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Review Article (Pages: 1339-1354)

Effects of Vitamin A in Neonates and Young Infants

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Abstract

Vitamin A is the generic name given to a group of fat-soluble compounds including retinol (the alcohol form), retinyl esters, retinaldehyde and retinol acid. Deficiency, first recognized in 1912, can damage the epithelial cells lining the respiratory tract. It can also affect immunocompetence, the reproductive function, growth and vision. The dose of vitamin A for neonates is 5,000 IU given intramuscularly 3 times weekly for 4 weeks. Retinol concentrations < 0.70 µmol/l in serum and <1.05 µmol/l in milk are indicative of vitamin A deficiency.

The supplementation of vitamin A to pregnant women with deficiency of vitamin A has protective effects against neonatal morbidity and mortality and has a positive impact on maternal vitamin A status. High cord vitamin A levels increase placenta weight and birth weight and length of the newborn. Vitamin A has been considered a therapeutic alternative in the reduction of the rate of bronchopulmonary dysplasia. The kidneys are target organs for vitamin A action. The vitamin A status of the mother profoundly affects the kidney organogenesis of the newborn. Retinoic acid regulates nephron mass. Intramuscular vitamin A (10,000 IU) 3 times weekly improves retinal sensitivity in preterm neonates. Vitamin A increases the neonatal body size. A dose of ≤10,000 IU vitamin A is not teratogenic.

Key Words: Effects, Infants, Neonate, Vitamin A.

*Please cite this article as: Maria Pacifici G. Effects of Vitamin A in Neonates and Young Infants. Int J Pediatr 2016; 4(2): 1339-54.

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Received date Dec 22, 2015 ; Accepted date: Jan 22, 2016

1-INTRODUCTION

Vitamin A deficiency remains common in developing countries where it contributes significantly to mortality and morbidity in both mothers and infants. By contrast, in more affluent countries, vitamin A deficiency is uncommon and almost exclusively confined to older subjects with significant malabsorption. One exception to this is the preterm neonate; they are born with low stores of vitamin A and are usually given insufficient amounts to meet their ongoing needs (1).

Vitamin A is used to reduce the risk of chronic lung disease in high risk premature neonates with vitamin A deficiency. Vitamin A is necessary for normal lung growth and the ongoing integrity of respiratory tract epithelial cells. Preterm infants have low vitamin A status at birth and this has been associated with increased risk of developing chronic lung disease. Supplementing very-low-birth weight with vitamin A is associated with a reduction in oxygen requirement among survivors at 36 weeks post-menstrual age (2).

Dietary deficiency of fat-soluble vitamin A results in squamous metaplasia of the tracheal and bronchial epithelium. Infants with vitamin A deficiency have a high incidence of respiratory problems. Levels of two intracellular proteins binding specifically retinol (vitamin A alcohol) and retinoic acid (vitamin A acid) change dramatically during perinatal lung development. Prematurely born infants hospitalized for respiratory problems have low serum concentrations of retinol and retinol-binding protein. Postnatal supply of vitamin A by parenteral alimentation may not be adequate, as large quantities of vitamin A are absorbed by the tubing. Careful assessment of vitamin A status in postnatal nutrition management of premature infants is desirable (3). The pulmonary histopathologic changes of bronchopulmonary dysplasia and vitamin A deficiency are remarkably similar. Retinol metabolites exhibit potent and site-specific effects on gene expression and on lung growth and development. Retinol is supplied in the diet as retinyl esters (4).

Vitamin A acts on the kidneys and the status of vitamin A in the mother affects the kidney organogenesis of the neonate. Infants born to mothers with vitamin A deficiency have significantly lower mean size of the kidneys. The maternal serum retinol concentrations are positively correlated with the cord retinol concentrations and newborns born to mothers with retinol deficiency have lower kidney size. Also, vitamin A increases the body weight of term infants (5, 6).

Of concern, is the fact that a significant proportion of pregnant women fails to achieve the recommended vitamin A intakes in a number of undeveloped countries where it contributes significantly to mortality and morbidity in both mothers and infants. Postpartum vitamin A supplementation is used to combat vitamin A deficiency and the World Health Organization (WHO) recommends a dose of vitamin A of 200,000 IU to mothers and the supplement of vitamin A will have a protective effect against infant mortality (7). Hypovitaminosis A is a candidate risk for infant bronchopulmonary dysplasia, low kidney size and reduced neonatal retinal sensitivity. Vitamin A is responsible for formation of the retina's photosensitive visual pigment.

Green vegetables, carrots, tomatoes, fruit and eggs provide vitamin A. Deficiency of vitamin A is rare in developed countries, but in developing countries, it is still a common cause of blindness due to xerophthalmia: it increases the mortality associated with pregnancy and with measles in the first 2 years of life. A 50,000 IU dose of vitamin A at birth by mouth reduces infant mortality. Vitamin A is toxic in excess and also teratogenic, and women planning to become pregnant

should avoid an intake of vitamin A in excess of 8,000 IU per day. Toxicity might also develop in a breastfed neonate whose mother had taken an excess of tretinoin (TT) and isotretinoin (ITT) (1).

