THE IMPORTANCE OF VITAMIN A DURING EARLY LIFE AND THE IMPACT ON INFANT MORTALITY

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ABSTRACT

The Under-Five Mortality Rate (MMR5) measures the number of deaths per thousand live births in this age group, reflecting aspects such as malnutrition and quality of maternal and child health care. Despite global efforts, the 5MWR is still high in developing countries, and about 48.1 million deaths are projected in this population by 2030. In Brazil, the 5MMR presents a worrying situation due to its slower reduction in recent years, with a high occurrence of deaths from preventable diseases. Vitamin A (VA) is essential for the immune system, cell development, and maintenance of the body. Vitamin A deficiency (VAD) mainly affects pregnant women, newborns and children under five years of age, and can cause blindness, infections and congenital malformations. Globally, millions of children and pregnant women suffer from VAD, which negatively impacts child growth and survival. In Brazil, the prevalence of VAD is significant, with 10 to 20% of children at risk, and it is a moderate to severe public health issue. Measures are carried out at the government level, such as the promotion of breastfeeding, supplementation and food enrichment. However, few studies report the impact of the consumption of fortified foods in the country, there are controversies regarding the effectiveness of supplementation in the long term, especially after childbirth, and breastfeeding remains insufficient, factors that contribute to the permanence of VAD. It is essential to improve the maternal and child care system in Brazil to reduce infant morbidity and mortality, especially in the most vulnerable populations. The adequacy of the VA, both for the mother and the baby, is essential to ensure health during the first years of life.

Keywords: Vitamin A deficiency. Infant mortality. Child health.

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INTRODUCTION

Infant mortality, especially in children under five, is an important public health indicator. The mortality rate in this age group (5MMR), which includes neonatal and post-neonatal deaths, reveals the level of care and health of a population, in addition to serving as a basis for the development of prevention policies (UN, 2024a). Although global infant mortality rates are decreasing, the pace of this reduction is still insufficient in many countries, especially developing countries such as Brazil, which has experienced a slower decline in infant mortality since 2009 (UN, 2024b; WHO, 2023).

Among the main causes of death of children in Brazil are perinatal conditions, congenital malformations, and infectious diseases, highlighting the importance of targeted interventions (MOURA et al., 2022). In this context, proper nutrition in the first years of life plays a key role. The period of the first 2,200 days of life is recognized as fundamental for the child's future health (ALMEIDA et al., 2022).

Vitamin A (VA) emerges as one of the essential nutrients in this process, with a direct impact from conception to the first years of the child's life. Its functions include promoting healthy growth and preventing infectious diseases (MEZZANO et al., 2022). However, vitamin A deficiency (VAD) is a public health problem, with serious consequences for both pregnant women and children, and is a risk factor for infant mortality (WHO, 2011a).

Given the importance of vitamin A in child development and in reducing the risks associated with mortality, this book seeks to explore the mechanisms of vitamin A transmission throughout child development, as well as to discuss the implications of vitamin A deficiency for maternal and child health. Understanding this relationship is essential for the evaluation of supplementation policies and the implementation of preventive care measures aimed at reducing infant mortality.

MORTALITY IN CHILDREN UNDER FIVE YEARS OF AGE

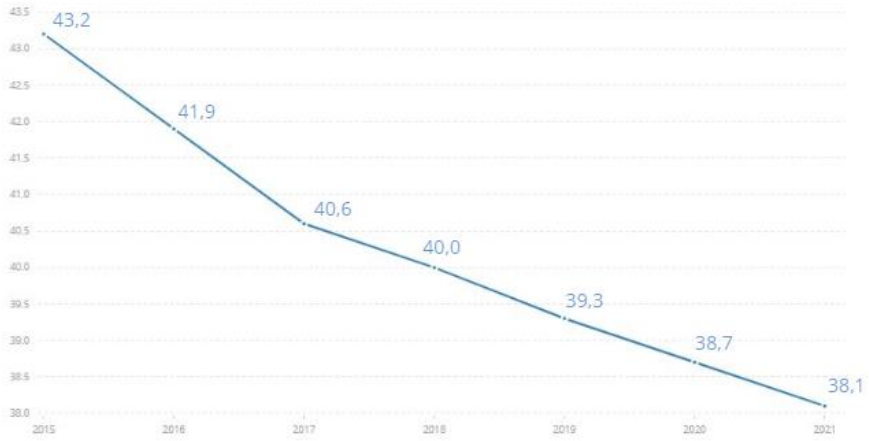
The 5MMR is defined as the number of deaths of children under five years of age, per thousand live births, in a population in the year considered. It expresses, in general, environmental aspects that condition child malnutrition, such as poverty, food insecurity, malnutrition during pregnancy, breastfeeding, complementary feeding, infectious diseases, water, hygiene and sanitation, as well as the infections associated with it, in addition to access and quality of resources available for maternal and child health care, determinants of mortality in this age group (WHO, 2024; DHAGE, 2024). This rate is a key indicator in assessing the health situation of a population, and is essential for the development of

preventive strategies aimed at reducing the risk of death in this age group (DHAGE, 2024; FRANÇA et al., 2017; BUGELLI et al, 2021)

It is possible to observe the importance of the 5RM through the global effort to reduce this index. In 2015, the United Nations (UN) General Assembly established the Sustainable Development Goals (SDGs), which include an infant mortality target, in which all countries must eradicate deaths in children under five years of age, in addition to achieving a 5MWR of 25 or fewer deaths per 1,000 live births by 2030. (DHAGE, 2024; UN, 2024a; SHARROW et al, 2022)

With these deployments, the worldwide RMT5 has been shrinking in recent years, however, there is still a long way to go. In 2015, when the SDGs were implemented, the rate was 43.2 per 1000 live births. In 2017, this rate was 40.6, indicating 5.7 million deaths per year. In 2021, this figure appears to have reduced to 38.1 (approximately five million deaths per year), but progress has been slow in recent years, particularly in developing countries *(Chart 1)* (UN 2024b; WHO, 2023). In 2022, 4.9 million deaths of children under five years of age were recorded, of which 2.3 million occurred during the first month of life and 2.6 million between 1 and 59 months of age (UNICEF., 2024). If current trends continue, 48.1 million under-five deaths are projected to occur between 2020 and 2030, almost half of them projected to occur during the neonatal period (UN, 2024b; WHO, 2023; SHARROW et al, 2022).

