treated women (RR = 0.30; 95% CI, 0.13–0.68). There was a 30% reduction in puerperal sepsis in women treated with zinc, but this was not significant (RR = 0.70; 95% CI, 0.37–1.47). The impact of vitamin A alone versus a placebo (RR = 0.21; 95% CI, 0.06–0.70) was similar to that of vitamin A and zinc versus a placebo (RR = 0.29; 95% CI, 0.10–0.84). These results, combined with those of the trial in Sheffield in 1931, strongly suggest that low-dose vitamin A given during the second and third trimesters of pregnancy can substantially reduce the risk of postpartum infections in populations of vitamin A–deficient women.

Vitamin A supplementation and maternal mortality

To date only a single trial has been published examining the impact of vitamin A and β-carotene in preventing maternal mortality [45]. This large, community-based, group-randomized, placebo-controlled trial was conducted in Nepal from April 1994 through September 1997. Women of reproductive age living in a ward (a local administrative area) were randomly assigned to one of three supplementation interventions: a single weekly oral supplement of 7,000 μg retinol equivalents of vitamin A, 7,000 μg retinol equivalents of β-carotene, or placebo. The supplements were provided over a period of 3½ years to 44,646 women, of whom 20,119 became pregnant once and 2,070 became pregnant twice during this period. Trained female fieldworkers delivered the supplements to trial participants and collected health information during weekly household visits.

The main trial outcomes were all-cause mortality in women during pregnancy up to 12 weeks postpartum (pregnancy-related mortality) and mortality during pregnancy to six weeks postpartum, excluding deaths apparently related to injury (maternal mortality ratio). Pregnancy-related mortality occurred at a rate of 704 per 100,000 pregnancies in the placebo group

(51/7,241), 426 in the vitamin A group (33/7,747), and 361 in the β-carotene group (26/7,201). These represent preventive effects, expressed as relative risks, of 0.60 (95% CI, 0.37–0.97) for vitamin A treatment and 0.51 (95% CI, 0.30–0.86) for β-carotene treatment. The maternal mortality was 645 per 100,000 live births in the placebo group (42/6,670), 407 in the vitamin A group (29/7,074), and 361 in the β-carotene group (23/6,643). The maternal mortality for vitamin A and β-carotene combined was 385 per 100,000 live births, giving a preventive effect with relative risk of 0.60 (95% CI, 0.39–0.93). The impact of each supplement alone on the maternal mortality ratio was not significant.

This trial was well designed and carefully executed. The investigators demonstrated that the vitamin A and β-carotene interventions did affect serum retinol and β-carotene concentrations in the treated women. In the women treated with vitamin A, there was an increase in serum retinol but no increase in serum β-carotene, whereas in the women treated with β-carotene, there was a smaller increase in serum retinol as well as an increase in serum β-carotene. There was an adequate sample size of 44,000 women and 22,000 pregnancies to examine the two *a priori* formulated hypotheses.

The limitations of the trial have been highlighted in an editorial [85] and correspondence about the study [86–88]. These concerns include some uncertainty about the impact of differential loss to follow-up on the numerators and denominators used in the analyses, the appropriateness of combining the vitamin A and β-carotene groups in analyses, the relevance of the main trial outcome, and the relevance of the findings to plausible supplementation programs.

One hundred fifty-seven women were lost to follow-up during the postpartum period (70 in the vitamin A group, 43 in the β-carotene group, and 44 in the placebo group). If all of these women had died, the impact of treatment with vitamin A on mortality would have been underestimated. However, if the mortality rate in these groups were the same as the average in the study population, there would have been no change on the reported efficacies of the interventions. Given the size of the trial, the loss to follow-up seems remarkably small and is unlikely to have altered the overall conclusions of the trial that vitamin A and β-carotene supplements in vitamin A–deficient women have an important impact on maternal mortality.

In several analyses, the authors combined the vitamin A and β-carotene groups; however, several commentators questioned this approach [86, 87]. The biological mechanisms by which these supplements might affect maternal mortality are likely to be different. Improved vitamin A status from supplementation with either preformed vitamin A or β-carotene might reduce mortality through a reduced risk of sepsis and possibly reduced levels of severe anemia. The antioxidant properties of β-carotene may have resulted in reduced rates of severe preeclampsia. In addition, these interventions should have different effects on biochemical indicators of vitamin A status, as was observed in the trial in Nepal. There is likely to be sufficient overlap in the mechanisms by which these two forms of vitamin A could potentially affect maternal mortality to justify conducting analyses with combined groups, provided the effects are also examined in each treatment group individually. Nonetheless, the study did not have adequate power to examine whether there was a significant difference in the level of impact between the preformed vitamin A and the β-carotene supplements. Finally, the authors state that they had planned combined analyses of these supplementation groups from the outset of the trial [45].

The investigators selected pregnancy-related mortality rather than maternal mortality as the primary endpoint for the trial. The later outcome is mortality restricted to the first six weeks following delivery and excludes deaths due to injuries and accidents. The investigators did attempt to determine the cause of death using a "verbal autopsy" method, although it was not clear whether this method had been validated in the study population. The investigators justified using an extended postpartum period for follow-up of 12 weeks because "maternal mortality related to malnutrition could extend beyond the conventional six weeks." However, this claim was not explained or justified by any supporting studies. The choice of trial outcome leaves open the possibility that the intervention resulted in a reduction in all-cause female mortality rather than an effect specific to maternal mortality [88].

The verbal autopsy data revealed little impact of the interventions on direct obstetric causes of mortality, and the largest relative impact was on deaths due to injuries. These findings are hard to reconcile with known potential mechanisms of maternal mortality, although it is possible that reductions in night-blindness were associated with lower injury-related mortality in the treated women postpartum. In summary, the reasons for selecting the main trial outcome, rather than the more conventional maternal mortality outcome, are not well developed in the report of the trial. If a more conventional trial outcome had been chosen, the impact of the intervention would have appeared less certain. The inclusion of the verbal autopsy data did not contribute to clarifying the interpretation of the findings. The validity of the verbal autopsy method used was uncertain, and there was insufficient power to detect the impact of the interventions on cause-specific mortality.

Suggestions that the investigators should have completed subgroup analyses based on the results of the verbal autopsy [87] are not appropriate, since the investigators used the only valid analysis strategy,

namely, an intention-to-treat analysis based on all deaths and pregnancies during the defined follow-up period and the *a priori* defined trial outcomes.

Lastly, the direct relevance of the trial findings for programs is unclear. Is the mortality-sparing effect of the interventions used in the trial only a consequence of their prolonged delivery starting prior to the onset of pregnancy? Supplementing all women of reproductive age with vitamin A is not a sustainable or plausible intervention in most countries with high levels of maternal vitamin A deficiency. Can the same impact be expected if the intervention is only provided during pregnancy through established health infrastructures used to deliver antenatal care services? Finally, it remains unclear which type of supplement, vitamin A or β-carotene, is more effective.

Despite these limitations, the NNIPS-2 trial has focused attention on the need to further examine the potential role of nutrition, especially improving vitamin A status, in preventing maternal mortality.

Vitamin A status of newborn

In most reports, infant cord blood serum retinol concentrations appear to be resistant to maternal supplementation with vitamin A during pregnancy [29, 35, 63, 67]. However, in populations with more severely vitamin A–depleted mothers of low socioeconomic status, oral supplementation with 30,000 IU of vitamin A during the last trimester of pregnancy resulted in higher infant serum retinol levels [19, 69].

It should be noted that fetal serum retinol concentrations are relatively independent of fetal liver vitamin A concentrations unless the liver stores are very low [89]. Thus, failure to alter cord blood concentrations may be masking substantial improvements in newborn liver vitamin A concentration, which are known to be low in newborns in many developing countries [40, 89].

Birthweight and duration of gestation

Several trials of vitamin A supplementation during pregnancy have reported no important impact of vitamin A supplements on birthweight [29, 67, 68, 84, 90]. This finding is not surprising, given the homeostatic mechanisms to support transfer of vitamin A to the fetus and the mechanisms to maintain fetal serum retinol concentrations [89]. Furthermore, vitamin A has been reported to have only a minor impact on postnatal infant growth, which is mainly limited to children with evidence of severe vitamin A deficiency.

A trial of vitamin A supplementation in HIV-positive pregnant women in South Africa has, however, reported a reduced rate of preterm delivery in vitamin A–supplemented women (17.4% in the placebo group to 11.4% in the vitamin A–treated group) [91]. It is possible that vitamin A will have different effects on gestation and birthweight in different populations. More work is needed to characterize the circumstances in which vitamin A supplementation might have a useful impact on birthweight and gestation

Neonatal morbidity and mortality

It is well established in industrialized countries that preterm infants have limited stores of vitamin A and that without supplementation with vitamin A, their suboptimal vitamin A status may persist for many months [8]. It has also been demonstrated that these infants have an increased risk of bronchopulmonary dysplasia and that this is prevented by appropriate postnatal vitamin A supplementation [92]. These observations have stimulated speculation that improving vitamin A status of newborn infants might have an impact on early respiratory illness frequently reported in infants in vitamin A–deficient populations.

Nonetheless, to date there have been no studies that examined the impact of maternal supplementation with vitamin A on neonatal morbidity or mortality. The NNIPS-2 trial [45] should eventually provide critical information about the impact of this intervention on neonatal survival in a vitamin A–deficient population.

Vertical transmission of human immunodeficiency virus (HIV) in pregnancy

Higher rates of vertical transmission of HIV from mother to child have been observed in developing countries [93], suggesting that either nutrition or differing breastfeeding practices may be an important influence [94]. Both pregnancy and HIV infection are known to be risk factors for vitamin A deficiency [95]. In addition, it is known that vitamin A plays an important role in immune function and in maintaining epithelial integrity of mucosal surfaces [95]. A detailed outline of the theories about why vitamin A may have a protective role against vertical transmission of HIV is beyond the scope of this review; however, it is well described by Semba [94].

Semba et al. [95] undertook a study to determine whether vitamin A deficiency played a role in the vertical transmission of HIV in a group of pregnant women in Blantyre, Malawi. This prospective cohort study showed that serum vitamin A levels, measured at the first antenatal care visit, of the mothers with HIV-infected offspring were significantly lower than those of mothers whose offspring were not affected by HIV. Following adjustment for maternal percentage of CD4 lymphocytes, maternal age, and body mass index, multivariate logistic regression models produced an odds ratio of 0.56 (95% CI, 0.37–0.85) for mother-to-

child transmission of HIV based on 0.45 μg/L increments in serum vitamin A. These authors estimated an attributable risk of vertical transmission of HIV of 0.25 for mothers with vitamin A levels below 0.70 μmol/L as compared with mothers with levels above 1.40 μmol/L.

This study was limited by a low follow-up rate, with only 286 of an original 567 pregnant women being included in the study. The others were excluded because their infants had died, they were lost to follow-up, or they declined to provide blood specimens. Additional criticisms have related to the methods of assessing breastfeeding status and the nonuniform timing of the lymphocyte subset measurements [96]. Despite these limitations, the study results indicated the need for further research, given the potential cost-effectiveness of providing dietary vitamin A to pregnant women [96].

A hospital-based cohort study [97] in Bangkok, Thailand, showed that lower levels of serum vitamin A and β-carotene are found in women with HIV than in controls. The reduction in the levels of these two nutrients was significantly correlated with the percentage of CD4 lymphocytes, CD4 count, and CD4/CD8 ratio. Subsequent research has suggested that a possible explanation for the observed lower vitamin A concentrations in pregnant women with HIV may be due to an acute-phase response rather than a reflection of lowered body stores of vitamin A [98].

A study of two cohorts of pregnant women with HIV [99] showed no statistical association between maternal vitamin A levels in the third trimester and transmission of HIV. This study was conducted in the United States with third-trimester women from metropolitan New York and Los Angeles. However, as would be expected, vitamin A deficiency was uncommon among the pregnant women in this study from an industrialized country [96].

Two moderately large randomized control trials failed to show any significant protective effect of vitamin A in preventing vertical transmission of HIV. The first of these studies was a large randomized control trial in Dar es Salaam, Tanzania. A total of 1,075 pregnant women between 12 and 27 weeks of gestation were assigned to one of four treatment groups: multivitamin supplements with vitamin A, multivitamin supplements excluding vitamin A, vitamin A alone (30 mg of β-carotene plus 5,000 IU of vitamin A), or a placebo. Multivitamins had significant protective effects on the risk of low birthweight, severe preterm birth, and small size-for-gestational-age, but no significant associations were observed for vitamin A [90]. Despite significant increases in CD4, CD8, and CD3 counts for women who consumed multivitamins, no such increase was observed for women consuming vitamin A alone [90]. No direct evaluation of vertical transmission of HIV was described in this study.

More recently, Coutsoudis [91] conducted a randomized, controlled trial of placebo or retinol (5,000 IU of retinyl palmitate and 30 mg of β-carotene) in a group of 728 HIV-infected pregnant women from Durban, South Africa, over a three-year period. This study also showed that vitamin A was not effective in reducing HIV vertical transmission in the women examined. Despite these findings, a lower rate of HIV transmission at 28 days and a lower risk of preterm deliveries were observed. A 47% decrease in HIV transmission was observed among 80 preterm babies; however, wide confidence intervals were observed for the intervention (prevalence, 17.9%; 95% CI, 3.5%–32.2%) and control groups (prevalence, 33.8%; 95% CI, 19.8%–47.8%). A high response rate of 91.7% was achieved in this study, although the sample size may have limited the power to detect a significant difference. The results of other trials presently being conducted in Africa should allow pooling of the results to provide additional power to examine whether vitamin A has a protective effect against vertical HIV transmission. Further research may be considered on HIV transmission in preterm infants in view of the high rate of preterm deliveries in HIV patients [91]. This topic is also covered by Coutsoudis in this issue [100].

Conclusions and recommendations

Maternal health and nutrition

Maternal vitamin A status

Vitamin A deficiency, as evidenced by night-blindness and low serum retinol levels, especially in the third trimester, is most probably common in populations known to have vitamin A deficiency in children. More research is needed to establish the extent of the problem in populations in developing countries and to characterize the changes in serum retinol and vitamin A status during pregnancy in well-nourished populations, as well as in populations with inadequate intakes of vitamin A.

There is evidence that daily or weekly low doses of vitamin A supplements, starting in the second or even third trimester, can reduce the severity of the decline in maternal serum retinol levels during late pregnancy and reduce symptoms of night-blindness. Women who have night-blindness should be treated with vitamin A using previously recommended doses. Effectiveness trials of vitamin A supplementation or dietary interventions should be considered to identify the most appropriate interventions for future programs to control vitamin A deficiency in women of reproductive age, especially women who are pregnant.

Maternal anemia

There is good evidence that vitamin A supplementation, when combined with iron supplementation and treatment for intestinal parasites, can reduce the levels of mild to moderate nutritional anemia by approximately 30%. Further research would be warranted in populations with different disease profiles, for example, women from endemic malarious areas. In addition, research is needed to compare the effectiveness of increases in dietary vitamin A and iron intakes versus supplements with these nutrients on nutritional anemia in women of reproductive age and during pregnancy.

Maternal sepsis

Preliminary studies and research conducted in the 1930s suggested that vitamin A had a powerful effect on reducing the risk of postpartum sepsis in women. This is likely to be an important intervention for women who deliver in contaminated environments and who are vitamin A deficient. More research is required to confirm these findings and to identify the minimum size and duration of doses needed to provide this protection. There is enough evidence to consider effectiveness trials of vitamin A supplements linked to antenatal care programs to assess the impact on maternal postpartum sepsis. The role of vitamin A in reducing sepsis following delivery by cesarean section also needs evaluation.

Maternal mortality

The findings from the NNIPS trial in Nepal provide strong evidence that vitamin A deficiency is an important factor contributing to the immediate causes of maternal mortality. This trial needs to be replicated in other populations. However, it should be recognized that these replication trials are likely to take place in populations with severe malnutrition and vitamin A deficiency and most probably with low levels of health care services for pregnant women and are likely to represent a maximum impact of the intervention.

Newborn nutrition and health

Given the strong homeostatic mechanisms to maintain fetal levels of serum retinol and the modest increment in requirements for vitamin A during pregnancy, it is likely that benefits of vitamin A supplementation in pregnancy for the newborn will be limited to populations with severe maternal vitamin A deficiency.

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Supplementation of infants and/or their mothers with vitamin A during the first six months of life

Betty Kirkwood

Abstract

It has been clearly demonstrated that in endemic areas, improving the vitamin A status of children aged six months to five years can substantially reduce their risk of mortality and severe morbidity. This paper reviews the potential benefits of improving vitamin A status during the first six months of life by either supplementing the infant or indirectly by supplementing the mother, in order to increase the vitamin A content of her breastmilk. This focus is important, since a large proportion of childhood deaths occur before six months of age. Also, whether or not supplementation has a direct benefit during the first six months of life, it could have an indirect benefit later in life if it ensures that the infant enters the second six months of life with improved vitamin A status. It might thus lead to a reduced risk of mortality in later childhood. In particular, this review evaluates the evidence concerning the health benefits.

Introduction

Vitamin A deficiency has been identified by the World Health Organization (WHO) as a problem of public health importance in over 60 countries. About 250 million children are estimated to be at risk for this deficiency [1]. Several large-scale field trials have clearly demonstrated that in endemic areas, improving the vitamin A status of children can substantially reduce their risk of mortality and severe morbidity [2]. The vast majority of children recruited in these trials were aged six months to five years. It is thus in this age group that the impact has been demonstrated; on average, supplementation has been found to reduce mortality by 23% [2].

This review focuses on the first six months of life. It examines strategies to improve the vitamin A status of the young infant and the potential health benefits of so doing. This focus is important for two main reasons. First, a large proportion of childhood deaths occurs before six months of age. It is thus important to understand whether the efficacy of vitamin A supplementation extends to the younger infant. Second, whether or not supplementation has a direct benefit during the first six months of life, it could have an indirect benefit later in life if it ensures that the infant enters the second six months of life with improved vitamin A status. It might thus lead to a reduced risk of mortality in later childhood.

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Supplementation strategies

Improved vitamin A status of the young infant can potentially be achieved either directly, by supplementing the infant, or indirectly, by supplementing the lactating mother in order to increase the vitamin A content of her breastmilk and thus provide additional vitamin A to the breastfed infant.

This review evaluates the evidence concerning health benefits for the following vitamin A supplementation strategies:

Maternal supplementation
- » Large dose in the first few weeks after delivery
- » Regular small doses throughout lactation

Infant supplementation
- » Supplementation of newborns with 50,000 IU
- » Periodic supplementation of young infant with 50,000 IU
- » Immunization-linked supplements delivered at each of the contacts for diphtheria-polio-tetanus immunizations. The recommended scheduled for these is 6, 10, and 14 weeks of age

Combined maternal and infant supplementation

The evidence concerning potential health impact for the child is discussed for each of the three strategy approaches in the following three sections. The main

findings are summarized in table 1, which lists the related randomized, double-blind, placebo-controlled trials. The results are shown separately as impacts on the vitamin A status of mothers, on vitamin A status of the infants, and on infant health.

The review then seeks to draw on the presented evidence to discuss what might be recommended approaches for vitamin A supplementation during the first six months of life, summarizing what is known and highlighting any important gaps in knowledge. In so doing, it examines the potential role of linking supplements to immunization programs, which have established a delivery system that reaches a large proportion of children in areas where vitamin A deficiency is widespread.

Benefits of maternal supplementation

Three supplementation trials have been conducted that included maternal supplementation (table 1). The first, in Indonesia [3], evaluated a single large dose of vitamin A, equivalent to 300,000 IU given at one to three weeks postpartum, against a placebo. The second trial in Bangladesh [4] had three groups who received two different supplementation strategies and a placebo. All mothers were enrolled at one to three weeks postpartum and given an initial dose. They were then followed and given daily supplements until nine months postpartum. Mothers in the first intervention group received one large dose of 200,000 IU of vitamin A, followed by daily placebo doses until nine months postpartum. Those in the second intervention group received a single placebo dose followed by daily doses of 7.8 mg of β-carotene throughout. This was designed to approximate one US recommended dietary allowance (RDA) of vitamin A for lactating women in the first six months postpartum. Mothers in the control group received placebo doses at enrollment and throughout.

The third trial [9], a multicenter study carried out in Ghana, India, and Peru, evaluated a single large maternal dose of 200,000 IU given between 18 and 42 days postpartum combined with infant supplements of 25,000 IU delivered alongside the diphtheria, pertussis, and tetanus (DPT)/polio immunizations.

The trials in Indonesia and Bangladesh each involved a total of just 150 to 200 mother-infant pairs and were designed to evaluate the impact on both the mothers' and the infants' vitamin A status. The multicenter trial involved more than 8,000 mother-infant pairs and also gathered data on morbidity and mortality; vitamin A status was evaluated on a subsample.

Impact on maternal vitamin A status

The main results concerning the impact on maternal vitamin A status are presented in figure 1 for each of the three trials and are summarized in table 1. Three different indicators have been used for maternal vitamin A status: serum retinol concentration, modified relative dose response (MRDR) to provide an assessment of the adequacy of liver stores, and breastmilk retinol concentration. An impact on the latter is the most relevant for assessing whether maternal supplementation is likely to lead to benefits for the breastfed infant.

In the Indonesian trial, breastmilk retinol was compared between vitamin A and placebo groups at baseline (before dosing at one to three weeks postpartum) and then at each month of age until eight months. At baseline, the mean breastmilk retinol concentration was lower in the vitamin A group than in the placebo group: 2.30 ± 1.42 μmol/L ($n = 70$), as compared with 2.69 ± 1.53 μmol/L ($n = 66$). The frequency of mothers with breastmilk concentrations below the 1.05 μmol/L cutoff was also marginally higher in the vitamin A group (10% vs 8%). At each subsequent point in time, supplementation raised breastmilk retinol concentrations by 0.48 to 1.18 μmol/L higher than the placebo group. At one month of age, shortly after supplementation, only one mother in the vitamin A group had a breastmilk concentration below 1.05 μmol/L, compared with 16 mothers (24%) in the placebo group ($p < .0001$). At all subsequent times, the frequency of breastmilk concentrations below 1.05 μmol/L was significantly lower for mothers in the vitamin A group. At eight months, the difference was still substantial: 16% as compared with 28%.

This sustained impact of supplementation on breastmilk retinol concentration was not replicated in either of the other two trials. The Bangladesh trial involved a similar number of mothers in each group; it also included a third group receiving daily doses of β-carotene. The breastmilk vitamin A concentration was expressed both per volume and per gram of milk fat, and was analyzed by comparing means and by comparing percentages below cutoff values. Similar results were found in all cases [4]. The percentages below 1.05 μmol/L are shown in figure 1B. At baseline, values were not statistically significantly different between the three groups. At three months, the vitamin A group showed a benefit as compared with the placebo group (57% vs 79%, $p < .01$), but this benefit had disappeared by six months. Daily supplementation with β-carotene had no impact on breastmilk concentrations at three months and six months, but appeared better than the placebo at nine months, when the percentage below 1.05 μmol/L was 63% as compared with 80% ($p < .05$).

