Vitamin A in pregnancy

Abstract

Vitamin A is a fat-soluble vitamin which does not only perform a lot of systemic functions, but also plays an important role in organogenesis. There are three active forms of vitamin A: retinol, retinal and retinoic acid. Vitamin A deficiency is the main preventable cause of blindness worldwide and the primary cause of childhood morbidity and mortality in the developing world. Maternal vitamin A deficiency during pregnancy is associated with high rates of maternal and infant mortality and with a significant risk of premature birth, miscarriage or fetal death. Both deficiency and hypervitaminosis A during pregnancy are associated with congenital malformations, but the teratogenic effect was described only for a daily intake of more than 10,000 IU of preformed vitamin A supplements. In conclusion, vitamin A supplementation is recommended only for pregnant women from areas with endemic avitaminosis A, in order to prevent nyctalopia.

Keywords: *retinol, retinoic acid, congenital malformations, vitamin A deficiency, teratogenesis, hypervitaminosis*

Rezumat

Vitamina A face parte din categoria vitaminelor liposolubile care, pe lângă funcțiile exercitate la nivel sistemic, joacă un rol important în cadrul organogenezei. Vitamina A se prezintă sub trei forme active: retinol, retinal și acid retinoic. Deficitul de vitamină A este nu numai principala cauză prevenibilă de orbire la nivel mondial, dar și un factor etiopatogenic esențial în ceea ce privește morbiditatea și mortalitatea infantilă în țările în curs de dezvoltare. Deficitul matern de vitamină A în timpul sarcinii se asociază cu rate mari ale mortalității materne și infantile, dar și cu un risc semnificativ de naștere prematură, avort sau moarte fetală. Atât deficitul, cât și hipervitaminoza A pe parcursul sarcinii sunt asociate cu apariția malformațiilor congenitale, însă efectul teratogen este descris doar în cazul unui aport zilnic de peste 10.000 UI de vitamină A preformată provenind din suplimente. În concluzie, suplimentarea cu vitamină A este recomandată doar în cazul femeilor gravide din zone cu deficit endemic de vitamină A, cu scopul prevenției nictalopiei.

Cuvinte-cheie: *retinol, acid retinoic, malformații congenitale, deficit de vitamină A, teratogeneză, hipervitaminoză*

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Introduction

Vitamin A is an essential nutrient and a fat-soluble vitamin which performs a lot of systemic functions. Adequate vitamin A is required for erythrocyte production, tissue differentiation, normal development of bones and teeth, immune competence, reproduction, proper gastrointestinal activity and vision. It also has an important role during the embryonic development, being involved in organogenesis[1-4].

There are two forms of vitamin A: preformed vitamin A (retinol) and provitamin A (carotenoids), but the three active forms are: retinol, retinal and retinoic acid[3]. While the retinoic acid is responsible for growth and development, the retinol and retinal forms of vitamin A play an essential role in maintaining the reproductive functions and the normal vision[4].

Carotenoids may be converted to vitamin A in the liver, where they will be ultimately stored[5]. While preformed vitamin A comes from animal sources from the diet (liver, milk, eggs, cheese), the carotenoids intake is based on plant sources, consisting of fruits and vegetables (spinach, carrots, pumpkins, sweet potatoes)[2,3,6,7]. Taking into account that there is a reduced absorption of vitamin A coming from plant sources, it is quite useful the consumption of animal food products, in order to maintain an adequate level of vitamin A[5].

The need of vitamin A is increased during pregnancy because of its essential role in supporting the maternal metabolism and the fetal development. The recommended daily dose in pregnant women is 770 µg/dL[5]. Among populations with a low prevalence of vitamin A deficiency, it is considered that the hepatic stores are sufficient to ensure the daily requirement of this nutrient[5]. On the other hand, in case of an endemic vitamin A deficiency, it is recommended daily or weekly supplementation, in order to prevent nyctalopia[8].

Avitaminosis A is a severe public health problem in many geographical regions, being considered the main preventable cause of blindness[1]. It is estimated that vitamin A deficiency leads to blindness in 250-500 million children worldwide, half of these children dying within a year of vision loss[7]. It is also a predisposing factor for multiple comorbidities, such as: respiratory diseases, measles, diarrhea, anemia, convulsive cough, thyroid dysfunction, some dermatological lesions, and moderate-severe forms of malnutrition in children[1,9,3]. Thus, vitamin A deficiency is the primary cause of childhood morbidity and mortality in the developing world, especially in Africa and Southeast Asia[7].