Graph 1 - World mortality rate, children under five years of age per 1,000 live births

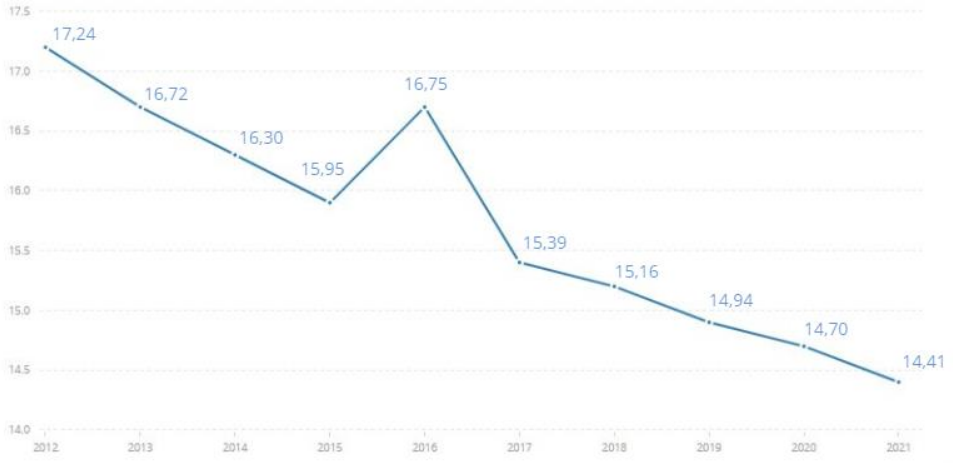


Source: Adapted from WHO, 2023 and ONE, 2024b

Despite being one of the countries that met the SDG target, the mortality of children under five years of age in Brazil foreshadows a worrying situation. The 5RM in Brazil shows a decreasing pattern (UN, 2024b; WHO, 2023; FRANÇA et al, 2017), however, since 2009, Brazil has been experiencing a slower decline in infant mortality, which has remained at high levels and has significant regional disparities. In 2016, the country recorded an

increase in the mortality of children under five years of age, which interrupted a 25-year period of downward trend (Graph 2) (UN, 2024b; WHO, 2023; BUGELLI et al, 2021).

Graph 2: Mortality rate in Brazil, children under five years of age per 1,000 live births



SOURCE: Adapted from WHO, 2023 and UN., 2024b

Deaths from communicable diseases, maternal, neonatal and nutritional disorders are the main causes of death in children under five years of age in Brazil, and in general can be considered preventable. On the other hand, congenital anomalies, with relatively stable rates in Brazil, occupy the first place among the causes of death, especially in states with lower mortality rates, approaching the profile found in high-income countries (SECRETARIA DE VIGILÂNCIA EM SAÚDE E AMBIENTE, 2022; FRANÇA et al, 2017).

METABOLIC ASPECTS OF VITAMIN A

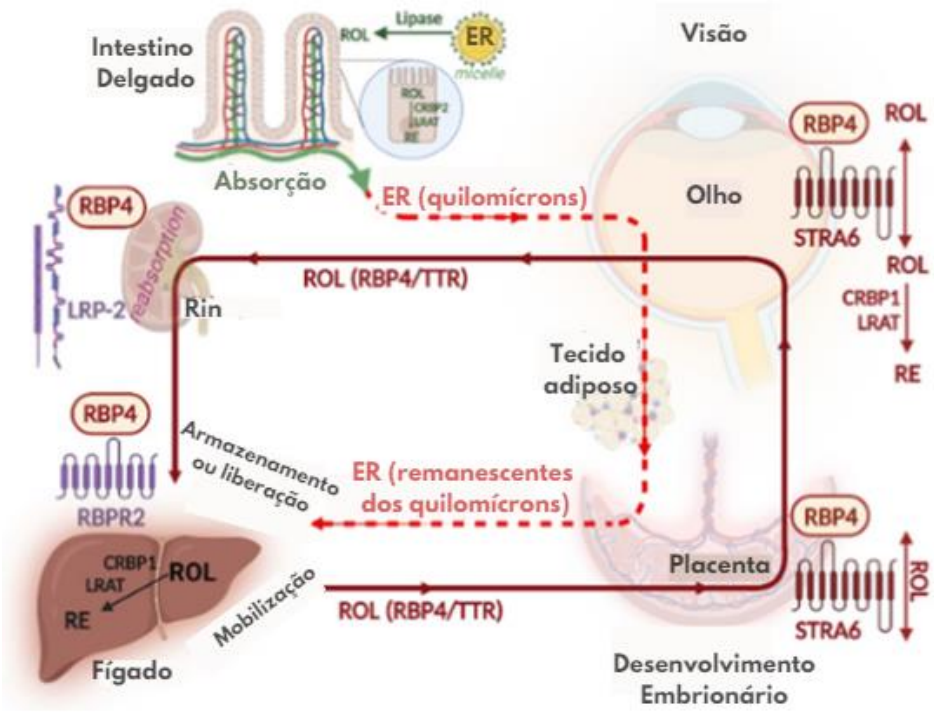
Dietary molecules with VA activity exist in two forms: preformed VA and provitamin A. Preformed VA molecules are mainly retinol and retinyl esters, usually obtained from animal-derived foods, while provitamin A carotenoids are obtained from plant-derived foods, which are later converted to the active form (CHEN et al, 2023; YADAV, 2022; CARAZO et al, 2021; TANUMIHARDJO et al, 2016)

ABSORPTION

The illustrative schematization of the absorption, transport and metabolism of the AV is shown in Figure 1. In the lumen of the intestine preformed VA and provitamin A carotenoids are released from the food matrix and emulsified with dietary fatty acids and bile acids, forming mixed micelles that reach the border membrane in intestinal brush (O'CONNOR, 2022; EFSA, 2015).

