Public Health Impact of Preventing Vitamin A Deficiency in the First Six Months of Life

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Introduction

Vitamin A is required for normal human growth and development, with nuclear receptors for this nutritional ligand detectable in embryonic life. Acting via its (retinoic) acid metabolites and associated nuclear receptors that direct protein synthesis [1, 2], vitamin A participates in regulating cell differentiation, growth, proliferation, and spatial patterning. Through these processes vitamin A is required for normal development of the heart and cardiovasculature [3, 4], respiratory [5, 6], gastrointestinal and genitourinary tracts, central nervous [7], immune [8] and renal [9] systems, cartilage, bone, and the eye [3, 10]. Experimental depletion of vitamin A in the dam results in fetal resorption and neonatal death [2, 9, 11]. Either severe maternal depletion or excess of vitamin A early in gestation can lead to teratogenesis [12]. In humans most congenital evidence relates to excess periconceptional exposure to vitamin A or its therapeutic analogs [13, 14], while data on teratogenicity of maternal vitamin A deficiency remains lacking. Placental-fetal acquisition of vitamin A appears to proceed in a regulated manner throughout a range of maternal vitamin A intakes and levels of status [2, 15]. Yet, despite fetal liver accumulation of vitamin A that normally occurs during the third trimester, term newborns have low vitamin A stores [10, 16] that predispose infants to poor vitamin A status and potential consequences of deficiency early in life. Preterm birth especially jeopardizes newborn vitamin A status due to even less hepatic retinol accumulation [17, 18]. For infants born preterm in developing countries, nutritional compromise coupled with
inaccessible and poor health care and less successful feeding, amplify the risk of vitamin A deficiency.

Postnatally, breast feeding appears to protect against moderate to severe vitamin A deficiency and its ocular disorders (xerophthalmia) from early infancy [19] throughout the highly vulnerable preschool years [20, 21]. However, mothers from poorly nourished societies have lower breast milk vitamin A content than found in industrialized countries [22–24] which limits accrual of infant hepatic vitamin A stores from breast-feeding alone [25–27]. Widespread maternal [28, 29] and infantile [26] vitamin A deficiency, coupled with emerging evidence of potential health and survival benefits to both mother [30] and newborn [31–33] from vitamin A prophylaxis, suggest that vitamin A deficiency may be a critical public health problem for the maternal-infant dyad in the developing world. Preventing deficiency in these groups, however, also raises concerns about safety, especially when supplementing women with vitamin A in the periconceptional period [12] or delivering high-potency vitamin A directly to young infants.

This chapter reviews evidence on: (1) vitamin A status; (2) health consequences attributable to vitamin A deficiency; the (3) health and survival benefits, and (4) safety concerns related to preventing this deficiency during the first 6 months of life.

**Vitamin A Status at Birth and during Early Infancy**

Building on previous treatises [10, 34] the reader is referred to excellent, recent reviews dealing with vitamin A deficiency and its prevention during pregnancy and infancy\(^1\) [25–27, 35, 36].

**Fetal and Neonatal Liver Vitamin A Stores**

The level of vitamin A nutriture at birth is largely a function of materno-placental transfer, fetal hepatic storage and utilization of retinol during gestation. Direct estimates of liver stores are based on several biopsy studies of small numbers of aborted fetuses, stillborns and deceased infants whose gestational and postnatal ages varied and whose population representativeness was uncertain, and unlikely. Notwithstanding, the mean ± SD liver retinol concentrations of 19 ± 10 (median 4) \( \mu \text{g/g liver wet weight} \) among neonates [37] and 22 ± 26 (median 11) 16 ± 16 (median 11) \( \mu \text{g/g liver wet weight} \) among term and preterm neonates have been reported from the United States [16].

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\(^1\) These papers and others dealing with vitamin A deficiency control appeared in comprehensive supplements to the Food and Nutrition Bulletin of the United Nations (September 2000) and Journal of Nutrition (September 2002) that summarized the proceedings of a World Health Organization Technical Consultation held in Yverdon-les-Bains, Switzerland, in March 2000 and the 20th International Vitamin A Consultative Group (IVACG) Meeting held Hanoi, Vietnam in February 2001, respectively.
Nearly half and one fourth of sampled newborns were deemed to have had inadequate and deficient stores\(^2\), respectively. Average hepatic retinol stores at birth were estimated to be sufficient to support an infant’s requirements for only \(~10\) days\(^3\). However, only \(~25\%\) of liver samples of US infants had an inadequate concentration at 6 months and virtually all sampled infants at 1 year of age had normal vitamin A stores [16], likely reflecting dietary vitamin A adequacy throughout infancy. Swedish fetuses and newborns have been reported to have even higher liver retinol concentrations of \(47 \pm 44\) (median \(37\)) \(\mu g/g\) [38], which would be sufficient to meet infant needs for the first 2 months of life [26]. Unlike term infants, those born preterm are likely to have smaller liver concentrations and total stores of vitamin A [16, 18, 39] placing them at high risk of deficiency in the absence of prompt and effective vitamin A therapy.

In developing countries, fetuses and newborns have equally precarious liver retinol stores as in North America, but usually with less opportunity to rapidly establish postnatal reserves. Among urban, middle-income groups in Thailand [40] and India [41, 42], the fetal liver vitamin A concentration and total content appear to rise with gestational age at least through the second trimester; however, the Thai data suggest that the mean liver retinol content decreases thereafter until term [40]. In fetuses of undernourished, lower-income mothers, as seen in India [41] and Ethiopia [38], the absolute hepatic retinol concentrations are markedly lower than in better nourished groups with little or no rise with gestational age, leading to average estimates of \(6–14\ \mu g\) of retinol/g of liver by the third trimester [34, 38, 41]. These patterns are consistent with biochemical [43] and clinical [44] evidence that moderate-to-severe maternal vitamin A deficiency late in pregnancy can be expected to leave infants in a near-deficient state at birth.

