REVIEW

Vitamin A and preterm infants: what we know, what we don't know, and what we need to know

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Vitamin A is essential for optimal growth and development. In the developing world, vitamin A supplementation of the newborn infant reduces mortality. In the developed world, extremely preterm infants are born with low body stores of vitamin A and are at high risk of vitamin A deficiency. Optimal vitamin A supplementation for this population is not clearly defined, however, and, despite evidence of benefit, early vitamin A supplementation of extremely preterm infants is not uniformly practised in the United Kingdom. There is an urgent need for studies in preterm infants that include quantification of hepatic stores and functional assessment of vitamin A status as well as long term outcome.

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Vitamin A is one of the most important micronutrients affecting the health of children. Recognised for nearly 90 years as an essential dietary constituent, it is necessary for orderly growth and differentiation of tissues.[1] [2] In the developing world, vitamin A supplementation programmes significantly reduce infant mortality as well as the incidence of xerophthalmia, respiratory infection, and morbidity from gastrointestinal disease.[3–5] Supplementing newborn infants with vitamin A within 48 hours of birth reduces infant mortality by almost a quarter, with the greatest benefit to those of low birth weight.[6] The World Bank estimates that vitamin A supplementation is one of the most cost effective health interventions available.[7] In the developed world, most infants and children are vitamin A sufficient. Term infants are well supplied with vitamin A in utero (at the expense of maternal stores), and both human milk and infant formulae contain adequate amounts of vitamin A for normal growth and health in the first six months.[8] Clinical vitamin A deficiency occurs rarely, and almost exclusively in children with malabsorptive disorders.

PRETERM BABIES

Unfortunately, vitamin A sufficiency cannot be assumed for preterm infants. This important subgroup of our infant population is born with inadequate body stores of vitamin A, is often unable to tolerate routine oral supplementation, and is prone to diseases of the eye and respiratory and gastrointestinal tracts. Preterm infants have low plasma concentrations of both retinol and retinol binding protein (RBP) at birth compared with term infants,[9–12] and this reflects low hepatic stores.[13–15] Plasma concentrations of retinol remain low during the infant's stay in the neonatal unit, and throughout the first year of life,[11] [16] [17] especially in preterm infants of multiple births.[17] [18] These issues have been recognised for over 20 years. Yet preterm infants (particularly those of extremely low birth weight (ELBW)) remain at risk of vitamin A deficiency because neither is optimal intake known nor are methods to assess vitamin A status properly defined.

UPTAKE AND METABOLISM OF VITAMIN A

The term vitamin A refers to a group of compounds, including retinol, retinaldehyde, and retinoic acid. Retinol may be obtained directly from foods of animal origin or be formed in the body from metabolism of β-carotene. Absorption of dietary retinyl esters is complex, involving hydrolysis and complexation with bile acids in the gut lumen before uptake by enterocytes[19] (fig 1). Metabolism of vitamin A within these cells and subsequent transfer into the lymphatic system depends on a specific carrier protein, cellular retinol binding protein type 2, the availability of which may be limited in the preterm infant.[20] [21] After absorption, retinol is bound to RBP in the liver and transported in plasma as the retinol-RBP complex, bound in a 1:1 ratio with transthyretin. Circulating retinol is delivered to target tissues via a specific membrane receptor and is oxidised within the cell to its active metabolite, retinoic acid. The precise mechanisms by which retinoic acid affects intracellular activity are complex and incompletely defined.[22] [23] Some 90% of the body's reserve of vitamin A is stored in the liver as retinyl esters; other sites of major vitamin A storage include the eye and the lung. In the retina, reversible oxidation of vitamin A produces a second active metabolite, retinaldehyde. Retinaldehyde is an essential constituent of the visual pigment rhodopsin, photoisomerisation of which induces a phototransduction cascade in response to light, the first stage in the process of vision.