The multicenter trial assessed breastmilk vitamin A concentration for a random subsample of approximately 1,500 mothers in each of the two trial groups at enrollment. Three different subsamples of these were selected to be reassessed at two, six, and nine months,

TABLE 1. Summary of trials of vitamin A supplementation to mother or child during first six months of life

Supplementation strategy	Study site	Study participants	Impact on vitamin A status		Impact on infant health
			Mothers	Infants	
Maternal supplementation					
1–3 wk postpartum: 312 μmol retinol palmate (300,000 IU)	Indonesia [3]	77 vs 76 mothers and their infants	↑ Breastmilk retinol (1–8 mo) ↑ Serum retinol (3 and 6 mo) ↔ Liver stores	↑ Serum retinol and liver stores (6 mo)	—
1–3 wk postpartum: 200,000 IU of vitamin A	Bangladesh [4]	74 vs 73 mothers and their infants	↑ Liver stores (3 and 9 mo, but not at 6 mo) ↔ Serum retinol ↑ Breastmilk retinol (3, ?6, and ?9 mo)	↑ Serum retinol and liver stores (6 mo)	—
1–3 wk postpartum, to 9 mo: daily doses of β-carotene	Bangladesh [4]	73 vs 73 mothers and their infants	↑ Liver stores (3, 6, and 9 mo) ↑ Serum retinol (3, 6, and 9 mo) ↑ Breastmilk retinol (3 and 9 mo, but not at 6 mo)	↑ Liver stores (6 mo) ↔ Serum retinol (6 mo)	—
Infant supplementation					
50,000 IU of vitamin A, 1st day of life	Indonesia [5]	1,034 vs 1,033 infants	Not relevant	—	64%↓ infant mortality Some morbidity ↓ (birth–4 mo)
4-monthly vitamin A supplements, 50,000 IU at <1 mo, 100,000 IU at 1–5 mo	Nepal (Sarlahi) [6]	6,086 vs 5,832 infants (1st dosed at <6 mo)	Not relevant	—	Mortality in 4 mo following dose: ↑ when given at <4 mo of age, ↓ when given at 4–5 mo
Single dose of 100,000 IU of vitamin A at 1–11 mo	Nepal (Jumla) [7, 8]		Not relevant	—	↔ Mortality 1–5 mo ↓ Mortality 6–11 mo
Maternal and infant supplementation					
Mothers: 18–42 days postpartum: 200,000 IU of vitamin A. Infants: 4 doses of 25,000IU at 6, 10, and 14 wk with 1st 3 doses of DPT/polio immunization, and at 9 mo with measles immunization	Ghana, India, and Peru multicenter study [9]	4,212 vs 4,227 mothers and their infants	↑ Breastmilk retinol (2 and 6 mo, but not at 9 mo)	↑ Serum retinol and liver stores at 6 mo, but not at 9 or 12 mo[a]	Up to 9 mo: ↔ mortality ↔ morbidity ↔ anthropometry At 12 mo[a]: ↔ mortality ↔ anthropometry

a. Placebo group received 100,000 IU at 9 mo.

giving between 280 and 340 measurements per group at each follow-up. The impact of vitamin A was apparent at two months (21.4% vs 27.8%, $p = .06$) and most marked at six months (30.0% vs 40.7%, $p = .004$), but had disappeared by nine months (fig. 1C). When data were analyzed separately by country (table 2), it can be seen that in India, where the percentage of women with low breastmilk retinol concentration was highest, the impact of vitamin A supplementation displayed its largest impact much earlier at two months.

It is worth noting that at baseline, about four times as many mothers in the Bangladesh trial as in the Indonesian trial had a breastmilk retinol concentration below the 1.05 μmol/L cutoff. In fact, percentages even at baseline in Bangladesh were higher than at eight months in Indonesia. By three months, this percentage exceeded 50% in all groups. Thus, the population was considerably vitamin A deficient. In addition, it should be noted that the vitamin A dose used was 300,000 IU in the Indonesian trial, as compared with 200,000 IU in the other two.

The Indonesia and Bangladesh trials also assessed

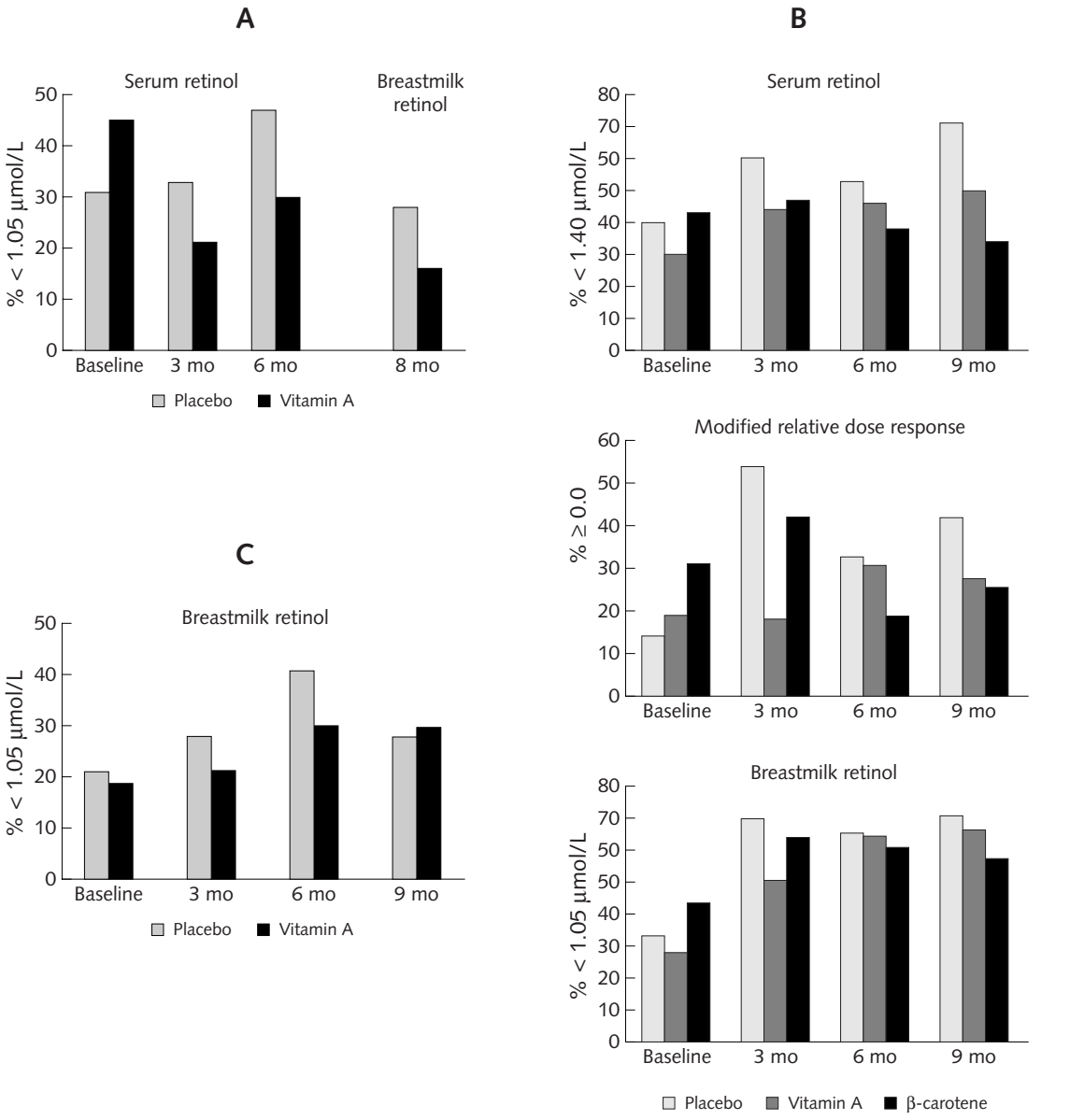

FIG. 1. (A) Impact of maternal supplementation on maternal vitamin A status: Indonesia trial. Source: ref. 3. (B) Impact of maternal supplementation on maternal vitamin A status: Bangladesh trial. Source: ref. 4. (C) Impact of maternal supplementation on maternal vitamin A status: multicenter study. Source: ref. 9

the impact on the maternal serum retinol and liver stores. For completeness, they are also summarized in table 1 and figure 1A and 1B. Only the β-carotene group in the Bangladesh trial showed an impact on both indicators. The 300,000 IU of vitamin A supplement in Indonesia impacted positively on serum retinol levels at both three months and six months, but had no clear impact on liver stores. The 200,000 IU of vitamin A supplement in Bangladesh, in contrast, had no demonstrated impact on serum retinol. It showed an inconsistent impact on liver stores; these were improved at three months and at nine months, but not at six months.

Impact on the infant's vitamin A status

The Indonesia and Bangladesh trials both included an assessment of the impact on the infant's vitamin A status at six months of age (tables 1–3). In the Indonesian trial, the investigators used a cutoff of <0.52 μmol/L to calculate the prevalence of low serum retinol; this is midway between the two more usual cutoffs of <0.35 μmol/L (severe deficiency) and <0.70 μmol/L (moderate deficiency), generally adopted as standards for young children. Using these cutoffs, a clear impact of maternal supplementation on the prevalence of low serum retinol was found. This was 15% in the vitamin A group at age six months, as compared with 36% in the placebo group ($p < .005$). The prevalence of low vitamin A stores, assessed by relative dose response (RDR), was also significantly lower in the vitamin A group (10% vs 23%, $p < .03$).

The Bangladesh trial used <0.70 μmol/L as the serum retinol cutoff level, and the modified relative dose response (MRDR) rather than RDR to assess liver stores. Smaller impacts were observed for maternal vitamin A supplementation than in the Indonesia trial (table 2); the differences did not reach statistical significance. The β-carotene group showed a marginally and nonsignificantly lower prevalence of low liver stores, but a higher prevalence of low serum retinol.

The multicenter study combined maternal and immunization-linked supplementation. It therefore does not provide an independent assessment of the impact of maternal supplementation on the infant's vitamin A status. The combined impact is discussed below.

TABLE 2. Immunization-linked vitamin A trial: impact on breastmilk retinol concentration by country

	Baseline		2 mo		6 mo		9 mo	
Country	% breastmilk retinol <1.05 μmol/L	*n*	% breastmilk retinol <1.05 μmol/L	*n*	% breastmilk retinol <1.05 μmol/L	*n*	% breastmilk retinol <1.05 μmol/L	*n*
Ghana								
Vitamin A	5.4	539	13.8	123	17.4	121	21.3	94
Placebo	5.1	534	16.1	124	26.3	114	15.4	78
p	.811		.611		.096		.323	
India								
Vitamin A	24.4	460	23.9	92	45.3	106	39.4	94
Placebo	24.1	464	41.9	86	56.1	107	40.6	106
p	.880		.011		.115		.862	
Peru								
Vitamin A	12.2	492	28.0	107	29.2	113	28.4	88
Placebo	13.0	501	30.3	99	40.7	113	24.1	112
p	.711		.721		.700		.491	

TABLE 3. Impact of maternal supplementation on the infants' vitamin A status at six months

	Indonesia trial [3]			Bangladesh trial [4]		
Supplement group	*n*	Serum retinol concentration % <0.52 μmol/L	RDR % ≥20%	*n*	Serum retinol concentration % <0.70 μmol/L	MRDR % ≥0.06
Placebo	70	36	23	70	34	93
Vitamin A: large dose at 1–3 wk postpartum	68	15	10	69	25	87
Daily β-carotene	—	—	—	69	41	84

RDR, Relative dose response; MRDR, modified relative dose response.

Impact on infant health

No trial has been identified that provides data on the impact of maternal supplementation shortly after delivery on infant morbidity and mortality.

Benefits of infant supplementation

Supplementation of newborns: Impact on morbidity and mortality

To date just one trial has been conducted in which vitamin A supplementation focused on newborns [5] (table 1). A group of 2,067 neonates was randomized to receive either 50,000 IU of vitamin A or a placebo on their first day of life. The infants were followed up at one year of age to determine the impact of the intervention on infant mortality. Outcome was confirmed for 89% of infants. Overall there were 19 deaths in the placebo group and 7 in the vitamin A group, yielding a relative risk of 0.36 with a 95% confidence interval from 0.16 to 0.87. This is equivalent to a 64% reduction in mortality, with a 95% confidence interval from 13% to 84%.

A substantial impact was clearly demonstrated. Examination of the survival curves, reproduced here in figure 2, shows that all of the reduction occurred in the first five months of life; there were no deaths after this.

A subsample of 470 infants underwent a more intensive follow-up, with morbidity questionnaires administered at 4, 6, and 12 months. One-week period prevalences of common morbidities among the infants in this subsample showed no significant differences between the vitamin A and placebo groups at 4, 6, or 12 months. However, between birth and age 4 months, significantly fewer infants in the vitamin A group were taken for medical care for cough (14.2% vs 24.6%, $p = .008$) and fever (13.7% vs 20.7%, $p = .063$). There were no differences between treatment groups in the proportion of infants seeking treatment for diarrhea, difficult breathing, ear infection or *pilek* (a local term referring to upper respiratory tract symptoms such as runny nose) [5]. Between 4 and 6 months and between 6 and 12 months of age, there were no differences between groups in care-seeking for any diagnosis.

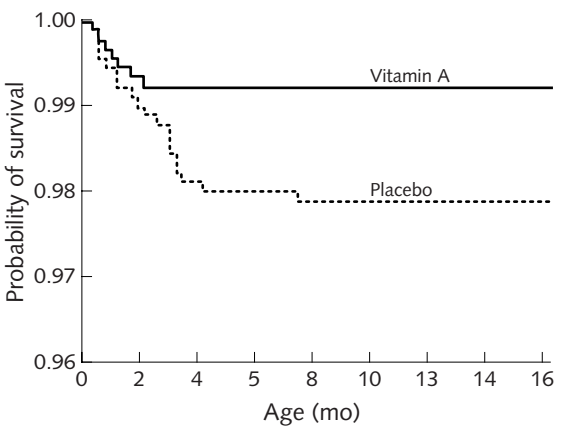

FIG. 2. Impact of neonatal vitamin A supplementation on infant mortality. Source: ref. 5

Periodic supplementation of young infants: Impact on mortality

A metaanalysis [8] carried out to ascertain the impact of vitamin A supplementation on childhood pneumonia also included an analysis of the impact of vitamin A supplementation on all-cause mortality in the first and second six months of life. The results are reproduced in table 4. The mortality reduction of 31% for the 6- to 11-month age group (RR = 0.69; 95% CI, 54–0.90 CI) was consistent with that reported for older children in the metaanalysis conducted by Beaton et al. [2]. However, no reduction was observed for the 0- to 5-month age group.

Two of the large-scale field trials of periodic supplementation of young children provided sufficient data on the mortality impact of periodic supplementation of young infants in both of these age periods. These are the Sarlahi [6] and Jumla [7, 8] trials in Nepal. The results are summarized in table 1. In the Sarlahi study, infants recruited into the study at one of the regular four-monthly home visits were given 50,000 IU of vitamin A if they were less than 1 month old and 100,000 IU if they were aged 1 to 5 months, the same dose that was given to infants aged 6 to 11 months. The Jumla study recruited children from 1 month of age; infants were also given 100,000 IU of vitamin A. Both showed an impact in the second 6 months of life but not the first (table 4).

The vast majority of the data available for periodic supplementation of infants derive from the Sarlahi study. Reproduced in table 5 is a detailed analysis carried out by the investigators [6] to assess the impact on mortality of age of dosing according to month of age in the first six months of life. The mortality rates compared are those during the four months following dosing. Thus the deaths, child-years of follow-up, and mortality rates given for infants aged, for example, two months at the time of dosing will be based on data for them from two months to six months. Note that this is in contrast to table 4, where deaths and follow-up are shown according to the time period in which they occurred, and not according to age of dosing. This analysis clearly shows no impact on subsequent four-month mortality of dosing infants in the first four months of life. The impact seen in older children starts to be apparent for doses given at five months of age.

TABLE 4. Metaanalysis of impact of vitamin A supplementation on all-cause mortality among zero- to five-month-old infants

	Vitamin A		Placebo		Comparison	
Study	Deaths	Child-years	Deaths	Child years	Rate ratio	Design-effect[a]
Jumla	20	120.2	19	112.9	0.99	1.416
Madurai	0	17.5	0	17.8	—	1.329
Sarlahi[b]	98	1,748.0	96	1,670.0	0.97	1.187
Sudan	0	5.0	0	2.5	—	1.000
Vast-CSS	0	8.0	0	10.0	—	2.003
Summary	118	1,884.7	116	1,797.2	0.97 (0.73–1.29)	

a. Empirical design effect based on Beaton et al. [2].
b. Based on the first 16 months of data out of a total of 24 months of follow-up.
Source: ref. 8.

TABLE 5. Effect of vitamin A on cumulative four-month mortality of infants under six months of age at time of dosing

	Age at time of dosing (mo)					
Group	<1	1	2	3	4	5
Control						
Deaths	34	32	20	11	15	18
Child-years	256.9	490.8	444.7	415.7	446.8	462.2
Mortality rate	132.3	65.2	45.0	26.5	33.6	38.9
Vitamin A						
Deaths	38	46	22	15	15	15
Child-years	268.4	512.8	447.2	449.2	454.5	493.2
Mortality rate	141.6	89.7	49.2	33.4	30.8	30.4
Relative risk	1.07	1.38	1.09	1.26	0.92	0.78
95% CI	0.66–1.72	0.85–2.24	0.56–2.12	0.54–2.95	0.41–2.03	0.37–1.65

Immunization-linked supplements to young infants

The only data currently available to assess immunization-linked supplementation are from the WHO/CAH (Department of Child and Adolescent Health and Development) multicenter study [9], which combined this with maternal supplementation.

Benefits of combined maternal and infant supplementation

As immunization programs have established a delivery system that reaches a large proportion of young children, linking vitamin A supplementation to these programs could be one mechanism to achieve extensive coverage in vitamin A–deficient populations. An informal consultation [10] was convened by WHO's Nutrition Unit and the Expanded Program on Immunisations (EPI) in 1992 to assess the role of using immunization contacts to combat vitamin A deficiency. This recommended, in association with the International Vitamin A Consultative Group (IVACG), delivery of 25,000 IU of vitamin A with each of the first DPT immunizations (scheduled around 6, 10, and 14 weeks) and with measles immunization around 9 months. Among populations in which breastfeeding is common and prolonged, the group also recommended one large 200,000-IU dose to the mother during the safe period of postpartum infertility (about 60 days).

This particular schedule formed the basis of the WHO/CAH immunization-linked supplementation trial [9]. This was a multicenter study carried out in Ghana, India, and Peru. A total of 8,439 infants and their mothers were randomized to vitamin A or control groups. Infants in the control group received 100,000 IU at nine months at the time of their measles immunization.

The main findings are summarized in table 1. The impact of the maternal supplementation component on the mother's breastmilk vitamin A content has been discussed above. Figure 3 shows that the combined maternal and immunization-linked supplementation schedule achieved a modest impact on the infants' vitamin A status at 6 months. However, this effect was no longer apparent at age 9 months, and at age 12 months it was comparable to that achieved with the single large dose of 100,000 IU given to infants in the control group at 9 months.

No significant differences between groups in mortality were observed. The mortality curves for the vitamin A and control groups were extremely close up to nine months of age (fig. 4). The rate ratio to compare all deaths up to age nine months was close to 1 (RR = 0.96; 95% CI, 0.73–1.27). The mortality curves appear to diverge after 9 months, with mortality between 9 and 12 months higher in the control group. However, this divergence cannot be interpreted as a real difference in mortality between the two groups. First, the study was not designed to achieve a high precision in the between-group comparison of mortality rates, and the sample size was not sufficient to support subgroup analyses. Second, the overall mortality rates until age 12 months did not differ significantly between the two groups. Furthermore, subsequent surveillance in the Ghana site with periodic supplementation of 200,000 IU to older children found no difference in mortality rates at age two years.*

Finally, the intervention had no effect on overall or severe morbidity (tables 6 and 7) or on anthropometry. At no visit did the mean weight differ by more than 0.05 kg between the two groups, or the mean length by more than 0.1 cm.

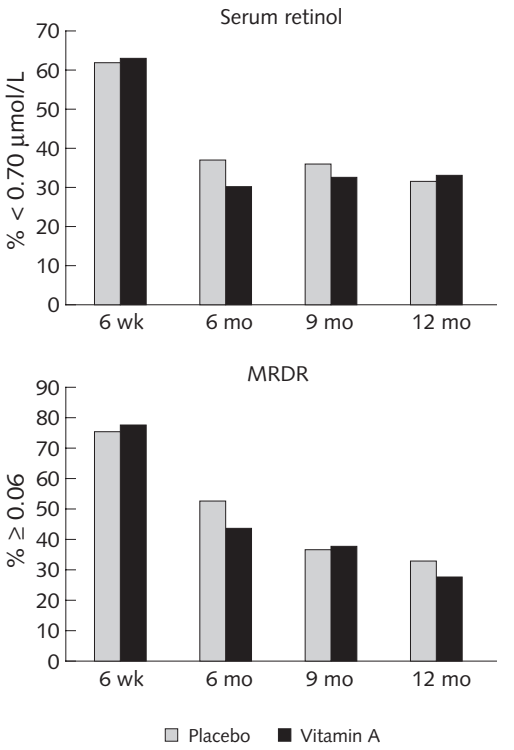

FIG. 3. Impact of immunization-linked vitamin A supplements on infants' vitamin A status. Source: ref. 9

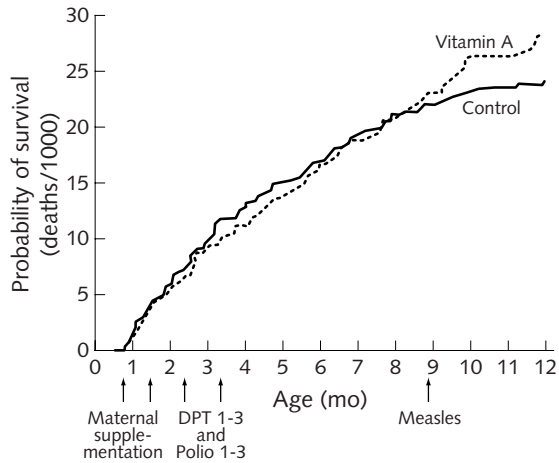

FIG. 4. Impact of immunization-linked vitamin A supplements on infant mortality. DPT, Diphtheria/pertussis/tetanus. Source: ref. 9

Summary and conclusions

Consideration of the above evidence suggests the following speculative summary and conclusions.

A single maternal dose of 200,000 IU or of 300,000 IU delivered shortly after delivery improves breastmilk vitamin A content, at least for six months. However, in many sites this intervention is unlikely to be sufficient to correct the underlying subclinical vitamin A deficiency in the mothers. For example, in Bangladesh at three months, although the percentage of mothers with low breastmilk vitamin A concentration was markedly reduced in the vitamin A group, at 57% it was still unacceptably high.

A single maternal dose of 200,000 IU or more taken shortly after delivery, either alone or in combination with immunization-linked small doses of 25,000 IU, has a demonstrable but limited impact on the infant's vitamin A status. Although there is some variation between sites, the impact at age six months and beyond is insufficient to make firm conclusions on the benefits of vitamin A supplementation during early infancy. The immunization-linked multicenter trial found almost identical infant mortality rates in the vitamin

* Personal communication, Paul Arthur, London School of Hygiene and Tropical Medicine, 2000.

TABLE 6. Impact of immunization-linked vitamin A supplementation on rates per child-year of clinic visits and hospital admissions in infants up to nine months of age

Event	Vitamin A	Control	Rate ratio (95% CI)
Clinic visits[a]			
Any visit	4.773	4.648	1.027 (0.982–1.074)
Acute lower respiratory tract infection or clinical pneumonia	0.879	0.838	1.050 (0.953–1.157)
Diarrhea	1.272	1.298	0.980 (0.913–1.053)
Persistent diarrhea	0.041	0.053	0.733 (0.562–1.063)
Dysentery	0.113	0.095	1.182 (0.948–1.473)
Hospital admissions			
Any admission	0.064	0.066	0.980 (0.775–1.238)
Acute lower respiratory tract infection	0.022	0.023	0.986 (0.639–1.521)
Acute diarrhea	0.018	0.016	1.089 (0.690–1.721)
Persistent diarrhea	0.002	0.001	1.286 (0.342–4.837)
Dysentery	0.001	0.000	Rate ratio and 95% CIs could not be assessed by the model

a. Data for India and Peru only.
Source: ref. 9.

TABLE 7. Impact of immunization-linked vitamin A supplementation on the point prevalence of acute lower respiratory tract infection and diarrhea during the previous 24 hours among children up to nine months of age

Illness	Vitamin A	Control	Rate ratio (95% CI)
Acute lower respiratory tract infection			
Cough + 2 respiratory rates above 60 or 50/min	0.036	0.034	1.058 (0.962–1.163)
Cough + 2 reported rapid breathings	0.024	0.027	0.920 (0.827–1.024)
Cough + 2 respiratory rates above 60 or 50/min + 1 of the following: lower chest indrawing, nasal flaring, fever	0.006	0.006	0.989 (0.810–1.207)
Diarrhea			
3 or more loose or watery stools	0.100	0.101	0.990 (0.939–1.045)
6 or more loose or watery stools	0.039	0.040	0.962 (0.883–1.048)
Diarrhea and blood in stools	0.003	0.003	1.035 (0.776–1.379)
Diarrhea and vomiting or fever	0.042	0.041	1.025 (0.994–1.114)
Diarrhea and refused breastfeeding	0.007	0.008	0.970 (0.802–1.172)

Source: ref. 9.