**Circulating Retinol Concentration in Early Infancy**

Cord blood analysis, taken to reflect circulating levels of vitamin A prior to and shortly after birth, consistently supports findings of low body stores at birth despite an apparent lack of correlation with fetal liver concentrations [40, 42]. Across a range of maternal vitamin A status, cord serum retinol concentrations are 25–60\% of that measured in mothers at delivery [45–51], likely reflecting placental [52, 53] and protein carrier-mediated [46] mechanisms that regulate materno-fetal transfer of vitamin A late in gestation. The low concentration range in healthy newborns suggests a need to reevaluate the validity of conventional cutoffs of <\(20\ \mu g/dl\) (0.70 \(\mu mol/l\)) and <\(10\ \mu g/dl\) (0.35 \(\mu mol/l\)) to

\(^2\) In young children, Olson et al. [16] suggested <\(20\ \mu g/g\) (0.07 \(\mu mol/g\)) and <\(5\ \mu g/g\) (0.0175 \(\mu mol/g\)) as cutoffs for hepatic vitamin A inadequacy and deficiency, respectively, which continue to be used [26].

\(^3\) Based on a basal daily requirement of \(120\ \mu g\) retinol equivalence (RE)/day to support growth and prevent xerophthalmia, increased to \(180\ \mu g\) RE/day to account for population variation in growth [59].
define low (hyporetinolemia) and deficient status, respectively [54], for perinatal assessment.

In well-nourished populations, plasma retinol levels rise in term-born infants with age. For example, in the United Arab Emirates, healthy newborns of South Asian descent had serum concentrations of 25.4 ± 5.5 µg/dl, nearly half that observed in mothers during the third trimester of pregnancy (~46 ± 13 µg/dl) and non-pregnant women (48.8 ± 13.9 µg/dl) within the same population (fig. 1). Thereafter, paralleling the positive trend in liver stores with age, serum retinol concentrations steadily rise to that of adult females before the 3rd year of life. In contrast, in developing countries where breast-feeding is nearly universal, vitamin A status may deteriorate following birth possibly reflecting the inadequate vitamin A content of breast milk [24] or complementary foods. In Bangladesh, infants <6 months of age had serum retinol concentrations of 17 ± 8 µg/dl, with 57% of values lying below 20 µg/dl.

**Fig. 1.** Serum retinol concentrations of South Asian pregnant women, infants, non-pregnant women and adult men residing in United Arab Emirates where vitamin A deficiency is not known to exist. Sampled groups from 2 hospitals include pregnant mothers in the third trimester (PM, n = 16), cord blood specimens from normal deliveries (CB, n = 20), healthy newborns on the 1st day of life (n = 44), infants 2–21 days of age (n = 20), 1–2 months of age (n = 23), 3–6 months of age (n = 34), 7–12 months of age (n = 24), and 13–21 months of age (n = 25), adult non-pregnant females (F, n = 24) and adult males (M, n = 19). Number of values at 40 days of age unspecified. Regression line depicts association between the serum retinol level and age for infants through 21 months of age [51].
Approximately 70% of the infants had inadequate hepatic vitamin A stores, reflected by an abnormal relative dose response\(^4\) [55]. In Nepal, more than 80% of infants at 3 months of age are hyporetinolemic [56] and in southern India infantile vitamin A deficiency continues to drive a low incidence of blinding keratomalacia under 6 months of age [19]. These patterns may be reflecting the difficulty in establishing normal vitamin A status through breast-feeding and complementary feeding practices at this age in rural south Asia [57]. Vitamin A-deficient preterm infants, born in unsupportive environs in many developing countries, are further disadvantaged with respect to achieving adequate vitamin A status due to additional metabolic stresses, poor absorption, and smaller volumes of milk intake.

Vitamin A Requirements and Dietary Adequacy of Vitamin A in Early Infancy

In developed countries, breast-feeding is usually adequate to meet the vitamin A needs of the young infant. In the United States, the Institute of Medicine (IOM) recently developed a new set of dietary requirements, the ‘dietary reference intakes’ [58]. Based on studies showing an average, daily breast milk volume of 0.78 liters and retinol concentration of 485 µg/l (excluding contributions from provitamin A carotenoids), the IOM recommended an intake rounded up to 400 µg of retinol activity equivalents (RAE)\(^5\) as ‘adequate’ for healthy North American infants. The Food and Agricultural Organization of the United Nations has previously estimated the daily ‘basal requirement’ and ‘safe level of intake’ to be 180 and 350 µg RAE for an infant of average weight at 3 months of age [59]. The basal value reflects the minimum daily amount needed to prevent xerophthalmia and permit growth, but not to build liver reserves, while the latter – from which the IOM ‘adequate intake’ is indistinguishable [58] – is intended to support all vitamin A-dependent functions and maintain adequate body stores. More recent mathematical modeling defends these recommendations [25–27, 36].

In industrialized cultures, daily breast milk intakes have been observed to rise from ~0.43 liters in the 1st week of life to ~0.81 liters by 5–6 months of age, with an average retinol equivalency that exceeds 700 µg/l and permits a daily intake of nearly 600 µg RAE from breast milk alone [23], an amount that is well above the ‘adequate intake’ level. In contrast, in developing countries, where breast-feeding is universal and complementary feeding often

\(^4\) In a test that assesses the relative adequacy of liver stores by calculating the change in serum retinol concentration 5 h following a small oral challenge with vitamin A, as a proportion of the 5-hour concentration \(\times 100\), a value >20% is indicative of low hepatic stores [54].