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Abbreviations: ELBW, extremely low birth weight; ERG, electroretinogram; RBP, retinol binding protein; RDR, relative dose response; ROP, retinopathy of prematurity; VLBW, very low birth weight
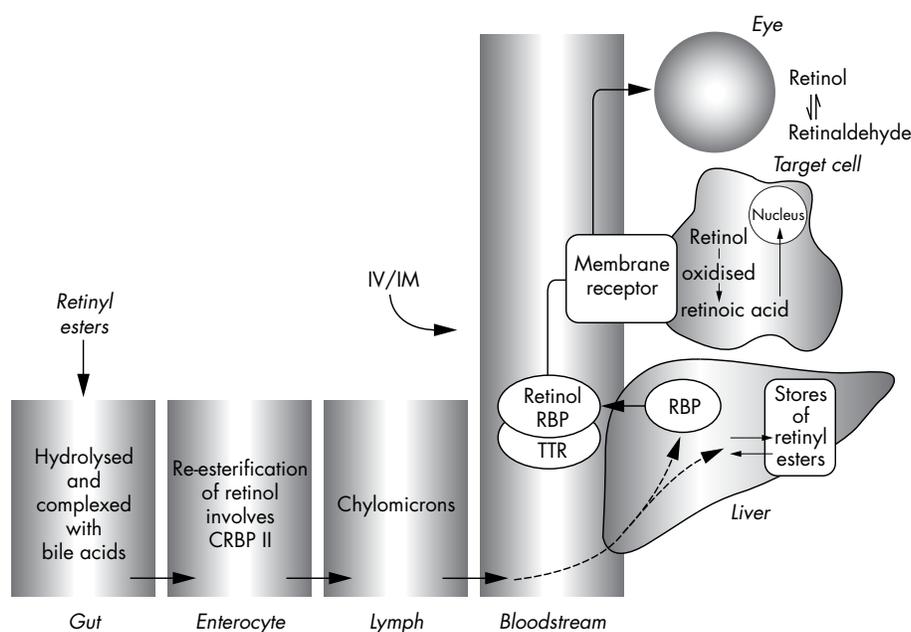
Figure 1 Uptake and metabolism of vitamin A. CRBP II, Cellular retinol binding protein type 2; IV, intravenous; IM, intramuscular; RBP, retinol binding protein; TTR, transthyretin.

BIOLOGICAL EFFECTS OF VITAMIN A IN THE PRETERM INFANT

Respiratory function

Vitamin A is required in the fetal lung for both cellular differentiation and surfactant synthesis.[23 24] In the rat, significant storage of vitamin A in the lungs occurs in the third trimester. These stores are rapidly depleted during late pregnancy and the early weeks of postnatal life as the lungs grow and develop.[25] Vitamin A and steroid hormones have similar effects on prenatal and postnatal lung development, operate through similar cell receptors, and may be inter-dependent.[23] The pathological changes of chronic lung disease are similar to those observed in vitamin A deficient experimental animals.[26–28] Plasma retinol concentrations were lower[11 29–31] and hepatic stores less[15 32 33] in preterm infants who developed bronchopulmonary dysplasia, supporting the hypothesis that vitamin A deficiency contributes to the development of chronic lung disease and/or respiratory tract infections in this population.[30 34] Observational and rando-mised studies of supplemental vitamin A produced conflicting results, attributable to a combination of factors, including small patient numbers, use of postnatal steroids, and variations in ventilatory management, baseline vitamin A status, and supplementation regimens.[35–41] Tyson *et al*[42] showed that giving intramuscular vitamin A to ELBW infants from day 2 lowers the risk of chronic lung disease at 36 corrected weeks, as well as reducing biochemical evidence of vitamin A deficiency. Thus there is a small, but significant reduction in death or oxygen dependency by 1 month of age in preterm infants supplemented with intramuscular vitamin A.[12]