Human breast milk contains 100-250 IU of vitamin A per 100 ml, and the term infants require no further supplementation whether artificially or breastfed. However, the fetal liver only accumulates vitamin A in the last trimester of pregnancy, and plasma levels are low in the newborn preterm neonates. Additional supplementation has been widely recommended for very preterm infant. Those who are receiving intravenous nutrition are often given a 900 IU/kg daily supplement with their Intralipid. A plasma retinol concentration of <0.35 mmol/l in a preterm infant almost certainly indicates depletion of hepatic stores. Most orally fed preterm infants are supplemented (1).

Nutrition vitamin A deficiency causes a progressive disease characterized by nyctalopia (night blindness), xerosis (dryness), and keratomalacia (corneal thinning), which may lead to corneal perforation. However, rapid, irreversible blindness ensues once the cornea perforates. Vitamin A also is involved in epithelial differentiation and may have some role in corneal epithelial wound healing (8). The aim of this study is to review the effects of vitamin A in neonates.

2- MATERIALS AND METHODS

2-1. Literature Search

The following databases were searched for relevant papers and reports: MEDLINE, CINAHL, Embase, Google scholar and PubMed as search engines; December 2015 were the cutoff point. Key references from extracted papers were also hand-searched.

2-2. Search Terms

Combinations of search terms from three categories ("Neonetes" keyword AND "Vitamin A" keyword AND "Effects" keyword AND "Infants" keyword) were used to search for the relevant literature. In addition, the books Neonatal Formulary (1) and NEOFAX by Young and Mangum (4) were consulted.

3-RESULTS

3-1. Monitoring

Assess regulatory for signs of toxicity: full fontanel, lethargy, irritability, hepatomegaly, edema, mucocutaneous lesions, and bony tenderness. Consider measuring plasma retinol concentration, especially if patients are also receiving glucocorticoid therapy. Desired concentrations are approximately 30 to 60 µg/dl. Concentrations <20 µg/dl indicate deficiency, while those >100 µg/dl are potentially toxic (4).

3-2. Dose and administration of vitamin A to neonates

For parental treatment of vitamin A to neonates give 5,000 IU intramuscularly 3 times weekly for 4 weeks. Vitamin A should not been administered intravenously to neonates (4).

3-3. Effects of vitamin A supplementation on infants and their mothers

Rotondi and Khobzi (7) assessed the relationship between the prevalence of vitamin A deficiency among pregnant women and the effect of neonatal vitamin A supplementation on infant mortality. Meta-regression analysis revealed a statistical linear relationship between the prevalence of vitamin A deficiency in pregnant women and the observed effectiveness of vitamin A supplementation at birth. In regions where at least 22% of pregnant women have vitamin A deficiency, giving neonates vitamin A supplements will have a

protective effect against infant death. These authors suggest that vitamin A supplementation can reduce infant mortality in regions where this micronutrient deficiency is common. Thus, neonatal supplementation programs may prove most beneficial in regions where the prevalence of vitamin A deficiency among pregnant women is high.

Martins et al. (9) assessed the impact of maternal vitamin A supplementation on the mother-infant pair. In a double blind, placebo-controlled study 33 women received 200,000 IU of vitamin A and 33 women received soy oil between 20th and 30th postpartum days. Maternal blood and milk samples were collected immediately before supplementation and 3 months after delivery, when blood was also collected from the infants. Retinol concentrations <0.70 µmol/l in serum and <1.05 µmol/l in milk were considered to indicate vitamin A deficiency. An increase in the serum retinol level was observed in the supplemented group compared to the pre-supplementation levels (1.05 and 1.17 µmol/l, respectively; P=0.026) and to the post-supplementation levels of the control group (1.02 µmol/l; P=0.032). Reduction in breast milk retinol was observed in the control group compared to the pre-supplementation levels (1.93 and 1.34 µmol/l, respectively; P=0.0001) and to the post-supplementation levels of the supplemented group (1.56 µmol/l; P=0.0003). There was a significant difference in the prevalence of vitamin A deficiency in breast milk after supplementation, 55.6% (15/27) in the control group and 16.1% (5/31) in the supplemented group (P=0.002). Vitamin A deficiency was present in 66.1% (39/59) of infants, with mean serum retinol levels of 0.64±0.30 µmol/l in the control group and 0.69±0.26 µmol/l in the supplemented group. Supplementation had a positive impact on maternal vitamin A status. No effect on infant status was detectable 2 months after supplementation with a single dose. Agarwal et al. (10) determined the relationship of various maternal and neonatal factors with serum vitamin A concentration in 100 matched mother-newborn pairs. Maternal serum vitamin A levels were not significantly affected by maternal age parity, hemoglobin level and presence of toxemia. Higher trends of maternal vitamin A concentrations (not significant) and statistically higher values of cord serum vitamin A levels (P<0.05) were seen in mothers who had received antenatal care. Significantly higher cord vitamin A levels were seen with increasing weight of the placenta, birth weight of the newborn as well as its gestational age and maturity. Weak but significant positive correlation was present between maternal and cord serum vitamin A levels. The present results show that prematurity and intrauterine growth retardation are associated with low neonatal vitamin A deficiency.