\(^5\) One RAE = 1 µg RE = 1 µg of all-trans retinol = 2 µg of supplemental all-trans β-carotene = 12 µg of dietary all-trans β-carotene = 24 µg of other provitamin A carotenoids in the diet [58].
unsatisfactory, infants are likely to consume inadequate amounts of vitamin A in the first 6 months of life, partly due to lower daily output of mature breast milk (~0.65 to 0.70 liters) [57, 60, 61] that has a retinol concentration of only 400–500 μg/l (range of reported averages 170–640 μg/l)\(^6\) [23, 34, 57]. These factors lead to average vitamin A intakes from breast milk of only ~300 μg/l/day, and considerably lower intakes among more impoverished groups. Under such conditions, one third to one half of infants in the developing world can be expected to have intakes of vitamin A that are inadequate to support all physiologic needs and sustain adequate liver stores [25]. Controlling this problem requires combinations of ‘fortifying’ breast milk through maternal vitamin A supplementation [62, 63], advocacy to feed vitamin A-rich colostrum, periodic dosing of infants with high-potency vitamin A [27, 36], regular feeding of adequate amounts of vitamin A-rich complementary foods (small amounts of dried milk, egg, liver, cheese or ripe yellow fruit, appropriately prepared) or provision of formula [57].

Health Effects of Vitamin A Interventions

Population-based evidence about the health effects of vitamin A supplementation during the first 6 months of life derives almost entirely from developing country experience where (a) the majority of infants born with low vitamin A stores fail to become replete during this time, and (b) policy interests and program resources are rising to prevent vitamin A deficiency in mothers and young infants. Health consequences that might be reduced through maternal and infant interventions, including (a) fetal and infant vitamin A deficiency, (b) low birth weight and poor postnatal growth, and (c) poor health and infant mortality, are reviewed below.

Impact on Infant Vitamin A Status and Deficiency

Infant vitamin A status can be improved by increasing the maternal intake of vitamin A (with transfer transplacentally and via breast milk) or by increasing vitamin A intake of infants through diet or supplementation. The effect of maternal vitamin A use on infant status was tested in a large, cluster-randomized field trial in rural Nepal, where breast-feeding is universal and antenatal and child health care minimal. Over 43,500 women of reproductive age received a placebo or an approximate recommended dietary allowance (RDA) of vitamin A, either preformed (7,000 μg REs) or as provitamin A β-carotene (42 mg), once weekly before, during and following pregnancy, among whom over 75% consumed at least half of their intended supplements [30]. During the trial a sample of 704 infants of 15,832 mothers who had had

\(^6\) Colostrum and transitional milk retinol concentrations of ~1,500 and 1,000 μg of retinol have been reported during the first month of lactation [23].
a live birth were selected to undergo biochemical and anthropometric assessment at ~3 months of age to evaluate impact on infant status (table 1). Maternal supplementation modestly raised infant serum retinol, evident by mean concentrations of 0.53 and 0.66 μmol/l and prevalences of hyporetinolemia (<0.70 μmol/l) of 83 and 62% among infants born to control and vitamin A-supplemented mothers, respectively (p < 0.0001 for both comparisons) [56]. Maternal β-carotene supplementation had even less of an impact, achieving a mean serum concentration in infants of 0.58 μmol/l (p = 0.07 vs. placebo) and prevalence of deficiency of 76% (p = 0.03).

Other maternal interventions in southern Asia have evaluated changes in the vitamin A status of infants whose mothers were given a dose of either 200,000 [64, 65] or 300,000 IU [62] of vitamin A within 3 weeks after delivery (table 1). Findings revealed that maternal high-potency vitamin A receipt could improve vitamin A status but not control deficiency throughout the first 6 months of life, with at least 25% of infants of vitamin A-supplemented mothers having hyporetinolemia (<0.70 μmol/l) at 6 months of age. Routine administration of β-carotene to mothers, either weekly [56] or daily [63],

Table 1. Differences in infant vitamin A status by type of maternal vitamin A supplement intervention

<table>
<thead>
<tr>
<th>Country/Design</th>
<th>Infants n</th>
<th>Age at assessment months</th>
<th>Serum retinol, μmol/l mean ± SD</th>
<th>% deficient1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nepal [56], weekly2</td>
<td>Vitamin A 224</td>
<td>3</td>
<td>0.66 ± 0.24***</td>
<td>62***</td>
</tr>
<tr>
<td></td>
<td>β-Carotene 277</td>
<td>3</td>
<td>0.58 ± 0.24*</td>
<td>76**</td>
</tr>
<tr>
<td></td>
<td>Placebo 203</td>
<td>3</td>
<td>0.53 ± 0.24</td>
<td>83</td>
</tr>
<tr>
<td>Bangladesh [63], single vs. daily3</td>
<td>Vitamin A 69</td>
<td>6</td>
<td>0.84 ± 0.23*</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>β-Carotene 69</td>
<td>6</td>
<td>0.80 ± 0.22</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>Placebo 70</td>
<td>6</td>
<td>0.77 ± 0.21</td>
<td>34</td>
</tr>
<tr>
<td>Indonesia [62], single4</td>
<td>Vitamin A 68</td>
<td>6</td>
<td>0.67 ± 0.19</td>
<td>15**</td>
</tr>
<tr>
<td></td>
<td>Placebo 70</td>
<td>6</td>
<td>0.65 ± 0.26</td>
<td>36</td>
</tr>
</tbody>
</table>

Treatment versus placebo comparisons: *p = 0.07; **p < 0.05; ***p < 0.0001.

1 Percent of infant serum concentrations <0.70 μmol/l in Nepal and Bangladesh, and <0.52 μmol/l in Indonesia.

2 Mothers given a weekly dose of 7,000 μg RE of vitamin A, 42 mg β-carotene or placebo throughout the trial (before, during and after pregnancy).

3 At 2 weeks postpartum mothers given a single dose of 200,000 IU vitamin A (60 mg RE) plus daily placebo thereafter, or placebo followed by 7.8 mg β-carotene daily thereafter, or placebo only through 9 months postpartum.

4 Mothers given a single 200,000 IU (60 mg RE) dose of vitamin A or placebo at 2 weeks postpartum.
performed even less well than single-dose, high-potency vitamin A in improving infantile vitamin A status.