Retinol is absorbed by enterocytes and esterified with fatty acids to generate retinyl esters (ER) (CHEN et al, 2023; YADAV, 2022; MOLTEDO et al, 2021). The most important enzyme involved in this synthesis in the gut, as well as in other tissues, is lecithin: retinol acyltransferase (LRAT) (O'CONNOR, 2022), along with cellular retinol-binding protein 2 (CRBP2). Retinyl esters are then incorporated into chylomicrons through the activity of microsomal triglyceride transfer protein (MTP) and transported in the lymph and blood. In peripheral tissues, chylomicrons undergo remodeling, and retinyl esters are hydrolyzed by lipoprotein lipase (LPL) and taken up by target organs, such as the eye, placenta, and adipose tissue, which retains 10 to 20% of the body's AV. However, most retinyl esters remain associated with chylomicron remnants and are metabolized by the liver (CHEN et al, 2023; YADAV, 2022; O'CONNOR, 2022; MOLTEDO et al, 2021; EFSA, 2015).

Figure 1- Scheme of vitamin A absorption, transport and metabolism. Enterocytes of the intestinal membrane absorb retinol and carotenoids from mixed micelles from the action of gastrointestinal lipases in the food matrix and convert them into ER by the action of the enzymes CRBP2 and LRAT, ER is incorporated into chylomicrons by MTP, where it circulates until it is captured by the target organs through the hydrolyzation of the enzyme LPL, the remaining ER is metabolized by the liver and converted into retinol that is associated with CRBP1, and can be released into the bloodstream bound to RBP4 (later forming the RBP4/TTR complex), or transported to the EHS where it is converted back into ER by LRAT for storage. The organ also produces the enzyme RBPR2, which catalyzes hepatic absorption of excessive circulating RBP4 and regulates its biliary excretion. In the kidneys, the elimination of retinoids is mediated by the reabsorption of RBP4 by the LRP-2 enzyme. In peripheral organs such as the eyes and placenta, retinol absorption is mediated by the enzyme STRA6, the interaction between STRA6 and RBP4 allows the bidirectional transport of retinoids to the intra- and extracellular medium. ER: Retinol ester, ROL: retinol, CRBP2: cellular retinol-binding protein 2, LRAT: lecithin: retinol acyltransferase. TTR: transthyretin, LRP-2: lipoprotein receptor-related protein 2 complex, RBP4: retinol-binding protein type 4, RBPR2:Retinol transporter protein receptor 2, CRBP1: retinol-binding cellular protein 1, STRA6: retinoic acid-stimulated receptor 6, CEH: hepatic stellate cell.



SOURCE: Adapted from O'CONNOR, 2022.

HEPATIC METABOLISM OF VITAMIN A

The liver is the main organ responsible for the storage, metabolism, and distribution of AV to peripheral tissues. Most of the AV (80-90%) is stored in the liver (CHEN et al, 2023; YADAV, 2022; CARAZO et al, 2021). Chylomicron-associated retinyl esters are taken up by hepatocytes via hepatic LPL and hydrolyzed to retinol, which is associated with cellular retinol-binding protein 1 (CRBP1). CRBP1 plays important roles in fine-tuning AV metabolism, including protecting retinol from degradation and ensuring its delivery to retinoid enzymes for oxidation or esterification (O'CONNOR, 2022). Hepatocytes are also responsible for RBP production and AR synthesis and catabolism (EFSA, 2015).

The retinol thus formed can follow different paths: a) bind to RBP and be released into the bloodstream; b) be oxidized to AR for cell signaling; c) be metabolized, in more polar forms, by the cytochrome P450 (CYP26) enzyme system, and conjugated with bile salts for excretion by bile; d) or else be transported to the CEH, where it will be stored. The individual's AV nutritional status determines the route to be followed (O'CONNOR, 2022; CARAZO et al, 2021).

CRBP1-bound retinol is transported to the HECs by hepatocytes, where it is converted by LRAT into retinyl esters and stored in large cytoplasmic lipid droplets of different sizes (Figure 1). The main storage site for AVs is the CEH (CZUBA, 2024; CHEN et al, 2023; YADAV, 2022). In the healthy liver, the bidirectional retinoic acid-stimulating receptor 6 (STRA6) transports the AV between the extra and intracellular retinoid-binding proteins (figure 1). The interaction of RBP4 with STRA6 allows for the bidirectional transfer of retinol into and out of cells (O'CONNOR, 2022).