Ambalavanan et al. (11) hypothesized that compared with the standard regimen of 5,000 IU vitamin A, 3 times per week for 4 weeks, a higher dose (10,000 IU 3 per week) would increase serum retinol and retinol binding protein and lower relative dose responses, and once-per-week dosing 15,000 IU would lead to equivalent levels of retinol binding protein, and relative dose response. Extremely low-birth-weight neonates (n=120, median gestational age was 25 weeks, and median birth weight was 689 grams) receiving O2, mechanical ventilation at 24 hours were randomly assigned to standard dose, higher dose, or once-per-week regimen. Possible toxicity was seen in <5%. The higher dose regimen did not increase retinol or retinol binding protein, decrease relative dose response, or improve outcomes. Infants in the once-per-week regimen had lower retinol levels and higher relative dose response without an effect on outcomes. Compared with the standard regimen, once-per-week dosing

worsened, and higher doses did not reduce vitamin A deficiency. Therefore, the standard regimen is recommended.

Postpartum vitamin A supplementation is used to combat vitamin A deficiency and seems to reduce maternal/infant morbidity and mortality. The World Health Organization protocol recommends a dose of 200,000 IU of vitamin A (1). This dose does not seem to provide adequate retinol levels in maternal breast milk, infant serum, and infant tissue. Fernandes et al. (12) compared the effect of postpartum maternal supplementation with 400,000 IU (International Vitamin A Consultative Group protocol) with 200,000 IU of vitamin A on infant morbidity. There were 276 mother-child pairs that were allocated to 2 treatment groups: 400,000 IU or 200,000 IU of vitamin A. They were followed up for >6 months to evaluate infant morbidity. Fever, diarrhea, otitis, acute respiratory infection, the need for intravenous rehydration, and use of antibiotic treatment did not differ significantly between the 2 treatment groups. These findings suggest that postpartum maternal supplementation with 400,000 IU of vitamin A does not provide any additional benefits in the reduction of illness in children aged <6 months. Therefore, these authors do not support the proposal to increase the standard vitamin A dose in the existing the World Health Organization protocol.

Semba et al. (13) conducted a prospective cohort study of 377 HIV-negative women and their infants in Blantyre, Malawi. Serum vitamin A levels were measured during the second or third trimester of pregnancy and infants were followed during the first year of life. From delivery until 12 months of age, 18 infants died (47.7 per 1,000). Mothers of infants who died had lower serum vitamin A levels during pregnancy (0.74 ± 0.13 mµmol/l) compared with mothers of infants who did not die (1.02 ± 0.03 mµmol/l), (P=0.055). Infants born to women whose vitamin A levels were in the lowest quartile (<0.32 mµmol/l) had three-fold higher likelihood of mortality than infants born to women whose vitamin A levels were in the higher quartiles (P<0.03). These results suggest that maternal vitamin A deficiency during pregnancy may contribute to higher infant mortality rates.

Klemm et al. (14) assessed the effect of supplementing newborns with 50,000 IU of vitamin A on all-cause infant mortality through 24 weeks of age. The study was a community-based, double-masked, cluster-randomized, placebo-controlled trial conducted in 19 unions in rural Northwest of Bangladesh. Maternal consent to dose was obtained from 17,116 live-born infants (99.8% of all eligible) among whom 15,937 (93.1%) were visited to be supplemented <30 days after birth and for whom vital status at 24 weeks of age was known. Dosed infants (n=15,902[99.8%]) received their study supplement at a median age of 7 hours. Relative to control subjects, the risk of death in vitamin A-supplemented infants was 0.85, reflecting a 15% reduction in all-cause mortality. Protective relative risks were indistinguishable by infant gender, gestational age, birth weight, age at dosing, parity, or across the 3 treatment arms of the maternal supplemental trial. Vitamin A improved infant survival through the first 6 months of life in Bangladesh. Vitamin A supplementation shortly after birth can reduce infant mortality.

3-4. Effects of vitamin A supplementation on neonatal lungs

Prematurity and the associated risk of bronchopulmonary dysplasia remain a significant threat to extremely-low-birth weight infants. Vitamin A has been considered a therapeutic alternative in reducing the rate of bronchopulmonary dysplasia and mortality in infant. Meyer et

al. (15) investigated whether early additional oral doses of vitamin A (5,000 IU/kg/day) supplementation for 28 days in extremely low birth-weight infants is more efficient in reducing bronchopulmonary dysplasia than placebo treatment. The end point was the proportion of children who died before 36 weeks' postmenstrual age or developed moderate or severe bronchopulmonary dysplasia. The results of Neo vitamin A trials provide robust data with regard to the efficacy of high-dose oral vitamin A supplementation in reducing the incidence of bronchopulmonary dysplasia or death at 36 weeks' postmenstrual age in extremely low birth-weight infants.

Parenteral administration of vitamin A to the newborn is the current recommended preventive therapy for bronchopulmonary dysplasia (16). Supplementation of vitamin A in late pregnancy increases the cord blood vitamin A concentration and decreases the incidence of bronchopulmonary dysplasia in newborns. This can be an effective adjunct to postnatal preventive therapy. Vitamin A supplementation in late pregnancy carries no risk of teratogenicity unlike that in early pregnancy. Moreover, vitamin A deficiency in pregnancy is associated with depressed immune function leading on to increased infectious morbidity which can cause intrauterine growth retardation, low birth weight and anemia in newborns. Combining antenatal vitamin A supplementation to the mother with postnatal supplementation to the newborn can effectively prevent bronchopulmonary dysplasia better than the traditional postnatal preventive therapy alone.