Maternal vitamin A deficiency during pregnancy is associated with high rates of maternal and infant mortality and with a significant risk of miscarriage, fetal death or premature birth[9,10-12]. In addition, both deficiency and

exposure to high doses of vitamin A during pregnancy (over 10,000 IU/day) are related to many fetal congenital malformations[3,10,12,15]. Ensuring an adequate and balanced diet in pregnancy has an essential role in the prevention of avitaminosis A, since the toxicity of vitamin A is often described in case of dietary supplements intake, especially for those with preformed vitamin A[5].

Vitamin A deficiency in pregnancy

The vitamin A deficiency in pregnancy is an important problem in public health system from developing countries, affecting around 19 million pregnant women worldwide, while other studies have shown an estimated 15% of pregnant women in low-income countries[1,11,14,15]. Vitamin A deficiency can result in malnutrition and inflammation, affecting growth, development and functional outcomes. It has an essential role for the maintenance of vertebral identity, the prevention of malformations and for the development of skeletal elements during embryogenesis[4]. It is associated with numerous factors, such as: low educational and socioeconomic status, unhealthy lifestyle during pregnancy consisting in smoking and alcohol consumption, as well as an advanced gestational age. Also, vitamin A deficiency is still considered the main preventable cause of night blindness, 8% of pregnant women having vitamin A deficiency high enough to lead to this ocular consequence[1,14].

The avitaminosis A is owing to an inadequate intake of preformed vitamin A from animal food sources or carotenoids from fruits and vegetables[3]. Subclinical vitamin A deficiency is defined by serum retinol concentrations below 0.70 μmol/L (20 μg/dL), while severe defiency is characterized by plasma retinol concentrations below 0.35 μmol/L (10 μg/dL)[3,4,9,14,16].

Some studies have shown that the serum level of retinol can be used as a predictive factor for preeclampsia, being reported low concentrations of plasma retinol in pregnant women with preeclampsia and eclampsia. However, the role of vitamin A in the etiopathology of pregnancy-induced hypertension is not completely known[9]. Although there are some studies which have been found that vitamin A and other antioxidants supplementation in pregnancy led to a reduction in absolute risk for preeclampsia with 3%, these results were statistically insignificant[17].

Maternal deficiency of vitamin A during pregnancy is associated with high rates of maternal and infant mortality in the first year of life[11]. Also, subclinical deficiency of vitamin A in the third trimester of pregnancy increases the risk of preterm birth and maternal anemia[9]. Thus, there is recommended the vitamin A supplementation in pregnant women with a low socioeconomic status, avitaminosis A being associated not only with an 1.8-fold increased risk of maternal anemia[4,9,18], but also with a low level of serum hemoglobin concentration in newborns[9]. Some studies have found that the supplementation with β-carotene or any form of vitamin A during pregnancy reduces the risk of anemia (Hb<11 g/dL) by 19%[19]. The mechanisms of anemia occurrence are related to some of the effects of vitamin A, including: anti-infectious role, the modulation of iron metabolism, and the increase of circulating level of erythropoietin[9].

More than half of pregnant women with vitamin A deficiency have nyctalopia, with a higher prevalence during the third trimester of pregnancy, because of the acceleration of fetal growth[3,20]. Nyctalopia is one of the first clinical manifestations of vitamin A deficiency, along with conjunctival xerosis and Bitot spots (keratin debris in the conjunctiva), subsequently leading, in case of a severe and prolonged vitamin A deficiency, to corneal scars, keratomalacia (drying and clouding of the cornea with ulceration) and permanent blindness. Another specific ocular manifestation owing to avitaminosis A is xerophthalmia (dry eyes and failure to produce tears)[2,3,21,22]. Taking into account that half of children with blindness due to vitamin A deficiency are dying within one year from the occurrence of blindness, promoting vitamin A supplementation in endemic deficit areas is an important public health method which reduces the infant mortality[13,23,24].