A and control groups during the first nine months of life. In addition, no differences in morbidity or anthropometry were found.

Analysis of data concerning the first year of life from the large-scale field trials of periodic vitamin A supplementation suggests that dosing the infant during the first four months of life, even with 100,000 IU of vitamin A, has no impact on subsequent mortality. This impact starts to become apparent when dosing takes place at five months of age.

A dramatic 64% reduction in mortality in the first five months of life was achieved in the Indonesia trial [3], following administration of 50,000 IU of vitamin A to newborns on their first day of life. This finding is in marked contrast with that of the immunization-linked multicenter trial and certainly needs to be substantiated. In summary, more evidence is needed to justify starting vitamin A supplementation any earlier in infancy than five months.

Given the potential for wide coverage that would be afforded by linking vitamin A supplementation to immunization programs, this further suggests that the possibility of giving 100,000 IU alongside the third DPT vaccine should be explored. Several countries have recommended schedules in which the third DPT is given at five months. Even in countries where there are opportunities earlier (say at 14 weeks), natural delays will mean that a large proportion of children are likely to actually receive this dose closer to five months.

In order to consider what might be optimal linkages between vitamin A supplementation and immunization schedules, data concerning the actual age patterns of immunization contacts need to be considered in conjunction with recommended vitamin schedules. It is important both to ascertain the likely coverage

with possible linking schedules and to assess the risks to children of receiving too frequent high doses. A close watch should be kept on the Zvitambo* trial in Zimbabwe. This trial started in 1998 and is due to be completed in 2002. It will recruit 14,000 mothers and their infants delivered at one of seven recruitment sites in greater Harare. They will be randomized into four treatment groups: 50,000 IU of vitamin A given to the neonate; 400,000 IU of vitamin A given to the mother during the immediate postpartum period; a combination of maternal and neonatal doses; and a placebo group.

To date, no mortality trials of vitamin A supplementation have been completed in areas with high HIV prevalence and high incidence of vertical (mother-to-child) HIV transmission. It is possible that early infant vitamin A supplementation may have a more important role in HIV endemic areas and that different vitamin A supplementation approaches need to be developed. A substudy of the Zvitambo trial is designed to evaluate in detail the impact of vitamin A supplements to the mother and/or child at birth on vertical HIV transmission during lactation, and on horizontal HIV transmission to HIV seronegative women during the immediate postpartum period.

* Zimbabwe Vitamin A for Mothers and Babies Project (ZVITAMBO). A collaborative project between the University of Zimbabwe, Faculty of Medicine, Department of Pediatrics, Obstetrics, and Immunology, Faculty of Science, Department of Nutrition, and the City of Harare Health Department, Harare, Zimbabwe; Johns Hopkins University, Center for Human Nutrition and Division of Disease Control, Department of International Health, School of Hygiene and Public Health, Baltimore, Md., USA; and the Montreal General Hospital Research Institute, Center for the Study of Host Resistance, Montreal, Quebec, Canada.

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A review of the evidence for the benefits and safety of adding vitamin A to the treatment of six common health problems in children

Lisa McNally and Andrew Tomkins

Abstract

It has been more than 70 years since vitamin A was first reported to play a role in the treatment of measles. The addition of vitamin A to the treatment of other common childhood illnesses remains controversial, with differing guidelines. This review analyzes the strength of the evidence for the role of vitamin A in six common childhood illnesses. We found no published papers on the use of vitamin A in chickenpox or malaria. There is strong published evidence for the use of adjuvant vitamin A in children requiring hospital admission for measles and some evidence for its use in acute shigellosis. The available evidence does not support a role for adjuvant vitamin A in acute lower respiratory tract infections or acute watery diarrhea. There is insufficient evidence on the role of vitamin A in the treatment of persistent diarrhea, acute measles not requiring admission, and protein-energy malnutrition to guide policy

Introduction

Population-based studies have shown that vitamin A supplementation can reduce childhood mortality rates in considerably vitamin A–deficient communities [1–4]. Vitamin A was first reported to play a possible role in reducing the mortality from complications of measles nearly 70 years ago [5]. The current Integrated Management of Childhood Illness guidelines recommend the use of vitamin A in children presenting to health-care workers with measles or severe protein-energy malnutrition [6]. However, other guidelines from the World Health Organization (WHO) have also suggested adjuvant treatment with high-dose vitamin A in children presenting to health care workers with diarrhea, respiratory disease, or chicken pox [7]. The purpose of this review is to analyze the strength of the evidence for the role of vitamin A in acute childhood illness.

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Methods

The medical literature databases Medline, Popline, and Embase were searched for published articles on the use of vitamin A in the treatment of the following six childhood illnesses: diarrhea (acute, persistent, and dysentery), acute lower respiratory tract infections, measles, malaria, chickenpox, and severe protein-energy malnutrition.

Searches were performed using the above terms and for all years available for each database. For Medline this was from 1966, for Popline from 1970, and Embase from 1988 to date. The abstracts for each of the identified studies were read by one of the authors (LMN), and articles relevant to the present review were noted. These papers were then read in full, and those reporting original studies examining the role of vitamin A in the treatment of the six childhood illnesses were included. The bibliographies of review articles were also searched for additional papers not found on preliminary literature review.

We included only original papers reporting randomized clinical trials of adjuvant treatment with vitamin A in children with acute illness [8]. Three studies did not fit into this category but are still included in this review [9–11]. One paper from Cape Town (South Africa) reported on a retrospective record review of children under 15 years old admitted to the hospital with measles [9]. The authors analyzed the morbidity and mortality data for children admitted over two nonconsecutive time periods before and after the introduction of routine high-dose vitamin A in the acute treatment of measles at their hospital. The authors had already published the results of a randomized clinical trial that is also included here [12] and performed the retrospective analysis to evaluate the efficacy and tolerance of high-dose vitamin A in routine clinical use.

In order to evaluate the tolerance of high-dose vitamin A in children, two randomized, placebo-controlled community trials are included in the review [10, 11]. Both of these papers stated that their primary aim was to evaluate the tolerance of vitamin A in children and are included here because the larger study populations ensure a greater power to detect rare side effects.

The other studies that are included are double-blind, randomized clinical trials, including two that were published as letters [13, 14]. However, there has been no standard dose or type of vitamin A used; the studies include different ages and inclusion criteria, and outcome measures are not standardized. This makes an overall statistical analysis of the evidence difficult, and we have therefore chosen to summarize the results of the studies as tables. The discussion summarizes the available data and focuses on further research required.

Results

Table 1 illustrates the number of studies identified by each of the databases and the number of studies included in this review. The number of articles available on each of the subjects is not equally distributed. We found no publications on the use of adjuvant vitamin A in acute malaria, and there was only one published letter on the role of vitamin A in chickenpox. We identified 6 articles on diarrhea, 12 on acute lower respiratory tract infections, 8 on measles, and 1 on severe protein-energy malnutrition. The authors of one of the papers included in all three of these sections [15] conducted a randomized clinical trial of the use of vitamin A in children presenting to their hospital in the Democratic Republic of the Congo. The majority of the children in this study had severe protein-energy malnutrition, and outcome measures included the morbidity from diarrhea or respiratory tract infections. The results are summarized in tables 2 to 7.

TABLE 1. Literature database searches for the use of vitamin A in childhood illness

Illness	Medline 1966 to date	Popline[a] 1970 to date	Embase[a] 1988 to date	Included in results
Diarrhea	189	243 (23)	226 (64)	6
ALRI	348	162 (28)	146 (79)	12
Measles	188	150 (20)	180 (105)	8
Malaria	47	133 (3)	57 (19)	0
Chickenpox	4	0 (0)	6 (1)	1
PEM	257	129 (16)	476 (39)	1

a. The numbers in parentheses are the numbers of duplicated papers found on search.

ALRI, Acute lower respiratory tract infection; PEM, protein-energy malnutrition.

Conclusions

Diarrhea

Six published articles of trials of vitamin A in children with diarrhea were found (table 2). Four evaluated the role of vitamin A in children with acute watery diarrhea, one in children with acute shigellosis, and one diarrhea in malnourished children. A study from Dhaka, Bangladesh, used a randomized, controlled trial with factorial design to compare the use of vitamin A, zinc, or both with a placebo in children with diarrhea of less than three days' duration [19]. The authors used logistic regression analysis to reduce confounding variables. Children were given 4,500 IU of vitamin A per day for 15 days, and no reduction in the mean duration of diarrhea was observed. There was, however, a trend towards a reduction in the risk of prolonged diarrhea (>7 days) in this group, but it was not significant ($p = .09$).

Another study from New Delhi, India, evaluated the role of vitamin A supplementation in children between the ages of six months and five years presenting with acute diarrhea of less than three days' duration [17]. The authors used the standard WHO dose of vitamin A of 200,000 IU (100,000 IU for infants and children weighing less than 10 kg or younger than one year) but again found no reduction in the mean duration of diarrhea. However, on subgroup analysis, children who had preexisting vitamin A deficiency (defined as conjunctival impression cytology stage 3/5 or above) had a significant reduction in the duration of diarrhea. Henning et al., in another study from Bangladesh, also failed to find a decrease in the duration of acute watery diarrhea in children supplemented with 200,000 IU of vitamin A [16], as did a Turkish study using 100,000 IU of vitamin A in children 6 to 12 months old [20]. In contrast, Hossain et al. gave 200,000 IU of vitamin A to children with acute shigellosis in Bangladesh and reported an increase in the proportion of children who were clinically cured at five days in the supplemented group [18].

A study from the Democratic Republic of the Congo failed to find a reduction in diarrhea among malnourished children given 200,000 IU of vitamin A [15]. However, when severely malnourished children were given a low-dose regimen of 5,000 IU of vitamin A each day during their admission, there was a significant reduction in the incidence, but not the duration, of severe diarrhea.

Donnen et al. reported that children with no edema who were given the high-dose vitamin A had an increased risk of severe nosocomial diarrhea (RR = 2.42; 95% CI, 1.15–5.11) [15]. In the other four studies, there were no reported adverse effects from vitamin A.

The addition of zinc to the treatment regimen does

TABLE 2. Diarrhea

Author and publication	Site	Objectives	Vitamin A dose	No.	Age	Inclusion criteria	Exclusion criteria	Results: placebo vs vitamin A	Subgroup analysis: adverse events
Henning et al. Eur J Clin Nutr 1992;46: 437–43 [16]	Dhaka and Matlab, Bangladesh	To evaluate whether a large dose of vitamin A affects the severity and duration of acute episodes of diarrhea or induces adverse manifestations	200,000 IU	83	12–60 mo	Watery diarrhea <48 h Male sex	Female sex Cholera Other serious illness Severe malnutrition Vitamin A within previous 3 mo Clinical vitamin A deficiency	No significant difference between the two groups Total duration of diarrhea (h): 54.6 (41.7) vs 52.1 (29.4) Total stool output (g/kg/episode): 143.6 (160.7) vs 143.0 (133.2) Emesis in first 24 h (g/day): 16.5 (46.1) vs 24.9 (59.8) Numbers are means (SD)	No adverse events noted
Dewan et al. Indian Pediatr 1995;32:21–5 [17]	New Delhi, India	To evaluate whether vitamin A supplementation early in a diarrheal episode alters the mean duration of diarrhea	100,000 IU <10 kg 200,000 IU >10 kg or >1 yr	216	6–60 mo	>3 stools/day for <72 h	No vitamin A within previous 3 mo No measles in preceding 6 wk	Duration of diarrhea (h): 110.49 (49.08) vs 100.74 (43) ($p = .11$) Numbers are means (SD)	Duration of diarrhea (h) in patients with the following conditions: CIC stage 3/5 or above: 128.46 (40.85) vs 95.89 (19.79) ($p = .009$) Malnutrition with CIC 3/5 or above: 131.33 (26.76) vs 8.33 (22.34) ($p = .025$) Dysentery: 75.2 (47.09) vs 86.16 (72.29) No adverse effects Numbers are means (SD)
Donnen et al. Am J Clin Nutr 1998; 68:1254–60 [15]	Katana, Democratic Republic of Congo	To examine the effects of either a single high-dose or daily low doses of vitamin A on recovery from diarrhea and ALRIs, including nosocomial diarrhea and ALRIs in children with moderate to severe vitamin A deficiency	High dose: 200,000 IU >12 mo, 100,000 IU <12 mo stat –or– Low dose: 5,000 IU every day of admission	900	0–72 mo	Consecutive cases admitted to Lwiro Pediatric Hospital within age range	Coma Vitamin A within previous 4 mo	No effect on duration of moderate or severe diarrhea Duration of diarrhea (days): Moderate diarrhea: High dose 3.27 Low dose 3.03 Placebo 2.42 Severe diarrhea: High dose 5.41 Low dose 4.28 Placebo 4.06	In children without edema, risk of nosocomial diarrhea was higher in both high-dose ($p < .05$) and low-dose (NS) groups Low dose significantly reduced incidence of severe diarrhea in severely malnourished children RR = 0.21 (95% CI, 0.07–0.62)

continued

TABLE 2. Diarrhea *(continued)*

Author and publication	Site	Objectives	Vitamin A dose	No.	Age	Inclusion criteria	Exclusion criteria	Results: placebo vs vitamin A	Subgroup analysis: adverse events
Hossain et al. BMJ 1998;316:422–6 [18]	Dhaka, Bangladesh	To evaluate the efficacy of a single large oral dose of vitamin A in treating acute shigellosis in children in Bangladesh	200,000 IU	83	1–7 yr	Bloody mucoid stools for <72 h >20 pus cells and erythrocytes per high-power field *Shigella* sp isolated	Other acute or chronic illness *Entamoeba histolytica* Antibiotics for current illness Vitamin A in previous 3 mo Weight-for-age <75%	Clinical cure by day 5: 20% vs 45% ($p = .02$) Bacteriological cure by day 3: 39% vs 38% ($p = .93$)	No adverse events noted
Faruque et al. Acta Paediatr 1999;88:154–60 [19]	Dhaka, Bangladesh	To evaluate the role of zinc or vitamin A supplementation as adjunct therapy of acute infantile diarrhea in developing countries	4 groups received one of the following daily for 15 days: Zinc (14.2 mg) Vitamin A (4,500 µg) Zinc plus vitamin A (doses as above) Placebo After 60% of patients had been recruited to study, dose of zinc was increased from 14.2 to 40 mg	684	6–24 mo	<3 day history >3 liquid stools/day with some dehydration	Severe dehydration Severe marasmus ± edema Systemic illness	Mean duration of diarrhea (h): Vitamin A: 159.7(129.5) vs 157.3(129.5) ($p = .82$) Zinc: 169.5 (122.4) vs 147.6 (122.4) ($p = .03$) In zinc-supplemented group, risk of diarrhea episodes lasting >7 days was markedly reduced by 43% (95% CI, 9%–65%) ($p = .017$) Trend toward reduction in prolonged diarrhea in vitamin A group RR = 0.67 (95% CI, 0.42 – 1.07) ($p = .089$) Numbers are means (SD)	Adverse events not stated
Yurdakok et al. J Pediatr Gastroenterol Nutr 2000;31:234–7 [20]	Hacettepe, Turkey	To examine the effect of single high-dose vitamin A supplementation on duration of acute diarrhea	100,000 IU	120	6–12 mo	Acute diarrhea <5 days	Chronic disease Malnutrition (<10th percentile) Associated infectious disease Prior antibiotic use Dysentery	Total duration of diarrhea (days): 7.8 (3.1) vs 7.4 (3.2) Numbers are means (SD) Persistent diarrhea (>14 days): 6.6% vs 6.6%	No children with bulging fontanelle or other signs of hypervitaminosis A

CIC, conjunctival impression cytology; ALRI, acute lower respiratory tract infection.

appear, however, to significantly reduce the mean duration of the diarrhea and the risk of prolonged diarrhea. A subgroup analysis of zinc use in stunted children was associated with a 19.3% reduced risk of diarrhea [19].

Acute lower respiratory tract infections

Twelve published papers were found evaluating the role of adjuvant therapy with vitamin A in children with acute lower respiratory tract infections. Four studies examined the role of high-dose vitamin A in children with laboratory-confirmed respiratory syncytial virus (RSV) disease (table 3). Three of these were from the United States (including one multicenter trial)[14, 21, 22] and one from Santiago, Chile [23].

In all three papers from the United States, children given high-dose vitamin A had longer lengths of stay than children given a placebo. This difference was statistically significant only in the paper by Bresee et al., which had the largest study numbers [21]. They suggested that their results were due to subtle vitamin A toxicity. The differences in length of stay were most significant in those children at low risk of severe RSV disease and those over 12 months of age. Older children with RSV disease generally have a milder illness than young children, and in combination with much higher doses of vitamin A in this age group, this may explain the adverse effects of vitamin A in this age group [21].

The study from Santiago, Chile, showed no overall benefit from vitamin A in children hospitalized for RSV infection. However, vitamin A recipients were less likely to receive oxygen, bronchodilators, and steroids after enrollment and spent fewer days in the hospital. However, none of these differences were statistically significant. For the subgroup of children with significant hypoxemia on admission (room air oxygen saturation level < 90%), those given vitamin A had a more rapid resolution of tachypnea ($p = .01$) and a shorter duration of hospitalization ($p = .09$) [23]. Children in Santiago are well nourished, and xerophthalmia and clinical vitamin A deficiency are not known to occur. In addition, baseline vitamin A levels were not lower in the Chilean study than in the US studies. The authors suggest that the younger age of the children in the Chilean study may be important, since the prolongation of hospital stay in the US multicenter trial was seen in those subjects older than 12 months of age. The authors concluded that if vitamin A is effective for the treatment of RSV, the effect is small and may only be seen in subgroups of children with severe disease [23].

Neuzil et al., in a letter to the Pediatric Infectious Diseases Journal, reported on results from a trial in Nashville, Tenn., USA [14]. After an initial safety trial, they began a randomized controlled trial of 50,000 IU of vitamin A on two consecutive days in children under 12 months old admitted to their hospital with RSV. Early in their study, a seven-week-old child with a mild respiratory illness developed a bulging fontanelle and an associated vitamin A level of 115 μg/dl six hours after receiving the first 50,000 IU of vitamin A. The second dose was not administered. By 24 hours, the serum vitamin A concentration had returned to normal, and by 48 hours, the fontanelle was flat. At this point they reduced their vitamin A dosage to 25,000 IU on two consecutive days. The first child to receive this new dose (three months of age) also developed a bulging fontanelle and a serum vitamin A concentration of 95 μg/dl six hours after the dose was given. Again the level returned to normal within 24 hours, and the fontanelle had flattened by 48 hours. All 22 subsequently enrolled children were given two consecutive doses of 12,500 IU of vitamin A without further evidence of toxicity. The children who received vitamin A in this study also had a higher mean length of stay, although this was not statistically significant, possibly because of small sample sizes [14].

Nonspecific acute lower respiratory tract infections

Kjolhede et al. gave 200,000 IU of vitamin A to children admitted to a hospital in Guatemala City with radiographically confirmed acute lower respiratory tract infections and found almost identical mean respiratory rates and temperatures in those children treated and not treated with adjuvant vitamin A [24] (table 4). The authors commented that their study population was relatively replete compared with populations used for the vitamin A mortality trials, and thus the subjects might not be expected to respond to vitamin A. They suggested repeating similar trials in areas where vitamin A deficiency is more prevalent and severe [24]. Three other studies used the higher dose of 400,000 IU of vitamin A in children with lower respiratory tract infections and found no decrease in days to resolution of fever, resolution of tachypnea, hospital stay, or response to first-line antibiotic [25–27]. However, on subgroup analysis, Nacul et al. found that Brazilian children not receiving vitamin A required a change of their first-line antibiotic earlier [25].

Donnen et al., in their study of malnourished children from the Democratic Republic of the Congo, found no effect of vitamin A on the length of an episode of lower respiratory tract infection, either for a single dose of 200,000 IU or for the low-dose regimen of 4,500 IU daily [15]. Fawzi et al. also found no effect of vitamin A in Tanzanian children, even those in the lowest decile of dietary intake [27].

There is some evidence that the use of vitamin A supplementation in the treatment of pneumonia could have adverse effects. Stephensen et al. gave adjuvant vitamin A to 95 Peruvian children hospitalized with

TABLE 3. Lower respiratory tract infections

Author and publication	Site	Objectives	Vitamin A dose	No.	Age	Inclusion criteria	Exclusion criteria	Results: placebo vs vitamin A	Subgroup analysis: adverse events
A. Acute lower respiratory tract infections									
Bresee et al. Pediatr Infect Dis J 1996;15: 777–82 [21]	Multicenter trial, USA	To determine whether high-dose vitamin A could reduce morbidity associated with RSV in children	50,000 IU 1–5 mo 100,000 IU 6–11 mo 200,000 IU >12 mo	239	1–72 mo	Admitted to hospital with laboratory confirmed RSV infection	Had RSV but hospitalized for a different reason Received high-dose vitamin A within preceding 3 mo Clinical vitamin A deficiency Known liver disease Hydrocephalus Increased intracranial pressure	Mean hospitalization (days): 4.4 vs 5.0 ($p = .01$) Mean duration of oxygen (days): 5.0 vs 5.3 ($p = .25$) Mean ICU stay (days): 6.4 vs 6.1 ($p = .82$) Died: 0% vs 1% ($p = .33$)	Vomiting <72 h after drug: 23% vs 33% ($p = .12$) No patients had bulging fontanelles Vitamin A levels inversely proportional to severity of illness
Quinlan and Hayani Arch Pediatr Adolesc Med 1996;150:25–30 [22]	Chicago, USA	To determine the benefit of oral vitamin A supplementation for acute RSV infection	100,000 IU	32	2–58 mo	Admitted with laboratory-confirmed RSV infection LRTI defined as 1 or more of the following: RR > 60, abnormal lung auscultation, CXR shows new lung infiltrate	Weight <4 kg Receiving vitamin A in doses >US RDA Known liver disease Clinical evidence of liver disease	No outcome measure was notably different between those who received vitamin A and placebo Supplemental oxygen days: 2.7 vs 5.5 ($p = .11$) Mean ICU days: 3 vs 10.3 ($p = .36$) Mean days to discharge or severity score 0: 3.5 vs 6.6 ($p = .8$)	Mean vitamin A and RBP levels were lower in RSV-infected inpatients than in outpatient controls Mean vitamin A and RBP levels were lower in RSV patients admitted to ICU than in those on ward No adverse events
Dowell et al. Pediatr Infect Dis J 1996;15: 782–6 [23]	Santiago, Chile	To determine whether high-dose vitamin A is effective in the treatment of RSV disease	50,000 IU 1–5 mo 100,000 IU 6–11 mo 200,000 IU >12 mo	180	1–72 mo	Admitted with laboratory-confirmed RSV infection	Had RSV but hospitalized for a different reason High-dose vitamin A within preceding 3 mo Xerophthalmia Known liver disease Hydrocephalus Increased cranial pressure	No significant benefit from vitamin A in treatment of the overall group	Children with severe hypoxemia on admission (SpO_2 < 90%): More rapid resolution of RR ($p = 0.01$) Hospital stay (days): 9.3 vs 5.5 ($p = .09$) No adverse events were seen
Neuzil et al. Pediatr Infect Dis J 1997;16: 84–5 (letter) [14]	Nashville, Tenn, USA	To investigate the safety and efficacy of a high dose of vitamin A in children with RSV	Initially 2 doses of 50,000 IU, reduced to 2 doses of 12,500 IU (see text)	33	<12 mo	Not stated	Not stated	Hospital stay (days): 2.9 vs 3.5 ($p = .16$)	