Vitamin A supplementation for very low birth-weight infants, beyond that routinely given in multivitamin preparation, is associated with a reduction in death or bronchopulmonary dysplasia (17). So, parenteral administration of vitamin A to the newborn is one of the current recommended preventive therapies for bronchopulmonary dysplasia. The information on the long-term neurodevelopmental status suggests no evidence of either benefit or harm. Nowadays, it seems that administration of antenatal vitamin A to the mother in late pregnancy associated with neonatal supplementation can better prevent the development of bronchopulmonary dysplasia in areas of endemic vitamin A deficiency.

Eleven infants, median gestational age 24 weeks, developed chronic lung disease. Their results were compared to 11 infants who, although they required mechanical ventilation for at least 48 hours, did not develop chronic lung disease. The median gestational age of this latter group was 30 weeks. The median vitamin A level of the infants who developed chronic lung disease was 0.62 µmol/l (range, 0.41-0.95), which was significantly ($P<0.05$) higher than the median level of the infants who did not develop chronic lung disease, which was 0.36 µmol/l (range, 0.13-0.89). Chan et al. (18) conclude that preterm infants who develop chronic lung disease are not predisposed to develop chronic lung disease by low vitamin A levels at birth.

Shenai et al. (19) conducted a randomized, double-blind, controlled trial to determine whether vitamin A supplementation from early postnatal life could reduce the morbidity associated with bronchopulmonary dysplasia in very-low-birth weight neonates. Forty neonates (700 to 1,300 grams birth weight, 26 to 30 weeks gestational age), were given by the intramuscular route either supplemental vitamin A (retinyl palmitate 2,000 IU) or saline solution on postnatal day 4 and every other day thereafter for a total of 14 injections over 28 days. Bronchopulmonary dysplasia was diagnosed in 9 of 20 infants given vitamin A supplementation and in 17 of 20 control

infants (P=0.008). The need for supplemental oxygen, mechanical ventilation, and intensive care was reduced in infants given vitamin A supplement compared with controls. Vitamin A supplementation at the dosage used not only improves the infant vitamin A status but also appears to promote regenerative healing from lung injury, as evidenced by a decrease in the morbidity associated with bronchopulmonary dysplasia.

Vitamin A deficiency may increase the responsiveness of the respiratory tract and increase the risk of respiratory tract infection, resulting in airway obstruction and wheezing. Luo et al. (20) investigated the relation between vitamin A deficiency and infant wheezing. The severity of vitamin A deficiency was related to the course of wheezing. A total of 331 hospitalized infants who suffered from wheezing were enrolled in the study. In the persistent wheezing group 14 patients (34.1%) were diagnosed as having severe vitamin A deficiency and 16 patients (39%) as having moderate vitamin A deficiency; among the acute wheezing group, 18 patients (16.4%) were diagnosed as having severe vitamin A deficiency and 32 patients (29%) having moderate vitamin A deficiency. Comparison of the two groups revealed that there was a significantly higher rate of moderate and severe vitamin A deficiency in the persistent wheezing group than in the acute wheezing group (P<0.01). The severity of vitamin A deficiency was related to the infants' wheezing severity. Severe vitamin A deficiency was found in 24 patients (47%) in the severe wheezing group and 8 (8%) in the mild and moderate wheezing groups. The rate of severe vitamin A deficiency was significantly higher in patients with severe than in those with mild and moderate wheezing (P<0.01). Serum vitamin A deficiency could be commonly found in infants with wheezing. The severity of vitamin A deficiency might be related to the course of wheezing and the infants' wheezing severity.

Tyson et al. (21) performed a multicenter, blinded, randomized trial to assess whether the effectiveness and safety of 5,000 IU vitamin A administered intramuscularly three times per week for four weeks was more effective than the lower doses given in past trials. These authors performed a multicenter, blinded, randomized trial to assess the effectiveness and safety of this regimen compared with sham in 807 infants in need of respiratory support 24 hours after birth. The mean birth weight was 770 grams in the vitamin A group and 769 grams in the control group, and the respective gestational ages were 26.8 and 26.7 weeks, respectively. The primary outcome of death or chronic lung disease at 36 weeks' postmenstrual age occurred in significantly fewer infants in the vitamin A group than in the control group (55% vs. 62%; relative risk, 0.89; 95% confidence interval 0.80 to 0.99). Overall, one additional infant survived without chronic lung disease for every 14 to 15 infants who received vitamin A supplements. The proportion of infants with serum retinol values below 0.70 µmol/l was lower in the vitamin A group than in the control group (25% vs. 54%; P<0.001). Intramuscular administration of 5,000 IU of vitamin A three times per week for four weeks reduced biochemical evidence of vitamin A deficiency and slightly decreased the risk of chronic lung disease in extremely low birth-weight infants.

