Vitamin A supplementation of young infants

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A meta-analysis of several large trials established that vitamin A supplementation of 6-month-old to 5-year-old children living in areas where vitamin A deficiency is a problem can reduce their risk of dying by an average of 23%. However, published studies are less conclusive about whether supplementation in the first 6 months of life is needed, safe, or provides any benefit. The most recent contribution to this debate was the Expanded Programme on Immunisation (EPI)-linked placebo-controlled trial in which breastfeeding mothers received 200 000 IU vitamin A (1 µmol=286 retinol equivalents=953 IU) at delivery and their infants were given 25 000 IU with all of three immunisation contacts before 5 months of age. The regimen was safe but there was no impact on infant morbidity or mortality, and only a very modest, short-lived improvement in infant vitamin A status. Should vitamin A supplementation of young infants be abandoned? We will argue that infant vitamin A supplementation should be increased rather than abandoned.

Do young infants need vitamin A supplementation?

Young infants are often vitamin A deficient. Studies from Bangladesh, Brazil, and Indonesia reported that a quarter to over 90% of the 6-month-old infants studied had inadequate liver stores. A necropsy study of American infants reported deficient liver vitamin A concentrations (≤0.07 µmol/g) in two-thirds of infants under 3 months of age, in a quarter of 4–6-month-old infants, but in none of 6–12-month-old infants. All infants are born with very limited vitamin A stores—about 6 µmol—which is less than a 2-week supply. During the first 6 months of life, healthy, well-nourished infants more than double the size of their liver and increase by five-fold its vitamin A concentration, increasing total vitamin A stores more than ten-fold to 70 µmol. They do this by drinking an adequate volume of breastmilk from a well-nourished mother, or commercial infant formula. Over the first 6 months of life a healthy, well-nourished baby ingests about 302 µmol of vitamin A, absorbs 90%, uses 202 µmol for daily needs, and stores the rest (70 µmol). Basal and “safe” daily dietary vitamin A requirements between birth and 3 months are 40 µg/kg and 78 µg/kg, respectively; between 3 and 6 months they are 26 µg/kg and 50 µg/kg, respectively. Assuming an average weight of 4.6 kg during the first 3 months of life, and of 6.9 kg during the second 3 months, basal and safe requirements for the entire first 6 months of life are 117 and 225 µmol, respectively. Thus, 202 µmol represents 173% and 90% of the basal and safe requirements.

Average breastmilk vitamin A concentrations of mothers in developing countries are about half that of well-nourished mothers, or about 1.05 µmol/L. Infants drinking this milk can be expected to absorb only 123 µmol, using nearly all of that for daily needs (105% basal and 55% safe requirements) and storing hardly any. Thus, vitamin A “deficiency” is physiological at birth and during early infancy, but is normally overcome by 6 months of age. However, many breastfed infants of undernourished mothers will remain vitamin A deficient at 6 months and will need additional vitamin A to attain normal physiological stores.

Safety

The most common acute side-effect of large doses of vitamin A is bulging of the fontanelle. The rate of bulging fontanelle attributable to vitamin A varies from 0 to 8%. This side-effect is not only uncommon, but also without significant consequence. It is very rarely associated with other symptoms and usually resolves spontaneously within 72 h. High doses of vitamin A transiently increase intracranial volume, but the volume pressure curve is such that mild to moderate increases in volume do not result in increases in pressure. Two studies looked for long-term developmental consequences at 3 years and found none.

Benefit

In one study in Indonesia, a single 50 000 IU dose of vitamin A given on the first day of life reduced infant mortality by 64%, and during the first 4 months of life, clinic visits for cough and fever suggestive of pneumonia, the major cause of death in this age group, were reduced. However, no impact was observed in two studies in which vitamin A was given after 3 weeks of age. Two replications of the Indonesian trial are currently underway in south India and Zimbabwe.

Although the impact of vitamin A supplementation given during the first 6 months of life on mortality remains inconclusive, vitamin A supplementation given during the second 6 months of life reduces mortality by an average of 24%. This suggests that if interventions given during early infancy can optimise infant vitamin A status by 6 months of age, they might reduce mortality during the second 6 months, irrespective of any protective effect during the first 6 months. The most important outcome of interventions targeted to young infants may be whether participating infants attain sufficient vitamin A status by 6 months of age.