B. Pneumonia or nonspecified acute lower respiratory tract infections									
Kjolhedeet al. J Pediatr 1995; 126: 807–12 [24]	Guatemala City, Guatemala	To test the efficacy of high-dose vitamin A as adjuvant treatment for radiographically confirmed ALRI requiring inpatient care	<1 yr 100,000 IU >1 yr 200,000 IU	263	3–48 mo	Radiographically confirmed ALRI: pneumonia or bronchiolitis	Asthma Tuberculosis Xerophthalmia Measles Multivitamins or vitamin A supplements within 4 mo Severe malnutrition (<70% weight-for-age)	No difference between treatment groups in return to normal of respiratory rate, temperature, or SpO_2 No difference in change of antibiotics No difference in survival analysis	No significant difference in adverse events
Nacul et al. BMJ. 1997;315: 505–10 [25]	Recife, Brazil	To evaluate the impact on clinical recovery and severity of the addition of large doses of vitamin A in the standard treatment for childhood pneumonia	<1 yr 200,000 IU >1 yr 400,000 IU Total dose (divided equally and given on days 1 and 2 of admission)	472	6–59 mo	Clinical diagnosis of pneumonia, either admitted or seen as outpatient	Xerophthalmia Readmission with same illness Renal failure Measles Other major concurrent infection Other active lung disease	Similar patterns of recovery in the 2 treatment groups Median duration of episode (days): 7.5 vs 7.6 Fever on day 3 (%): 26.4 vs 16 ($p = .008$) Other signs of pneumonia at 2 days showed no difference Response to first-line antibiotic: RR = 0.71; 95% CI, 0.50–1.01; $p = .054$	Placebo children in hospital needed change of antibiotic earlier: RR = 0.56; 95% CI, 0.35–0.92; $p = .02$ No significant difference in adverse events
Si et al. Acta Paediatr 1997; 86:1052–5 [26]	Ho Chi Minh City, Vietnam	To determine the effect on morbidity and mortality of high-dose vitamin A in children hospitalized with moderate or severe pneumonia	<1 yr 200,000 IU >1 yr 400,000 IU Half on admission and half next day	592	1–59 mo	Moderate or severe pneumonia as defined by WHO	High-dose vitamin A within last month Raised ICP Suspected tuberculosis Empysema Lung abscess Severe heart disease Malignancy Steroids Severe malnutrition (weight-for-age < 60% expected) Xerophthalmia	Days to resolution: Placebo / Vitamin A Fever ($p = .43$) 4.14 / 4.61 Normal RR ($p = .44$) 4.81 / 5.29 Hospitalization ($p = 0.87$) 7.47 / 7.38	Moderately malnourished patients: Hospital stay (days): 8.64 vs 6.82 ($p = .04$) but no difference in duration of fever or tachypnea No side effects reported but not on data forms Side effects most pronounced in children without malnutrition
Fawzi et al. Am J Clin Nutr 1998;68:187–92 [27]	Dar es Salaam, Tanzania	To determine whether large doses of vitamin A given to Tanzanian children admitted with non-measles pneumonia would reduce the severity of respiratory disease	<1 yr 200,000 IU >1 yr 400,000 IU Total dose (divided equally and given on days 1 and 2 of admission)	687	6–60 mo	Admitted with pneumonia as defined by WHO	Vitamin A in preceding 4 mo Weight-for-age <60% Measles Pulmonary tuberculosis Diphtheria Whooping cough Xerophthalmia	Mortality RR (vitamin A vs placebo) = 1.63; 95% CI, 0.67–3.97; $p = .28$ No difference in duration of hospital stay, days of fever, RR, or hypoxia	Vitamin A not associated with an adverse event No effect of nutritional status

continued

TABLE 3. Lower respiratory tract infections *(continued)*

Author and publication	Site	Objectives	Vitamin A dose	No.	Age	Inclusion criteria	Exclusion criteria	Results: placebo vs vitamin A	Subgroup analysis: adverse events
Donnen et al. Am J Clin Nutr 1998;68:1254–60 [15]	Katana, Democratic Republic of the Congo	To evaluate effect of high- and low-dose vitamin A on recovery from morbidity and recovery from nosocomial infections of hospitalized children To evaluate effect of vitamin A on ALRI recovery	High dose 200,000 IU –or– Low dose 5,000 IU daily during admission	900	0–72 mo	Admission to hospital ? malnourished >2 days of cough and RR > 40 or cough and temperature > 38.5°C	Coma Vitamin A in previous 4 mo	Length of episode (%): 1 day >1 day High dose 72.7 27.3 Low dose 66.0 34.0 Placebo (NS) 79.6 20.4 No effect	
Stephensen et al. Pediatrics. 1998; 101:e3:915–916 [28]	Lima, Peru	To test the hypothesis that high-dose vitamin A supplements will enhance recovery of children hospitalized for the treatment of community-acquired pneumonia	<1 yr 100,000 IU followed by 50,000 IU the next day >1 yr 200,000 IU followed by 100,000 IU the next day	95	3 mo–10 yr	Admission to hospital with X-ray confirmed community-acquired pneumonia	Immunodeficiency Regular vitamin A supplements Weight-for-height <70% Bronchial asthma Suspicion of tuberculosis Underlying chronic disease	Mean blood oxygen level at 24 h lower in vitamin A group ($p = .03$) Rate of decrease in prevalence of retractions greater in placebo group ($p < .0005$) Mean RR, heart rate, and aggregate severity score all greater in vitamin A group over time ($p < .05$) Mean duration of hospital stay (days): 6.0(4.9) vs 5.9(3.5) ($p = .74$) Numbers in parentheses are SD	
Julien MR. Trop Med Int Health 1999:4: 794–800 [29]	Maputo, Mozambique	To test the potential of routine vitamin A supplementation on admission to speed recovery from ALRI and to decrease levels of morbidity 6 wk after discharge	100,000 IU <1 yr 200,000 IU >1 yr	164	6–72 mo	Inpatient admission for ALRI defined as: Cough Temperature >37.5°C RR > 50 Creps or bronchial breathing	Measles or measles vaccination in preceding 4 wk Clinical vitamin A deficiency Kwashiorkor or marasmus Other severe diseases	Mean hospital stay (days): 4 vs 3 (NS) Clinical discharge by day 5 74.2 % vs 88.4% ($p = .023$) No difference in ARI, fever, or other illnesses at 6 wk follow-up	Clinical discharge day 5 <1 yr old 69.4% vs 100% ($p = .002$)

ALRI, Acute lower respiratory tract infection; CXR, chest X-ray; ICP, intracranial pressure; ICU, intensive care unit; LRTI, lower respiratory tract infection; NS, not significant; RBP, retinol-binding protein; RDA, recommended daily allowance; RR, rapid respirations; RSV, Respiratory syncytial virus.

radiographically confirmed pneumonia [28]. The children given vitamin A had a longer duration of clinical signs and a greater need for supplemental oxygen. These adverse effects were not so severe as to require longer hospitalization, produce untoward clinical outcomes, or produce significant differences in chest X-ray findings at the follow-up examination, but they did result in more nursing time and higher costs of care. There was a tendency toward a longer duration to normalization of respiratory rate in Vietnamese children without malnutrition [26].

However, a paper from Mozambique published after the initial review was presented to WHO reported a significant difference in the percentage of children discharged before day five among those given 200,000 IU of vitamin A on admission for acute lower respiratory tract infections. This difference was particularly important in children less than one year of age. They found no significant difference in this criterion between the two groups at six weeks of follow-up. They concluded that it is likely that response to vitamin A is only significant in societies with low mean vitamin A levels such as theirs, and that although there was no significant clinical difference at six weeks, a reduction in hospital stay would have important financial implications [29].

Large doses of vitamin A may be beneficial in some children with underlying hypovitaminosis, but there is no evidence that it should be used in all children, since there is a high rate of adverse effects in children hospitalized for acute lower respiratory tract infections.

Measles

The evidence for a role of adjuvant vitamin A in the treatment of measles is strong, and its use has become standard practice. There are, however, differences in the dose recommended by WHO and the dose used in the initial trials. Barclay et al. and Hussey et al., in two separate randomized, clinically controlled trials, gave 200,000 IU of vitamin A on two consecutive days to children admitted to the hospital for acute measles [12, 30] (table 4). Both studies showed significant reductions in measles-associated morbidity and mortality. In the study from Tanzania, there was a reduction in mortality from measles from 13% in the treatment group to 7% in the control group, although this was not significant. The largest decrease in mortality was seen in the under two-year-old children and in those children who had measles-related complications, especially croup [30]. Hussey and Klein followed up this randomized, controlled trial by showing in a retrospective records review that the introduction of vitamin A regimen in their hospital had led to significant reductions in mean stay, admission to the intensive care unit, and death from measles in children under 15 years old [9].

Another study from South Africa used the WHO-recommended dose of vitamin A in 60 children admitted to the hospital for measles complicated by pneumonia or diarrhea. There was a significant improvement in recovery and in the children's integrated morbidity scores [31].

Rosales et al. studied the effect of a WHO dose of vitamin A on the outcome of acute measles in 200 Zambian children not requiring hospital admission [33]. There was no difference in measles complications during the acute stage of the illness. On cross-sectional analysis at four weeks, there was a significant reduction in cough and pneumonia in the vitamin A group, but when longitudinal analyses were performed, there was no statistically significant benefit from the use of vitamin A.

No adverse effects were found in children with measles treated with high-dose vitamin A, probably because these children had low serum levels of the vitamin.

Chickenpox

In a letter to the Journal of Pediatrics, Özsoylu et al. published results of a clinical controlled trial of the use of vitamin A in chickenpox [13] (table 5). They gave 200,000 IU of vitamin A to 47 children with acute chickenpox and none to 46 controls. Crusting of the lesions occurred significantly earlier in the study group (5.34 as opposed to 6.37 days, $p < .01$). They concluded that vitamin A should be given to all children with acute chickenpox on the first day of the eruption. However, the confidence intervals were very wide (95% CI, 3.82–6.86 days in treated children and 5.03–7.71 days in the untreated), and we are therefore unsure as to the statistical validity of their conclusions. We found no other studies evaluating the role of vitamin A in chickenpox.

Severe protein-energy malnutrition

The only published trial on the use of vitamin A in malnourished children was from the Democratic Republic of the Congo [15] (table 6). However, the inclusion criteria stated only that the children were admitted to the Lwiro Pediatric Hospital. Although most children admitted to the hospital are malnourished, not all of them are. The study evaluated the effect of vitamin A given in two different doses on mortality from, duration of, and incidence of acute lower respiratory tract infection or diarrhea and all-cause fevers. Neither vitamin A regimen had an effect on the case fatality rates, median length of stay, or incidence of all-cause fevers. As mentioned previously, in children with severe protein-energy malnutrition, a daily dose of 5,000 IU significantly reduced the incidence, but not the duration, of severe diarrhea.

TABLE 4. Measles

Author and publication	Site	Objectives	Vitamin A dose	No.	Age	Inclusion criteria	Exclusion criteria	Results: placebo vs vitamin A	Subgroup analysis: adverse events
Ellison JB. BMJ 1932;2: 708–11 [5]	London	To determine whether a liberal supply of vitamins A and D early on in measles is able to exercise a favorable influence on the course of the disease	300 IU vitamin A and 2,000 IU vitamin D for 7 and 21 days, depending on severity of disease	300	<5 yr	Hospital admission for measles		Overall case fatality rates 8.7% vs 3.7% Pneumonia cases 34/300 vs 32/300 Case fatality rates for pneumonia 68% vs 31% No difference in cases of otitis media 28 vs 29 cases	No signs of hypervitaminosis were detected in any of the children
Barclay et al. BMJ 1987;294: 294–6 [30]	Dodoma, Tanzania	To determine the effect of high-dose vitamin A taken during early infection with measles on subsequent mortality in African children	400,000 IU divided equally and given on 2 consecutive days	180	Not stated	Hospital admission with acute measles	Corneal ulcers Death within 24 h Vitamin A before admission	Mortality 13% vs 7% ($p = .13$; $p < .05$ in children <2 yr) Complications: Pneumonia 51% vs 43% (NS) Croup 22% vs 22% (NS)	Mortality <2 yr: 22% vs 0% ($p < .05$) Mortality in those with complications: Pneumonia 15% vs 8% Croup 31% vs 0% Adverse effects not stated
Coutsoudis et al. Am J Clin Nutr 1991;54:890–5 [31]	Durban, South Africa	To determine the effect of WHO dose of vitamin A on measles-associated morbidity, pneumonia, and diarrhea. Examined at 8 days, 6 wk, and 6 mo Inpatients	Vitamin A 54.5 mg (100,000 IU) (<12 mo) or 109 mg (200,000 IU) (>12 mo) at admission and 6 wk or placebo	60	4–24 mo	Measles complicated by pneumonia and diarrhea		Recovery (days) from: Pneumonia 5.7 ± SE:0.79 vs 3.8 ± SE:0.40 ($p = .037$) Diarrhea 4.5±SE: 0.35 vs 3.2 ± SE0.71 (NS) Fever 4.2 ± SE:0.50 vs 3.6 ± 0.30 NS Recovery <8 days: 65% vs 96% ($p = .002$) Integrated morbidity scores: 1.37 vs 0.24 ($p = .006$)	Adverse events not stated
Hussey and Klein N Engl J Med 1990;323:160–4 [12]	Cape Town, South Africa	To determine the effect of oral vitamin A on morbidity and mortality in children requiring hospital admission for acute measles	400,000 IU divided equally and given on 2 consecutive days	189	<13 yr	Hospital admission for acute measles	Vitamin A before admission Xerophthalmia Rash >4 days Lack of consent	Relative risk (vitamin A to placebo): Death 0.21 (95% CI, 0.05-0.94) ($p = .046$) Pneumonia >10 days 0.44 (95% CI, 0.24-0.80) ($p = .008$) Diarrhea >10 days 0.40 (95% CI, 0.19–0.86) ($p = .023$) Croup 0.51(95% CI, 0.28-0.92) ($p = .033$)	No clinical adverse effects

								Duration of pneumonia 12.37 vs 6.53 days ($p < .001$) Duration of diarrhea 8.54 vs 5.61 days ($p < .001$) Duration of hospital stay 15.24 vs 10.52 days ($p = .004$)	
Hussey and Klein J Trop Pediatr 1993; 39: 342–5 [9]	Cape Town, South Africa	Retrospective study to determine whether high-dose vitamin A reduces measles-associated morbidity and mortality in routine hospital setting	400,000 IU given in 2 equally divided doses on 2 consecutive days Historical control group: 3,000 IU vitamin A daily during hospital stay	1,720	<15 yr	Hospital admission for measles	None	Hospital stay 13 vs 10.1 days ($p < .001$) ICU admission 10.5% vs 4.3% ($p < .001$) Death 5% vs 1.8% ($p < .001$)	No adverse events
Madhulika et al. J Trop Pediatr 1994;40:305–7 [32]	Ahmedabad, India	To detemine the effect of vitamin A on post-measles complications	400,000 IU orally divided equally and given on 2 consecutive days or half this dose given i.m.	177	Not stated	Measles in last 2 wk Survived >72 h in hospital	Previous measles vaccination Active tuberculosis	Mortality 32% vs 16% ($p < .02$); SE not given	Mortality in: Severe malnutrition 57% vs 54% (NS) Encephalopathy 50% vs 63% (NS) Adverse events not stated
Rosales et al. Am J Epidemiol 1996;143: 413–22 [33]	Ndola, Zambia	To determine the effect of WHO-recommended dose vitamin A on outcome of acute measles in nonhospitalized patients	Single dose 200,000 IU vitamin A	200	Not stated	Acute measles, clinical, confirmed by antibody titres	Requiring hospital admission Xerophthalmia Severe undernutrition	Cross-sectional analysis: Only difference at 4 wk in children admitted with: No ARI 93% vs 78% Cough 10% vs 7% Pneumonia 12% vs 0% ($p = .005$) Longitudinal analysis: No statistically significant benefit from vitamin A	Adverse events not stated

continued

TABLE 4. Measles *(continued)*

Author and publication	Site	Objectives	Vitamin A dose	No.	Age	Inclusion criteria	Exclusion criteria	Results: placebo vs vitamin A	Subgroup analysis: adverse events
Ogaro et al. Trop Geogr Med 1993;45:283–86 [34]	Nairobi, Kenya	To determine whether high-dose vitamin A in acute measles reduced the incidence or severity of diarrheal and respiratory complications	<6 mo: 50,000 IU 6–12 mo: 100,000 IU >12 mo: 200,000 IU	294	<5 yr	Hospital admission for acute measles	Moribund Another major illness Xerophthalmia	Pneumonia on admission: No difference in resolution between groups Diarrhea on admission: Resolution <5 days 38% vs 55% ($p = .04$) Severe diarrhea: 32% vs 18% ($p = 0.03$) Complications after admission: Diarrhea 36% vs 41% (NS) Croup 24% vs 23% (NS) Pneumonia 18% vs 19% (NS) Otitis media 15% vs 4% ($p = .03$)	Side effects not stated

Safety and tolerance

Children between one and six months of age given 100,000 IU of vitamin A in a community study in Nepal had a 1.6% excess risk of vomiting (statistically significant) and a 0.5% excess risk of bulging fontanelles (not significant) (table 7). There was no increased risk of vomiting or a bulging fontanelle in infants under one month old. There was no increased risk of irritability or fever in either group [10]. Infants in this study were examined only at 24 hours. It is possible that if they had been examined earlier, the side effects might have been greater [11].

Older children aged one to six years given 200,000 IU of vitamin A in the Philippines complained of nausea, vomiting, and headache four times more often than children given placebo [9]. The effect was dose related, since children given 200,000 IU complained twice as much of symptoms as children given 100,000 IU of vitamin A [10].

Policy conclusions regarding efficacy

The evidence for a beneficial effect of large-dose vitamin A in acute pediatric illness has been reviewed in published reports. There is:

» Strong evidence that high-dose vitamin A is beneficial in the treatment of complicated measles requiring hospital admission;
» Some evidence that high-dose vitamin A is beneficial in the treatment of acute shigellosis;
» Evidence that high-dose vitamin A is not beneficial in the treatment of acute watery diarrhea or acute lower respiratory tract infections;
» Insufficient evidence on the role of high-dose vitamin A in the treatment of persistent diarrhea, acute measles not requiring hospital admission, and protein-energy malnutrition;
» No published information on the use of vitamin A in the treatment of chickenpox or acute malaria.

Policy conclusions regarding safety

» There is some evidence for worsening of clinical indicators for acute lower respiratory tract infections among children receiving high-dose vitamin A.
» There is no evidence for deterioration of clinical status of other childhood illnesses when high-dose vitamin A is given as adjuvant therapy.

TABLE 5. Chickenpox

Author and publication	Site	Objectives	Vitamin A dose	No.	Age	Inclusion criteria	Exclusion criteria	Results: placebo vs vitamin A	Subgroup analysis: adverse events
Özsoylu et al. J Pediatr 1994; 125(6):1017–8 (letter) [13]	Ankara, Turkey	No clear statement	200,000 IU	93	Not stated	Clinical chicken-pox	Clinical evidence of vitamin A deficiency	Crusting of all lesions 6.37 vs 5.34 9 days ($p < .01$) Complications 5/47 vs 0/46	Adverse events not stated

TABLE 6. Severe protein-energy malnutrition

Author and publication	Site	Objectives	Vitamin A dose	No.	Age	Inclusion criteria	Exclusion criteria	Results: placebo vs vitamin A	Subgroup analysis: adverse events
Donnen et al. Am J Clin Nutr 1998;68:1254–60 [15]	Katana, Democratic Republic of Congo	To determine the effect of high- and low-dose vitamin A on recovery from morbidity and recovery from nosocomial morbidity of hospitalized children To determine the effect of high- and low-dose vitamin A on diarrhea, ALRI, and all- cause fevers Hospital admits malnourished children, most of whom have severe PEM	High dose: 200,000 IU or 100,000 <12 mo stat Low dose: 5,000 IU daily	900	0–72 mo	Hospital admission	Coma Vitamin A within 4 mo	Case fatality rates: High dose 8.0% Low dose 8.4% Placebo (NS) 8.9% Hospital days (median): High dose 10 Low dose 9 Placebo (NS) 8	Duration (days): Moderate diarrhea (NS) High dose 3.27 Low dose 3.03 Placebo 2.42 Severe diarrhea (NS) High dose 5.41 Low dose 4.28 Placebo 4.06 In children without edema on admission, risk of severe nosocomial diarrhea was higher in vitamin A-supplemented groups RR of diarrhea: High dose 2.42* Low dose 1.87 In children with kwashiorkor, daily low dose significantly reduced risk of severe diarrhea, but high dose did not RR: High dose 0.91 Low dose 0.21 No effect on ALRI or all-cause fever Adverse events not stated

* Statistically significant difference.

TABLE 7. Safety

Author and publication	Site	Objectives	Vitamin A dose	No.	Age	Inclusion criteria	Exclusion criteria	Results: placebo vs vitamin A	Subgroup analysis: adverse events
West et al. Bull WHO 1992; 70(6):733–9 [11] Sarlahi District,	Nepal	To investigate the incidence and severity of acute side effects among neonates and infants who received a large oral dose of vitamin A; note that this is a prophylactic dose and not treatment dose	<1 mo 50,000 IU 1–6 mo 100,000 IU in oil	2,840	<1 mo 1–6 mo	Random allocation of infants in 261 village wards to placebo or vitamin A	Absent from house or refusal of consent	<1 mo: No difference in incidence of morbidity 24 h after receiving vitamin A No increase in bulging fontanelles 1–6 mo: RR following dose Vomiting 1.67* Fever No effect Loose stool No effect Bulging fontanelle: excess risk 0.5% (–0.1% to 1.1%) % rate difference in irritability (NS): 0–1 mo 0 1–6 mo 0.2 (–0.6 to 1.0)	
Florentino et al. Am J Clin Nutr 1990;52:694–700 [10]	Rizal, Philippines	To evaluate the incidence of side effects from high-dose vitamin A before commencing a community trial of vitamin A prophylaxis 24 hr and 1 wk after dosing	60 or 30 mg	2,471	1–6 yr	All children of defined age in chosen villages	Clinical vitamin A deficiency Nausea, vomiting, diarrhea, fever or headache in previous 24 h	Symptoms (%): High dose / Medium dose / Placebo: Nausea/vomiting 8.8* / 3.6 / 2.2; Headache 5.9 / 2.0 / 0.8; Diarrhea 6.0 / 5.5 / 5.4; Fever 7.9 / 6.1 / 5.3 Symptoms (%): <24 h / 1–7 days: At least 1 symptom — High-dose 17.2* / 5.6; Medium dose 9.6 / 4.6; Placebo 7.9 / 4.5 At least 2 symptoms — High dose 4.1 / 0.7; Medium dose 1.4 / .0; Placebo 0.6 / 0.5	Nutritional status: consistent trend towards occurrence of symptoms with deteriorating nutritional status Symptoms (%) according to nutritional status: High dose / Medium dose / Placebo: Nausea/vomiting — Normal 5.8 / 1.3 / 2.2; 1 8.7 / 4.0 / 8.7; 2 11.8 / 3.9 / 11.8; 3 20.0 / 16.7 / 6.2 Headache — Normal 4.7 / 0.6 / 1.1; 1 6.3 / 2.4 / 1.2; 2 5.9 / 2.2 / —; 3 10.0 / — / —

*Statistically significant difference.

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Safety of vitamin A supplementation of postpartum women and young children

Jean H. Humphrey and Rebecca N. Ichord

Abstract

It is now known that the previous World Health Organization (WHO) recommendation for vitamin A supplementation of postpartum women (200,000 IU) is not sufficient and that larger doses are well tolerated. The new recommendation is to give women 400,000 IU during the first eight weeks postpartum, as two 200,000-IU doses separated by at least 24 hours. The most common side effect of large doses of vitamin A in young infants is bulging of the fontanelle. This side effect is rare (0%–8%), spontaneously resolves within 72 hours, and is not associated with significant short- or long-term clinical consequences. A 50,000-IU dose is safe for young infants, but doses greater than 50,000 IU may be harmful, especially for infants under four months of age. The revised WHO recommendation for infants zero to five months old is 150,000 IU as three doses of 50,000 IU with a one-month interval between doses.

Safe dose of vitamin A for postpartum women

Vitamin A deficiency is common among women of reproductive age living in deprived situations* [1] and may be associated with a substantial increase in maternal mortality [2]. The immediate postpartum period represents both a programmatic and a biological window of opportunity to provide reproductive-aged women with a large dose of vitamin A, since a large proportion of women come into contact with the health care system for childbirth or immediately afterward, and because at that time pregnancy can be reliably ruled out. This intervention not only benefits the mother by improving her own vitamin A status (as reflected by plasma and breastmilk retinol concentrations), but also improves the status of her breastfed infant [3].

Since 1982, the World Health Organization/United Nations Children's Fund/International Vitamin A Consultative Group (WHO/UNICEF/IVACG) has recommended supplementing postpartum women living in areas where vitamin A deficiency is a public health problem with 200,000 IU of retinol equivalent (RE) [4–6]. This group's most recent recommendation also extended the safe time frame to eight weeks postdelivery for breastfeeding women, when the risk of pregnancy is nil. The recommended dose was based primarily on the availability of 200,000-IU capsules in the community.