Visual function

Vitamin A is necessary for the health of the anterior eye and is also an essential constituent of visual pigment (and therefore the developing photoreceptors). Deficiency in older children and adults presents as xerophthalmia, signs and symptoms of which include night blindness, corneal ulcers, and keratomalacia.[43] Microscopic conjunctival changes consistent with vitamin A deficiency have been noted in preterm babies, but the relation to vitamin A status was not explored.[44] The preterm infant retina at birth contains several times less rhodopsin than at term birth[45]; how rapidly rhodopsin is subsequently accreted, and how this is related to total body stores of vitamin A, is not known. The rhodopsin content of the developing rat retina is dependent on vitamin A sufficiency and is reduced by early exposure to light.[46 47] Dark adapted (rod photoreceptor) retinal sensitivity is dependent on retinal vitamin A sufficiency, and impaired dark adaptation is one of the earliest manifestations of vitamin A deficiency.[48–50] Rod photoreceptor sensitivity can be assessed electrophysiologically and correlates with subjective testing.[51] Retinal sensitivity, as measured by the electro-retinogram (ERG), increases dramatically between 30 and 50 postmenstrual weeks,[52 53] and preliminary data suggest that retinal sensitivity in preterm infants correlates with hepatic stores of vitamin A.[54] Dark adapted retinal sensitivity is less in ex-preterm infants at term corrected age than in newborn term infants; the reason for this is not clear[55] (fig 2).

Vitamin A and retinopathy of prematurity (ROP)

Low plasma vitamin A concentrations have been associated in some studies with the development of ROP,[11 38] and abnormal conjunctival impression cytology (reflective of poor
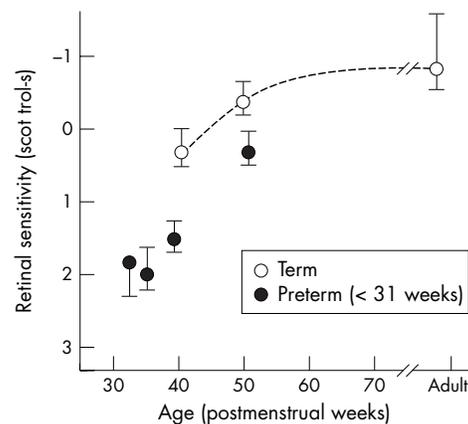

Figure 2 Increase in retinal sensitivity with age (retinal sensitivity defined as the retinal illuminance of the flash which produces a half-maximal electroretinogram).

retinol status in adults) has been associated with ROP requiring treatment.[44] Pooled data show a non-significant trend towards a reduction in ROP in vitamin A supplemented infants.[12] The pathogenesis of ROP is complex and includes free radical mediated oxidative damage to the developing retina which could in theory be ameliorated by the antioxidant properties of vitamin A.[56 57] ROP adversely affects the developing photoreceptors[58 59]; whether this is influenced by the availability of vitamin A and/or rhodopsin is unknown. The incidence of threshold ROP in a group of ELBW infants who received 10 000 IU intramuscular vitamin A three times a week was nil, compared with 16% in those who received half this dose.[60] Although this result did not achieve statistical significance, it suggests that higher doses of vitamin A than those associated with improved respiratory outcome in preterm infants may have a beneficial effect on the incidence of ROP.

Cardiovascular system
Vitamin A is required in early gestation for normal cardiopulmonary development, and postnatally it accelerates the development of oxygen induced contraction of the ductus arteriosus in the rat model.[61] In a small group of ventilator dependent preterm infants weighing 500–1500 g, intramuscular vitamin A did not affect the spontaneous closure rate of patent ductus arteriosus. The dose used was, however, less than that shown to improve respiratory outcome.[62]

Immune competence
There is some evidence that vitamin A supplementation reduces the risk of airway infection,[38] and pooled data show a non-significant trend towards reduction of culture positive nosocomial sepsis in vitamin A supplemented infants.[12]

Other effects
The incidence and severity of intraventricular haemorrhage is higher in infants born with low hepatic stores of vitamin A.[15] Postnatal vitamin A supplementation of ELBW infants was not, however, associated with a significant reduction in the incidence of intraventricular haemorrhage.[42]