Vitamin A is necessary for normal lung growth and the ongoing integrity of respiratory tract epithelial cells. Preterm infants have low vitamin A status at birth and this has been associated with increased risk of developing chronic lung disease (2). Supplementing very low birth-weight infants with vitamin A is associated with a reduction in death or oxygen requirement at one month of age and oxygen requirement among survivors at 36 weeks

postmenstrual age, with this latter outcome being confined to infants with birth weight less than 1000 grams. Information on long-term neurodevelopmental status suggests no evidence of either benefit or harm from the intervention.

A National Institute of Child Health and Human Development National Research Network randomized trial showed that vitamin A supplementation reduced bronchopulmonary dysplasia or death in extremely low birth-weight neonates (relative risk: 0.89). Of 807 enrolled infants, 133 died before and 16 died after discharge. Five hundred seventy-nine (88%) of the 658 remaining infants were followed up. Neurodevelopment impairment or death by 18 to 22 months occurred in 190 of 345 (55%) infants in the vitamin A group and in 204 of 342 (60%) of the control group (relative risk: 0.94; 95% confidence interval: 0.80 to 1.07). Relative risks for low Bayley Mental Index, low Psychomotor Index, and Cerebral Palsy were <1.0. Ambalavanan et al. (22) found no evidence that neonatal vitamin A supplementation reduces hospitalizations or pulmonary problems after discharge. Vitamin A supplementation for extremely low birth-weight infants reduces bronchopulmonary dysplasia without increasing mortality or neurodevelopmental impairment at 18 to 22 months.

Kaplan et al. (23) examined and characterized variations among neonatal intensive care unities in the use of vitamin A supplementation for the prevention of bronchopulmonary dysplasia in extremely-low-birth-weight infants. Among 4,184 eligible infants cared for in 30 neonatal intensive care units, 1,005 infants (24%) received vitamin A. Eighteen centers (60%) used vitamin A for some patients. Infants discharged in 2007 (odds ratio: 2.7 [95% confidence interval: 1.4 to 5.3]) and 2008 (odds ratio: 2.8 [95% confidence interval: 1.4 to 5.8]), compared with 2005, were more likely to receive vitamin A. Neonatal intensive care unit medical directors from centers using vitamin A, compared with centers that did not adopt vitamin A supplementation, reported stronger beliefs in the efficacy of vitamin A to reduce the incidence of bronchopulmonary dysplasia (83% vs.33%; P=0.03) mjand in the ease with which vitamin A could be implemented (75% vs. 22%; P=0.02). Although the use of vitamin A is increasing, marked variation across neonatal intensive care units remains. Provider attitudes and systemic characteristics seem to influence vitamin A adoption.

3-5. Effect of vitamin A on neonatal kidneys

Vitamin A (retinol) and its analogs (retinoids) are important regulators of cell proliferation, differentiation, immune function, and apoptosis (24). The kidneys are target organs for vitamin A action. Retinoic acid, a vitamin A metabolite, is involved in embryonic kidney pattering through the control of receptor tyrosine kinase expression, which modulates ureteric bud branching morphogenesis. Vitamin A status of the mother profoundly affects kidney organogenesis of the newborn. Retinoic acid regulates nephron mass, its optimal availability during nephrogenesis. Maternal vitamin A deficiency during pregnancy is widespread in developing countries and segments of these populations may be exposed to low vitamin A during fetal life when the nephron number is determined. Infants born with subpopulation nephrons may develop primary hypertension later in life. Because retinoic acid regulates nephron mass, its optimal availability during nephrogenesis is critical. Retinoic acid levels in the embryo are affected by several factors, such as maternal vitamin A nutrition and disturbances in retinol metabolism. Although maternal vitamin A

deficiency is not common in developed countries, the congenital nephron number nevertheless varies widely, indicating low retinoic acid levels due to common variants of the enzyme that convert retinol to retinoic acid.

A study was performed to assess the vitamin A status of a cohort of Egyptian pregnant women and their newborns and to determine the potential effect of maternal vitamin A deficiency during pregnancy on the neonatal kidney size (25). The maternal and cord blood samples were collected for the measurement of retinol concentration. Within the 3 days after delivery, an abdominal ultrasound was performed in all the newborns to determine the renal dimensions and volume. Sixteen (20%) mothers had vitamin A deficiency. The newborns delivered to vitamin A deficiency mothers had significantly lower mean values of cord retinol concentrations and dimensions of both kidneys than the newborns delivered to mothers with vitamin A sufficiency. The maternal serum retinol concentrations were positively correlated with the cord retinol concentrations, the dimensions of both kidneys, and the combined renal volume of their respective newborns. Maternal vitamin A deficiency during pregnancy may decrease renal size in the infant at birth.

Goodyer et al. (26) designed a pilot study to determine the prevalence of maternal vitamin A deficiency in Montreal (Canada) and Bangalore (India) and the usefulness of newborn renal volume as a surrogate for nephron endowment. Among 48 pregnant Montreal women two (4%) had one isolated mid-gestation retinol level slightly below the accepted limit on normal (0.9 mμmol/l), whereas 25 (55%) of 46 pregnant women in Bangalore had at least one sample below this limit. Average estimated retinol intake was correlated with mean serum retinol in pregnant women from Bangalore. In Montreal where maternal vitamin A deficiency was negligible, Goodyer et al. (26) found that newborn renal volume (estimated by renal ultrasonography at 2-6 weeks of age) was correlated with surface area at birth and was inversely correlated with serum creatinine at one month. Renal volume adjusted for body surface area in Montreal (184 ± 44 ml/m^2) was significantly greater than in Bangalore (114 ± 33 ml/m^2) $P<0.01$. Definitive studies are needed to establish whether maternal vitamin A deficiency accounts for subtle renal hypoplasia in Indian newborns.