Theoretical calculations and recent studies suggest this dose is too small and that a larger dose would be well tolerated. The demands of the mammary gland over the first year of lactation are twice the WHO dose, or about 400,000 IU (assuming a milk vitamin A concentration of 1.75 μmol/L, and volumes of 750 ml/day for the first six months and 600 ml/day for the second six months). This requirement is in addition to the needs of the mother herself (800 μg RE/day [7] or 292,000 μg RE [950,000 IU]/year). Preschool children have been safely given 200,000 IU for many years. A 50-kg woman's body weight, her plasma volume to accommodate the absorbed dose, and her liver size to process and store the dose are about three to four times greater than those of a preschool child. Thus, it is reasonable to assume that women would tolerate doses at least twice those given to preschool children. These theoretical calculations are substantiated by three recent studies. In Bangladesh, 200,000 IU was not enough to maintain adequate levels of serum retinol among the women or to build adequate vitamin A stores in their breastfed infants during the first six months of life [8]. The authors concluded

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* Bloem MW, Matzger H, Huq N. Vitamin A deficiency among women in the reproductive years: an ignored problem. Report of the XVI IVACG Meeting, Chaing Rai, Thailand, 1994.

that the current WHO dose is too low. In Indonesia, a 300,000-IU maternal dose was sufficient to raise breastmilk vitamin A concentrations to the normal range and allow the majority of infants to build adequate vitamin A stores by six months of age, but was not enough to prevent a fall in maternal serum retinol concentrations over the period of lactation [3]. Based on these calculations and data, Iliff et al. tested the tolerance of a single 400,000-IU dose by 398 postpartum women as compared with 390 placebo-treated women using a double-blind randomized design [9]. Rates of headache, nausea, vomiting, blurred vision, and drowsiness were low among all women (<5%) and were not different between treated and control groups ($p > 0.1$).

Together, these data suggest that the WHO-recommended dose for postpartum women is too low and that a higher dose (i.e., twice the current dose) is well tolerated. A theoretical risk remains, however, that higher maternal doses may result in high breastmilk concentrations of retinoic acid and its metabolites, which could be harmful to the infant. Measurement of these metabolites in breastmilk and the time course of clearance from plasma and breastmilk following maternal dosing is therefore a research priority. Until this information is available, postpartum breastfeeding women living in areas where vitamin A deficiency exists should receive 400,000 IU of vitamin A during the first eight weeks postpartum, given as two 200,000-IU doses separated by at least 24 hours. Women who are not breastfeeding should receive the first 200,000-IU dose, but not the second.

Safe dose of vitamin A for young infants

All infants are born with very limited vitamin A stores of about 6 μmol,* or a few days' supply. Over the first six months of life, breastfed infants of well-nourished women increase their vitamin A stores more than 10-fold to about 70 μmol (275 g liver weight × 0.26 μmol/g) [11]. They do this by ingesting about 130 L [10] of vitamin A–rich milk yielding approximately 300 μmol of vitamin A (18 L × 3.7 μmol of vitamin A per liter during the first month + 112 L × 2.1 μmol of vitamin A per liter during months 2 to 5). Therefore, vitamin A stores are physiologically nil at birth but accrue to normal concentrations during the first six months of lactation in healthy breastfed infants of well-nourished mothers.

Breastfed infants in developing countries are born with the same minimal stores but then consume breastmilk that, on average, contains only half the vitamin A concentration of breastmilk from privileged mothers [13]. Over the first six months of life, many of these infants will ingest the same volume, but receive just enough vitamin A to meet basal needs and store virtually none. Studies from Bangladesh [8, 14], Brazil [12], and Indonesia [3] reported that one-quarter to over 90% of the six-month-old babies studied had inadequate liver stores (defined by direct liver biopsy, relative dose response, or modified relative dose response). Many infants in developing countries will remain vitamin A–deficient at six months of age and require additional vitamin A.

Despite this physiological basis, vitamin A supplementation of young infants (less than six months of age) has been controversial, because the literature has been inconclusive about both its benefits and its safety [15–19]. These two issues may be related: concerns about safety have perhaps led to the use of smaller than optimal doses, which have then failed to achieve measurable benefit.

What is the highest safe dose for infants less than six months of age? A national trial in Nepal tested a 100,000-IU dose among infants 2 to 11 months of age. Compared with infants receiving a placebo, the supplemented infants had a 1.6% excess rate of vomiting, a 0.5% excess rate of bulging fontanelle, and a nonsignificant trend toward slightly (~1%) less breastfeeding and sleeping and more crying [19]. The authors concluded that the observed side effects were sufficiently uncommon and mild so as to be unlikely to deter compliance with a community-based supplementation program. However, longer follow-up of these infants suggested that this dose was too high for infants less than six months of age, especially those younger than four months [17].

The relative risk of mortality exceeded 1.0 among the vitamin A recipients as compared with controls for the 1-month-olds (RR = 1.38; 95% CI, 0.85–2.24), 2-month-olds (RR = 1.09; 95% CI, 0.56–2.12), and 3-month-olds (RR = 1.26; 95% CI, 0.54–2.95). By 4 months, the relative risk of mortality was less than 1.0 among the vitamin A recipients as compared with controls (RR = 0.92 and 95% CI, 0.41–2.03 for 4-month-olds; RR = 0.78 and 95% CI, 0.37–1.65 for 5-month-olds; RR = 0.78 and 95% CI, 0.49–1.25 for 6- to 11-month-olds who also received 100,000 IU). The adverse effect of the 100,000-IU dose among the 2- to 4-month-old infants appeared to be greater among the better-nourished children: there was a dose-response increase in the relative risk of mortality with increasing mid-upper-arm circumference among supplemented children.

* Liver weight at birth is 125 g [10]. The liver vitamin A concentration of all infants at birth is ~0.05 μmol/g [11, 12]. Thus, stores at birth are estimated at 6 μmol (125 g × 0.05 μmol/g). The Food and Agriculture Organization defines basal and safe vitamin A requirements for infants from birth to three months as 40 μg/kg/day and 78 μg/kg/day, respectively. Thus, for a 3.3-kg neonate, the daily requirement is 0.5 to 0.9 μmol, so the 6-μmol stores will last for 7 to 12 days.

A 50,000-IU dose was first recommended for neonates by WHO in 1982 [4]. In their most recent publication, this dose was again recommended specifically for neonates being breastfed by mothers who were not given postpartum vitamin A supplementation and those not breastfed [6]. Six placebo-controlled studies have assessed acute side effects following a single 50,000-IU dose in young infants* [9, 16, 19], and three additional studies have assessed side effects following a single 25,000-IU dose [20–22]. In these studies, the most common side effect, and the only side effect to raise concern, was bulging fontanelle. The following section will address the clinical significance of vitamin A–induced bulging fontanelle and conclude that this sign is self-limited, benign, and not associated with acute or long-term neurodevelopmental sequelae.

Therefore, for infants less than six months old, there is substantial evidence that the currently recommended dose of 50,000 IU is safe. However, based on the findings from the Nepalese trial mentioned above, doses exceeding 50,000 IU should not be given to young infants, especially those under four months of age.

The mechanism and clinical significance of bulging fontanelle following vitamin A supplementation

Bulging fontanelles have been the most common and least understood side effect of vitamin A supplementation in young infants. Table 1 lists nine controlled studies that assessed acute side effects among young infants following 25,000-IU or 50,000-IU doses of vitamin A given at birth or in concert with immunizations. Bulging of the fontanelle was the most common side effect: six of the nine studies reported excess rates of 0.5% to 8.4% of this sign, which was statistically significant in three [16, 20, 23].

This section addresses the clinical significance of bulging fontanelle following prophylactic doses of vitamin A when given as a public health intervention in regions of the world where deficiency is a problem. To best understand this, the neurological consequences of severe vitamin A toxicity—when clearly toxic doses of vitamin A have been ingested—will be reviewed, as the extreme situation of this condition. Understanding the mechanism and consequences of severe vitamin A toxicity provides an appropriate context within which to interpret the significance of transient bulging fontanelles occurring with infant vitamin A supplementation in the public health setting. Finally, the long-term neurodevelopmental status in infants with vitamin A–induced bulging fontanelles will be reviewed.

Physiology of intracranial pressure

Intracranial pressure obeys the mechanics of noncompressible fluid within a minimally expansile container. The relationship of pressure and volume defines the compliance of the cranium and can be depicted as a compliance curve (fig. 1A). Pressure at the lower limit of the container's volume capacity is low, and increases exponentially as volume is added. Under normal physiological conditions, the system functions on the lower flat part of the curve, in which a small increase in volume (V_1) produces essentially no increase in pressure (P_1). Mild abnormalities, such as early hydrocephalus or a small subdural hematoma, may cause a modest increase in volume (V_2), leading to a small increase in pressure (P_2).

As the system reaches the upper limit of its volume capacity, a small increase in volume produces a large increase in pressure. This pressure-volume relationship of the human cranium has been well documented, from infancy through adulthood [24, 25]. Infants differ from adults in that their open sutures and fontanelles allow the capacity of the skull to expand over a short time period (hours to days). The resulting shift in the compliance curve allows the infant skull to accommodate larger volumes without increasing pressure [26] (fig. 1B). Thus, a small increase in intracranial volume can elevate the fontanelle, thereby expanding the volume without necessarily significantly increasing the intracranial pressure. Progressively larger volume increases would cause the fontanelle to bulge and become more tense and ultimately cause intracranial pressure to rise.

The clinical significance of raised intracranial pressure depends on the cause, location, and severity of the increase. The cranial contents can be viewed simplistically as three volume compartments (fig. 2): brain, blood, and cerebrospinal fluid (CSF). Brain volume increases physiologically with growth and development, or pathologically as a result of acute injury or tumor formation. Blood volume changes physiologi-

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TABLE 1. Controlled studies of infant vitamin A supplementation with and without immunization

Authors	Country	Age at dosing	Dose (μmol)	Immunization	Bulging fontanelle				Other side effects
					Vitamin A		Control		
					n	%	*n*	%	
Thanangkul, et al. 1974 [21]	Thailand	Birth	52	No	0/62	0	0/59	0	None
West, et al. 1992 [20]	Nepal	<1 mo	52	No	0/112	0	1/111	0.9	None
		1–6 mo	105	No	10/1349	0.7	3/1265	0.2	Vomiting
Akib, et al. 1994 [22]	Indonesia	6 wk	26	DTP/OPV-1	0/158	0	0/156	0	Not reported
		6 wk	52	DTP/OPV-1	1/155	0.5			
de Francisco et al. 1993 [23]	Bangladesh (rural)	6.6 wk	52	DTP/OPV-1	4/95	4.2	0/96	0	None
		11.2 wk	52	DTP/OPV-2	4/95	4.2	0/96	0	
		15.9 wk	52	DTP/OPV-3	8/95	8.4	1/96	1.0	
Agoestina et al. 1994 [17]	Indonesia	Birth	52	No	46/1034	4.4[a]	28/1033	2.7[a]	None
					46/1030	4.5[b]	25/1027	2.4[b]	
Baqui et al. 1995 [24]	Bangladesh (urban)	6.5 wk	26	DTP/OPV-1	0/86	0	0/81	0	Anorexia, fever, vomiting
		11.8 wk	26	DTP/OPV-2	3/86	3.5	0/81	0	
		17.0 wk	26	DTP/OPV-3	9/86	10.5	2/81	2.5	
Rahman et al. 1995 [25]	Bangladesh	10 wk	26	DTP/OPV-1	2/99	2.0	0/98	0	None
		14 wk	26	DTP/OPV-2	3/88	3.4	0/85	0	
		18 wk	26	DTP/OPV-3	3/76	3.9	1/70	1.4	
WHO/CHD 1998 [26]	Ghana, Peru, India	6–8 wk	26	DTP/OPV-1	12/4582	0.3	5/4596	0.1	None
		10–12 wk	26	DTP/OPV-2	26/4481	0.7	7/4496	0.2	
		14–16 wk	26	DTP/OPV-3	37/4388	0.8	13/4404	0.4	
Iliff et al. 1999 [10]	Zimbabwe	Birth	52	No	7/398	1.8	5/390	1.3	None

a. 24 h after dosing.
b. 48 h after dosing.
c. Denominator excludes infants with closed fontanelles.

cally in response to the brain's metabolic demands, or pathologically from hemorrhage or systemic disease conditions (e.g., hypoxia). CSF volume is determined by a dynamic equilibrium between production, primarily by the choroid plexus, and absorption, primarily in the arachnoid villi into the dural venous sinuses [27].

Changes in volume of a localized nature, such as from a hemorrhage in one hemisphere or from expansion of obstructed ventricles, produce localized pressure gradients. Localized pressure gradients produce shifts of brain structures (herniation syndromes), with resulting life-threatening compression of vital structures in the brain stem. Benign intracranial hypertension (BIH) is a disorder of CSF dynamics leading to raised intracranial pressure without localized pressure

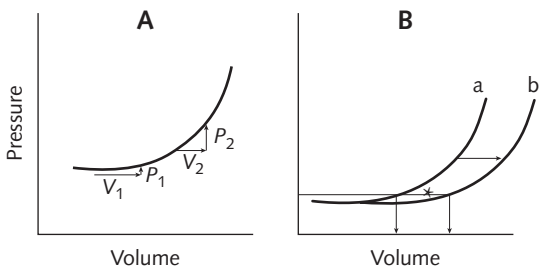

FIG. 1. A. Intracranial compliance: Increased volume on the low-pressure end of the curve (V_1) causes a minimal pressure change (P_1). Increased volume on the high-pressure end of the curve (V_2) causes a large pressure increase (P_2). B. The infant's cranium expands as represented by a shift in the compliance curve from *a* to *b*. Expansion can occur via elevation of the fontanelle in the span of minutes, or via separation of sutures in the span of hours or days, and through skull growth in the span of weeks and months. The expanded cranium can accomodate a larger volume without a significant increase in pressure, illustrated by *.

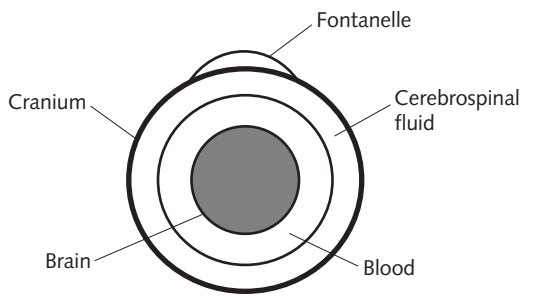

FIG. 2. Physiology of intracranial pressure: A rigid container with 3 compartments.

gradients. In BIH the CSF volume increases as a result of disturbed equilibrium between CSF production and absorption. Intracranial pressure is equally distributed throughout the cranial vault and does not cause herniation. BIH, also known as pseudotumor cerebri, has many diverse causes [28–30]. It is defined clinically as the presence of elevated intracranial pressure with no mass lesion or hydrocephalus on neuroimaging and no abnormalities of CSF composition [30]. When vitamin A toxicity produces neurological dysfunction, it does so by causing benign intracranial hypertension.

Severe vitamin A toxicity: A cause of BIH

The role of severe vitamin A toxicity as a cause of BIH is well established in the neurological literature [31, 32]. Vitamin A toxicity may occur acutely as a result of ingesting massive doses for one to several days, or chronically as a result of ingesting moderately high doses for months or years. The neurological disorder caused by acute or chronic vitamin A toxicity has been described in both infants and adults, and it conforms closely to BIH. In children these symptoms most commonly include anorexia, irritability, and vomiting, in addition to bulging of the fontanelle [33]. Intracranial pressure, as measured by lumbar puncture, is elevated, and CSF composition is normal [31, 34–39]. Neuroimaging by pneumoencephalography, ventriculography, or computerized tomography reveals no parenchymal abnormalities and ventricles that may be normal or mildly dilated [31, 32, 36–41]. Changes in the electroencephalogram (EEG) are rare [32, 38, 41–43].

The mechanism by which vitamin A causes an increase in CSF volume is poorly understood. During vitamin A toxicity, circulating vitamin A exceeds the carrying capacity of retinol-binding protein [44]. The resulting free vitamin A (not bound to retinol-binding protein) can penetrate the central nervous system [45], where it either alters the capillary permeability of the arachnoid villi [46], thereby decreasing the rate of CSF resorption, or alters the cellular integrity of the choroid plexus, thereby increasing CSF formation [47]. Interestingly, vitamin A deficiency can also cause bulging fontanelles and other signs and symptoms of BIH in infants, which are all reversible with vitamin supplementation [48, 49].

An important and consistent observation in numerous case reports is that the elevated intracranial pressure is reversible upon elimination of excess vitamin A, regardless of how long the condition has been present [31, 36–38, 41, 43, 50]. The associated neurological signs and symptoms are all reversible, with one important exception. Adults or adolescents with chronic vitamin A intoxication may develop permanent visual loss if the intracranial hypertension is sufficiently severe and long lasting (usually on the order of months and, in some cases, years) to cause chronic papilledema or optic atrophy [31].

In preadolescent children, transient papilledema has been reported during severe vitamin A toxicity [51–55]. However, permanent visual loss has never been reported in preadolescent children with vitamin A–induced BIH. Among infants, transient papilledema appears to be a very unlikely sequela of even severe vitamin A toxicity resulting from extremely high intakes. The literature contains reports of nine infants who received total doses of vitamin A ranging from 364 μmol (350,000 IU) to 7,020 μmol (6,750,000 IU) over periods of one day to nine months and underwent ophthalmic examination [34–37, 40]. All presented with bulging fontanelles and other concomitant toxic signs and symptoms, including vomiting [34, 36, 40], irritability [35, 40], skin lesions [35–37], hepatomegaly [35], and skeletal lesions [36, 37]. All, however, had normal optic discs. Thus, the only potentially irreversible sequela of BIH induced by chronic vitamin A toxicity, namely, visual loss secondary to chronic papilledema, has not been reported in infants, even those with severe vitamin A toxicity.

Bulging fontanelles following infant vitamin A supplementation of infants at risk for deficiency

Table 1 summarizes existing reports of side effects from vitamin A supplementation of infants in developing countries where vitamin A deficiency exists. In three studies, rates of bulging fontanelle were significantly higher among vitamin A–treated subjects than among placebo-treated subjects. It is also important to evaluate whether observed bulging fontanelles were associated with symptoms of intracranial hypertension (e.g., vomiting, irritability, and lethargy), as has been reported with universal regularity in severe vitamin A toxicity. Bulging of the fontanelle was associated with other symptoms (fever, vomiting, and anorexia) in one study [20]; in all other studies, bulging fontanelles were isolated signs. These observations can be fully explained by a small increase in CSF volume: the cranium can accommodate a small increase in CSF volume, and bulging of the fontanelle can occur without significant associated increase in intracranial pressure. This could occur if intracranial compliance parameters were on the flat part of the pressure-volume curve (fig. 1A). This interpretation is supported by the one study that objectively assessed intracranial pressure by Doppler resistive index (RI) and reported no measurable increase in intracranial pressure in newborns with vitamin A–induced bulging fontanelles [16]. The reliability of the RI as a relative indicator of intracranial pressure has been demonstrated in experimental and clinical settings [56–58], and it would be expected to detect clinically significant intracranial hypertension.

The studies reviewed in table 1 suggest that higher rates of vitamin A–induced bulging fontanelle may be expected when the vitamin is given concurrently with a DTP (diphtheria/tetanus/pertussis) immunization, especially with the third dose* [20]. There are two reports of infants who developed bulging fontanelles following DTP alone (without concurrent vitamin A supplementation). In both cases, the first two DTP doses had been well tolerated, and the bulging fontanelle occurred following the third dose of DTP [59, 60]. The mechanism of DTP-induced bulging of the fontanelle is not known. When considered in the light of an understanding of the physiological basis for vitamin A–induced neurological symptoms, the results of these studies can be viewed as reassuring.

Long-term neurodevelopmental consequences of vitamin A–induced bulging fontanelle

The literature contains a few reports of long-term neurodevelopmental outcomes in infants after chronic severe vitamin A intoxication. All describe normal outcomes [36, 37]. Two long-term developmental follow-up studies have been conducted following single doses of 50,000 IU of vitamin A. The first [61] was among children who had participated in the Expanded Programme on Immunization (EPI)–linked vitamin A supplementation trial conducted in Bangladesh [23]. A total of 71 children were evaluated for neurological, physical, and developmental abnormalities at three years of age. The Denver Developmental Screening Test, adapted to local cultural and field conditions, was used to assess development. Of the 71 children, 35 received vitamin A during the trial and did not develop a bulging fontanelle, 25 received a placebo and had a normal fontanelle, and 9 and 2 developed a bulging fontanelle after receiving vitamin A and a placebo, respectively. There were no neurological abnormalities identified in any child and no differences in anthropometric indices or developmental scores between groups.

A second and larger study [62] was conducted among children who had been enrolled in the Indonesian vitamin A supplementation trial [16], in which neonates received 52 μmol of vitamin A or a placebo on the first day of life. Ninety-one children who developed a bulging fontanelle after either vitamin A or a placebo and 432 children who had a normal fontanelle were evaluated at three years of age by the Bayley Scales for Infant Development II. In regression models predicting each developmental score of the Bayley Scales when one outlier child who had been injured since birth was removed from the analysis, the effect of bulging fontanelle was small and not significant in any model. Thus, this study provided no evidence of any biologically significant adverse developmental sequelae of neonatal vitamin A supplementation, whether accompanied by a bulging fontanelle or not. Indeed, vitamin A supplementation had a small beneficial effect on all developmental scores, which was significant for one scale, and for two when the outlier child was removed.

In summary, the bulging fontanelles observed during vitamin A public health intervention programs can be interpreted as a reflection of altered CSF volume without significant effect on intracranial pressure in the vast majority of infants given vitamin A supplements. In rare instances in which bulging fontanelles do occur with subjective symptoms, the effect is self-limited, with no significant acute neurological sequelae. Adverse long-term neurodevelopmental sequelae have not been observed and would not be expected in infants who have transient bulging fontanelles following vitamin A supplementation in doses described in these reports.

Conclusions

For postpartum women

» Vitamin A deficiency is common among pregnant and lactating women living in deprived areas and is associated with substantial increased risk of maternal mortality.
» The current WHO-recommended dose for postpartum women (200,000 IU) is not sufficient to attain and maintain normal maternal or infant vitamin A status for most women in developing countries.
» A 400,000-IU dose has been well tolerated, but it carries the theoretical risk of resulting in high breastmilk concentrations of retinoic acid and/or its metabolites, which may be harmful to the infant. Measurement of the concentrations and time course of clearance of these metabolites in human milk following single doses of 200,000 IU, 300,000 IU, and 400,000 IU is a research priority.
» The current recommendation for postpartum breastfeeding women should be increased to 400,000 IU given within eight weeks postpartum as two 200,000-IU doses given at least 24 hours apart.

For young infants

» All infants are born with very small vitamin A stores. Well-nourished normal infants accrue stores of about 0.26 μmol/g by six months of age. Breastfed

* de Francisco A, Yasui Y, Chakraborty J. Vitamin A supplementation given to mothers after delivery reduces infant mortality and increases symptoms of morbidity. Presented at the XVI International Vitamin A Consultative Group (IVACG) Meeting, 24–28 October 1994, Chaing Rai, Thailand.

infants of vitamin A–deficient mothers consume approximately half the vitamin A of their well-nourished peers and remain vitamin A–deficient at six months of age.

» One trial provided evidence that doses greater than 50,000 IU may be associated with increased risk of mortality, especially for the best-nourished infants and for those under four months of age. Therefore, doses over 50,000 IU of vitamin A should not be given to infants under six months of age.

» Acute side effects of the 50,000-IU dose have been assessed in six controlled trials, which demonstrated that the most common side effect of this dose in this age group is bulging fontanelles. The trials reported bulging fontanelle rates of 0.5% to 8.4%.

