

## Vitamin A and Related Compounds in the Prenatal and Postnatal States: A Maternal-Neonate Focused Review

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### Abstract

**Background:** It is generally accepted that vitamin A is critical to fetal and infant development. However, vitamin A has many related compounds, including lutein, carotenes, and lycopene, and recent evidence has shown they may also be important in maternal-infant health. Much less is known about the impact of vitamin A related compounds on maternal and newborn outcomes.

**Methods:** The following article presents a review of maternal vitamin A and related compounds on the fetus and newborn, particularly in the brain and retina. Dietary intake and supplementation will be examined in their relationship to breast milk and formula levels of vitamin A and related compounds. Finally, deficiencies in developed and developing countries are discussed.

**Results:** Vitamin A related compounds, such as lycopene, carotenes, and lutein, may impact maternal-infant outcomes independent of retinol status. High-risk groups, including preterm infants, have been shown to be particularly susceptible. Studies also show that vitamin A deficiency remains a problem in developing nations and may be a concern in disadvantaged populations in developed nations.

**Conclusion:** This review indicates a need to better understand the influence of maternal vitamin A and related compounds in order to improve interventions to maintain homeostatic levels in mothers and neonates.

**Keywords:** Vitamin A; Carotenes; Lutein; Diet; Infancy; Pregnancy

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### Introduction

It is generally accepted that vitamin A is important for fetal and neonatal development and is essential for tissue growth and development, reproduction, immune health, and vision [1]. Vitamin A adequacy in the fetus and newborn is largely dependent upon the mother via placental transfer, or post-partum via breast milk or formula. Maternal vitamin A status is then particularly relevant to fetal development and newborn outcomes. However, Vitamin A Deficiency (VAD) remains a significant public health concern; worldwide, VAD is estimated to affect 19 pregnant women and 190 million preschool children [2].

Vitamin A related compounds, particularly lycopene and lutein, may have important biological properties in newborn and unique roles in eye and brain development that are independent of retinol status. Other biologically significant carotenoids include

$\alpha$ -carotene,  $\beta$ -carotene, and  $\beta$ -cryptoxanthin, all of which have pro-vitamin A activity. All of these compounds are also potent anti-oxidants, which may be relevant in newborn infants, especially premature infants, who are at high risk for adverse events related to oxidative stress. However, very little is known about the role of these compounds in maternal and infant outcomes.

Vitamin A comprises a family of molecules containing a 20 carbon structure with a methyl substituted cyclohexenyl ring and a tetraene side chain with a hydroxyl group (retinol), aldehyde group (retinal), carboxylic acid group (retinoic acid), or ester group (retinyl ester) [1]. The term retinoids refers to retinol, its metabolites, and synthetic analogues that have similar structure [1]. Recent biochemical evidence suggests that cellular uptake of vitamin A from the retinol binding protein is facilitated by a membrane receptor. This receptor, identified as the Stimulated

by Retinoic Acid Gene 6 (STRA6) gene product, is highly expressed in epithelia that constitute blood– tissue barriers, including eye and brain [3,4].

Vitamin A related compounds include carotenes,  $\beta$ -cryptoxanthin, lycopenes, and lutein. Fifteen to 30 naturally occurring carotenoids have been found in serum and breast milk, the most abundant being lutein, lycopene, and  $\beta$ -carotene [5]. These vitamin A related compounds are thought to have a variety of different actions, including antioxidant activity, immune-enhancement, inhibition of mutagenesis and transformation, inhibition of premalignant lesions, quenching of non-photochemical fluorescence, and activity as pigment in the primate macula [6].

## Vitamin A in the Neonate

Deficiency of vitamin A is related to significant morbidity and mortality from common childhood infections, as well as being the world's leading preventable cause of childhood blindness. In children 6-71 months of age, low serum retinol is defined as 0.70  $\mu\text{mol/l}$  (200  $\mu\text{g/L}$ ) or below, which is used to identify children with both clinical and sub-clinical VAD status. VAD has also been shown to increase susceptibility to infection, due to impaired humoral and cellular immunity. All-trans-retinoic acid and 9-cis-retinoic acid are the two most important forms of vitamin A in immune system function, regulating the development, differentiation, and apoptosis of immune cells to shape innate and adaptive immunity [7]. Retinoic acid functions to maintain the structure of keratinocytes in the skin, modulate lactoferrin expression, and regenerate mucosal barriers broken down by infection. Thus, VAD causes deficiencies in both the humoral and cell-mediated immunity [8]. VAD can also cause impairment in the function of lymphocytes, natural killer cells, and neutrophils, as well as decrease cell proliferation in antibody production [9]. Cumulatively, VAD can increase the risk of infection, duration of disease, and child mortality [8], and indeed, VAD in children is shown to be strongly associated with depressed immune function and higher morbidity and mortality due to infectious diseases such as respiratory infections and diarrhea [10].