Vitamin A deficiency is a major cause of childhood morbidity and mortality, being associated with severe immunodepression, which predisposes to a high incidence of respiratory infections and other infectious diseases, such as diarrhea and measles[3,16]. In children with avitaminosis A, measles is a predisposing factor for conjunctival and corneal affliction, this being associated with higher mortality rate compared with cases of measles among children with normal vitamin A status[3,25,26]. Neonatal vitamin A supplementation increases the resistance at infections, reduces the incidence and severity of measles, with a significant impact on cases of neonatal diarrhea, which are responsible for about 30% of neonatal deaths[3,15].

Some studies showed that vitamin A deficiency in mothers with HIV infection is associated with a 3-4-fold increased rate of mother-to-child transmission[3,16,27]. However, other studies including pregnant women and women during breastfeeding have not shown significant benefits of vitamin A supplementation on the rate of transmission of HIV infection from mother to child[3,28].

A study which included 138 children with combined iodine and vitamin A deficiency has demonstrated increased thyroid hormone and TSH concentrations, as well as an increased risk of goiter, related to the severity of vitamin A deficiency[3,29]. Even without supplementation of iodine deficiency, vitamin A administration led to reduced TSH and thyreoglobulin concentrations, as well as a decrease in thyroid gland volume[3,30].

It has been shown that vitamin A deficiency in pregnant women interacts with iron deficiency, which is another major micronutrient. This can be explained not only by the role of vitamin A in supporting the mobilization and the transport of iron, but also by its importance in hematopoiesis, a process requiring large amounts of iron. In addition, it was found that simultaneous use of vitamin A and iron supplements is more effective in preventing the iron deficiency anemia than the use of either of these nutrients alone[4].

Vitamin A deficiency is also associated with other conditions, including follicular hyperkeratosis, characterized by

excessive keratin synthesis in the hair follicles, with initial localization at the extremities, but with the possibility of generalization[3,31,32].

Another symptom of vitamin A deficiency is bronchopulmonary dysplasia, which is a form of chronic disease with an unfavorable prognosis, occurring in approximately one third of preterm infants less than 28 weeks of gestation. It has been shown that intramuscular administration of 5000 IU of vitamin A three times per week during four weeks in preterm infants has been associated with a significant reduction in the risk of developing bronchopulmonary dysplasia[3,32,33].

Animal studies have shown that severe vitamin A deficiency in pregnancy induces abortion, fetal death and fetal birth defects, mostly consisting in microphthalmia, anophthalmia and abnormalities of the lung, cardiac and urogenital systems. There have also been reported facial, renal and diaphragmatic malformations, along with severe enamel and dentin dysplasia. Other animal studies have been found a relationship between the maternal vitamin A deficiency and the occurrence of ocular defects, such as: coloboma, penetration of the retina by mesodermal tissue, retinal eversion, defects in the iris and low insertion of the optic stalk[34]. Subsequently, human studies have also demonstrated a direct relationship between maternal vitamin A deficiency during pregnancy and the development of congenital ocular defects[4,10,12,16].

Hypervitaminosis A in pregnancy and teratogenesis

Although vitamin A supplementation during pregnancy can have many benefits, it has been shown that a daily intake of more than 10,000 IU of preformed vitamin A derived from supplements is associated with the occurrence of congenital defects in 1 of 57 children. The teratogenic risk is correlated with the intake of high doses of vitamin A before the 17th week of gestation. In addition, the congenital defects were mainly observed in the tissues derived from neural crest cells. There were described congenital malformations such as transposition of the great vessels, ventricular septal defect, multiple cardiac defects, hydrocephalus, craniosynostosis, and cleft lip[13,16].

For a daily intake of less than 10,000 IU of preformed vitamin A supplements there was no risk of congenital malformations, and β-carotene was also related with no risk of teratogenic effects. However, isotretinoin – a synthetic derivative of retinol – is contraindicated during pregnancy, leading to a large number of major congenital defects[3,35,36].

It was found that 20% of fetuses who were exposed to isotretinoin during pregnancy had craniofacial, cardiac, thymic and central nervous system malformations. While there were observed cranial malformations such as microcephaly, hydrocephaly, micro- and macro-cerebellar dysgenesis, the craniofacial anomalies included facial asymmetry, cleft palate, micrognathism, stenosis or atrophy of the external auditory canal and other malformations of the external ear[36,37].