3-6. Effects of vitamin A supplementation on preterm infant retinal sensitivity

Preterm infants show reduced retinal sensitivity at term corrected age compared with newborn term infants. Mactier et al. (27) tested the hypothesis that retinal sensitivity in preterm infants is improved by an early intramuscular vitamin A dose of 10,000 IU 3 times weekly from day 2 for a minimum of 2 weeks or until establishment of oral feeding. Eighty-nine infants (42 supplemented and 47 controls) were recruited. The infants had a gestational age <32 weeks and a body weight <1501 g. Plasma retinol was higher in supplemented infants at 7 and 28 days (median, 1.0 versus 0.5 μmol/l and 0.7 versus 0.6 μmol/l; $P<0.001$ and 0.03, respectively). Neither plasma retinol nor relative dose response differed between groups at 36 weeks' postmenstrual age. Retinal sensitivity was greater in supplemented infants ($P<0.03$) and was not related to relative dose response. Early high-dose intramuscular vitamin A supplementation for infants at risk of retinopathy of prematurity improves retinal function at 36 weeks' postmenstrual age.

3-7. Effects of vitamin A on neonatal body size

Low levels of vitamin A have a major impact on growth, development, and immunity. Rondò et al. (5) determined the relationship between cord concentrations of vitamin A and neonatal anthropometry in 711 neonates born at term in Brazil. Concentrations of vitamin A in cord blood correlated significantly (P<0.001) with birth weight (r=0.24), length (r=0.20), chest circumference (r=0.24), and mid-upper arm circumference (r=0.23), triceps skinfold thickness (r=0.26), and head circumference (r=0.12) of neonates. The anthropometric measurements of infants were sorted by the vitamin A concentrations and divided into quartiles. Differences between the quartiles were tested by analysis of variance. Infants in the bottom length, head circumference and triceps skinfold thickness quartiles had lower mean vitamin A concentrations than those of quartiles two, three and four. Infants in the bottom birth weight, chest and mid-upper arm circumferences quartiles had lower mean vitamin A concentrations than those of quartiles three and four (P = 0.003). These data show that smaller/shorter infants had lower concentrations of vitamin A than heavier/longer infants, probably reflecting the important role of this micronutrient on growth.

Of 105 neonates, 53 (50.5%) were males and 49 (49.5%) were females. Mean cord plasma vitamin A level of the male neonates was significantly lower (P<0.05) than that of the female neonates (12.2±4.6 vs. 14.7±5.2 µgrams/dl, respectively). The mean body weight of premature neonates (2,186±530 grams) was significantly lower (P<0.05) compared with the mean body weight of full term neonates (3,279±459 grams). The mean body weight of male neonates was slightly greater than that of female neonates (3,271±575 vs. 3,139±552 grams). The cord plasma of preterm neonates had mean value vitamin A significantly lower (P<0.05) than full term neonates (8.3±3.2 versus 13.8±4.5 µgrams/dl). A trend of increasing birth weight with increasing cord plasma vitamin A level is evident (6).

3-8. Lack of teratogenicity following ≤ 10,000 IU doses of vitamin A to pregnant women

Miller et al. (28) state that doses of 10,000 IU per day or less of preformed vitamin A (retinyl esters and retinol) are considered safe, doses >10,000 IU per day as supplements have been reported to cause malformation. Daily periconceptional exposure greater than 25,000 IU per day of preformed vitamin A, have not been sufficiently studied to establish specific risk. Because no study reports adverse effects of 10,000 IU per day preformed vitamin A supplements and this dose is more than the Recommended Dietary Allowance for pregnant women (2,670 IU per day), Miller et al. (28) recommend that women living in industrialized countries or who otherwise have nutritionally adequate diets may not need to ingest more than the Recommended Dietary Allowance of preformed vitamin A supplements. Human epidemiologic studies do not establish at what level vitamin A becomes teratogenic; however, pharmacokinetic data indicate that blood levels of retinoids from women taking 30,000 IU per day of preformed vitamin A are not greater than retinoid blood levels in pregnant women during the first trimester who delivered healthy neonates.

Of 22,748 women, 339 had neonates with birth defects; 121 of these neonates had defects occurring in sites that originated in the cranial neural crest (29). For defects associated with cranial-neural-crest tissue, the ratio of the prevalence among the infants born to women who consumed more than 15,000 IU of preformed vitamin A per day from food and supplementation to the prevalence among the infants whose mothers consumed 5,000 IU or less per

day was 3.5 (95% confidence interval, 1.7 to 7.3). For vitamin A from supplements alone, the ratio of the prevalence among the neonates born to women who consumed more than 10,000 IU per day to that among the infants whose consumed 5,000 IU or less per day was 4.8 (95% confidence interval, 2.2 to 10.5). Using a smoothed regression curve, Rothman et al. (29) found an apparent threshold near 10,000 IU per day of supplemental vitamin A. The increased frequency of defects was concentrated among the neonates born to women who consumed high levels of vitamin A before the seventh week of pregnancy. High dietary intake of preformed vitamin A appears to be teratogenic. Among the babies born to women who took more than 10,000 IU of preformed vitamin A per day in the form of supplements about 1 infant in 57 had a malformation attributable to the supplement.