EXTRA-LIVER METABOLISM OF VITAMIN A

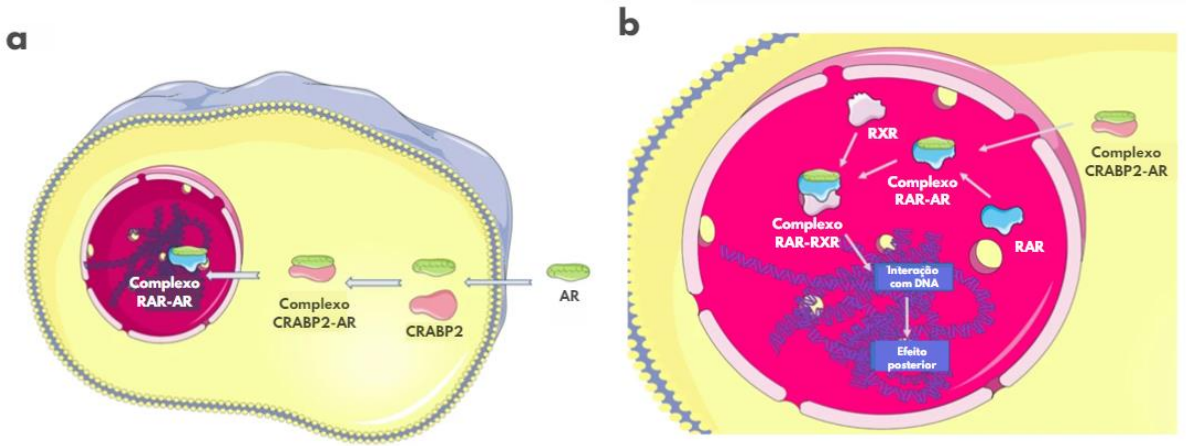
Retinol storage is under strict AR feedback regulation. The expression of LRAT and RBP1 in the liver is induced by RA, thus acting to direct the flow of retinol for storage in times of AV sufficiency. AV metabolism also responds to regulators of liver lipid metabolism (O'CONNOR, 2022). As demand increases, stocks of hepatic retinol are mobilized. As required, retinyl esters from CEH are hydrolyzed by various hepatic lipases to retinol and transferred to hepatocytes. Hepatocytes secrete retinol bound to retinol-binding protein (encoded by RBP4) (O'CONNOR, 2022; YADAV, 2022). This retinol-RBP4 complex is designated holo-RBP4 or holo-RBP, in contrast to apo-RBP4 which is not bound to retinol (YADAV, 2022). Holo-RBP4 circulates as a complex with transthyretin (TTR) (O'CONNOR, 2022; YADAV, 2022). Blood VA levels are homeostatically regulated to maintain a narrow range, through hepatic co-secretion of RBP-bound retinol (LOUNDER et al, 2017)

Retinol-bound RBP4 interacts with specific receptors expressed by target tissues (O'CONNOR, 2022; YADAV, 2022). Retinol uptake in tissues can be mediated by passive diffusion or active uptake via STRA6 (YADAV, 2022). STRA6 is a high-affinity holo-RBP4 receptor expressed by many blood tissue barrier sites, such as pigmented cells of the retina, placenta, yolk sac, choroid plexus, and Sertoli cells (O'CONNOR, 2022). In addition to protein-mediated transport, a considerable fraction of VA can be transported by lipoproteins that deliver retinoids to many target tissues, including the placenta (YADAV, 2022). The elimination of retinoids occurs through the kidneys or liver into the bile. RBP4 is reabsorbed from the proximal tubule of the kidney via the lipoprotein receptor-related protein 2 (LRP-2) complex (figure 1) (O'CONNOR, 2022).

VITAMIN A CELL SIGNALING

Active retinoids can be generated in tissues from retinyl esters, retinol, or β-carotene. All-trans-retinoic acid, or AR, is the major bioactive metabolite of retinol (CZUBA, 2024; CHEN et al, 2023; YADAV, 2022; O'CONNOR, 2022). AR is transported from the cytosol to the nucleus by binding to retinoic acid binding protein type 2 (CRABP2) (Figure 2a), where it binds to members of the retinoic acid nuclear receptors (RAR), forming an AR-RAR complex that stimulates the narrowing of RAR binding with the retinoid X receptor (RXR), forming RAR/RXR heterodimers, which subsequently bind to specific retinoic acid response elements (RARE), thus initiating the transcription of target genes and promoting the regulatory effects of AV (figure 2b), acting on lipid metabolism, fatty acid oxidation, gluconeogenesis, and extracellular matrix remodeling, among other functions (CZUBA, 2024; BURZYŃSKI et al, 2023; CHEN et al, 2023).

Figure 2 - Retinoic acid signaling. a) Transport of retinoic acid through the membrane and cytoplasm. b) Retinoic acid signaling in the nucleus. a) AR is transported from the cytosol to the nucleus by binding with CRABP2, where it binds to RAR, forming the AR-RAR complex, b) this complex stimulates the narrowing of the RAR bond with RXR, forming RAR/RXR heterodimers, which subsequently bind to RARE, promoting the regulatory effects of RAR. AR: RA retinoic acid, CRABP2: retinoic acid type 2 binding protein, RAR: retinoic acid receptor, RXR: retinoid X receptor, RARE: specific elements of response to retinoic acid.



FONTE: Adaptado de BURZYŃSKI et al, 2023.

MAIN FUNCTIONS OF VITAMIN A

Retinal and AR are the two major metabolites that mediate the physiological functions of AV. The retinal is the chromophore of visual pigments, a critical component of the visual cycle. On the other hand, AR is an activator of nuclear receptors, which are transcription factors that respond to variations in ligand levels, so VA acts on several cellular factors that influence growth, immunity, among other aspects (CHEN et al, 2023)

GROWTH AND DEVELOPMENT

AV is an essential micronutrient for human beings, especially in times of intense growth and development (DALLAZEN et al, 2023; ZHAO et al, 2022). Findings from experimental studies suggest that VA may affect growth through the regulation of growth hormone (GH) and thyroid-stimulating hormone beta genes. RA deficiency is associated with reduced GH secretion by the pituitary gland, resulting in somatic growth failure, particularly in preschool-aged children (SSENTONGO et al, 2020).

Children who do not achieve their full development do not achieve adequate learning, behavior, and mental and physical well-being; perform worse in school; and earn lower wages as adults. This perpetuates a cycle of poverty and continuously undermines human development (CORREIA et al, 2019). In low- and middle-income countries, 36.8% of children aged three to four years performed poorly on developmental tests (CORREIA et al, 2019). It is estimated that, worldwide, more than 200 million preschool children are not developing properly (CORREIA et al, 2019). Short stature, weight loss, and low weight are responsible for more than 45% of mortality in children under five years of age and impaired

cognitive development and are associated with multiple risk factors, including fetal growth restriction, enteric and systemic infections, diarrheal diseases, and poverty, highly concomitant factors in individuals with VAD (SSENTONGO et al, 2020).