Directly dosing infants under 6 months of age with high-potency vitamin A is likely to modestly raise serum retinol. In a randomized trial among 9,424 infants carried out by WHO in Ghana, India and Peru, supplementation with 25,000 IU at ~6, ~10 and ~14 weeks of age during immunization visits left serum retinol concentrations only slightly and nonsignificantly higher than levels in placebo recipients at ~6 months of age (0.84 vs. 0.80 μmol/l). Testing for relative liver content also revealed nonsignificantly smaller percentages of infants with inadequate stores (43 vs. 52%, respectively) [66]. These findings are consistent with observations in older children showing only modest, sustained elevations in serum retinol following high potency vitamin A delivery [21], even in populations where preschool child mortality reduction is, nonetheless, likely to be substantial [28].

**Impact on Birth Size and Infant Growth**

Given the requirement of vitamin A for mammalian growth [3], one might expect to observe, at the minimum, associations between fetal vitamin A status and size at birth. Indeed, the cord serum retinol concentration has been shown to be correlated with term newborn length, weight, and head circumference in Brazil [67], Saudi Arabia [68], India [69] and multiethnic groups in the United Kingdom [70], with coefficients (r) ranging from 0.20 to 0.42 that explain 4.5–6.5% of variance (r²) in birth size. However, many such cross-sectional studies fail to adequately adjust for the confounding effects of gestational age. That is, the correlation that exists between cord blood retinol and gestational age among infants born preterm (and thus low weight) [69] also exists throughout the conventional ‘term’ age stratum of 37–41 weeks (r = 0.15–0.36) [67, 69], leaving the possibility for residual confounding to explain this association.

The evidence to date suggests that fetal vitamin A status does limit growth in most human populations. Placebo-controlled trials generally show little to no effect of maternal or infant vitamin A supplementation on growth through the first 6 months of life. Neonates born to marginally nourished Nepalese mothers randomized to receive a weekly RDA of vitamin A, preformed or as β-carotene, failed to show differences in size by 7–14 days of age compared to infants of placebo-recipient mothers (table 2). Indonesian infants of mothers supplemented daily during and following pregnancy with 4,800 μg RE failed to show an advantage in weight or length through 6 and 12 months of age over infants of non-vitamin A-recipient mothers [71]. Better ponderal and linear growth was observed through 6 months of age in infants with adequate (>0.70 μmol/l) vs. low retinol concentrations at ~4 months of age, but these effects may have been due to other factors that promote both adequate vitamin A status and growth. Similarly, directly dosing young infants appears to have little effect on growth. In the randomized trial carried out by
the WHO in Ghana, India and Peru, ponderal and linear growth of infants supplemented with 25,000 IU of vitamin A at ~6, 10 and 14 weeks of age was nearly identical to that of placebo recipients at both 6 and 12 months of age [66].

In HIV-infected populations, maternal vitamin A deficiency is associated with low birth weight and poor postnatal growth [72] but the effects of intervention have been mixed. In a randomized trial in Malawi, daily antenatal supplementation of HIV-infected mothers with 3,000 μg RE of vitamin A during pregnancy improved weight at birth (+90 g) and at 6 weeks of age (+169 g) over controls [73] whereas, in Tanzania, daily antenatal vitamin A (1,500 μg RE) plus β-carotene (30 mg) use by HIV-infected mothers failed to affect birth weight [74].

**Impact on Infant Health and Survival**

A number of studies have attempted to reduce early infant morbidity and mortality by targeting the delivery of vitamin A to (a) mothers antenatally and postnatally, (b) newborns and neonates, and (c) infants from 1 to 6 months of age. This section reviews findings from trials that have tested the delivery of vitamin A at each of these ages, and discusses the biologic plausibility of observing effects of vitamin A on infant survival that depend on severity of maternal deficiency, age of infant at receipt and possibly size of dosage.

Maternal Vitamin A Supplementation

In Nepal, a randomized, placebo-controlled trial that supplemented women each week prior to, during and following pregnancy with vitamin A or β-carotene reduced maternal mortality related to pregnancy by ≥40% [30] but failed to benefit overall fetal or infant survival, with relative risks (RRs) close to 1.0 for each outcome [56]. An exception, however, occurred among offspring

<table>
<thead>
<tr>
<th>Measure</th>
<th>Placebo</th>
<th>Vitamin A</th>
<th>β-Carotene</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg</td>
<td>n(^1)</td>
<td>mean SD</td>
<td>n(^1)</td>
<td>mean SD</td>
</tr>
<tr>
<td>Length, cm</td>
<td>273</td>
<td>2.71 0.44</td>
<td>338</td>
<td>2.72 0.49</td>
</tr>
<tr>
<td>Arm circumference, cm</td>
<td>265</td>
<td>9.10 0.80</td>
<td>327</td>
<td>9.15 0.94</td>
</tr>
<tr>
<td>Chest circumference, cm</td>
<td>270</td>
<td>30.16 1.98</td>
<td>339</td>
<td>30.19 2.15</td>
</tr>
<tr>
<td>Head circumference, cm</td>
<td>270</td>
<td>33.10 1.44</td>
<td>337</td>
<td>33.14 1.50</td>
</tr>
</tbody>
</table>


\(^{1}\) Number restricted to infants measured between 7 and 14 days of age in each treatment group.
of ~8% of mothers who had developed night blindness during pregnancy. The 6-month mortality of infants whose mothers developed this condition, despite being given vitamin A on a regular basis, was 25% lower (74 per 1,000) than that among infants born to night-blind mothers in the control group (99 per 1,000) [75]. β-Carotene receipt, on the other hand, only modestly (and nonsignificantly) reduced maternal night blindness [76] and mortality among infants of affected mothers [75]. In accord with an overall lack of supplement impact, infants of non-night-blind women experienced the best survival, regardless of treatment group (fig. 2). Notably, no effect on infant mortality was observed in offspring of HIV-infected mothers receiving vitamin A daily in Tanzania [77]. A 38% increase in HIV transmission from mother-to-child was also reported [77] which awaits assessment in at least one other HIV-positive population in Africa (J. Humphrey, personal communication, 2002).