» When vitamin A toxicity produces neurological dysfunction, it does so by causing benign intracranial hypertension (BIH). BIH results when free circulating vitamin A penetrates the central nervous system and alters either the production or the resorption of cerebral spinal fluid (CSF), resulting in a transient increase in CSF volume. The human cranium can accommodate small increases in CSF volume without measurable increase in intracranial pressure. This is especially true for infants with open sutures and fontanelles, in whom a small increase in CSF can elevate the fontanelle without increasing the intracranial pressure. Larger CSF increases cause the fontanelle to bulge and intracranial pressure to increase. Vitamin A–induced elevated intracranial pressure is always reversible following elimination of the excess vitamin A. Bulging fontanelles induced by a single 50,000-IU dose spontaneously resolve within 72 hours of dosing and are nearly always an isolated sign, not associated with other signs and symptoms of increased intracranial pressure. One study that objectively assessed intracranial pressure in newborns with vitamin A–induced bulging fontanelle found no measurable increase. Two studies have looked for adverse developmental sequelae at three years of age among infants who had vitamin A–induced bulging fontanelles and found none. Thus, the 50,000-IU dose is safe: acute side effects are nearly always limited to transient isolated bulging fontanelles, which are self limited without acute or long-term neurological sequelae.

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Vitamin A and carotenoid toxicity

Rune Blomhoff

Abstract

Large differences in time and dose needed to induce hypervitaminosis A have been observed. High doses of vitamin A in food and oily solutions are well tolerated, whereas emulsified preparations have higher toxicity. Chronic hypervitaminosis seems to be induced following daily doses of 300,000 to 600,000 IU of vitamin A (90–180 mg of retinol) in oily preparations for many months or years, whereas teratogenicity may be induced by daily doses as low as 40,000 IU of vitamin A (12 mg of retinol) in oil during the first trimester. For the provitamin A, β-carotene, serious adverse effects have been reported in large-scale prospective randomized trials: four years of supplementation with 20 to 30 mg β-carotene per day was associated with increased risk of lung cancer and cardiovascular disease among smokers and workers exposed to asbestos. These results strongly suggest that high doses of β-carotene should not be recommended for any group until the safety of such doses can be established.

Introduction

Humans need vitamin A for normal functioning of the retina, maintenance of epithelial surfaces, immune competence, growth, development, and reproduction. The fat-soluble vitamin A is obtained either from preformed vitamin A present in milk, eggs, butter, and fish liver oils, or as provitamin A carotenoids in dark-green leafy vegetables, red palm oil, and red- or orange-colored fruits and vegetables, such as carrots, mangoes, papayas, and sweet potatoes. Most of the absorbed vitamin A is transported from the small intestine to the liver, where it is stored as retinyl palmitate. It is released into the bloodstream in combination with a specific binding protein, from which target cells throughout the body take it up.

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When the intake of vitamin A is inadequate to meet the body's needs, the liver stores are depleted to maintain serum retinol at a normal concentration. If intake is low over a prolonged period of time, the serum retinol concentration will decrease. A consequence of vitamin A deficit in target cells is clinical vitamin A deficiency, which is characterized by ocular features (Bitot's spots, night-blindness, and xerophthalmia) and keratomalacia leading to corneal drying (xerosis), corneal ulceration, and corneal necrosis. Generalized impaired resistance to infection is also reduced.

Vitamin A deficiency is a public health problem in over 120 countries. It is estimated that about 100 million children are subclinically vitamin A deficient, 3 million are clinically vitamin A deficient, and over 1 million childhood deaths are associated with vitamin A deficiency annually. At least 5 million children develop xerophthalmia each year, of whom up to half a million go blind. In vitamin A–deficient areas, women of childbearing age are also at high risk for vitamin A deficiency because of increased vitamin A requirements during pregnancy and lactation [1].

Trials indicate that wherever vitamin A deficiency exists, routine vitamin A supplements given between 6 and 72 months of age can be expected to reduce mortality by an average of 23%, based on eight field studies [2]. In addition, vitamin A supplements as part of measles management can reduce the mortality by more than 50% [3]. Recent studies in areas where vitamin A is suboptimal also suggest that vitamin A supplements given to mothers immediately after birth will improve their vitamin A status and the vitamin A content of their breastmilk, which in turn seem to contribute to improved health outcomes of both mothers and infants. Due to these developments, research in this field is now focusing not only on the efficacy of vitamin A interventions but also on the assessment of the sustainability of vitamin A interventions [2].

Several strategies are needed to ensure adequate vitamin A intakes for all people, including the use of periodic large doses, weekly or daily, of vitamin A supplements, fortification of commonly consumed

foods, and educational programs to improve the diet. In areas of vitamin A deficiency, it is believed that correcting vitamin A deficiency is likely to have an impact on reducing childhood mortality that is at least as great as that of any single immunization. Because vitamin A is stored in the liver, the impact of large-dose supplementation is relatively long lasting, and the appropriate dosages could potentially be given weekly, monthly, or more infrequently [1, 2].

The present international practice has been to use 100,000 IU of vitamin A (30 mg of retinol) for infants 6 to 12 months of age and 200,000 IU of vitamin A (60 mg of retinol) for children aged 12 months and over, given up to once every six months. For vitamin A supplementation to the mothers, a 200,000-IU (60 mg of retinol) dose has been given, preferably at the time of delivery but no later than within six weeks of delivery.

The last review of vitamin A safety was done by the International Vitamin A Consultative Group (IVACG) several years ago [4], and since then important new developments have taken place and have justified an update. In addition, UNICEF, the World Health Organization (WHO), and other nongovernmental organizations have put a lot of effort into vitamin A deficiency control since the Montreal Conference on Hidden Hunger in 1989. The increasing use of vitamin A supplements has raised questions regarding the safety of vitamin A, particularly in young children (less than six months old) and pregnant women and in connection with immunizations. We aim to review the safety of vitamin A and carotenoids related to such intervention strategies. For evaluating the safety of vitamin A and carotenoids, it is helpful to have an insight into their metabolism and functions in the body. This report will therefore first give a short introduction to these aspects.

Metabolism of vitamin A and carotenoids

Vitamin A is a term reserved to designate any compound possessing the biological activity of retinol [5] (fig. 1). The term *retinoids,* which was introduced in 1976 by Sporn et al. [6], was designated by the International Union of Pure and Applied Chemistry–International Union of Biochemistry (IUPAC-IUB) [5] to include "compounds consisting of four isoprenoid units joined in a head-to-tail manner; all retinoids may be formally derived from a monocyclic parent compound containing five carbon-carbon double bonds and a functional terminal group at the terminus of the acyclic portion." By this definition, retinoids would include both the naturally occurring forms of vitamin A and the many synthetic analogues of retinol, with or without biological activity. One problem with this definition is the fact that several

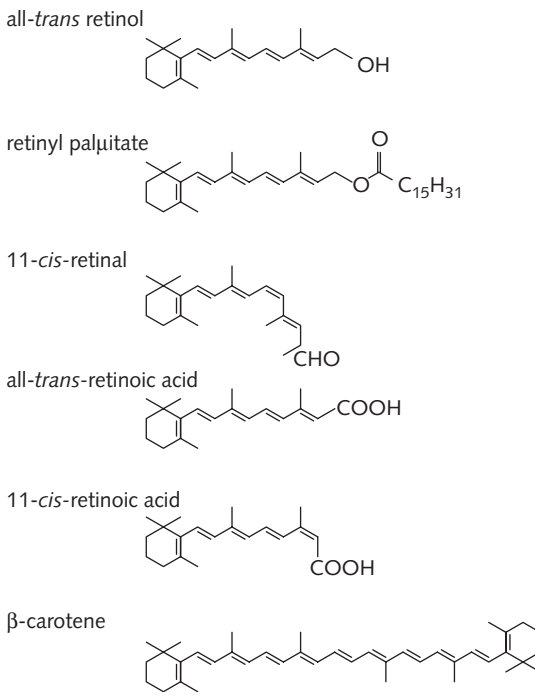

FIG. 1. Structural formulas of some natural retinoids and beta-carotene

synthetic compounds, such as TTNN and Ch-55* [7], which do not fit into this definition of retinoids, have been shown to be much more active than retinol or retinoic acid in assays for vitamin A or retinoid activity. Sporn and Roberts [7] proposed in 1985 that "a retinoid should be defined as a substance that can elicit specific biologic responses by binding to and activating a specific receptor or set of receptors." In practice, most researchers today use a combination of these two definitions, that is, the class of retinoids consists not only of retinol analogues (with or without biologic activity), but also of several compounds that are not closely related to retinol but elicit biologic vitamin A or retinoid activity.

Retinol (molecular weight, 286 daltons) and its derivatives are hydrophobic compounds that are highly unstable in the presence of oxygen and yield a mixture of dehydrated and double-bonded rearrangement products in acids. Light catalyzes double-bond isomerization of most retinoids.

Vitamin A exists in the plant world only in the form of precursor compounds, such as β-carotene. This is a member of a large class of naturally occurring carotenoids, with about 50 compounds with vitamin A activity. In all cases, it is a requirement for vitamin

* TTNN: 6-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-2-naphthalene carboxylic acid.

Ch-55: (E)4-[3-(3,5-di-tert-butylphenyl)-3-oxo-1-propenyl]-benzoic acid.

A activity that after a split of the molecule at least one intact molecule of retinol or retinoic acid can be obtained.

The dietary sources of vitamin A are provitamin A carotenoids from vegetables and preformed retinyl esters from animal tissues. Traditionally, one international unit (IU) of vitamin A is defined as 0.3 μg of all-*trans*-retinol. For nutritional purposes, a better term is *retinol equivalents* (RE), which is used to convert all sources of vitamin A and carotenoids in the diet into a single unit. Thus, 1 μg of all-*trans*-retinol equals 1 RE. Generally, 1 μg of retinol has been assumed to be biologically equivalent to 6 μg of β-carotene or 12 μg of mixed dietary carotenoids [4]. However, the basis for these conversion factors is weak. Recent findings from population intervention studies with vitamin A status endpoints (serum retinol response and total body vitamin A by isotope dilution) suggest that the current conversion estimate of 6:1 is a gross overestimate of the bioavailability of β-carotene in most foods [8–10].

During absorption, essentially all of the retinyl esters are enzymatically converted to retinol in the intestinal lumen prior to absorption by intestinal cells. Carotenoids, on the other hand, are internalized unchanged by the absorptive cells, where they are partially converted to retinol (fig. 2). Retinol is then esterified to long-chain fatty acids, forming retinyl esters, before incorporation into chylomicrons. Chylomicrons consist of aggregates of thousands of molecules of triacylglycerol and phospholipids packed together in a characteristic manner with carotenoids, retinyl esters, and other fat-soluble vitamins and cholesteryl esters and a few specific apolipoproteins. These huge lipoproteins (100–2,000 nm in diameter) are exocytosed into the intestinal lymph and then move into the general circulation, where several processes, such as triacylglycerol hydrolysis and apolipoprotein exchange, result in the formation of chylomicron remnants. Almost all retinyl esters and carotenoids present in the chylomicrons remain with the particle during conversion to chylomicron remnants [11–14](fig. 2).

Although chylomicron remnants are mainly cleared by the liver, extrahepatic uptake of remnants may be important in the delivery of retinol and carotenoids to extrahepatic tissues, such as bone marrow, peripheral blood cells, spleen, adipose tissue, skeletal muscle, and kidney. In light of the importance of retinoids for regulating gene expression and cellular differentiation, chylomicrons may be an important transport complex for delivering retinol and carotenoids to tissues with intensive cell proliferation and differentiation, such as bone marrow and spleen [12, 13]. Since this delivery of vitamin A to tissues increases relatively linearly with the dietary intake of preformed vitamin A (but not carotenoids), acute toxic effects of preformed vitamin A might also be mediated by this uptake rather than retinol bound to retinol-binding protein (RBP) or free retinol or retinoic acid in plasma (fig. 2).

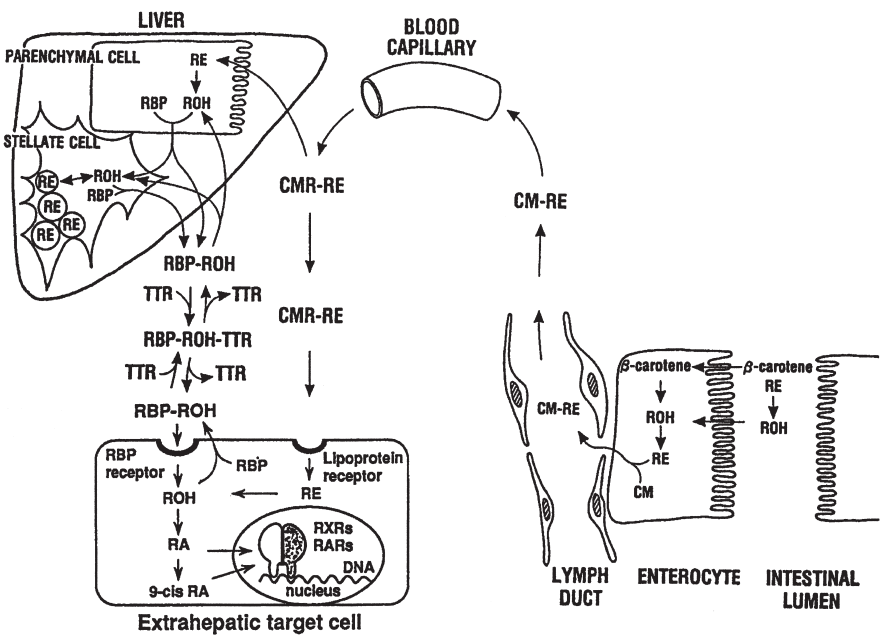

FIG. 2. Major pathways for retinoid transport in the body. ROH, Retinol; RE, retinyl ester; CM, chylomicron; CMR, chylomicron remnant; RBP, retinol-binding protein; TTR, transthyretin; RA, retinoic acid; RAR, retinoic acid receptor; RXR, retinoic X receptor

Most of the absorbed dietary vitamin A is, however, delivered to hepatic parenchymal cells (hepatocytes). The retinyl esters are hydrolyzed, and retinol may be transferred to RBP, which is found in high concentration in endoplasmic reticulum. Binding of retinol to RBP apparently initiates a translocation of retinol-RBP from endoplasmic reticulum to the Golgi complex, followed by secretion of retinol-RBP from the cells [11–14].

In vitamin A–sufficient states, most of the chylomicron remnant retinyl esters taken up by hepatocytes are transferred as RBP-bound retinol to perisinusoidal stellate cells in the liver for storage [15, 16]. In mammals, 50% to 80% of the body's total retinol (retinol plus retinyl esters) is normally present in the hepatic stellate cells. Ninety-eight percent of the stellate cell vitamin A is present in the form of retinyl esters packed together in cytoplasmic lipid droplets. The normal reserve of vitamin A in stellate cells is adequate to last for several months [17, 18]. The normal massive storage of retinyl esters in stellate cells and the cells' ability to control mobilization of retinol ensures that the blood plasma retinol concentration is defended close to 1 to 2 μM, in spite of normal fluctuations in daily vitamin A intake.

The transport of carotenoids has been described in much less detail. The fractions of carotenoids that are absorbed from the diet in an unchanged form enter the lymphatics in association with chylomicrons and follow their transport mainly to the liver. Following processing of chylomicron remnant carotenoids in parenchymal cells, some of the carotenoids are probably converted to retinoids. The carotenoids do not accumulate in liver cells but are mobilized as components of the very-low-density lipoprotein (VLDL) particles that are converted to VLDL remnants and low-density lipoproteins (LDL) in the circulation by a process resembling chylomicron remnant formation. Thus, no specific transport protein exists for carotenoids in plasma. The carotenoids may to a certain degree accumulate in adipose tissues following ingestion of large doses [19, 20].

Physiological function of vitamin A and carotenoids

We learned from early research that vitamin A functions as a chromophore in the visual process, and that vitamin A deficiency and vitamin A excess dramatically change the differentiation of epithelial cells. As early as 1925, Wolbach and Howe [21] showed that vitamin A deficiency in rats led to the replacement of differentiated mature epithelium with squamous keratinizing epithelial cells in tissues from various parts of the body. Twenty-eight years later, Fell and Mellanby [22] reported that the phenotype of chick epidermis in organ culture could be changed from keratinized to mucus-producing tissue by treatment with retinol or retinyl acetate. During the last 15 years, the ability of retinoids to affect the gene expression and differentiation of epithelial cells *in vivo* and *in vitro* has been studied in great detail.

The importance of retinoids for the proper function of both male and female reproductive organs has also been well documented. Classically, it has been assumed that retinol and retinoic acids perform separate functions and that both are needed for normal reproduction. Recent data indicate, however, that retinoic acid alone may fulfil all functions of retinoids in this process [23]. Present evidence clearly indicates that retinoids can influence growth and differentiation of various hematopoietic progenitor cells. It is also evident that retinoids play an important role in the complex interplay of cells and soluble factors that constitute the immune system [24].

Vitamin A deficiency, as well as vitamin A excess, produces a number of malformations of the embryo of all vertebrates. These abnormalities involve almost all organs in the body (e.g., the central nervous system, eye, face, dentition, ear, limbs, urogenital system, skin, lungs, heart, and hematopoietic system, as well as body axis development). Thus, retinoids are regarded as essential molecules that orchestrate many aspects of normal embryonic development [25].

Thus, today we know that vitamin A is of central importance for many biological processes, such as cell differentiation, proliferation, and apoptosis, and that the mechanism of action of vitamin A in these processes involves regulation of gene expression. This is mediated by nuclear receptors that are specific for vitamin A metabolites that regulate gene expression by binding to short DNA sequences in the vicinity of target genes [11, 12].

In addition to the role of carotenoids as vitamin A precursors, the carotenoids have a separate function as antioxidants. Oxidative stress is believed to play a role in cancer and respiratory tract infections. Therefore, the antioxidant function of carotenoids turns out to be another interesting facet of the function of this family of molecules [26].

Requirements of vitamin A and carotenoids

In most societies, vitamin A needs are met by the combined consumption of carotenoid precursors of vitamin A in plants and preformed vitamin A (retinol and retinyl esters) in animal foods. There has been no consensus in different countries as to the amount of vitamin A and carotenoids that should be consumed in order to maintain optimal health. Whereas no recommendations are generally given for carotenoids, most countries have based their recommendations between

500 and 1,000 μg of retinol equivalents (RE) for adults [27–29]. The recommendations are also based on a surprisingly small number of studies.

Much of the world relies on WHO and the Food and Agriculture Organization (FAO) to publish and disseminate the technical information that is used for national dietary allowances or as a basis for producing national nutrient requirement standards. The establishment of human nutrient requirements is a prerequisite for countries to develop food-based dietary guidelines for their populations. During the 1980s, WHO and FAO reviewed the literature on vitamin A requirements. However, progress in vitamin A research since then requires updating knowledge of the subject. WHO and FAO are now in the process of revising their recommendations. Table 1 presents the recommended dietary intake of vitamin A from WHO/FAO, the European Union, and Recommended Dietary Allowances/National Academy of Sciences.

Symptoms of hypervitaminosis A

Symptoms of hypervitaminosis A may occur in the skin, nervous system, musculoskeletal system, circulation (e.g., plasma proteins), and internal organs. The toxicity varies with dose and body mass, age, sex, disease conditions, concurrent drug administration, and environmental chemical exposures.

Toxic reactions provoked by large doses of vitamin A are well known to occur following either intake of liver rich in vitamin A (e.g., polar bear, seal, halibut, or whale) or excessive administration of vitamin A preparations [30–34]. It is useful to differentiate between the acute vitamin A intoxication caused by short-term ingestion of excessive amounts of vitamin A [35–38] and the chronic hypervitaminosis A resulting from long-term intake of more moderate vitamin A doses [39–42]. Thus, acute hypervitaminosis A can be defined as any toxicity manifested following the ingestion of a single very high dose or several repeated very high doses over a few days. Furthermore, chronic hypervitaminosis A can be defined as any symptoms resulting from continued ingestion of high doses for months or years. Toxicities associated with acute and chronic excess of vitamin A intake have been extensively reviewed [43, 44]. The symptoms of acute and chronic hypervitaminosis A are summarized in table 2.

TABLE 1. Comparison of recommended dietary intakes of vitamin A (RE/day)

Group	Age (yr)	FAO/WHO 1988 [27]	EU 1992 [28]	Food and Nutrition Board, NAS, RDA 1989 [29]
Infants	0–1	350	350	375
Children	1–3	400	400	400
Children	4–6	400	400	500
Children	7–10	400	500	700
Males	11–12	500	600	1,000
Males	12–15	600	600	1,000
Males	15+	600	700	1,000
Females	11–12	500	600	800
Females	12–15	600	600	800
Females	15+	500	600	800
Pregnant		600	700	800
Lactating	1st 6 mo	850	950	1,300
Lactating	2nd 6 mo	850	950	1,200

Sources: refs. 27–29.

TABLE 2. Symptoms of hypervitaminosis A

Acute hypervitaminosis A
Increased CSF pressure. Bulging of fontanelle in infants, headache and blurred vision in adolescents and adults
Loss of appetite, nausea, vomiting, abdominal pain
Peeling of skin, cheilitis, loss of hair
Fatigue, lassitude, vertigo, somnolence, disturbance of consciousness, occasionally meningeal irritation
Hemorrhages, nose bleeding
Edema
Occasionally tenderness of the long bones
Occasionally hepatomegaly and splenomegaly
Chronic hypervitaminosis A
Desquamation and peeling of the skin, erythema, pruritus, disturbed hair growth
Desquamation of mucous membranes: cheilitis, angular stomatitis, gingivitis, glossitis
Pain and tenderness of the bones: restricted movement
Radiological detectable bone changes (hyperostosis corticalis)
Increased CSF pressure, headache predominantly in the occipital region
Hyperirritability, sleep disturbance: EEG changes only exceptionally
Papillary edema, diplopia
Anorexia and loss of weight
Hepatomegaly, sometimes with splenomegaly
Edema and swelling
Clinical-chemical findings
Retinyl ester concentration in plasma is always increased
Increased serum retinol dependent of dose
Calcium concentration in serum is often increased
Activity of serum alkaline phosphatase is often increased
SGOT and SGPT activities are occasionally increased with chronic intoxication

Source: refs. 30–44.

Lowest dose needed to induce acute and chronic hypervitaminosis A

The large differences in time and dose needed to induce hypervitaminosis A from supplements may at first glance look surprising and may lead erroneously to the assumption that individual tolerance to vitamin A varies over a wide range. Much of the variance may, however, be related to the physical formulations of the ingested preparations, that is, whether vitamin A exists in an oily solution or is emulsified in an aqueous and equivalent formulation. If vitamin A is ingested as an oily solution, fairly high doses seem to be tolerated—independently of age—until hypervitaminosis A symptoms appear. As reviewed by Korner and Vollm [45] and presented in figure 3, a daily intake of 5,000 IU of vitamin A (1.5 mg of retinol) per kilogram of body weight for 3.5 years is necessary before symptoms appear. In contrast, in the case of aqueous emulsions, the period before symptoms appear after administration is only approximately seven months with identical doses. Therefore, one may have to take into account an approximately sixfold higher toxicological activity for emulsified vitamin A preparations as compared with oily preparations. Thus, it is impossible to draw conclusions on the safe dose of vitamin A when literature reports do not present details of the vitamin A preparation administered. It would very important for further studies to validate the suggestions from Korner and Vollm [45].

Both graphs in figure 3 show a clear relation between the daily ingested amount of vitamin A and the duration of intake with regard to the appearance of hypervitaminosis A symptoms. Administration of very high doses significantly reduces the time before onset of hypervitaminosis A, whereas "moderate" doses prolong the lag period [45].

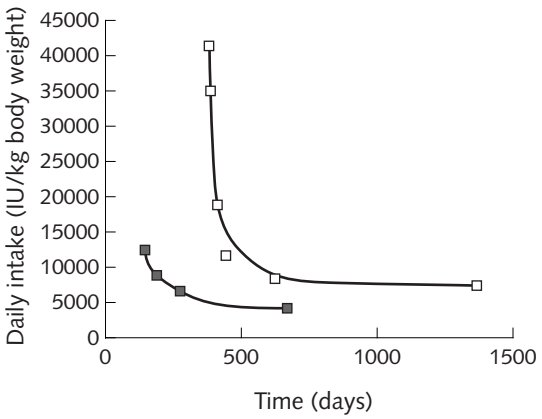

FIG. 3. Time until the appearance of chronic hypervitaminosis A after daily doses of preformed vitamin A in oily solution (□) and water-soluble preparations (■). Source: modified from ref. 45

It is known from a series of other experimental studies that vitamin A is absorbed much better from emulsified than from oily solutions. Early studies in experimental animals, infants, children, and adults demonstrated that aqueous emulsions of retinol and retinyl esters resulted in higher plasma peak values, higher liver values, and lower fecal losses than oily vitamin A preparations [46–48]. These observations have recently been confirmed [49–52].