Czeizel and Rockenbauer (30) determined the human teratogenic risk of vitamin A supplementation during pregnancy. Paired analysis of cases with congenital abnormalities and matched healthy controls was performed in a large population-based data set. Of 35,727 pregnant women who had control infants without defects, 3,399 (9.5%) were treated with vitamin A. Of 20,830 pregnant women who had case offspring with congenital abnormalities, 1,642 (7.9%) were treated with vitamin A, a rate that is significantly lower than that of the control group ($P<0.001$). The case-control pair analysis also showed a lower rate of vitamin A treatment during pregnancy and in the first trimester of gestation in most congenital abnormalities groups. Thus, the use of low or moderate doses of vitamin A (<10,000 IU) during the first trimester of pregnancy (i.e., organogenesis) is not teratogenic but presents some protective effects to the fetus. Mills et al. (31) determined whether moderate doses of vitamin A are teratogenic. Women whose pregnancies produced offspring with neural tube defects (n=548) or major malformations other than neural tube defects (n=387) and normal control subjects (n=573) were interviewed to determine periconceptional vitamin A defects. The proportion of women consuming doses of vitamin A between 8,000 and 25,000 IU was no greater in the major malformations group or the group with neural tube defects than in the normal control group.

No association between periconceptional vitamin A exposure at doses >8,000 or >10,000 IU per day had odds ratios for major malformations of 0.79 (95% confidence interval 0.40 to 1.53) and 0.73 (95% confidence interval 0.27 to 1.96), respectively, compared with women consuming <5000 IU. The results for neural tube defects were similar. For cranial neural crest defects the odds ratios were 0.76 (0.22 to 2.56) and 1.09 (0.24 to 4.98) for exposure to >8000 and >10,000 IU, respectively, versus exposure to <5000 IU. Mills et al. (31) found no association between periconceptional vitamin A exposure at doses >8000 IU or >10,000 IU per day and malformations in general, cranial neural crest defects, or neural tube defects. If vitamin A is a teratogen, the minimum teratogenic dose appears to be well above the level consumed by most women during organogenesis.

Johansen et al. (32) evaluated the association between the maternal intake of vitamin A from diet and supplementations and the risk of having an infant with orofacial cleft. Data on maternal dietary intake were available from 535 cases (188 with cleft palate only and 347 with cleft lip with or without cleft palate) and 693 controls. The adjust odds ratio for isolated cleft palate only and 347 with cleft lip was 0.47 (95% confidence interval: 0.24, 0.94) when comparing the fourth and first quartiles of maternal intake of total

vitamin A. In contrast, there was no appreciable association of total vitamin A with isolated cleft lip with or without cleft palate. An intake of vitamin A above 95th percentile was associated with a lower estimated risk of all isolated with cleft lip with or without cleft palate. An intake of vitamin A above the 95th percentile was associated with a lower estimated risk of all isolated clefts compared with the 40th-60th percentile (adjusted odds ratio=0.48, 95% confidence interval 0.20, 1.14). Maternal intake of vitamin A is associated with reduced risk of cleft palate only, and there is no evidence of increased risk of clefts among women with the highest 5% of vitamin A intake.

4-DISCUSSION

Prematurity is associated with bronchopulmonary dysplasia and vitamin A is an alternative therapy to reduce bronchopulmonary dysplasia morbidity and mortality. Intramuscular administration of 5,000 IU of vitamin A three times per week for 4 weeks decreased the risk of chronic lung disease in extremely-low-birth infants (21). Bronchopulmonary dysplasia was diagnosed in 9 of 20 infants given vitamin A supplementation and 17 of 20 control infants (P=0.008) (19).

Supplementation of vitamin A in late pregnancy increases the cord blood vitamin A concentration and decreases the incidence of bronchopulmonary dysplasia in newborns. Combining antenatal vitamin A supplementation with postnatal supplementation to the newborn prevents bronchopulmonary dysplasia better than the postnatal preventive therapy alone. Vitamin A deficiency may increase the responsiveness of the respiratory tract infection, resulting in airway obstruction and wheezing (20).

Preterm infants have low vitamin A status at birth and this has been associated with increased risk of developing chronic lung disease (2). Infants with serum retinol values below 0.70 µmol/l were significantly ($p<0.001$) lower in the vitamin A group than in the control group. In regions where at least 22% of pregnant women have vitamin deficiency of vitamin A, giving neonates vitamin A supplements will have a protective effect against death (7). Reduction in breast milk retinol was observed in the control group compared with the pre-supplementation levels (1.93 and 1.34 µmol/l, respectively; P=0.003) (9). Postpartum vitamin A supplementation is used to combat vitamin A deficiency and to reduce maternal and infant morbidity and mortality. The World Health Organization recommends a dose of 200,000 IU of vitamin A to pregnant women. Infants born to women whose vitamin A levels were in the lowest quartile (<0.32 µmol/l) had three-fold higher likelihood of mortality than infants born to mothers whose vitamin A levels were in the higher quartiles ($P<0.03$). These results suggest that maternal vitamin A deficiency during pregnancy may contribute to higher infant mortality rates (13). Klemm et al. (14) observed that supplementation of vitamin A reduces by 15% mortality compared with controls.