Carotenes have shown the potential to have important roles in the developing eye. A study conducted by Rubin et al. indicates that carotenoids may be important for fetal development of the retina and macula, a 5-6 mm diameter region in the posterior pole of the retina [11]. This study compared plasma carotenoid levels and retinal health in preterm infants fed diets with and without added lutein, lycopene, and  $\beta$ -carotene. They found that plasma carotene levels were higher in the supplemented group, and this group also had lower inflammatory biomarkers and greater rod photoreceptor sensitivity [11]. Lutein and its isomer zeaxanthin deposit at high levels selectively in the retinal fovea, the central region of the macula. This is believed to occur within the final months of gestation, and is highly influenced by maternal carotenoid levels, especially zeaxanthin [12]. The fovea contains the highest concentration of carotenoids (lutein and zeaxanthin) in the body, which could indicate an important role in vision [13]. These compounds also appear to play a role in cognitive function as well in this population, based on a finding

that macular pigment optical density is positively correlated with cognitive function [14].

In regards to brain development, vitamin A related compounds may also play a significant role. In a unique study using cadaveric brain samples, Vishwanathan et al demonstrated that lutein was the predominant carotenoid in the infant brain, specifically in the frontal cortex, hippocampus, auditory cortex, and occipital cortex, during the first year of life [15]. Another study conducted by Wang et al. indicates that lutein directs differentiation of cultured human stem cells into neural progenitor cells [16]. Preterm infants have lower carotenoid levels compared to full term infants, which indicates that the deposition of carotenoids in neural tissues occurs in the later months of gestation [15]. This implies that adequate levels of maternal carotenoids may be critical to neurodevelopment. These findings correlate with macular pigment detection of infants, which was not detectable in the retina of preterm infants but was present in term infants [17,18]. These findings were accompanied by significantly low concentrations of serum and skin carotenoids [18]. Lutein and zeaxanthin also appear to affect neural functioning, as macular pigment density is positively correlated to neural visual processing function [19].

## Vitamin A Compounds and Infant Feeding

Prior to 6 months of age, breast milk or formula is the only source of vitamin A for infants [20]. Human milk contains preformed vitamin A, mainly in the form of retinyl palmitate and retinyl stearate. Vitamin A is delivered by chylomicrons from the intestine to breast milk in the form of retinyl esters. Because this process is not highly regulated, it is believed that breast milk levels of vitamin A can shed some light on the maternal status of vitamin A. Women in developing nations with nutrient-poor diets have low breast-milk vitamin A concentrations (i.e., 1  $\mu\text{mol/L}$ ), versus women in industrialized nations who have nutrient-rich diets or take vitamin A supplements (i.e., 2  $\mu\text{mol/L}$ ).

Carotenes and lutein in human breast milk occur in levels that are proportional to the maternal intake of these carotenoids [21,22], however these levels are impacted by other maternal lifestyle factors. Alcohol intake, obesity and smoking are factors secondary to diet that affect carotenoid levels in breast milk [23,24]. Due to these factors, carotenoid intake for infants on breast milk is variable, which may manifest as highly variable macular pigment density in the infant retina [25].