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How much vitamin A supplementation is needed?

Intakes associated with adequate liver stores at 6 months of age

Two studies done before the EPI-linked trial assessed liver vitamin A stores as an index of status in 6-month-old infants and measured the vitamin A concentration of the breastmilk they consumed during the first 6 months of lactation. A third study measured vitamin A concentrations in necropsy samples from US infants, who we assume were fed commercial infant formula or breastmilk with a vitamin A concentration similar to that measured in other populations of well-nourished women. We estimated the total vitamin A received by the infants in these studies from birth to 6 months of age and correlated this finding with the proportion of infants with adequate vitamin A status at 6 months (table 1). Mean total intakes under 150 µmol left most infants deficient, whereas 90% of infants with mean intakes of 300 µmol or more attained adequate vitamin A status by 6 months of age. We postulate that the percentile intake corresponding to the proportion of infants with adequate vitamin A stores at 6 months approximates to the intake required by the infants in each study population to attain adequate liver vitamin A stores by 6 months of age. For example, among Bangladeshi infants whose mothers received placebo, 7% were vitamin A sufficient so the 93rd percentile of vitamin A intake (233 µmol) represents the amount needed by these infants to attain sufficiency by 6 months. Table 1 suggests that infants need 135–237 µmol of vitamin A during the first 6 months of life; the variability probably reflects differences in morbidity rates. However, an intake of at least 237 µmol during the first 6 months of life would allow nearly all infants to achieve sufficient vitamin A stores by 6 months of age.

Table 2 (upper part) shows how infants drinking mature breastmilk with a vitamin A concentration of 0.70–1.75 µmol/L (a range typical in developing countries) at the 10th, 50th, and 90th percentiles of breastmilk intake, are 58 µmol, 130 µmol, and 160 µmol/L, respectively (table 2).

Dose delivered by maternal supplement

Four placebo-controlled studies compared breastmilk vitamin A response to maternal supplementation with either 200 000 IU or 300 000 IU. Mean vitamin A intakes were estimated for the supplemented and control infants in each study. The difference in the mean intakes between the groups for each study was taken as the estimated amount of vitamin A delivered to the infants by the maternal supplement. A 200 000 IU maternal dose delivered 45 µmol to the infant in urban Bangladesh, but only 18 µmol in rural Bangladesh, whereas a 300 000 IU maternal dose delivered 22 µmol in the Thai study and 109 µmol in the Indonesian study. Biological variability may reflect differences in maternal vitamin A status, morbidity experience, and body size. We have conservatively assumed that a maternal dose of 200 000 IU or greater will provide an additional 25 µmol to the infant drinking a volume at the 50th percentile.

Dose delivered by infant supplement

About 50% of a 200 000 IU dose is absorbed and retained by 2–6-year-old children, so doses of 25 000 IU and 50 000 IU given to infants will provide 13 µmol and 26 µmol additional vitamin A, respectively.

Estimated intakes of infants receiving vitamin A in the EPI-linked trial and drinking at the 10th, 50th, and 90th percentiles of breastmilk intake, are 58 µmol (19 µmol from maternal dose+39 µmol [3×13 µmol] from infant doses), 64 µmol, and 70 µmol, respectively (table 2). The intervention increased infant vitamin A intake. However, most infants of mothers whose milk before supplementation contained no more than 1-05 µmol/L and those who drank low volumes of milk which contained 1-40 µmol/L before supplementation may have failed to achieve adequate vitamin A stores by 6 months of age. Since the median concentration of breastmilk vitamin A among women in developing countries is often only 1.05–1.40 µmol/L, infants with inadequate intakes will make up one-third to one-half of infants in these countries. This is consistent with the 43% of supplemented infants who remained vitamin A deficient at 6 months of age in the EPI-linked trial.
A regimen in which mothers are given 200 000 IU vitamin A at delivery and their infants receive four doses of 50 000 IU (ie, at birth and with their immunisation contacts) would allow nearly all infants to enter the second half of infancy in adequate vitamin A status (table 2).

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