Another synthetic derivative of vitamin A is etretinate, which can cause cardiac, thymic or limb congenital defects. In addition, it has a very long half-life of 120 days and accumulates in the body, through storage especially in the adipose tissue. This explains the persistence of teratogenic risk in pregnant women over a long period of time after cessation of exposure to this substance[37].

In addition to teratogenic risk, exposure to high doses of vitamin A (25,000-33,000 IU/day) for long periods may cause symptoms related to chronic toxicity, characterized by headache, anorexia, weight loss, pruritus, bone and joint pain, hepatomegaly and splenomegaly, hemorrhage or even coma[3].

Recommendations regarding vitamin A supplementation during pregnancy

Vitamin A supplementation during pregnancy is not routinely recommended in order to prevent maternal and infant morbidity and mortality[38]. World Health Organization recommends vitamin A supplementation only for pregnant women from areas where avitaminosis A is a severe public health problem, in order to prevent nyctalopia[8]. The reason is represented by the severe outcomes of night blindness, which was associated with a significantly increased risk of both postpartum and pregnancy-related mortality, and also with a five-fold increased risk in infection-related causes[39].

Vitamin A supplementation of deficient populations is also important in the prevention of anemia, being found that the use of supplements for a period longer than two weeks raises the hemoglobin concentrations by 0.2-1 g/dL[19].

In pregnant women with suspected low vitamin A status, it can also be prescribed a well-balanced diet rich in β-carotene-containing vegetables[16]. Also, studies performed on Indonesian women have showed that large-scale oil fortification with vitamin A improved the vitamin A status of people living in poverty, being a cost-effective way to reduce vitamin A deficiency and its severe consequences[40].

Vitamin A deficiency is considered a severe public health issue if at least 20% of pregnant women in the population have serum retinol levels below 0.7 μmol/L, or at least 5% of women have a history of nyctalopia during a pregnancy which has occurred in the last 3-5 years[8].

The main forms of vitamin A found in dietary supplements are retinyl acetate and retinyl palmitate, but retinoids (retinol, retinal and retinoic acid) or carotenoids (most commonly β-carotene) can also be found[5]. The recommended vitamin A doses can be up to 10,000 IU/day or up to a maximum dose of 25,000 IU/week[38,41].

The recommended daily dose in pregnant women is 770 μg/dL[5]. The Teratology Society of United States of America recommends that the daily total intake of vitamin A should not exceed 8000 IU/day[16].

The administration of more than 25,000 IU of single-dose vitamin A supplements between the 15th and the 60th day post-conception has a teratogenic effect. In addition, this kind of administration is considered insecure, not being recommended[2,8,41].

The main goal during pregnancy is to ensure a healthy and balanced diet for the pregnant woman, considering that dietary supplementation, along with the weight gain during pregnancy and the mother's preconception nutritional status are highly associated with the cranial circumference, the weight and the length at birth[42]. So, the vitamin A supplementation is not a mandatory measure. Moreover, if the daily intake of vitamin A exceeds 8000 IU, it is no longer recommended the administration of additional doses[2,8,41].

Conclusions

Vitamin A plays an essential role in embryonic development, the maternal deficiency of this micronutrient during pregnancy being associated with the occurrence of ocular congenital malformations, abortion or fetal death.

The vitamin A deficiency has a higher prevalence in the third trimester of pregnancy among pregnant women with low educational and socioeconomic status and an unhealthy lifestyle, this being considered one of the most preventable causes of blindness worldwide. Other comorbidities associated with avitaminosis A are: anemia, respiratory disease, measles, diarrhea, thyroid dysfunction and hyperkeratosis.

It has been shown that the daily intake of more than 10,000 IU of preformed vitamin A supplements before the 17th week of gestation has teratogenic effect, being associated with the occurrence of congenital malformations such as: transposition of the great vessels, ventricular septal defect, multiple cardiac defects, hydrocephalus, craniosynostosis and cleft lip. The teratogenic risk has not been described for β-carotene or for doses of vitamin A lower than 10,000 IU/day.

Considering this toxicity, vitamin A supplementation is not routinely recommended, although it plays an important role in reducing maternal and infant morbidity and mortality. World Health Organization recommends supplementation only for pregnant women from areas with endemic vitamin A deficiency, in order to prevent nyctalopia. Therefore, the healthy and balanced diet of the pregnant women is the main method of preventing avitaminosis A in pregnancy. ■

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