PLASMA CONCENTRATIONS OF VITAMIN A IN PRETERM INFANTS
Problems in interpretation
In older human subjects and in animals, plasma concentrations of retinol are maintained at the expense of hepatic stores and reflect body stores only in states of critical depletion or excess.[43 63 64] In vitamin A deficient subjects, supplemental vitamin A may be used to produce clinical benefit without necessarily improving plasma concentrations or body stores.[40] Furthermore, the pharmacokinetics of vitamin A are likely to vary between infants, and it is not clear whether the peak or trough plasma retinol value is more important in terms of vitamin A status.[60] Plasma retinol may reflect the availability of its carrier protein, RBP, which is typically low in the preterm infant.[10 16]

What is an acceptable plasma vitamin A concentration?
Vitamin A sufficiency in older children and adults is defined as plasma concentrations in the range 0.7–2.8 µmol/l. Plasma concentrations of retinol <0.35 µmol/l (100 µg/l) are associated with reduced hepatic stores, and clinical signs of vitamin A deficiency and are considered to indicate severe deficiency.[64–66] Milder biochemical deficiency in childhood, although not manifest as xerophthalmia, is associated with increased morbidity and mortality.[43] Studies of vitamin A supplementation in the preterm infant population suggest that plasma retinol concentrations ≥0.7 µmol/l indicate vitamin A sufficiency,[38 39] but these data were confounded

by the use of postnatal steroids. Most even relatively healthy preterm infants have plasma retinol concentrations <0.7 µmol/l throughout their stay in the neonatal unit, and 20% of ELBW babies who have not received intramuscular vitamin A have plasma retinol concentrations <0.35 µmol/l at 28 days.[11 16 42 67] The significance for preterm infants, in terms of functional vitamin A status, of low plasma concentrations of vitamin A is not, however, clear.

Effects of corticosteroids
Antenatal and postnatal corticosteroids significantly increase plasma concentrations of retinol in preterm infants.[11 15 68–70] Administration of antenatal steroids may contribute to higher plasma values measured soon after birth in the most immature preterm infants (own observations).[11 16] In the rat model, the increase in serum retinol in response to steroids is at the expense of hepatic stores.[71] Hepatic and pulmonary stores of vitamin A were increased in ELBW infants who had received postnatal corticosteroids,[42] but numbers were small, and babies undergoing postmortem examination may not be representative of the population. It is likely that the beneficial pulmonary response to postnatal steroids may be mediated, at least in part, by vitamin A.[23 70]

ASSESSMENT OF VITAMIN A STATUS IN PRETERM INFANTS
Clearly therefore assessment of vitamin A status in preterm infants should include consideration of body stores as well as (or perhaps instead of) circulating concentrations of retinol.

Liver
Indirect measure of hepatic stores can be achieved in vivo by means of the relative dose response (RDR), and this test has been successfully applied to preterm infants.[15 32 33 72] Hepatocytes deficient in vitamin A rapidly take it up from the circulation after an oral or intramuscular dose, and secrete it as retinol complexed to RBP.[73] Measurement of either retinol or RBP can be used to calculate the RDR. The RDR is the percentage difference between the predose plasma retinol or RBP concentration and the plasma concentration five hours after the dose. The test distinguishes between low plasma retinol concentrations due to vitamin A deficiency (high RDR) and low plasma retinol concentrations due to other factors (low RDR). In healthy preterm infants ready for discharge, the RDR correlates with the predose retinol concentration, suggesting that low plasma retinol concentrations in these preterm infants reflect reduced hepatic stores of vitamin A.[32 72] Even when the plasma retinol concentration has been increased by intramuscular supplementation, the RDR may indicate reduced hepatic stores.[32]