**Fig. 2.** Probability of survival from birth through 6 months of age among Nepalese infants stratified by whether or not mothers developed night blindness during pregnancy and weekly supplement group among mothers who developed night blindness. VA = Vitamin A (7,000 μg RE); BC = β-carotene (42 mg); PL = placebo. Log rank test p value = 0.015 comparing all groups [75].

Neonatal Vitamin A Supplementation

A potential may also exist to improve infant survival by directly dosing neonates with vitamin A, supported by findings from two double-masked, placebo-controlled trials in south Asia. The first study (a) randomized 2,067 Indonesian, hospital-born infants to receive a single 50,000 IU oral dose of
vitamin A receipt was associated with a 64% reduction in mortality (RR = 0.64; 95% confidence interval (CI) 0.16–0.87). Most of the mortality difference was observed by the 4th month of life (fig. 3a), by which time there had also been a 34 and 43% decline in clinic attendance rates for fever (p = 0.06) and cough-related (p = 0.008) illnesses, respectively, among vitamin A-supplemented infants [31]. A recently completed, community-based trial in Tamil Nadu, India, followed up on these findings by randomizing 11,617 infants to receive either vitamin A (24,000 IU on 2 consecutive days) or placebo within 48 h after birth [33].

**Fig. 3.** a Probability of survival from birth into the 2nd year of life among Indonesian infants randomized to receive vitamin A (50,000 IU) or placebo at birth [31]. b Probability of survival from birth through 6 months of age among south Indian infants randomized to receive vitamin A (24,000 IU on 2 consecutive days) or placebo within 48 h after birth [33].
or placebo within 48 h after birth. After 6 months, mortality in vitamin A-supplemented infants was reduced by ~23%, reflected by a RR = 0.77 (95% CI 0.62–0.96; fig. 3b). The effect was restricted to infants born low in birth weight (<2,500 g) [33], suggesting there may have been disproportionate benefit among preterm infants. Although point effect estimates from these 2 studies vary, both suggest that infant mortality can be reduced by orally dosing newborns with a large dose (~50,000 IU) of vitamin A.

Postneonatal Supplementation with Vitamin A

In contrast to the potential survival benefits of dosing infants at or shortly after birth, and the dramatic and consistent reductions in mortality that have been shown to occur when older infants and children are supplemented with vitamin A [21], several trials have failed to show a favorable effect of high potency vitamin A on survival when infants are dosed between 1 and 5 months of age. In Nepal, 11,918 infants born during an ongoing community trial [78] received 50,000 IU of vitamin A or placebo if recruited as a neonate and 100,000 IU or placebo if 1–5 months of age at the time of 4-monthly household visits by field teams. There was no overall effect of vitamin A on mortality as reflected by RR = 1.11 (95% CI 0.86–1.42; fig. 4a) [79]. Subgroup analyses, however, did reveal nonsignificant increases in mortality of 38, 9, and 26% among infants who were dosed with 100,000 IU (30 mg RE) at 1, 2, and 3 months of age, respectively. Infants dosed at 4 and 5 months of age had nonsignificant 8 and 22% reductions in mortality risk, compatible with improved survival when vitamin A was given at 6 months of age and older [78]. Also, while absolute mortality markedly decreased with the size of the infant at every age (assessed by arm circumference), there was an increase in mortality among vitamin A recipients of better nutritional status relative to controls [79], an interaction for which there is presently no clear explanation. In the large WHO 3-country trial, there were no significant differences in survival to 6 months of age or beyond among infants given either vitamin A (25,000 IU) or placebo at their ~6, ~10 and ~14 week immunization visits (fig. 4b) [66]. These findings suggest that, while high-potency vitamin A (up to 50,000 IU) given from the late neonatal period through the 6th month of life can be expected to improve liver retinol stores [36], a reduction in early infant mortality should not be expected.

Plausible Biological Mechanisms

Effects of vitamin A on infant mortality appear to be governed by complex interactions involving dosage, severity of deficiency, comorbidity that may exist, recipient of the dose and, in the event it is the infant, age or developmental stage at which exposure to vitamin A occurs. Giving a RDA of vitamin A prophylactically to pregnant and lactating women may not markedly affect infant survival in a population. However, susceptible groups may benefit. Specifically, survival of infants of moderately to severely vitamin A-deficient mothers (defined as pregnant women with a previous history of maternal
night blindness or who become night blind during a current pregnancy) may improve following routine maternal vitamin A receipt. Findings from Nepal suggest that such effects could be reflecting ‘nutrient partitioning’, whereby routine maternal supplementation with an RDA of vitamin A was insufficient to replete deficient maternal tissues, revealed by the occurrence of night

Fig. 4. a Probability of survival over a 4-month period among Nepalese infants who were cluster-randomized to receive vitamin A (50,000 if <1 month of age; 100,000 IU if 1–5 months of age at time of dosing). Age at follow-up ranges from 4 to 9 months [79]. b Probability of survival among Ghanaian, Peruvian and Indian infants through 12 months of age randomized to receive vitamin A (25,000 IU) or placebo in conjunction with each immunization visit at ~6, ~10 and ~14 weeks and ~9 months of age (at which controls also received 100,000 IU), denoted by arrows [66].
blindness, but sufficient to improve infant survival [32]. It is possible that low birth weight [33], preterm infants born in undernourished, under-served societies may favorably respond to maternal vitamin A supplementation or dosage receipt at birth. Providing high-potency vitamin A to low birth weight, and perhaps especially developmentally immature, preterm infants born with precariously low nutrient reserves may also reduce mortality risk in under-served populations where causes of early infant death are often unknown.