IMMUNITY AND OXIDATIVE STRESS

Another aspect that deserves to be highlighted is the fact that AV is closely linked to the immune system (CHEN et al, 2023; GURGEL et al, 2018). Considered among all micronutrients as most closely associated with infectious diseases (RAMALHO, 2017). AV plays a key role in maintaining mucosal integrity, differentiation, growth and function of neutrophils, Natural Killer (NK) cells, monocytes, dendritic cells and T and B lymphocytes, modulation of phagocytic cell response, stimulation of phagocytosis, expression of mucin, keratin and cytokines, production of immunoglobulins, participation in hematopoiesis, oxidation-reduction reaction, healing, in the apoptosis process and in the regulation of genes that influence immunity (CHOOBDAR et al, 2023; CARAZO et al, 2021; ZHANG et al, 2019; LOUNDER et al, 2017; EFSA, 2015) and also participates in the activation of cell-mediated cytotoxicity and the increase in the response of thymocytes to specific mitogens (RAMALHO, 2017).

AR increases the percentage of lymphoid cells expressing T-helper lymphocyte surface markers, while β-carotene increases lymphoid cells expressing NK cell markers, which suggests a differentiated action of the various retinoids on specific cellular immunity (CHOOBDAR et al, 2023).

In the inflammatory state, the AV is significantly reduced in approximately 72 hours. This fact can be explained by the deviation of protein synthesis, prioritizing the production of acute phase proteins to the detriment of the reduction of the pool of circulating visceral proteins (including the retinol transporter protein - RBP), high consumption of antioxidants, exacerbation of oxidative stress caused by inflammation and infection; and increased urinary excretion during the acute phase of infection, which causes depletion of the stores of this vitamin (TANUMIHARDJO et al, 2016).

VA is a fat-soluble antioxidant, carried in conjunction with LDL cholesterol (LDL-c) and protects the polyunsaturated fatty acid against oxidation. When there is depletion of antioxidants in the LDL-c molecule, lipid chain peroxidation occurs, so that the presence of antioxidants in this lipoprotein delays the onset of this process (O'CONNOR, 2022; CARAZO et al, 2021). Retinol through its antioxidant activity combines with peroxyl radicals preventing the formation of hydroperoxides (CARAZO et al, 2021).

Carotenoids are efficient in fighting free radicals and act as singlet oxygen deactivators and peroxyl radical scavengers, reducing DNA and lipid oxidation (MIZAEK et al, 2022), in addition to protecting LDL-c molecules from oxidation (O'CONNOR, 2022; CARAZO et al, 2021), with β-carotene being the most well-known and studied carotenoid due to its antioxidant potential, especially in relation to the protection of LDL-c molecules (MIZAEK et al, 2022; BOHN et al, 2019). As an anti-infective vitamin, VA adequacy is necessary to support rapid growth and resistance to infections in the pediatric public, where this condition can lead to critical consequences (CHOOBDAR et al, 2023).

VAD affects the immune system on several levels, including destroying the integrity of the mucosal epithelial membrane, which acts as a protective barrier in the gastrointestinal, respiratory, and urinary systems. It causes metaplasia and destruction of the defense mechanism of the squamous layer of the airways, epithelium, and microbial invasion. DVA also leads to weakened immunity by dysfunction of macrophages and natural killer cells, monocytes, neutrophils, and dendritic cells. It also increases the severity of enterovirus infections by reducing the concentration of interferon alpha and IgM (CHOOBDAR et al, 2023; ZHANG et al, 2019)element.

VISUAL CYCLE

In the eye, the retina is the structure responsible for visual perception, including its transmission to the brain. This perception is mediated by specific structures in the retina: rods and cones. Rods are sensitive to low light and are therefore crucial for vision in dark situations (e.g., night vision), while cones are responsible for high-intensity light (color vision) (YADAV, 2022; CARAZO et al, 2021; TANUMIHARDJO et al, 2016). This important function of the rods is linked to the size of the pupil, which opens in the dark to allow light to reach the back of the eye and becomes smaller in bright light (TANUMIHARDJO et al, 2016).

VA has a role in the regeneration of visual pigment. The active derivative of VA 11-cis-retinal is associated with the protein opsin, a G-coupled protein receptor in the retina. The complex is known as rhodopsin, which is the crucial pigment for light perception. Under light stimuli, the 11-cis-retinal is transformed into all-trans-retinal and initiates a chain of reactions whose final consequence is the transmission of optical perceptions through the optic nerve to the brain. After this reaction, part of the *all-trans-retinal* can be transformed back into 11-cis-retinal , allowing the recycling of this key molecule. The remaining *all-trans-retinal* can be transformed into retinol, which can be

stored in the epithelial cells to be later reused or converted into AR (HODGE, 2023; YADAV, 2022; CARAZO et al, 2021)

The visual system requires a constant supply of retinol precursor to maintain vision (O'CONNOR, 2022) otherwise, a lack of retinol supply can lead to night blindness, due to poor regeneration of visual pigment in the retinal rods (HODGE, 2023; O'CONNOR, 2022). In individuals with VAD, the ability of the rods to adapt in the dark and for the pupils to properly measure light inside and outside the eye may be impaired (TANUMIHARDJO et al, 2016). As the severity of the deficiency worsens, signs of xerophthalmia develop with Bitot's spots (conjunctival, triangular, or oval, foamy lesions) and conjunctival xerosis (appears as conjunctival wrinkling). If VAD persists, its later stages present as corneal xerosis, corneal ulceration, and eventually keratomalacia as the corneal ulcers heal, resulting in corneal scarring and blindness (HODGE, 2023; WHO, 2009).

EVALUATION OF THE NUTRITIONAL STATUS OF VITAMIN A

The nutritional status of AV is defined by the balance between the proportion of the micronutrient ingested and its use by the body (MCLAREN, 2012). Its evaluation can be made through dietary, biochemical, functional and clinical indicators. Each method has its strengths and limitations, for the choice of use, its usefulness must be evaluated according to the purpose and target group established (TANUMIHARDJO et al, 2016; MCLAREN, 2012).