Eye
Ocular stores of vitamin A influence both dark adapted retinal function and the health of the corneal epithelium. ERG provides objective assessment of retinal function and can be applied to preterm infants from 31 weeks after conception.[52–55 74] Changes in the dark adapted ERG are present in adults and children with vitamin A deficiency and may be a more accurate reflection of vitamin A status than plasma retinol.[75 76] Except in the most severe cases, ERG changes can be reversed with vitamin A supplementation.[76 77] In animal studies, both the dark adapted ERG threshold and the amplitude of the ERG reflect retinal vitamin A status.[63 78] Reduced retinal sensitivity in preterm infants at term corrected age may reflect vitamin A deficiency, although other confounding effects of preterm birth on the developing retina have not been studied in detail. The long term consequences, if any, are unknown. Conjunctival impression cytology has been used to assess vitamin A status in adults[79] and can be easily incorporated into ROP screening[44]; its

relation to vitamin A status in the preterm infant has, however, not yet been fully explored.

Lungs

Pulmonary stores of vitamin A in preterm infants cannot, of course, be measured in vivo, and postmortem data may not reflect the situation in life. The preterm human infant's lungs may be deficient in vitamin A at birth, but whether this can be modified by supplementation of either mother or newborn infant is unknown. We do not know how lung concentrations of vitamin A relate (if at all) to either plasma retinol or RDR. Intramuscular supplementation did not significantly increase pulmonary stores of vitamin A in a small group of ELBW infants.[42] Animal and adult human studies have shown increased vitamin A consumption and depletion of hepatic stores in inflammatory disease of the lungs.[80 81] Currently unanswerable questions include whether low pulmonary stores of vitamin A reflect deficiency or increased use, and whether use of vitamin A in the developing lungs of the preterm infant is limited only by supply.

VITAMIN A SUPPLEMENTATION

Vitamin A can be given enterally, intramuscularly, or intravenously. In term infants, vitamin A is well absorbed enterally (except in malabsorptive states), and supplemental vitamin A is given enterally to infants and children of all ages. In very low birth weight (VLBW) infants, vitamin A given orally in conjunction with early feeds can achieve comparable plasma concentrations of retinol to vitamin A given intramuscularly if sufficiently generous oral doses are given.[82] In ELBW infants, however, even very large enteral doses of vitamin A from birth do not significantly increase plasma concentrations of vitamin A or improve outcome.[83 84] Given that these are the very infants most likely to benefit from additional vitamin A, they must be supplemented by a parenteral route, at least in the early days of life.

Intravenous administration of vitamin A is problematic. Vitamin A degrades in light, and there is significant adsorption to the tubing.[85] Mixing vitamin A with lipid emulsion before infusion increases efficacy of delivery,[86] and this is the recommended method of intravenous administration. The practice of delivering a multivitamin preparation in an amino acid/dextrose mix, as still occurs commonly outwith the United Kingdom, is strongly to be discouraged. In the United Kingdom, supplementary vitamin A is generally given as Vitlipid N (Fresenius Kabi Ltd, Runcorn, Cheshire, UK), at a recommended dose of 4 ml/kg/day. This provides 910 IU/kg/day (280 µg/kg/day) vitamin A in addition to vitamins D, E, and K, equivalent to the approximate daily retinol intake of a term, breast fed infant of a well nourished mother during the first week of life.[87] Although this dose increased the mean plasma retinol in seven VLBW infants, the plasma retinol concentration was not consistently maintained above 0.7 µmol/l.[88] The American Society for Clinical Nutrition subsequently recommended 910 IU/kg/day as the minimum dose suitable for preterm infants, and suggested evaluation of a higher dose.[89] Increasing the vitamin A content of intravenous fat emulsion by two to threefold (total vitamin A intake 2700 IU/day) increased mean plasma retinol in a group of VLBW infants, although no difference in clinical outcome was noted.[90] Infants were not all at significant risk of bronchopulmonary dysplasia, however, and numbers were small. Pilot data from our unit suggest that the currently recommended intravenous dose of supplemental vitamin A does not improve plasma concentrations of vitamin A in VLBW infants.[67]