The safe dose of vitamin A is therefore related to the physical form of the vitamin A preparation. It is conceivable that preparations of vitamin A blended with a detergent or water, or lyophilized and packed in dry tablets, have a lower threshold for toxicity than vitamin A in oily emulsions or in foods such as liver. This knowledge seems to have been forgotten by most investigators in the field and has not been taken into account when considering the toxicity and teratogenicity of vitamin A in almost all more recent studies.

In agreement with the threshold levels presented in figure 3, controlled studies aimed at secondary cancer prevention also demonstrated that daily doses of 300,000 to 600,000 IU of vitamin A (90–180 mg of retinol) as retinol in oily preparations for many months or years are usually required to produce signs of hypervitaminosis A [53] in adults. However, toxic symptoms developed earlier when similar doses of emulsified water-soluble formula were used, as in an Italian study [54] in which doses of 300,000 IU of retinol (90 mg of retinol) were given daily for 12 months to patients with resected stage I non-small-cell lung cancer. Serum levels of γ-glutamyltranspeptidase rose during treatment but were significantly higher only after two years. Serum triglyceride levels increased 63% over the first year of treatment and were significantly higher than those of controls at 8 and 12 months [55, 56]. The majority of adverse events in the Italian study were dermatological (dryness, desquamation, and itching).

Higher toxicity with emulsified preparations than with oily preparations was also observed in the Indian National Program in the 1970s [57]. Reversible toxic reactions were too frequently reported when an annual oral dose of 200,000 to 300,000 IU (60–90 mg of retinol) was given as an emulsified preparation. However, these effects were nearly eliminated when the program changed to comparable amounts of vitamin A in an oily solution.

May vitamin A intake marginally above the recommended dietary intake increase the risk of osteoporosis?

Recently, Melhus et al. [58] in an epidemiological study found that subject-reported dietary intakes of

retinol greater than 5,000 IU (1.5 mg of retinol) per day were associated with reduced bone mineral density and increased risk of hip fracture. The relation was dose-dependent, and no attenuation of the effect of excess vitamin A on the risk of hip fracture was seen in multivariate analyses that adjusted for major risk factors for osteoporosis. These results are consistent with experimental data from both *in vitro* and *in vivo* studies. Animal studies [59–61] have shown the importance of vitamin A in the bone remodeling process. Vitamin A deficiency results in retarded bone growth [60], and hypervitaminosis A and pharmacological doses of retinoids are associated with accelerated bone resorption, bone fragility, and spontaneous fracture [59, 62–65].

It was surprising that Melhus et al. [58] observed these effects at a dose of over 5,000 IU of vitamin A (1.5 mg of retinol) per day. Results from animal experiments and clinical experience with retinoids would suggest that much higher doses are needed to induce these adverse effects. A limitation of the study by Melhus et al. [58] is the possibility of information bias resulting from the retrospective questioning of vitamin A intake. The study probably had a high degree of random error in the assessment of retinol intake. Other limitations were possible confounding factors, such as lack of data on thyroid hormone therapy, physical activity after hip fracture had occurred, and family history of osteoporosis. Moreover, the possibility of other unidentified dietary confounders cannot be excluded. This epidemiological study must therefore not be taken as a proof for a cause-and-effect relationship between retinol intake and the risk of hip fracture. Further studies are required.

Preformed vitamin A and birth defects

As early as 1953, Cohlan [66] observed that the administration of large doses of retinoids to pregnant experimental animals resulted in a variety of embryonic malformations. Although well known to experimental scientists, it came as a shock to dermatologists when they observed similar teratogenic effects in patients with keratinizing disorders treated with high doses of retinoids. Doses of 13-*cis*-retinoic acid (isotretinoin) and all-*trans*-retinoic acid (tretinoin) of 0.4 to 2.0 mg/kg/day in the first trimester of pregnancy caused spontaneous abortions and serious birth defects, including malformations of the brain, heart and major arteries, craniofacies, and thymus [67].

Lowest teratogenic dose in experimental animals

High doses of preformed vitamin A (retinol and retinyl esters) undoubtedly cause birth defects in experimental animals. The teratogenic dose of retinol and retinyl ester varies substantially among species [67, 68]. It is therefore not easy to predict the lowest teratogenic dose in humans from these data.

In animal experiments, hypervitaminosis A produced malformations in almost all organ systems. The type and incidence of malformation depends on the stage of gestation and dose and, to a lesser extent, on the species and strain. Reported structural defects in animals include defects of the brain, spinal cord, face, eye, all parts of the ear, teeth, salivary glands, aortic arch, heart, lungs, gastrointestinal tract, liver, gallbladder, urinary system, genitalia, pituitary, thyroid, thymus, skull, vertebrae, ribs, extremities, muscles, and situs inversus [43, 44, 67–69].

It is not always easy to trace how the dose was given in each experiment. Because the physical form of the vitamin A preparation has a significant effect on the dose-effect curve, these data may represent an underestimation of the doses needed for adverse effects when compared with vitamin A in oily solutions and in foods such as liver.

The lowest teratogenic dose of vitamin A and retinoids reported in experimental animals is given in table 3. The lowest dose in rabbits causing teratogenic effects was 5.5 mg/kg/day or 18,300 IU/kg/day. A comparable dose for a 50-kg pregnant woman would represent an intake of 915,000 IU/day (277 mg of retinol). Thus, if humans are as sensitive to the teratogenicity of vitamin A as the most sensitive experimental animal, the data would tend to suggest that doses of several hundred IU are needed to induce adverse birth defects.

TABLE 3. Lowest teratogenic dose of retinoids (mg/kg/day) in animals and humans

Retinoid	Rat	Mouse	Rabbit	Hamster	Cynomolgus monkey	Human
Retinol	50–90	25–50	5.5	15	6	Not determined
All-*trans*-retinoic acid	0.4–2.0	3	2	7	7.5	Not determined
13-*cis*-retinoic acid	150	100	10	25	2.5–5.0	0.4

Source: refs. 43, 44, 67–69.

When animal data are extrapolated to humans, safety factors are usually applied to the animal doses. Typically, a 10-fold factor is applied for species differences and a further 10-fold factor for interhuman differences. If this commonly used, but somewhat arbitrary, 100-fold safety factor is applied, a daily intake of 9,150 IU (2.8 mg of retinol) for a 50-kg woman is the upper safe limit. This intake is, however, only 3.5 times higher than the recommended daily vitamin A intake for pregnant women in many countries (800 μg of retinol) and is very close to the actual average daily intake for women in many areas of the world. Thus, the ordinary safety evaluations used by toxicologists to set limits for xenobiotic and pollutant exposures are doubtful for establishing a safe level of vitamin A for humans.

Plasma threshold levels of preformed vitamin A causing teratogenic effects

An alternative approach would be to determine the lowest serum level of retinoid metabolites that corresponds to the teratogenic effect observed following isotretinoin (13-*cis*-retinoic acid) treatment in humans. It should then be possible to give human volunteers various doses of vitamin A to determine the intake causing teratogenic levels in human plasma. Following dosing of 0.4 mg of 13-*cis*-retinoic acid per kilogram in humans, peak plasma concentrations of 13-*cis*-retinoic acid between 50 to 150 ng/ml have been observed [70–72] (table 4). Although it has not been demonstrated conclusively, all-*trans*-retinoic acid and 13-*cis*-retinoic acid are generally believed to be responsible for the teratogenic effect in humans [67].

Serum concentrations of retinyl palmitate metabolites in humans following administration of vitamin A in liver or various types of supplements have been studied (table 4). It should be noted that vitamin A intake from liver varies with diet and species. The normal concentrations of all-*trans*-, 13-*cis*-, 4-oxo-all-*trans*-, and 4-oxo-13-*cis*-retinoic acid in human serum are somewhat higher than in rats: 1, 1, 0.5, and 2–4 ng/ml, respectively. When volunteers were given 10,000 to 25,000 IU of vitamin A (3–7.5 mg of retinol) in oil, plasma peak levels were in the normal range. After dosing of 50,000 to 500,000 IU of vitamin A (15–150 mg of retinol) in oil or 250,000 to 346,000 IU of vitamin A (75–104 mg of retinol) in liver, plasma concentrations of the retinyl palmitate metabolites increased somewhat but were still much lower than the expected teratogenic threshold. High plasma concentrations comparable to a teratogenic dose were observed when retinyl esters were administered in a water-soluble physical form. These data suggest that the physical form that is used to administer the vitamin is an important determining factor and that the following order of potencies exists: liver < oily solutions < water-soluble forms. Furthermore, it is unlikely that the teratogenic threshold is reached when humans are dosed with 10,000 to 500,000 IU (3–150 mg) of retinol in oil or liver, in contrast to 500,000 IU (150 mg) of retinol in water-soluble or emulsified form.

TABLE 4. Plasma peak concentrations following dosing with retinoids (ng/ml)[a]

Dose	All-*trans*-retinoic acid	13-*cis*-retinoic acid	4-oxo-all-*trans*-retinoic acid	4-oxo-13-*cis*-retinoic acid
Lowest teratogenic dose of 13-*cis*-retinoic acid (0.4 mg/kg) [70–72]	Not determined	50–210	Not determined	600–800
Normal plasma concentration [73, 74]	1	1	0.5	2–4
Dosing of humans with 10,000 IU (3 mg) retinol in oil for 60 days [75]	2	2	Not determined	3
Dosing of humans with 25,000 IU (7.5 mg)retinol in oil for 60 days [75]	2	2	Not determined	5
Dosing of humans with 50,000 IU (15 mg) retinol in oil for 20 days [73]	4	10	Not determined	19
Dosing of humans with 250,000 IU (75 mg) retinol in fried liver [76]	2	22	1	32
Dosing of humans with 500,000 IU (150 mg) retinol in fried liver [74]	4	31	6	43
Dosing of humans with 346,500 IU (104 mg) retinol in oil [77]	5	13	Not determined	Not determined
Dosing of humans with 500,000 IU (150 mg) water-soluble retinol [74]	87	68	17	64

a. In these studies, retinol was administered as retinyl palmitate, which has similar teratogenicity to retinol.

Duration of treatment needed for teratogenic effect

The timing during embryonic development that the threshold levels of teratogenic retinoids are exceeded is another parameter to be considered in risk assessments. To obtain abnormal second visceral arches in rat embryos, it is necessary to expose embryos *in vitro* to teratogenic concentrations of 13-*cis*-retinoic acid for three to six hours during the sensitive period [78]. Exposure for less than three hours did not cause abnormal arches, even if the concentration of 13-*cis*-retinoic acid was greatly increased. It is not known whether this finding applies to other retinoids. This might suggest that in humans teratogenic retinoids would need to exceed threshold levels for a certain period of time to cause teratogenicity. This is characteristic of isotretinoin exposure in the human, where plasma 13-*cis*-retinoic acid and 4-oxo-13-*cis*-retinoic acid are continuously elevated due to the twice-daily dosing regimen. This repeated exposure in the human is associated with teratogenicity [78].

The necessary duration of exposure in the human is unknown, but it is most likely to be an important parameter. The area under the curve has been used to determine teratogenicity, but this variable may be inappropriate without consideration of the duration of exposure above the threshold level. Malformations may be induced only when the threshold level is exceeded during a certain period.

Case reports of teratogenicity from preformed vitamin A

Several anecdotal reports exist on malformations in infants whose mothers consumed supplements with 25,000 to 150,000 IU (7.5–45 mg) of retinol per day during pregnancy. In 1985, Rosa et al. [79] reviewed the literature and found 18 suspicious birth defect outcomes from pregnancies with high vitamin A dose exposure. Some of these were reported in proceedings from meetings, some had been reported to the Food and Drug Administration (FDA), and six had been reported earlier in scientific journals [80–85]. All but one of the 18 birth defects reported with a high dosage of vitamin A occurred with long-term exposure continuing past conception of 25,000 to 150,000 IU (7.5–45 mg) of retinol per day. The single exception was a massive accidental exposure (500,000 IU or 150 mg of retinol) occurring in the first month of pregnancy [83]. Some of the exposures were in combinations with high dosages of other vitamins, such as vitamin D and E, and there is no information about dietary intake of vitamin A in combination with supplementary intake. In addition, very little information is available as to the physical form of the vitamin A supplements used. Although these case reports are inconclusive, they are useful for planning well-controlled prospective studies.

No further case reports have been published since 1985 on the teratogenic effect of vitamin A in humans, in spite of widespread use of high-dose vitamin A supplements. Several million capsules, each with doses of 25,000 to 200,000 IU of vitamin A (7.5–60 mg of retinol), are consumed each year in a number of countries [79].

It is important to note that there have been no case reports of birth defects from vitamin A exposure due to dietary sources [79]. Intake from a dinner with 150 g of liver would represent about 100,000 to 200,000 IU of vitamin A (30–60 mg of retinol) [86], but liver is not likely to be consumed frequently.

Case-control studies of teratogenicity from preformed vitamin A

Several case-control studies have been published that focused on the relation between vitamin A consumption and birth defects in humans. Martinez-Frias and Salvador [87] evaluated 11,293 cases of congenital malformations in Spain with controls who were matched for sex, hospital, and day of birth. Maternal intake of vitamin A from diet and from supplementation during pregnancy was assessed by a questionnaire. The authors found no statistically significant association between exposure to vitamin A and birth defects. The odds ratio for birth defects from exposure to vitamin A in multivitamin complexes (mean dose, 20,263 IU of vitamin A = 6.1 mg of retinol) was not statistically different from 1, whereas exposure to vitamin A supplements alone (mean dose, 63,636 IU of vitamin A = 19.1 mg of retinol) had an odds ratio of 9.9 (p = .006). When they compared birth defects in children of mothers exposed to supplements containing various doses of vitamin A with children of mothers not taking any supplement, they observed a decrease in birth defects, although it was not significant in the group exposed to up to 40,000 IU of vitamin A (12 mg of retinol) daily. In the group consuming more than 40,000 IU of vitamin A (12 mg of retinol), a significant increase in birth defects (OR = 2.7, p = .06) was found. This study therefore suggests that daily doses of up to 40,000 IU are safe, whereas doses of more than 40,000 IU may increase the risk of birth defects. One should, however, be cautious when drawing a conclusion based only on the 16 of 11,293 cases of birth defects that had been exposed to doses of vitamin A of 10,000 IU (3 mg of retinol) or more in this study.

Werler et al. [88] conducted a study in the United States of 2,658 infants with birth defects possibly due to abnormal development of cranial neural crest cells

and 2,609 controls. Vitamin A supplementation was defined as daily use for at least seven days of retinol alone or with vitamin D, or fish oils. Information on the vitamin A dose and dietary intake was not available. Women who used vitamin A supplements in early pregnancy had approximately a twofold increased risk of giving birth to an infant with malformation of cranial neural crest-derived structures. However, since these findings were based on few exposed controls, risk estimates were unstable and were also compatible with no association. Since supplements containing 25,000 to 100,000 IU of vitamin A (7.5–30 mg of retinol) were common during the years when the infants in the study by Werler et al. [88] were born, it is reasonable to suggest that the users of vitamin A supplements included some who consumed doses up to 100,000 IU (30 mg of retinol) per day.

In a geographically based case-control study in the United States, Mills et al. [89] interviewed women whose pregnancies produced offspring with neural tube defects ($n = 548$) or major malformations other than neural tube defects ($n = 387$) and normal control subjects ($n = 573$) to determine periconceptional vitamin A supplement exposure levels. The proportion of women consuming doses of vitamin A between 8,000 and 25,000 IU (2.4–7.5 mg of retinol) was no greater in any malformation group than in the normal control group. Thus, Mills et al. [89] found no association between periconceptional vitamin A exposure at doses consumed by most women during organogenesis.

Recently, Czeizel and Rockenbauer [90] performed a paired analysis of cases with congenital abnormalities and healthy controls in a large population-based data set of the Hungarian Case-Control Surveillance of Congenital Abnormalities. Of 35,727 pregnant women who had control infants without defects, 9.5% received vitamin A. Of 20,830 pregnant women who had offspring with congenital abnormalities, 7.9% consumed vitamin A supplements, a rate that is significantly lower than that of the control group. Thus, this study indicated that low or moderate doses of vitamin A (<10,000 IU) during the first trimester of pregnancy are not teratogenic but have some protective effect on the fetus.

Another case-control study [91] in the United States of conotruncal heart defects, which arise in part from cranial neural crest cells, found a lower risk among women who used multivitamin preparations that included vitamin A during the periconceptional period than among those who did not. Botto et al. [91] identified 158 infants with conotruncal defects and 3,026 unaffected, randomly chosen control infants born to mothers residing in metropolitan Atlanta, Georgia, USA. Periconceptional multivitamin use was defined as regular use from three months before conception through the third month of pregnancy, as reported by the subject. Mothers who reported periconceptional multivitamin use had a 43% lower risk of having infants with conotruncal defects than did mothers who reported no use. Thus, periconceptional multivitamin use is associated with a reduced risk of conotruncal defects.

Prospective cohort study of teratogenicity from preformed vitamin A

In a nonrandomized, prospective cohort study, Rothman et al. [92] obtained information on the diets of 22,748 pregnant women during their first trimester of pregnancy. Information on the outcome of pregnancy was obtained 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. The proportion of total birth defects and cranial neural crest-derived birth defects appeared to be relatively constant for the women who had total intakes of 0 to 15,000 IU of vitamin A (0–4.5 mg of retinol) per day (table 5).

For defects associated with cranial neural crest tissue, the ratio of the prevalence among the babies born to women who reported consuming more than 15,000 IU of preformed vitamin A (4.5 mg of retinol) per day from food and supplements, as compared with the prevalence among babies whose mothers consumed 5,000 IU (1.5 mg of retinol) or less per day, was 3.5 (95% CI, 1.7–7.3). For vitamin A from supplements alone, the ratio of the prevalence among the babies born to women who consumed more than 10,000 IU of vitamin A (3 mg of retinol) per day to that among the babies whose mothers consumed 5,000 IU

TABLE 5. Birth defects in the prospective cohort study of Rothman et al.[92]

Daily dose (IU)	Total pregnancies (no.)	Cranial neural crest defects (%)	Total birth defects (%)
Total intake			
0–5,000	6,410	0.5	1.3
5,001–10,000	12,688	0.5	1.5
10,001–15,000	3,150	0.6	1.3
≥15,001	500	1.8	3.0
From food			
0–5,000	21,755	0.5	1.5
5,001–10,000	805	0.6	1.7
≥10,001	188	1.1	2.7
From supplements			
0–5,000	11,083	0.5	1.3
5,000–8,000	10,585	0.5	1.6
8,001–10,000	763	1.2	1.7
≥10,001	317	2.2	3.2

of vitamin A (1.5 mg of retinol) or less per day was 4.8 (95% CI, 2.2 to 10.5). Since the mean vitamin A intake in this group of women was 21,675 IU per day, it is likely that some women took supplements with much more than 25,000 IU per day. It would be helpful to know just how much of the apparent association between vitamin A consumption and birth defects in this study resulted from the consumption of vitamin A at these higher levels.

Although the risk estimate is statistically significant, it is important to note that it is based on just five excess defects in the high-supplement group. Other factors that could have given rise to any or all of these five events include diagnostic misclassification (especially when a quarter of all reports were based solely on maternal reports and were not verified further); maternal abuse of other vitamins, drugs, or noxious agents (since most women who took a vitamin A supplement also consumed other vitamins at unstated doses); and, of course, chance.

This study therefore indicated that intake of supplements at some level above 10,000 IU of vitamin A (3 mg of retinol) increases both total and cranial neural crest-derived defects. Rothman et al. [92] suggested that an apparent threshold for birth defects occurs near 10,000 IU (3 mg of retinol) from supplements per day. However, this threshold is not consistent with other data on teratogenicity [90], and the study has been criticized on several scientific grounds [93–96].

Furthermore, no information is available as to the physical form of supplements consumed in the various case-control studies or the prospective study. Water-soluble forms, which might have been responsible for a major fraction of the birth defects described, are about six times more toxic than vitamin A in oily solutions, but this has not been considered in any of these studies.

Safe dose of carotenoids

Experimental studies in animals have shown that β-carotene is not mutagenic or teratogenic. Doses up to 180 mg of β-carotene per day have been used for many years to treat patients with erythropoietic protoporphyria, with no evidence of vitamin A toxicity and without the development of abnormally elevated blood vitamin A concentrations [97, 98]. This is due to the observation that conversion of β-carotene and other provitamin A carotenoids seems to be regulated by the vitamin A status of individuals. Therefore, high intakes of carotenoids do not lead to abnormally high vitamin A concentrations or symptoms of hypervitaminosis A [99].

Hypercarotenemia, or high serum concentrations of carotene, may occur when individuals take supplements containing 20 mg or more of β-carotene for extended periods. Hypercarotenemia has been seen in people who consume large quantities of food rich in β-carotene, such as carrots. These individuals also develop yellow palms and soles, a condition technically known as hypercarotenodermia. This condition can be clearly differentiated from jaundice, because the whites of the eyes are yellow only in patients with jaundice. These symptoms disappear with reduced intake [100]. A rare genetic inability to convert β-carotene to vitamin A [101, 102], hypothyroidism, diabetes mellitus, and hepatic and renal disease can cause hypercarotenemia [98]. High lycopene intake also produces hypercarotenodermia; however, a deeper orange is usually observed than with β-carotene [100].

Canthaxanthin is an approved food color additive, but it has been used without regulatory approval for attaining a skin color similar to a suntan. Excessive intake produces discolored plasma and feces, which probably has no physiological significance; however, crystalline deposits occurred in the retinas of all subjects who ingested 60 mg, and a change in retinal function after long-term treatment was observed in a few persons with such deposits [103]. The dose of canthaxanthin required for this ocular response appears to be more than 30 mg/day [104]. The changes in retinal function are corrected over a period of months or years [103, 105]. Similar canthaxanthin retinopathy induced in monkeys was not associated with retinol dysfunction or abnormal morphology [106].

The retinas of 26 patients with protoporphyria who received treatment with β-carotene (200 30-mg capsules per month for several months) for periods of 1 to 10 years were not found to have crystalline deposits. Asymptomatic retinopathy, consisting of multiple, bright-yellow, glistening crystalline deposits in and around the maculae, was observed in 6 of 50 patients who had ingested more than 200 30-mg doses of canthaxanthin as a photoprotectant and systemic skin colorant [107].

Experimental and epidemiological investigations have suggested that food rich in β-carotene might reduce the risk of cancer, particularly lung cancer and coronary heart disease. Therefore, several trials have tested whether large doses of supplementary β-carotene might reduce the incidence of these diseases. Although most of these trials have reported no toxic effects, serious adverse effects were reported in four large-scale prospective randomized trials.

In the ATBC (α-Tocopherol and β-Carotene Supplements) Study, 29,133 Finnish men aged 50 to 69 years who smoked five or more cigarettes daily were randomly assigned to receive α-tocopherol (50 mg), β-carotene (20 mg), α-tocopherol and β-carotene, or a placebo daily for five to eight years (median, 6.1 years) [108]. Disappointingly, however, the results showed that β-carotene supplementation was associated with an increase in lung cancer risk of about 20%.

Similar findings were observed in the CARET (Beta-carotene and Retinol Efficacy Trial) Study l [109], which tested the combination of 30 mg of β-carotene and 25,000 IU of retinyl palmitate taken daily against a placebo in 18,314 men and women at high risk of developing lung cancer. The CARET intervention was stopped 21 months early because of clear evidence of no benefit and substantial evidence of possible harm; there were 28% more lung cancers and 17% more deaths in the active intervention group receiving the daily combination of 30 mg of β-carotene and 25,000 IU of retinyl palmitate.

The CARET study also observed that the active-treatment group had a 26% increase in the relative risk of death from cardiovascular disease [110]. Thus, after an average of four years of supplementation, the combination of β-carotene and vitamin A had no benefit and may have had an adverse effect on the incidence of risk of death from lung cancer, from cardiovascular disease, and from any cause in smokers and in workers exposed to asbestos.

Rapola et al. [111] studied the frequency of major coronary events in 1,862 men enrolled in the ATBC Study (smokers aged between 50 and 69 years) who had had a previous myocardial infarction. In agreement with the CARET study, there were significantly more deaths from coronary heart disease in the β-carotene groups than in the placebo group.