For infants that are not breastfed, their only source of vitamin A comes from infant formulas. Vitamin A levels in formula are highly regulated to maintain levels that are effective enough for infant development, without producing vitamin A toxicity. Currently, the Expert Panel recommends a minimum preformed vitamin A level in infant formulas of 200 IU/100 kcal (60  $\mu\text{g RE}/100$  kcal), which is double the recommendation for healthy breast-fed infants, who have a recommended concentration of 100 IU/100 kcal in human milk. This increased level is to account for the potential increased bioavailability of vitamin A esterase in human

milk, due to the presence of bile-salt-stimulated lipase. The maximum vitamin A content in infant formulas is 500 IU/100 kcal (150 µg/100 kcal) [26]. Infant formula is fortified with vitamin A in the form of retinyl acetate or retinyl palmitate, which are both more stable due to their decreased susceptibility to oxidation [27]. The expert panel of the Life Sciences Research Office (LSRO) of the American Society for Nutritional Sciences recommended maximum vitamin A content in infant formulas of 500 IU/100 kcal [26]. Once infant formulas are opened, the exposure to light and oxidation will cause vitamin A loss over time. This is accounted for with over-fortification of vitamin A to ensure that the labeling reflects actual vitamin A content. After 70 days of storage after opening, adequacy levels ranged from 100% to 106% [28]. Over-fortification of vitamin A is regulated due to possible toxicity. A study conducted by Delgado-Zamarreno et al. studied four different infant formulas, and retinol acetate levels ranged from 0.59-0.74 mg RE/100 g, which corresponds to an adequacy level between 113% and 120% [29].

The majority of infant formula contains only trace amounts of lutein and zeaxanthin [21]. A study conducted by Johnson et al. indicates that at birth, breastfed infants and formula-fed infants had the same levels of plasma lutein and zeaxanthin at birth. After 1 month, lutein and zeaxanthin plasma carotenoid levels increased significantly for breastfed infants, and decreased for formula fed infants [30]. Infants on lutein-supplemented formula have been shown to exhibit better photoreceptor sensitivity and decreased retinopathy compared with controls [11].

Infant foods typically consumed in the first year of life, such as apples, pears, carrots, sweet potatoes, and peas, are not high in lutein [15]. A National Health and Nutrition Examination Survey III from 1988–1994 indicates that lutein constitutes 12% of total carotenoids consumed in the United States' infant's diet during the first year of life, and β-carotene and lycopene together constitute roughly 70%. However, lutein constitutes 59% of total carotenoids in the infant brain. β-carotene and lycopene constitute 20% of total carotenoids in the brain, indicating the preferential uptake and/or conservation of lutein from ages 0-1 [15]. Even in full term infants consuming formula that was not supplemented with lutein, it was still the predominant carotenoid in the infant brain, indicating that term infant brains are able to maintain measurable levels of lutein despite limited intake.

Vitamin A supplementation during pregnancy has been utilized to improve maternal vitamin A levels for proper fetal growth, with beneficial outcomes on physical development. In chronically undernourished populations, vitamin A supplementation during pregnancy has been associated with decrease hearing loss due to ear infections in the offspring [31] and improved growth outcomes [32]. Supplementation of vitamin A during pregnancy in an undernourished population in Nepal has also been associated with improved offspring lung function [33], however; it did not decrease risk of asthma [34]. Supplementation of newborns with vitamin A in Bangladesh improved infant survival [35], however other studies have shown no effect of vitamin A supplementation on infant or maternal survival [36,37]. A 2016 birth cohort study was conducted to assess the effects of vitamin supplementation

during pregnancy on child behavior. Over 1,000 (n=1,271) pairs of Japanese women and their newborns were followed from pregnancy to 3 years of age. The results of this study indicated that supplemental vitamin A or β-carotene prior to and/or during pregnancy can lead to behavioral problems in the child at age 3 (p=0.003), as assessed with a Child Behavior Checklist. This statistically significant difference held true even when variables such as age, number of deliveries, infertility treatment, diet, smoking status, maternal and paternal education levels and income, gestational age, weight, height, head circumference, and body circumference [38]. The exact percentage of people taking vitamin A supplements in Japan was unknown, but it is estimated that 25% took supplements containing vitamin A, and that 5% took supplements containing vitamin A only. In the United States, it has estimated that greater than 75% of the population may take more than the recommended dietary level of vitamin A [39]. There was, however; no evidence that these levels of intake resulted in toxicity, and they were below the lowest level of intake at which adverse effects have been reported [39]. A 2012 systemic review conducted by Marik and Flemmer indicates that neonatal benefits derived from vitamin A supplementation, such as improvements in tissue development and growth may only occur in a nutrient-poor population [40].