The optimal intramuscular dose is similarly unclear. To increase serum retinol concentrations, the minimum effective dose in ELBW infants is of the order of 5000 IU three times a week.[84] This regimen improves respiratory outcome in ELBW infants, but considerable numbers of treated infants still have borderline plasma retinol concentrations and biochemical evidence of low hepatic stores.[42] Doubling this dose did not significantly increase mean plasma retinol in ELBW infants nor improve hepatic stores; there was, however, a wide range of plasma retinol concentrations within the treatment groups.[60] Intramuscular administration is painful, and the justification of giving 12 injections to every ELBW infant for modest improvement in short term respiratory outcome has been questioned.[91] Despite evidence of benefit, intramuscular supplementation of vitamin A is not widely practised, even in the United States.[92] Intramuscular injections once a week are associated with worse biochemical vitamin A status than the same dose of vitamin A in divided doses three times a week.[60] For the smallest, sickest infants, parenteral administration of vitamin A is more efficacious than enteral administration, but it is not clear how intravenous administration of vitamin A in lipid emulsion compares with intramuscular administration. No published study to date has directly compared intramuscular with intravenous administration of vitamin A in VLBW infants, in terms of morbidity, mortality, or vitamin A status.

Most neonatal units administer oral vitamin supplements to preterm infants once enteral feeding has been established, but doses vary and are not generally adjusted in favour of the smallest, most immature infants. Many neonatologists will not be aware that the vitamin A content of ABIDEC (Pfizer Ltd, Walton Oaks, UK) has been reduced by two thirds so that the recommended dose of 0.3 ml daily provides only 666 IU retinol. A further 550 IU retinol is provided by 180 ml low birthweight infant formula (Wyeth Pharmaceuticals, Maidenhead, UK). Oral supplementation of 4000 IU/kg/day has been recommended for VLBW infants from establishment of full enteral feeding until discharge from the neonatal unit,[93] and the Canadian government has recently approved increased vitamin A in preterm formulae, up to 1420 IU per 100 kcal (equivalent to about 2100 IU per 180 ml).[94]

Inhalation of vitamin A in aerosol improved biochemical vitamin A status in a small group of preschool children in Ethiopia.[95] This novel method of administration has not yet been explored in infants.

VITAMIN A TOXICITY

Concerns about the potential toxicity of vitamin A have led to caution in the doses administered to preterm infants, but appear to be largely unfounded. There is no published evidence to suggest that parenteral supplemental vitamin A in preterm infants in doses of up to 8500 IU/kg/day is associated with significant side effects.[41 42 60] Neonatal vitamin A supplementation of larger infants is not associated with any adverse developmental sequelae, even when associated with bulging fontanelle.[96 97]

CONCLUSIONS

More than 20 years after it was first recognised that preterm infants may be functionally deficient in vitamin A, we still do not know how much to give, or by which route. There are considerable differences in clinical practice between North America and the United Kingdom. The smallest and sickest infants in our care are at highest risk of suffering from the sequelae of vitamin A deficiency, and it is increasingly clear that they should receive parenteral supplemental vitamin A within the first few days of life, and probably from day 1. Once enteral feeding is established, oral supplementation is preferred, but currently administered doses may be inadequate for VLBW preterm infants. To define optimal intake and mode of delivery of vitamin A, we need good quality research which includes quantification of hepatic stores as

well as assessment of retinal function and long term clinical outcome. Measuring plasma concentrations of retinol is not sufficient to assess vitamin A status properly in preterm infants. There is an urgent need for a comparison of the efficacy of intramuscular and intravenous administration and a review of the current practice of intravenous supplementation. Vitamin A supplementation of term born infants in developing countries has proved to be enormously beneficial and cost effective. The time has come to ensure that the most vulnerable infants in our own society are also given appropriate amounts of this essential micronutrient during the critical early weeks of life.

ACKNOWLEDGEMENTS

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Competing interests: none declared

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