The kidneys are target organs for vitamin A action (24). Retinoic acid, a vitamin A metabolite, is involved in embryonic kidney pattering. Vitamin A status of the mother affects kidney organogenesis of the neonate. Retinoic acid regulates nephron mass during nephrogenesis. The newborns born to mothers with vitamin A deficiency have significantly lower mean values of cord retinol concentrations and dimensions of kidneys than the newborns delivered to mothers with vitamin A sufficiency. The maternal serum retinol concentrations were positively correlated with the cord retinol concentrations, the dimensions of kidney, and the renal volume of their respective newborns. Maternal vitamin A deficiency during pregnancy may decrease renal size

in the infant at birth. Preterm infants have a reduced retinal sensitivity compared with term infants. Mactier et al. (27) administered intramuscularly a vitamin A dose of 10,000 IU 3 times weekly from day 2 for a minimum of 2 weeks. Retinal sensitivity was greater in supplemented infants than in controls (P<0.03). Early high-dose vitamin A supplementation for infants at risk of retinopathy of prematurity improves retinal function at 36 weeks' postmenstrual age.

Vitamin A increases the body weight of term infants. A statistically significant (P=0.001) correlation was observed between vitamin A concentration in cord blood and birth weight, length, chest circumference, mid-upper arm circumference, triceps skinfold thickness and head circumference of neonates (5). Tolba et al. (6) observed a trend of increasing birth weight with increasing cord plasma vitamin A.

Miller et al. (28) observed that doses of 10,000 IU vitamin A (retinyl esters and retinol) per day are safe and do not cause teratogenicity. Doses > 10,000 IU vitamin A per day, as supplements have been reported to cause malformations. Using a smoothed regression curve, Rothman et al. (29) found an apparent threshold near 10,000 IU per day of supplemental vitamin A. The increased frequency of defects was concentrated among neonates born to mothers who consumed high levels of vitamin A before the seventh week of pregnancy.

Czeizel and Rockenbauer (30) stated that doses of vitamin A (<10,000 IU) during the first trimester of pregnancy is not teratogenic but presents some protective effects to the fetus. Mills et al. (31) observed no association between periconceptional vitamin A exposure at doses >8,000 or >10,000 IU per day and malformations in general. If vitamin A is a teratogen, the minimum teratogenic dose appears to be well above the level consumed by most women during organogenesis. In conclusion, vitamin A consists of four fat-soluble compounds namely retinol (the alcohol form), retinyl esters, retinaldehyde and retinol acid. Vitamin A is used to combat bronchopulmonary dysplasia and mortality in infants. Preterm infants have lower vitamin A status than term infants at birth and this has been associated with increased risk of developing chronic lung disease. Supplementation of vitamin A to mothers and infants reduces the risk of infant mortality.

Vitamin A concentration correlates in cord and maternal sera. Retinoic acid regulates the nephron mass during nephrogenesis. Vitamin A deficiency reduces the dimensions of neonatal kidneys. Supplementation of 10,000 IU vitamin A increases the retinal sensitivity in preterm infants. Vitamin A cord concentration correlates with the neonatal body size. Doses of vitamin A ≤10,000 IU are not teratogenic. Although there are several studies on the effects of vitamin A in neonates and young infants, more studies are needed to administer vitamin A for an evidence-based treatment of neonates and infants with this vitamin.

5-CONCLUSION

Vitamin A deficiency remains a public health problem among women, affecting an estimated 19 million pregnant women (33), with the highest burden found in the WHO regions of Africa and South-East Asia. During pregnancy, vitamin A is essential for the health of the mother as well as for the health and development of the fetus. This is because vitamin A is important for cell division, fetal organ and skeletal growth, maintenance of the immune system to strengthen defences against infection, and development of vision in the fetus as well as maintenance of maternal eye health and night vision (34, 35). During pregnancy, serum retinol levels decline, particularly in the third

trimester; this may be due to the physiological increment in blood volume or due to an acute phase response, and it can be exacerbated by an inadequate vitamin A intake (36, 37). Night blindness, an early sign of vitamin A deficiency, is associated with infectious diseases (37, 38). In countries where vitamin A deficiency is a public health problem, WHO recommends periodic administration of high-dose vitamin A supplements to children 6–59 months of age to reduce mortality (39). Although vitamin A supplements are not recommended as part of routine antenatal care for the prevention of maternal and infant morbidity and mortality, they are recommended in pregnant women for the prevention of night blindness in areas where there is a severe public health problem of vitamin A deficiency (40).

6-CONFLICT OF INTERESTS

Prof. Gian Maria Pacifici declares no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts and honoraria.

7-ACKNOWLEGMENTS

The author thanks Dr. Patrizia Ciucci and Dr. Francesco Varricchio of the Medical Library of the University of Pisa for retrieving the scientific literature.

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