There are a number of vitamin A-responsive disease mechanisms occurring at specific stages of fetal and neonatal development that may partly explain these effects. The placenta and most organs of vertebrate species are affected by maternal vitamin A depletion when imposed at critical stages of fetal development [3, 7, 80], effects that presumably give rise to increased neonatal morbidity and mortality [8, 11, 81, 82]. For example, maternal vitamin A depletion, especially late in gestation, induces loss of gene expression for the structural protein, elastin, and causes keratinizing metaplasia in the perinatal rat lung [5, 9, 82, 83]. In very low birth weight preterms, bronchopulmonary dysplasia represents a potentially fatal lung disease that is exacerbated by vitamin A deficiency and which has been shown to be responsive to vitamin A therapy [6, 17, 84]. In animals, maternal supplementation with vitamin A accelerates closure of the ductus arteriosus after birth, which fails more often in preterm than term human infants [85]. Preterm birth coupled with poor nutrition, including vitamin A deficiency, may impede maturation and function of the gastrointestinal tract. For example, vitamin A supplementation ameliorates experimentally induced intestinal mucosal injury in newborn rats [86], suggesting a possible role for vitamin A in reducing the risk or severity of necrotizing enterocolitis to which preterm, low birth weight neonates are at high risk [84]. Dosing low birth weight newborns with vitamin A may also modify disease risk by accelerating maturation [8, 81] and subsequent responsiveness of the immune system to infection. The recent newborn vitamin A trial in southern India observed that infants born to night-blind mothers were 3 times more likely to have their nasopharynx colonized with *Streptococcus pneumoniae*, the leading cause of bacterial pneumonia in infants, than infants born to non-night-blind controls [87]. Further, newborn supplementation with vitamin A significantly reduced or delayed the risk of nasopharyngeal colonization at 4 months of age among infants not colonized at 2 months, suggesting that perinatal exposure to vitamin A may have enhanced epithelialization and immune defenses in the respiratory tract [88], consistent with known effects of vitamin A on pulmonary [5] and immune [89] function.

**Safety of Intervening with Vitamin A**

In countries with vitamin A deficiency, there is a need to assess health risks that may accompany public health vitamin A interventions directed to reach infants, either via the maternal route or directly.
Maternal Interventions

Previously, the WHO recommended that mothers living in undernourished populations receive a single 200,000 IU prophylactic oral dose of vitamin A within 6–8 weeks after delivery, to minimize the risk of periconceptional exposure [90]. Following randomized field trials in Indonesia [62] and Bangladesh [63], however, that found only modest improvements in breast milk vitamin A and infantile vitamin A status after mothers received 300,000 and 200,000 IU, respectively, the IVACG now recommends that mothers be given 200,000 IU on 2 different days (total dose of 400,000 IU) within 6 weeks after delivery [91]. This presumably more effective dosage also appears to be safe. A randomized double-masked trial of nearly 800 Zimbabwean mothers and infants recently found low and indistinguishable rates of maternal headache, nausea, vomiting, poor appetite, and other complaints between postpartum recipients of 400,000 IU and placebo controls [92]. Newborns co-randomized with mothers to receive high-potency vitamin A or placebo also showed low rates and no differences between groups in side effects [92].

Although not part of formal programs at this time, maternal use of vitamin A during pregnancy, alone or (more likely) in combination with other micro-nutrients, is likely to increase, raising concerns about teratogenicity [13]. Findings from a high-profile epidemiologic study in the USA of an increased risk of cranial neural crest defects among the offspring of women taking supplements of 10,000 IU or more [14] have not been confirmed by other investigators [12]. Further, normal circulating levels of retinoic acids (putative teratogens of vitamin A) have been observed in women taking up to 30,000 IU/day [12] with the minimum daily teratogenic dosage currently estimated to be \( \sim 50,000 \) IU of vitamin A. Oral vitamin A supplements up to 10,000 IU (3,000 \( \mu \)g RAE)/day or single doses of 25,000 IU (7,500 \( \mu \)g RAE)/week are considered to be safe for prophylaxis among women of reproductive age [58, 93].

Early Infant Interventions

Reasonable safety data exist for three approaches to vitamin A supplement under 6 months of age:

(a) Delivery of 25,000–50,000 IU at Diptheria-Pertussis-Tetanus and Polio Vaccine Visits: Three oral supplements can be given to infants at 6, 10 and 14 weeks of age. Currently 50,000 IU at each visit is recommended by IVACG/WHO [91]. Trials in Bangladesh [94–97] have reported differences of up to 7.4% in the risk of bulging fontanel (percent cases among vitamin A recipients – percent cases among controls) following this dosing regimen. In Ghana, Peru and India risk differences of <1% were observed [66]. In all studies, cases resolved spontaneously within 48 h of supplement receipt. One follow-up study revealed no developmental differences 3 years later between children who had vs. had not experienced a bulging fontanel following supplement receipt in early infancy [98].
(b) Dosing Newborns Orally with 50,000 IU of Vitamin A: This approach is not practiced at present, but shows promise in terms of infant survival [31, 33] while being safe, reflected by a ~2% excess risk over controls for a bulging fontanel (4.5 vs. 2.4% after 48 h) [99]. Importantly, the bulge that occurred in Indonesia was not associated with a differential rise in intracranial pressure, risk of intracranial hemorrhage or symptoms of irritability. A 3-year follow-up study revealed no long-term developmental sequellae associated with a vitamin A-supplement induced bulging fontanel [100].

(c) Dosing Infants with 50,000 IU of Vitamin A at Any Age Under Six Months: This approach might be most likely to be practiced in association with semi-annual high potency vitamin A delivery campaigns for under 5-year-old children in the community. In Nepal, there was a <2% excess risk of developing a bulging fontanel or vomiting within 48 h of being dosed with vitamin A (50,000 IU <1 month and 100,000 IU at 1–5 months of age) [101], suggesting minimal risk to exist following receipt of a single dose of 50,000 IU or less.