DIETARY ASSESSMENT

Dietary assessment methods include dietary records, 24-hour food recall, food frequency questionnaires, brief dietary assessment instruments, and dietary history (TANUMIHARDJO et al, 2016; MCLAREN, 2012). Deficiency is considered when the intake does not meet the needs established for the population, on the other hand, if the consumption remains above the recommendations, especially the pre-formed AV, it is possible to form reserves and maintain concentrations (TANUMIHARDJO et al, 2016).

Dietary assessment has the advantage of being non-invasive, inexpensive, and uncomplicated, so that many individuals can be readily seen and a profile of a population can be drawn, aiding possible subsequent dietary interventions. (MCLAREN, 2012). They also have great applicability, being widely used worldwide by professionals in governments, academia, health services and the food industry for a wide range of purposes, such as assessing the level of inadequacy by sex and age groups and assessing the potential of a food supply to meet the nutritional needs of a country (MOLTEDO et al, 2021).

However, it is important for the elaboration and application of these questionnaires to be aware of which foods are sources of AV available and consumed in the country or population of study, which are enriched, especially with preformed AV, as well as the seasonality of different fruits and vegetables sources of carotenoids (MOLTEDO et al, 2021; TANUMIHARDJO et al, 2016). Potential confounding factors such as self-report and use of supplementation should be considered, as well as methodological challenges such as inconstancy regarding the unit used to quantify consumption (International units 'IU' or Recommended mean estimate 'EAR') and the absence of a consensus regarding the system of conversion of provitamin A carotenoids into RAS (MOLTEDO et al, 2021; TANUMIHARDJO et al, 2016; MCLAREN, 2012).

FUNCTIONAL ASSESSMENT

Some measurements are able to assess the functional impact of AV, reflecting its influence on specific biological systems. These measurements seek to identify night blindness, which is the first functional indicator of VAD (CARAZO et al, 2021; WHO, 2009). Ocular symptoms associated with VAD have been shown to develop at concentrations less than <0.7 µmol/L (HODGE, 2023).

Among the main ones are dark adaptation tests, electroretinography, pupillary threshold test and conjunctival impression cytology (TANUMIHARDJO et al, 2016).

The dark adaptation tests and the pupillary threshold test are based on the conversion time of the rod to cone retinal receptors in the dark adaptation process, consisting of exposing the individual to lighting and then to a dark room for ten minutes. Although they are direct tests and do not require associated biomarkers, they have limitations due to the high degree of attention required by the test subject, and due to the set of factors that can cause confounding such as eye diseases, protein or zinc deficiency and age, being inappropriate for children and the elderly (TANUMIHARDJO et al, 2016).

Electroretinography measures the number of photoreceptors in the retina and their ability to regenerate rhodopsin after an exposure to bright, discolorating light. For this, the pupil dilation of the analyzed subject and direct contact with a measuring electrode are required. Conjunctival impression cytology, on the other hand, consists of taking a sample of the conjunctiva of the eye and staining the cells, in search of abnormality defined as absence of goblet cells and hyperplasia of epithelial cells. In addition to the limitations mentioned above, these methods are more restricted because they are invasive, being used only in clinical or research settings (TANUMIHARDJO et al, 2016).

A pilot study in 1980 proved the validity of the interview in relation to the objective test of night vision – scotopic vision and serum retinol (SOMMER et al, 1980). In view of the above, the World Health Organization (WHO) proposed a standardized interview, which is an algorithm to increase sensitivity and reduce the misclassification of night blindness, and which should be used prioritizing local language. For its application, the use of expensive equipment and specialized ophthalmological knowledge is not required (WHO, 1996). The proposed interview, in addition to being easy to apply, allows the detection of the problem in the population segment most vulnerable to nutritional deficiencies (ZHAO et al, 2022; YISAK et al, 2020).

Pereira et al. compared the diagnosis of night blindness through the proposed interview with electroretinography and the association of these diagnoses with serum retinol concentrations. Night blindness diagnosed by both methods showed an association with VAD according to serum retinol concentrations. The authors conclude that the standardized interview for the diagnosis of night blindness can be a good strategy to assess the nutritional status of AV, being a simple, non-invasive, and low-cost method (PEREIRA et al, 2020).

CLINICAL EVALUATION

In the clinical evaluation, some procedures can help estimate the status of AV, including the patient's historical survey, in the search for risk factors such as malabsorption, infectious diseases, impaired immunity, cirrhosis, pancreatic insufficiency, prematurity, low socioeconomic status, and current pregnancy or lactation in a context of malnutrition (HODGE, 2023). Likewise, it is of great value to perform the physical examination due to the possible identification of signs of deficiency such as conjunctival xerosis, keratinization of the mucous membranes of the respiratory, gastrointestinal, and urinary tracts, dryness, desquamation, and follicular thickening of the skin, and growth retardation in children (HODGE, 2023).

However, the most commonly used aspect to determine AV status is xerophthalmia, which titles the clinical spectrum of ocular manifestations of VAD; these range from the mildest stages of night blindness, Bitot's spots to the potentially permanent stages of xerosis, ulceration, and necrosis of the cornea (keratomalacia) (HODGE, 2023; WHO, 2009). The various stages of xerophthalmia are considered disorders and clinical indicators of VAD (WHO, 2009).

It is observed that the clinical manifestation of VAD occurs late, when the deficiency is already installed and the AV reserves are already seriously depleted, so its evaluation is

not effective to diagnose it previously, highlighting the importance of the subclinical diagnosis of VAD to minimize its consequences in the population. In addition, the identification of clinical signs can be influenced by factors such as the professional's interpretation and the population's access to the health service (MCLAREN, 2012; WHO, 2009).

BIOCHEMICAL EVALUATION

The most commonly used forms of biochemical measurement of AV status are the quantification of serum retinol and retinol transporter protein (RBP). VAD is defined as its concentration less than <0.7 µmol/L (HODGE, 2023; TANUMIHARDJO et al, 2016).