## Vitamin A Status of Maternal–Offspring Populations

Despite its importance in child development, VAD persists as a problem both for developed and developing countries. According to current estimates, 88 countries are classified as having a problem of moderate to severe public health significance with respect to biochemical VAD in pregnant women. Current estimates from the WHO indicate that approximately 190 million preschool children and 19 million pregnant women have this deficiency. Of these, 7 million children suffer from xerophthalmia, and 9-10 million women suffer from night blindness during pregnancy [2].

In India, the prevalence of subclinical VAD is considered high, ranging from 31% to 57% among preschool children [41]. A study conducted by Agarwal et al. reports that all infants are born with low vitamin A levels, including those born to well-nourished mothers with high vitamin A stores [41]. The reported proportion of infants with serum retinol below 0.7 µmol/L (200 µg/L) ranges from 0-89% in developing countries, compared to 0-29% in industrialized countries [41]. The higher deficiency in retinol is likely attributed to higher rates of preterm deliveries and low birth weight babies, both of which are high risk groups for VAD. However, a study conducted by Belvady on Indian infants indicates that even those fed by mothers with VAD whose breast milk contains as little as 120 ± 15 µg RE/day grow normally and have no clinical signs of VAD [42].

A recent study conducted at a public maternity hospital in Recife, Brazil, examined the serum retinol concentrations of 65 consecutive mother-newborn pairs at delivery from January to August 2008. Results showed that low (0.7 µmol/L, 200 µg/L) and inadequate (<1.05 µmol/L, 300 µg/L) serum concentrations were observed in 23.1% of newborns and 23.0% of mothers. Serum

retinol distribution was 0.04  $\mu\text{mol/L}$  lower in males ( $p=0.01$ ) than in females. Concentrations in mother-newborn serum retinol levels were correlated ( $r=0.27$ ,  $p=0.04$ ), but interestingly, maternal vitamin A status accounted for only 7% of the variance in retinol concentration in her newborn's cord plasma [43]. VAD prevalence is generally lower for Latin America, though it remains problematic in areas like Northeastern Brazil where it is associated with other medical conditions such as protein-energy malnutrition and anemia [43].

Industrialized countries such as the United States are often assumed to be vitamin A sufficient, based on gross domestic product. However, recently concerns have been raised about the diet quality of susceptible populations. A study using data from the 2003-2008 National Health and Nutrition Examination Survey (NHANES), which is considered a representative sample of the United States population, demonstrated that women of childbearing age in the United States are not consuming adequate amounts of vitamin A [44]. This is especially true for women in minority ethnic groups, as well as women of lower socioeconomic status [44]. In general, lower income individuals have less access to high quality, vitamin A-rich foods such as fruits and vegetables, as measured by the Alternate Healthy Eating Index, which is a summary score of 11 components that measures diet quality. Obtaining a nutrient rich diet is restricted by a myriad of factors, including lack of access to grocery stores and the higher costs associated with fresh produce. In addition to income, racial and ethnic minorities are also more likely to face these challenges, and as a result, have poorer nutrient intake and diet than whites [45]. Socioeconomic background and race has been shown to correlate with an increased risk of vitamin A deficiency in women of childbearing age. A study by Hanson et al. assessed serum

retinol concentrations from women 14-45 years of age ( $n=3170$ ) from the 2003-2006 National Health and Nutrition Examination Survey (NHANES). Results indicate that poverty score and race were significantly correlated with vitamin A status after adjusting for confounding variables like inflammation, estrogen use, and smoking status. Retinol concentrations of  $<1.05 \mu\text{mol/L}$  ( $300 \mu\text{g/L}$ ) were 1.85 times higher for those of lower socioeconomic status when compared to women of higher status. Non-Hispanic black and Mexican American females are more likely than non-Hispanic white females to have low serum retinol concentrations. Dietary vitamin A and lutein intake was statistically significantly lower in groups with higher poverty scores ( $p=0.004$ ); women of lower socioeconomic status took in an average of 93.9 less Retinal Activity Equivalents when compared with women of higher status [46].

## Conclusion

Vitamin A and related compounds impact maternal-child outcomes, and the effects of compounds such as lycopene, lutein, and carotenes may be independent of retinol. As these compounds are modifiable by maternal diet, more research into the impact of vitamin A and related compounds could have a beneficial impact on maternal and infant health.

## Author Contributions

ARW, AAB, and CH conceived and designed the concepts and wrote the paper.

## Conflicts of Interest

None of the authors have any conflicts of interest to disclose.



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