Conclusions

Vitamin A deficiency in early infancy is a public health problem in undernourished populations, attributed to marginal gestational nutrition leading to very low body stores and status at birth, preterm birth, low maternal breast milk vitamin A content, premature and inadequate complementary feeding and infection in the presence of high nutrient demand to support growth and development. Without adequate postnatal vitamin A intake, via breast milk, hygienically prepared formula or other nutritious complementary foods, infants remain vitamin A deficient. Subgroups of infants, born preterm or to moderately to severely vitamin A-deficient mothers, may be at increased risk of morbidity and mortality in the first 6 months of life. Dosing mothers prone to develop night blindness with low-level dietary vitamin A may lower risk of mortality for both mother and infant. Antenatal and postnatal use of supplemental vitamin A in HIV+ populations remains controversial. Supplementation of newborns with up to 50,000 IU and infants through the first 6 months of life with up to 50,000 IU during immunization visits appears also to be safe.

Research Challenges

(1) Review the pathophysiological relevance of conventional serological cutoffs of <10 μg/dl (<0.35 μmol/l) and <20 μg/dl (<0.70 μmol/l) presently used to define low and deficient vitamin A status in newborns.

(2) Develop full set of dietary reference intakes, including an estimated average requirement, RDA and tolerable upper intake level for infants
<6 months of age based on the effects on physiologic function, to eventually replace the currently used ‘adequate intake’ of 400 µg RAE as presently set by the IOM [58].

(3) Confirm and elucidate plausible mechanisms whereby high potency vitamin A may reduce infant mortality when newborns are dosed versus being dosed later in the first half of infancy (1–5 months).

(4) Develop an adequate base of evidence through epidemiologic studies to reveal the risk of birth defects that may be associated with maternal vitamin A deficiency in human populations.

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References

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Discussion

Dr. Stacy: There have been many articles in Cochrane review from Cochrane library in January 2002 Kussakandal, saying that giving vitamin A prophylaxis during the first 6 months of life reduces retinopathy of the premature infant and bronchopulmonary dysplasia. Do you have any comments on these data?

Dr. West: There are trials [1], on the impact of supplementing preterm babies with intramuscular vitamin A for a certain number of days throughout the neonatal period, showing a reduction in the risk of bronchopulmonary dysplasia, including requirements for mechanical ventilation and therapeutic oxygen. The first was published by Shenai et al. [2] in 1987 and was conducted at a time when surfactant was not being used to treat premature infants. With that now in use more recent trials have shown much more modest effects. A recent meta-analysis review of studies that have been done, including a larger trial that was published just a few years ago [3], suggested that there still may be a benefit with respect to reducing the dependence for therapeutic oxygen in preterm infants. So it is still holding up, but not as strong an effect as reported in the early and smaller trials.

Dr. Al Lamki: In Oman a few years back, we had a national health survey on children under 5 and it was recommended to give vitamin A supplements to all newborns based on the functional indexes of vitamin A deficiency. Do you think that it is enough without biochemical indexes as an indicator for supplementation, particularly as you mentioned the danger of toxicity from vitamin A?

Dr. West: It was 50,000 at birth?

Dr. Al Lamki: Yes, at birth.

Dr. West: Without knowing more about infant mortality and other risk factors it is hard to say definitively, but 50,000 IU at birth could become a recommendation in the future for infants in populations where the infant mortality rate is, for example, above 40–50/1,000 births. This approach could emerge to be more efficacious in reducing mortality than giving vitamin A at 6, 10 and 14 weeks of age. I would think it would be worthwhile to see vitamin A status data in the population as well.

Dr. Al Lamki: Actually this is based on various factors like high rates of prematurity plus the functional early clinical symptoms of vitamin A deficiency in this young population. I was wondering whether it was enough to give supplementation to all children?

Dr. West: There is no evidence of harm in the trials that have been done so far with dosing infants at birth and some evidence of benefit, so it may well be indicated. I think you have a very progressive-minded Minister of Health keeping tabs on some of these nutritional problems and trying to take preventive action.

Dr. Pettifor: You mentioned a study from the United Arab Emirates [4] on the vitamin A levels throughout the first 2 years of life, and it appeared that most children under 2 years of age had levels of <20 μg/dl, which is the cutoff point for subclinical vitamin A deficiency. Are you suggesting that there are different cutoff levels for children under 2 years of age for defining vitamin A deficiency if you are using serum retinol levels? Because you suggested that those infants were in fact healthy well-growing children, indicating that in fact the vitamin A status is probably adequate.

Dr. West: Not under 2 but in the early infancy, shortly after birth for the first few months of life, we don’t have a clear view of what the cutoff should be for defining deficiency by serum retinol levels. We take the 20-μg cutoff and extrapolate to that age group. In terms of defining the cutoff in the first 3 months of life, 20 μg/dl may be too low, but we don’t have good functional data to define that cutoff point right now.

Dr. Abbasy: First of all thank you for your elegant presentation. Secondly I would like to tell you about our experience in Egypt. In Egypt we give 100,000 IU vitamin A
in the form of a capsule during the childhood immunization program along with the measles shot at 9 months, and at 18 months of age 200,000 IU are given. With measles vitamin A is also given as scheduled by the World Health Organization. Several studies were done, one of them by myself in Alexandria, among the infants with acute respiratory infections and we found that vitamin A is very low and that vitamin A supplementation to those with acute respiratory infection might help them to decrease the mortality rate.

Dr. West: And what did you find? Did you find that the risk of severe illness went down with supplementation?

Dr. Abassy: No, we found that in those with acute respiratory infection, pneumonia, the vitamin A level is very low. So supplementation during treatment is very essential to decrease the mortality rate.

Dr. West: The relation between vitamin A and respiratory infection is a little perplexing. There are trials that have been submitted to pooled analysis. The relative risk pretty much comes out as 1 with respect to the incidence or severity of acute respiratory infection in children getting vitamin A versus not. But there are certainly other reasons for providing vitamin A to such children because they are often malnourished as well and ill from other points of view, so I think it is a wise move.

Dr. Al Frayh: The results which you showed in the reduction of infant mortality rate of 60% or above in Nepal and 30% in India are very encouraging. I wonder whether you have some details about those survivals: how many of them were prematures and how many of them had low birth weight or extremely low birth weight? What is the approximate percentage?