It is worth noting that both the ATBC and the CARET studies included only smokers and workers exposed to asbestos. The results of these four studies strongly suggest, however, that high doses of β-carotene (20–30 mg) should not be recommended for any group until the safety of such doses can be established.

Conclusions

When considering the toxicity of vitamin A, it is important to take into account the observation that emulsified preparations seem to be approximately six times more toxic than oily preparations or foods such as liver. Chronic hypervitaminosis seems to be induced following daily doses of 300,000 to 600,000 IU of vitamin A (90–180 mg of retinol) in oily preparations for many months or years, whereas teratogenicity may be induced by daily doses as low as 40,000 IU of vitamin A (12 mg of retinol) in oil during the first trimester of pregnancy. The controlled, periodic distribution of a single 50,000-IU dose of vitamin A (15 mg of retinol) confers no apparent acute risk on young infants, whereas a 100,000-IU (30 mg of retinol) dose is associated with a minimum risk of transient acute side effects.

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Vitamin A supplementation and the control of vitamin A deficiency: Conclusions

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It was the consensus among all meeting participants that their conclusions concerning vitamin A supplementation should be understood as applying to populations in countries or areas where vitamin A deficiency is a public health problem, including HIV-infected populations. Additionally, it was strongly emphasized that for success, a multipronged approach to the elimination of vitamin A deficiency is needed. Food fortification and dietary diversification, including an increased consumption of vitamin A–rich foods, are key components in any strategy to control vitamin A deficiency. Efforts to promote these strategies should be pursued while implementing supplementation activities.

Infants under six months and postpartum women

Liver stores of vitamin A at birth are sufficient to supply an infant's requirements for only a few days, even if the mother is well-nourished during pregnancy. Theoretical calculations and limited evidence suggest that intakes of 125 μg RE per day are needed to prevent xerophthalmia and faltering in growth, but are not enough to allow for accumulation of stores and may not prevent other functional consequences of vitamin A deficiency. Similar calculations and evidence suggest that intakes of 300 μg RE per day are needed to allow accumulation of adequate stores (at least 20 μg/g in the liver) by six months and to meet all other needs.

The breastmilk vitamin A concentration of well-nourished women is at least 50 μg/dl. In regions of the world where vitamin A deficiency is a problem, breastmilk vitamin A concentrations are lower. In most regions of the world, initiation of breastfeeding is nearly universal; however, exclusive breastfeeding for six months is very rare. Therefore, it is important to consider that when breastmilk vitamin A concentrations are below 50 μg/dl or when breastmilk intake volumes are less than 600 ml per day, vitamin A intakes will not be sufficient to promote adequate vitamin A stores by six months of age.

There are two options for improving the vitamin A status of breastfed infants: improving the vitamin A status of mothers, and thus the vitamin A content of breastmilk; or supplementing the infant. Both strategies should be employed. Breastfeeding mothers need to receive more vitamin A postpartum. The current policy of giving them 200,000 IU of vitamin A during postpartum is not enough to meet their increased vitamin A requirements for lactation during that period. Nonbreastfeeding women can also benefit from postpartum doses of vitamin A to replete their own liver stores.

It is considered that increasing the postpartum dose of vitamin A to 400,000 IU will be an effective way to increase the mother's vitamin A status and breastmilk content. The safety of a 400,000-IU (120,000 μg RE) dose has been confirmed. To avoid operational confusion, both breastfeeding and nonbreastfeeding women should receive the increased dose within their respective safe infertile periods.

The 400,000-IU (120,000 μg RE) vitamin A supplement should be administered either at the time of delivery or within the safe infertile postpartum period, that is, within eight weeks for breastfeeding women and within six weeks for nonbreastfeeding women. It should be given as two doses of 200,000 IU (60,000 μg RE) each, the first dose immediately after delivery and the second dose later on within the safe infertile postpartum period. It is important that the second dose be given at least 24 hours after the first dose, when the first dose will have been metabolized and taken up by the liver. However, a longer interval is preferred, because it will allow for better retention

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of the second dose. In situations where the mother cannot be recontacted any time soon after birth, a single dose of 400,000 IU (120,000 μg RE) could be given at once, but this should be considered as exceptional and avoided as much as possible, because the evidence that a single dose of 400,000 IU (120,000 μg RE) of vitamin A is safe is still limited and further investigation is needed.

Alternatively, the additional vitamin A can be given as a low dose, either on a daily basis, not exceeding 10,000 IU (3,000 μg RE), or on a weekly basis, not exceeding 25,000 IU (7,500 μg RE) at any time postpartum.

In the absence of cumulative evidence of a reduction in early infant mortality, the main rationale for supplementation of young infants with vitamin A is to achieve improvement in vitamin A status in the second half of infancy. There is ample evidence that an adequate vitamin A status by five months of age improves health and survival. Additional justification of young infant supplementation includes the following:

» Some children may not be breastfed (particularly in areas of high HIV prevalence where mothers may be opting not to breastfeed);
» There is benefit to premature and low-birthweight babies;
» There are immunological benefits to HIV-infected children.

Available data on retinol pharmacokinetics suggest that three doses of 50,000 IU (15,000 μg RE) given to infants under the age of six months would be safe and are likely to be more effective in achieving normal stores at six months of age than doses of 25,000 IU (7,500 μg RE), which have been tested and confirmed safe but insufficient for sustained improvement in status.

Recommendations

1. Exclusive breastfeeding for the first four to six months of life should continue to be promoted as the primary way to prevent vitamin A deficiency in young infants.
2. The postpartum dose of vitamin A to mothers should be increased to 400,000 IU (120,000 μg RE) and should be given as two doses of 200,000 IU (60,000 μg RE). Postpartum supplementation should be given to both breastfeeding and nonbreastfeeding mothers, within their respective safe infertile periods, i.e., within eight weeks of delivery for breastfeeding women and within six weeks of delivery for nonbreastfeeding women. Postpartum women should be screened for eligibility to receive vitamin A supplementation at any health contacts, in particular at the first postpartum visit within the first week following delivery or at the child immunization contact.
3. As an alternative to large-dose supplementation, mothers can receive vitamin A at any time postpartum, given as a low dose not exceeding 10,000 IU (3,000 μg RE) per day or 25,000 IU (7,500 μg RE) per week.
4. Infants should receive three 50,000-IU (15,000 μg RE) doses of vitamin A within the first six months of life. The three diphtheria-tetanus-pertussis (DTP) immunization contacts at 6, 10, and 14 weeks are thought to be some of the best opportunities to deliver and record these doses. However, all health contact opportunities, such as the Integrated Management of Childhood Illness Programmes (IMCI), growth monitoring and under-five clinics, mother's postpartum visit, and family planning consultations should all be used for screening to determine whether a child is up-to-date or is due to receive a vitamin A supplement. If the child is eligible, vitamin A should be administered and the dose recorded on the child's immunization or health card. An interval of one month between doses is recommended.
5. In children over 6 months of age, the current recommendations [1] are still applicable:
   » Between 6 and 11 months, a single large dose of 100,000 IU (30,000 μg RE) of vitamin A should be given. This dose is important to maintain adequate vitamin A status throughout the first year of life. Ideally, this dose can be given simultaneously with measles vaccine at 9 months, but additionally all health contacts should be seen as opportunities
   » In children over 12 months of age, a large dose of 200,000 IU (60,000 μg RE) of vitamin A should be given every 4 to 6 months at any health or immunization contact
6. The existing recommendation [2] for distribution of vitamin A with oral polio vaccine during National Immunization Days to all children 6 to 59 months of age, regardless of previous doses received, should be maintained and encouraged.
7. Any doses given should be carefully recorded on the mother's health card or on the child's immunization or health card. It is not recommended or necessary to record doses during National Immunization Days.

Pregnant women

At present there is no new evidence to justify changes in the current recommendations for safe vitamin A dosage during pregnancy [1].

HIV populations

Low serum retinol is commonly associated with HIV infection, although this does not appear to be a causal relationship. It is well established that vitamin A supplementation is safe in HIV-infected individuals in the usual recommended doses. There is no evidence that vitamin A increases HIV viral load, even in vitamin A–replete individuals. In HIV-infected children, vitamin A supplementation has been effective in improving health outcomes, particularly in reducing the incidence and severity of diarrhea. In populations where HIV is a public health problem, supplementation of children and mothers should follow the schedule described above.

Treatment of sick children

There are several reasons for providing vitamin A supplements to sick children at the health facility:

» There are specific diseases for which vitamin A supplementation has a beneficial effect on the clinical outcome of an acute illness.
» Each sick child visit should be considered an opportunity for ensuring that children are up-to-date with their regular vitamin A prophylaxis.
» Children with a current illness are often likely to experience a further episode in the near future, and vitamin A supplementation will decrease the incidence, prevalence, and severity of certain key childhood illnesses (comorbidity) and reduce mortality.

There is well-established evidence for a beneficial effect of vitamin A supplementation in the treatment of measles. Vitamin A treatment is also required in the management of severe malnutrition to prevent keratomalacia. Vitamin A has not been demonstrated to have a positive effect on the clinical outcomes of acute diarrhea but might help reduce the severity of future episodes. Vitamin A supplementation does not have a beneficial effect on pneumonia and is associated with a mild increase in respiratory symptoms, including cough, but not an increase in predisposition to pneumonia.

There are several conditions for which new information is required about the role of vitamin A supplementation in the management of childhood illnesses. These include persistent diarrhea, dysentery, tuberculosis, malaria, meningitis, leprosy, parasitic infections, septicemia, and all HIV-associated infections.

Recommendations

1. The current recommendations [2] of using vitamin A supplementation for the treatment of measles and severe malnutrition are fully supported.
2. There is endorsement for the existing IMCI guidelines of using any sick child contact to screen for previous doses of vitamin A supplements and administering a supplemental dose if it is due.

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In Memoriam

Vulimiri Ramalingaswami, 1921–2001

Vulimiri Ramalingaswami, known as "Rama" by his many colleagues and friends, died at his home in New Delhi on May 28, 2001 after a long battle with prostate cancer. He was born in 1921 in Andhra Pradesh, India and received his education locally including his M.B.B.S. from Andhra Pradesh University in 1944, and his M.D. from the same institution in 1946. He then obtained a D. Phil. from Oxford in 1951 and a D.Sc. from Oxford in 1967. He was a Fellow of the Royal College of Physicians and the Royal College of Pathology, both in London.

Rama received many honors during a remarkably distinguished career. These included Fellow of the Royal Society, London; Foreign Associate of the National Academy of Sciences of the United States; Foreign Member of the Academy of Medical Sciences, U.S.S.R; Fellow and President of the Indian National Science Academy; Honorary Fellow, American College of Physicians; and an Honorary Doctorate of Medicine from the Karolinska Institute, Stockholm. He was a Chairman of the WHO Global Advisory Committee of Medical Research (ACMR), Geneva.

His exceptional leadership qualities led to a series of posts of major responsibility and importance in India. From 1957 to1979 he was Professor and Chairman of the Department of Pathology in the All India Institute of Medical Sciences, New Delhi. From 1969 to 1979 he also served as Director of this leading medical institute in India. In 1978 he was a visiting member of the Thyroid Unit and Division of Pathology at the Massachusetts General Hospital. From 1979 to 1986 he was Director-General of the Indian Council of Medical Research. In 1986 he became a Scholar-in Residence in the Fogarty International Center of the U.S. National Institutes of Health, Bethesda, Maryland. This was followed by a year as a Visiting Professor of International Health Policy in the Harvard School of Public Health. In 1988 he became Special Adviser on Child Survival and Development to the Executive Director of UNICEF in New York. He was also a long time special advisor to the International Development Research Centre (IDRC) of Canada.

He returned to India in 1988 as National Research Professor Emeritus of the All India Institute of Medical Sciences, New Delhi, and was president of the National Institute of Immunology, New Delhi. In this period he made major contributions to the UN ACC Subcommittee on Nutrition (SCN). In 1992 he served as Secretary-General of the International Conference on Nutrition in Rome. At the time of his death he had been a member of the International Award Committee of the Prince Mahidol Award Foundation of Thailand for nine years although unable to attend last year.

His reputation rested not only on his outstanding contributions as a science administrator, but also on solid and significant research contributions. These include his early research on kwashiorkor, nutritional anemia, liver disease, and nutritional blindness. His animal seminal studies on liver disease in the tropics are summarized in the Heath Clark lectures at London University. However, he was best known for studies of the disorders arising from a nutritional deficiency of iodine. He played a major role in field studies in northern India, where severe iodine deficiency was highly prevalent. His advocacy greatly increased awareness of the problem and guided efforts toward eradication of these disorders in his own and other countries. As a founding member of the International Council for the Control of Iodine Deficiency Disorders (ICCIDD), he participated fully in its activities and contributed importantly to its subsequent growth and influence.

His more than 200 scientific publications have been influential, but are only a small part of his broad influence in the field of nutrition. Through his personal influence and charm he contributed significantly to almost every major nutrition meeting in the last 40 years. He influenced trends both in research and international nutritional health policies. As a member of the five-year International Commission for Health Research, he insisted on the involvement of national health professionals in every country in the work of the Commission and on their role in essential health research. Rama had remarkable personal qualities that in every situation provided synthesis and consensus.

He was a great conciliator. When, as often happened, sharp differences arose among participants in conferences and meetings, he could be counted on to settle the conflicting opinions and identify productive paths. His advice was invariably sought and his comments resolved differences and restored communication among participants. His role in this will not be easily filled. Sir Harold Walter, President of the World Health Assembly in 1976 in presenting him with the Leon Bernard Foundation award characterized him as a unique physician, research scientist, and humanitarian. To this description should be added outstanding medical educator, effective health research advocate, and international catalyst for progress in nutrition.

All who had the privilege of his friendship over the years profited from his wisdom and idealism, and have now suffered a grievous loss. The nutrition world, particularly in developing countries, owes Rama a great debt. He is survived by Prahba, his wife of 54 years, a daughter, Lakshme, a nutritional biochemist living in New York, a son, Jagdish now in Washington D.C. and three grandchildren.

Books received

Food hypersensitivity and adverse reactions: A practical guide for diagnosis and management. Edited by Marianne Frieri and Brett Kettelhut, Marcel Dekker, New York, 1999 (ISBN 0-8247-9903-87) 520 pages, hard cover. US$195.00

This book provides 25 state-of-the art chapters by internationally recognized experts on all major aspects of the topic. The basic science chapters cover the allergic and immunological basis for food hypersensitivity. The clinical section includes prevalence, diagnosis, prevention, and treatment. The final section covers the management of the hospitalized patient with food hypersensitivity by diet and hypoallergenic formulas. Several chapters contain detailed information on immunologic mechanisms including food allergen characterization, food contaminants, and unrecognized traces of allergenic substances in foods. Other topics covered include non-IgE mediated responses and atypical cutaneous manifestations. An integrated team approach to evaluating and managing the food-allergenic patient is presented. This book contains many useful tables and is indexed. It will be a valuable reference for any health worker confronted with issues of hypersensitivity to foods, from students and faculty to physicians, dietitians, and food scientists in industry.

Green tea: Health benefits and applications. Yukihiko Hara. Marcel Dekker, New York, 2001. (ISBN 0-8247-0470-3) 240 pages, hard cover. US$125.00.

Knowledge of positive relationship between the consumption of tea and health has been growing rapidly as recorded in scientific publications, reviews, symposia, and conferences. While both fermented and unfermented teas have been studied, attention has focused on green tea because of its greater antioxidant content. This book deals primarily with the health benefits of tea polyphenols – particularly tea catechins which are responsible for the pungency of green tea. It strongly promotes health benefits for green tea but does not provide a comprehensive review of global research. However, it is an interesting source of original data from the extensive research of the author and is well indexed.

Laboratory tests for the assessment of nutritional status. Second edition. Howerde E. Sauberlich. CRC Press, Boca Raton, Florida, 1999. (ISBN 0-8493-8506-7) 512 pages, hardcover. US$69.95/£46.00.

The first edition of this book was published in 1974 and for over a quarter of a century has continued to be the best single reference source for biochemical methodologies for the assessment of nutritional status. However, many more nutrients are now measured in nutrition studies, new assays have been introduced, and older methodologies improved. This is a very much needed, authoritative, updating of the former volume. Superbly written entirely by the author, it is comprehensive without overlapping. Nutrients covered include not only water soluble and fat soluble vitamins but also the semi- or quasi-vitamins - carnitine, choline, inositol, and taurine. Minerals covered in separate chapters include body electrolytes sodium, potassium, and chlorine, but also the macrominerals calcium, phosporus, and the trace elements iron, iodine, zinc, copper, selenium, manganese, chromium, and molybdenum. In addition, the ultra trace elements (arsenic, boron, fluorine, nickel, silicon, tin, vanadium, and sulfur) are covered in a single chapter. A short but adequate index is provided. This book should be in the library of every institution whose staff use biochemical measures for the evaluation of nutritional status. It will be as indispensable for the current generation of students and professionals doing nutrition field studies as its predecessor and is more complete.

Obesity: Preventing and managing the global epidemic. Report of a WHO consultation. WHO Technical Report Series No. 894. World Health Organization, Geneva, 2000. (ISBN 92 4 120894 5) 253 pages, paperback. Sw. fr. 56- /US$50.40. Price in developing countries Sw. fr. 39.20

Overweight and obesity represent a rapidly growing threat to the health of populations not only in most industrialized countries but also in many developing countries. Indeed they are now so common that they are replacing more traditional problems such as undernutrition and infectious diseases as the most significant causes of ill-health. Obesity co-morbidities include coronary heart disease, hypertension and stroke, certain types of cancer, non-insulin-dependent diabetes mellitus, gallbladder disease, dyslipidemia, osteoarthritis and gout, and pulmonary diseases, including sleep apnea. In addition, the obese suffer from social bias, prejudice, and discrimination, not only by the general public but also by health professionals. This may make them reluctant to seek medical assistance. WHO therefore convened a Consultation on obesity to review current epidemiological information, contributing factors, and associated consequences, and this report presents its conclusions and recommendations. In particular, the Consultation concluded that the fundamental causes of the obesity epidemic are sedentary lifestyles and high-fat energy-dense diets, both resulting from the profound changes taking place in society and the behavioral patterns of communities as a consequence of increased urbanization and industrialization and the disappearance of traditional lifestyles. It concluded that a reduction in fat intake to around 20 to 25% of energy is necessary to minimize energy imbalance and weight gain in sedentary individuals. While there is strong evidence that certain genes have an influence on body mass and body fat, most do not qualify as necessary genes, i.e., genes that cause obesity whenever two copies of the defective allele are present; it is likely to be many years before the results of the genetic research can be applied to the problem. Methods for the treatment of obesity are described, including dietary management, physical activity and exercise, and antiobesity drugs, with gastrointestinal surgery being reserved for extreme cases. It is well organized and referenced. This is a very valuable publication for everyone concerned with any aspect of public health and clinical nutrition.

Management of the child with a serious infection or severe malnutrition. Guidelines for care at the first-referral level in developing countries. Department of Child and Adolescent Health and Development, World Health Organization, Geneva, 2000. (ISBN 92 4 154531 3) 162 pages, paperback. Sw. fr. 15.-. Price in developing countries Sw.fr. 10.50.

This manual presents up-to-date clinical guidelines for inpatient and outpatient care in small hospitals where basic laboratory facilities and inexpensive essential medicines are available. The focus is on the inpatient management of the major causes of childhood mortality, such as pneumonia, diarrhea, severe malnutrition, malaria, meningitis, measles, and related conditions. It is consistent with the Integrated Management of Childhood Illness (IMCI) guidelines for outpatient management of sick children, which are applicable in most areas of the world and can be adapted to the needs specific to a country. This manual will be useful particularly for physicians and senior health workers responsible for care of young children at the first referral level in developing countries.

News and notes

Invitation to register and join the INF IDPAS Iron World Network

The United Nations University (UNU) and the International Nutrition Foundation (INF) have actively supported international work on micronutrients for almost 20 years. The INF has recently introduced the Iron Deficiency Project Advisory Service (IDPAS), a new short term project aimed at filling gaps in current needs to support technical information, technical assistance, and advocacy by officials, researchers, and program managers working to prevent and control iron-deficiency anemia and improve iron nutrition in developing countries and countries in transition.

The IDPAS Iron World is a major new IDPAS activity, supported by the Micronutrient Initiative of Canada. It is designed to complement and expand the support available to projects and individuals working on anemia by using multiple communication channels to learn about their efforts and to bring them specific information on technical issues, questions, and problems that constrain their work. IDPAS Iron World develops two-way information channels for projects and people. It proactively reaches out to participants to develop and maintain a technical dialogue that provides ongoing information support addressing specific information constraints and other needs of individual projects and activities.

IDPAS Iron World strives to provide rapid responses to requests for information on a wide range of technical questions. The IDPAS Project Office, located in the Tufts University School of Nutrition Science and Policy, maintains a comprehensive, up-to-date collection of over 1,200 published and unpublished articles, research reports, outcomes of technical meetings and consultations, and global and regional technical guidelines.

Beyond collection, IDPAS can rapidly search technical and medical databases and library collections for information addressing questions and information requests sent from the field. IDPAS also relies on professional and personal contacts with a wide group of recognized experts and researchers working on iron nutrition and advising programs in each region of the world. IDPAS also is linked to over 30 international organizations that can provide technical assistance and other support for those working to improve iron nutrition and to prevent and control iron deficiency and anemia.

IDPAS Iron World is proactive, regularly contacting participants to learn how projects are progressing, if there are information needs and if there are lessons learned that can be shared. IDPAS uses e-mail, fax, telephone, mail, and courier to develop and maintain contact with participants, deliver requested information, and seek out lessons learned that can be shared.

For additional information about IDPAS Iron World or to register as a participant, contact:

IDPAS
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Note for contributors

The editors of the *Food and Nutrition Bulletin* welcome contributions of relevance to its concerns (see the statement of editorial policy on the inside of the front cover). Submission of an article does not guarantee publication—which depends on the judgement of the editors and reviewers as to its relevance and quality. All potentially acceptable manuscripts are peer-reviewed. Contributors should examine recent issues of the *Bulletin* for content and style.

Language. Contributions should be in English.

Format. Manuscripts should be typed or printed on a word processor, , and with ample margins. Only an original typed copy or a photocopy of equivalent quality should be submitted; photocopies on thin or shiny paper are not acceptable.

When the manuscript has been prepared on a word processor, a diskette should be included with the manuscript, with an indication of the disk format and the word-processing program used.

Length. Ordinarily contributions should not exceed 4,000 words.

Abstract. An abstract of not more that 150 words should be included with the manuscript, stating the purposes of the study or investigation, basic procedures (study subjects or experimental animals and observational and analytical methods), main findings (give specific data and their statistical significance if possible), and the principal conclusions. Emphasize new and important aspects of the study or observations. Do *not* include any information that is not given in the body of the article. Do not cite references or use abbreviations or acronyms in the abstract.

Tables and Figures. Tables and figures should be on separate pages. Tables should be typed or printed out double-spaced. Submit only original figures, original line drawings in India ink, or glossy photographs. Labels on the figures should be typed or professionally lettered or printed, not handwritten.

Photographs. Ideally photographic materials should be submitted in the form of black and white negatives or black and white glossy prints. Photographs will not be returned unless a specific request is made.

Units of measurement. Preferably all measurements should be expressed in metric units. If other units are used, their metric equivalents should be indicated.

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1. Alvarez ML, Mikasic D, Ottenberger A, Salazar ME. Caracteristicas de familias urbanas con lactante desnutrido: un análisis critico. Arch Latinoam Nutr 1979;29:220–30.

—*corporate author:*

2. Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology. Recommended method for the determination of gammaglutamyltransferase in blood. Scand J Clin Lab Invest 1976;36:119–25.

Book or other monograph reference

—*personal author(s):*

3. Brozek J. Malnutrition and human behavior: experimental, clinical and community studies. New York: Van Nostrand Reinhold, 1985.

—*corporate author:*

4. American Medical Association, Department of Drugs. AMA drug evaluations. 3rd ed. Littleton, Mass, USA: Publishing Sciences Group, 1977.

—*editor, compiler, chairman as author:*

5. Medioni J, Boesinger E, eds. Mécanismes éthologiques de l'évolution. Paris: Masson, 1977.

—*chapter in book:*

6. Barnett HG. Compatibility and compartmentalization in cultural change. In: Desai AR, ed. Essays on modernization of underdeveloped societies. Bombay: Thacker, 1971:20–35.

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