However, these two parameters are not sensitive indicators of the nutritional status of AV and do not reflect hepatic reserve. This is because serum retinol is homeostatically controlled by liver reserves and only falls when liver reserves are very low (MEZZANO et al, 2022; TANUMIHARDJO et al, 2016; McCauley et al., 2015). Serum retinol and RBP tend to be lower in infants and young children than in adults, even in populations with adequate serum VA levels (TANUMIHARDJO et al, 2016). Difficulties also arise when assessing micronutrient deficiencies in countries where there is a high burden of infection as these biomarkers are altered by inflammation (MEZZANO et al, 2022; SHEFTEL et al, 2021; TANUMIHARDJO et al, 2016). In addition, there may be interference due to drugs, alcohol, and physiological conditions (CARAZO et al, 2021; SHEFTEL et al, 2021).

The retinol concentration of breast milk is an indicator of the vitamin status of both the mother and the infant, and has been shown to be a more sensitive marker of maternal nutritional status than the respective blood concentrations (MACHADO et al, 2019; SOUZA et al, 2015). The cut-off points adopted to identify VAD and adequate formation of hepatic reserve are <1.05 and >2.3 µmol/L, respectively (SOUZA et al, 2015; STOLTZFUS, 1995). However, the measurement by this method is hampered by the difficulty of standardizing the collection of breast milk samples, since the AV content of breast milk is very variable. Among the factors that cause this variability are: breastfeeding period, breast to be pumped, time of day, time elapsed since the last feeding, collection at the beginning or end of the feeding, and the mother's pre- or post-prandial state (DEMINICE et al, 2018; TANUMIHARDJO et al, 2016).

Hepatic AV reserves are considered a reference of excellence for the evaluation of this vitamin (CHEN et al, 2023; TANUMIHARDJO et al, 2016). Hepatic stellate cells store 50-80% of the total AV in the body in the form of retinyl palmitate in lipid droplets in the cytoplasm, being responsible for regulating the transport and storage of AV. A normal

reserve of the vitamin in these cells represents an adequate supply for most individuals for several weeks or months (TANUMIHARDJO et al, 2021; SENOO et al, 2017).

Hepatic reserve of AV can be measured indirectly through retinol *isotope dilution* (RID) or dose-response tests, such as *relative-dose-response* (RDR) and *modified-relative-dose-response* (MRDR), or they can be quantified directly from liver tissue, through biopsy or autopsy (SURI et al, 2023; TANUMIHARDJO et al, 2016). Direct measurement is the most reliable way to estimate the hepatic reserve of AV. It is not realistic to perform biopsies in living people, being used to evaluate retinol concentrations in humans only in special cases. Autopsy samples, on the other hand, should be considered for population monitoring, given that VAD is not considered a primary cause of death and its concentrations in the liver remain unchanged up to 48 hours postmortem (MEZZANO et al, 2022; TANUMIHARDJO et al, 2016; OLSON et al, 1984). Hepatic retinol reserve is considered *adequate* when the values are equal to or greater than 20µg/g (or 0.07µmol/g) of liver (OLSON et al, 1979).

VITAMIN A DEFICIENCY

VAD is a public health problem worldwide (ZHAO et al, 2022; DING et al, 2021; MIRANDA et al, 2018; HANSON et al, 2017; CRUZ et al, 2017a) that can increase maternal/perinatal mortality (CRUZ et al, 2018; 2017a; WHO, 2011a). The main causes of VAD include an insufficient intake of VA-rich foods, malabsorption, and loss of AV due to disease (ZHAO et al, 2022; GURGEL et al, 2018).

The most characteristic consequence of VAD is impaired vision. In the long term, VAD can cause xerophthalmia and, eventually, total blindness, which can be permanent. This circumstance is the most common cause of preventable blindness in developing countries. VAD is also characterized by epithelial modifications that directly affect various body systems, including respiratory, urogenital, reproductive, gastrointestinal, nervous, and skin systems, as well as increasing the risk of infections, malnutrition, and anemia (CARAZO et al, 2021; GURGEL et al, 2018).

The main victims of VAD are pregnant women, newborns, and children under five years of age who are males, in countries with a low sociodemographic development index (HODGE, 2023; ZHAO et al, 2022; MEZZANO et al, 2022; MIRANDA et al, 2018; HANSON et al, 2017). Many populations in these countries rarely eat meat, dairy, or carotenoid-rich vegetables, which makes it difficult to obtain sufficient amounts of VA (HODGE, 2023). Maternal and infant VAD not only affects individuals at these biological times, but also extends to long-term health in adulthood (ALMEIDA et al, 2022)

In the gestational period, VAD increases the risk of complications during pregnancy and in the postpartum period and has been positively associated with maternal infections, anemia, and birth defects (THOENE et al, 2020). The increased need for the vitamin, especially in women in the third trimester of pregnancy, when fetal growth is faster, can also lead to night blindness, a risk marker for pregnancy that is able to identify VAD in its subclinical stage (MACHADO et al, 2016). In addition, maternal VAD can lead to embryonic malformations, which are manifested by deficiencies of the cardiovascular and nervous system and less developed tissues, among other defects (CARAZO et al, 2021).

In children, VAD can cause growth and developmental deficits, vision loss, and be a potential risk factor for cognitive impairment and mental illness, as well as increase susceptibility to respiratory, parasitic infections, and diarrhea (ZHAO et al, 2022). The greater vulnerability of this age group to VAD is attributed to the rapid growth and development, characteristic of this phase of life and, consequently, the increase in the need for AV, which is often not met due to insufficient intake. This is coupled with greater susceptibility to diseases that reduce absorption, increase metabolic demands, and excretion of this vitamin. In this way, repeated infections further reduce the absorption of AV, resulting in a vicious cycle in this population (DALLAZEN et al, 2023; ZHAO et al, 2022).

There is a downward trend in the worldwide prevalence of VAD, with significant reductions reported since 1990 (ZHAO et al, 2022; MIRANDA et al, 2018). However, in 2019 its values remained high, reaching more than four hundred and eighty-nine million people (ZHAO et al, 2022). According to a WHO report, 190 million preschool-aged children and 19 million pregnant women have been exposed to VAD globally (ZHAO et al, 2022; THOENE et al, 2020). In several Latin American countries, VAD is still considered a serious public health problem (ZHAO et al, 2022).