Dr. West: I don’t have the numbers on the preterm delivery rate but the low birth weight rate is around 25–30%, about 30% are below 2,500 g.

Dr. Sazawal: The only thing in these populations and what we see in most of northern India as well as in the south of India, is that although the prematurity rate is the same as the Western world, about 9–10%, but effectively in all instances the babies would die even before you got there. So I would suspect from the experience that we have had in Delhi that most of those children are full-term rather than premature and there are hardly any or very few prematures because they don’t survive beyond the first 2 days given that there is no assistance.

Dr. West: There is a bias in the estimate of low birth weight which is exactly related to the timing of getting the birth weight. When, through great effort, we have measured birth weights in Nepal and Bangladesh, we found 40–50% low birth weight rates.

Dr. Young: To pursue further the question you asked me this morning: is there any evidence of a vitamin A inadequacy in infant populations in developing regions if the breast milk retinol concentration is 1.7 \( \mu \text{mol} \), i.e. the level that the Institute of Medicine (IOM) used to arrive at an adequate intake?

Dr. West: In broad strokes there is evidence. If you look at where vitamin A deficiency in children is historically, breast milk levels are lower than 50 \( \mu \text{g/dl} \), and often at or below 30 \( \mu \text{g/dl} \) for example. Both the breast milk and infant serum levels respond to supplementation. Through that kind of evidence you see breast milk vitamin A being related to the risk profile of infants and young children.

Dr. Young: So are you saying that the value that the IOM used as a basis for establishing the adequate intake for North American infants would be inadequate with respect to infants in developing regions?

Dr. West: It could be.

Dr. Young: Why could that be? I don’t quite understand.

Dr. West: In terms of infants possibly needing more than what the IOM recommends due to higher demands or, alternatively, when one considers smaller breast milk intakes that could require higher concentrations.
Dr. al Qabandi: I would like to ask about vitamin A deficiency in infants with cholestatic liver disease. I know this is a special group of infants with multiple deficiencies of all kinds of vitamins, but I find it extremely difficult to monitor their vitamin A levels. Especially with vitamin A, whatever dose is given you don't establish a normal level, and with vitamin A toxicity I find it more difficult than giving other vitamins. Is monitoring their serum level effective, and if it is effective, how often do we have to monitor the level of serum vitamin A in these babies?

Dr. West: How frequently, I don't know. Does anybody know the answer to that? It is a good question.

Dr. Endres: In our small part of the world there is an ongoing discussion between nutritionists dealing with the recommendation or non-recommendation of micronutrients during pregnancy. So when I look at the data from your study with 44,000 pregnant women in Nepal, it is very amazing that the pregnancy-related mortality was decreased so much by giving retinol. I would like to ask you, is this knowledge known to gynecologists? In general you are mainly dealing with ophthalmologists but I know that they do not recommend a lot: the minimum they recommend is only folate and iodine, the others they say are not necessary. But when I look at your data I think this is very encouraging.

Dr. West: We think so too but there is considerable equipoise about those estimates right now. If you read the letters to the British Medical Journal during the year following the studies, this uncertainty of opinion is sufficient to require other trials. So that is why in Bangladesh for example we have a trial in 55,000–60,000 pregnant women underway right now, we have 20,000 women already enrolled and being followed and dosed with vitamin A, β-carotene or a placebo, to try to replicate these findings in Bangladesh with the Ministry of Health and Welfare there. There is also a follow-up replicate trial underway in Ghana to look at the impact on maternal mortality. There are biologically plausible explanations related, for example, to the impact of vitamin A on maternal sepsis. One trial goes back to the 1930s and showed marked reductions in sepsis in London among women who were given cod liver oil in later pregnancy and the first several days postpartum [5]. So there are explanations that one can bring to bear on our findings, especially in a population that is undernourished and where the maternal mortality rate and the pregnancy-related mortality rate is 70 times higher than in Europe and the United States. So these are women who have considerable nutritional and health needs.

Dr. Barclay: In your studies on vitamin A supplementation in neonates have you looked at the effects of the iron status of these babies?

Dr. West: We haven't done it on the vitamin A studies but iron is being looked at in subsequent trials in these populations and in terms of severe anemia under 6 months of age, I think it is very low.

Dr. Young: Since we are on the topic of preventing vitamin A deficiency would you care to comment very briefly with respect to the role that agricultural biotechnology might play in this context?

Dr. West: I think it has a role. I think the genetic modification revolution has a fuse of probably 25 years before it really takes its place in the public health arena. Golden rice is an example. There is also rape seed oil modification that is going to increase the β-carotene content. The proof of concept is there but only a few bags of golden rice exist in the world and it is going to take some time to move these kinds of products into real life, have them grown, a slightly different color, educate the population, figure out the price structure, get farmers to adopt these crops, figure out what the inputs are so that the crop production does not go down and so forth. I think we are looking at easily 25 years but that is not to criticize it, these are steps that are being taken now that may yield real public health benefits in another 2 or 3 decades.
Dr. Allen: A few points of clarification, one is that serum retinol increases throughout the first 6 months of life even in well-nourished communities, the cutoffs are probably wrong for the vitamin A status indicators such as serum retinol and the modified relative dose response [6]. So this is a word of caution to people who are trying to evaluate the status of young infants using those measures. The second concerns the kinetics of vitamin A turnover. About 2% of the dose is lost from liver stores every day, and so a high dose disappears quite quickly. It is gone from liver stores in about 3 or 4 months after administration. Thirdly, in order to answer Dr. Young's question, I am pretty sure that the 400 μg/day that is recommended in the US and Canada during the first 6 months is enough to maintain liver stores unless infants are heavily infected, which is unlikely in the first 2 months of life even in very poor environments.

Dr. West: True, but I guess where it gets a little fuzzy is when breast milk production is not at 780 ml/day, frequently you get estimates of 500 or less. So if you take the 50 μg/dl times 5 or even times 4, then you start to get very low intakes of vitamin A from breast milk.

References