In Brazil, studies have identified prevalences of 10% to 20% of serum retinol levels below 0.70 µmol/L, a condition that characterizes VAD as a moderate to severe public health problem (MIRANDA et al, 2018). According to the Pan American Health Organization (PAHO) and the WHO, the country is considered to be an area of severe subclinical shortage of AV (ZHAO et al, 2022).

For children and infants, the recommended daily intake of VA ranges around 400-500 retinol activity equivalents (RAE), while for women, pregnant and breastfeeding women, the recommended levels range between 700 and 1300 RAE, with the highest for lactating women (HODGE, 2023; CARAZO et al, 2021). The minimum requirement to prevent symptomatic AVD in children from one to five years of age is about 200 micrograms/day (HODGE, 2023). There are no specific guidelines for increasing β-carotene intake or

indications for supplementation in breastfeeding mothers. The typical intake of β-carotene in a Western diet is six to eight mg per day (NICHH, 2022).

MATERNAL VITAMIN A TRANSFER

MATERNAL VITAMIN A TRANSFER DURING PREGNANCY

In the early intrauterine period, the developing embryo is totally dependent on maternal circulation for its AV supply (THOENE et al, 2020; QUADRO et al, 2020). The maternal/fetal retinol concentration is about 2:1 in mothers in the absence of severe retinol deficiency (TEKGÜNDÜZ et al, 2022). Maternal-fetal transport of retinoids relies on RBP4 (maternal- and fetal-derived) as well as lipoprotein-mediated pathways, both of which respond to AV status (O'CONNOR, 2022). The AV reaches the embryo by crossing the maternal-fetal barrier (placenta and yolk sac) (DEMINICE et al, 2018). Placental homeostasis plays a key role in the delivery of retinol to the fetus and is responsible for the storage of retinoids until fetal liver maturation is complete (TEKGÜNDÜZ et al, 2022).

Depending on the maternal dietary regimen, different metabolic pathways appear to be activated to maintain retinoid homeostasis in the placenta and control the amount of preforms and provitamin A that is transferred to the developing embryo, a process that the literature has recently reported to be possibly involved with lipid metabolism (QUADRO et al, 2020).

The literature also demonstrates relatively stable fetal AV levels , despite fluctuations in maternal retinol levels, this is justified by the transplacental passage of retinol that increases in cases of maternal retinol deficiency (TEKGÜNDÜZ et al, 2022; THOENE et al, 2020), which can increase even more when comparing retinol-deficient mothers compared to insufficient ones (THOENE et al, 2020). In addition, it appears that maternal RBP levels, and in turn placental retinol release, increase or decrease according to the intensity of the transplacental retinol passage to protect the fetus from a sudden change in retinol levels. Some factors can reduce maternal and umbilical cord RBP during pregnancy, such as malnutrition, gestational diabetes, preeclampsia, and anemia (TEKGÜNDÜZ et al, 2022).

Dietary AV appears to sufficiently support adequate embryogenesis if maternal hepatic stores are depleted or cannot be adequately mobilized, this may occur through a compensation with increased transport of retinyl esters in the absence of RBP-bound retinol induced by increased expression of placental LPL (QUADRO et al, 2020). It has been observed in animal models that even if maternal liver storage is inadequate, adequate dietary retinol intake may allow for normal fetal development (TEKGÜNDÜZ et al, 2022).

In cases of inadequate intake, serum retinol is maintained at the expense of the hepatic reserve to ensure adequate regulation of fetal transfer until the reserve is depleted, with depletion there is a decrease in serum concentrations and consequently fetal supply is impaired (TEKGÜNDÜZ et al, 2022; THOENE et al, 2020; AHMAD et al, 2018). Newborns born to mothers with deficient retinol concentrations have significantly lower retinol concentrations in their umbilical cord blood compared to those born to mothers with adequate concentrations (THOENE et al, 2020).

However, it has been suggested that the adequacy of maternal hepatic retinol may not guarantee the adequacy of fetal transfer, and consequently, prevention against all possible neonatal nutritional deficiencies is not guaranteed (THOENE et al, 2020).

Due to the physiological changes of pregnancy, such as increased blood volume and AV demand, there is a decrease in serum retinol levels in pregnant women, especially in the third trimester. This, together with a selective placental barrier that aims to avoid teratogenic effects, causes newborns to have a lower storage capacity for hepatic retinol, with a low reserve at birth (TEKGÜNDÜZ et al, 2022).

The transfer of AV to the fetus also influences other factors that affect the development of the fetus after birth, such as the placental transfer of antibodies from mother to baby, the control of maternal hormone expression signaling, and longitudinal growth, especially in the third trimester (AHMAD et al, 2018; GAMLIEL et al, 2016).

TRANSFER OF VITAMIN A VIA BREASTFEEDING

After birth, most serum retinol is transported to the breast by the RBP, reaching breast milk. From then on, the transport of VA into breast milk in the first six months of life provides 60 times more VA when compared to the placental route throughout pregnancy, increasing the physiologically low hepatic reserve of newborns. In addition, breast milk also transports active provitamin A carotenoids, which serve as additional nutrients for the baby (GAMLIEL et al, 2016).

The AV plays a role in mammary gland metabolism throughout lactation. RA is essential for the development of the mammary gland and in the secretory epithelium to achieve adequate milk production. Retinoids, through the RARα-dependent signaling pathway, have also been shown to regulate, at least in part, the weaning process, where epithelial cell death is coupled with tissue remodeling (CABEZUELO et al, 2020).

After the initial support by colostrum milk (<72 hours postpartum), the transitional milk (up to 15 days) supports the newborn, and milk production increases considerably to meet the nutritional and developmental needs of the rapidly growing baby, after 16 days,

the mature milk starts to support the infant. The bright yellow color of human colostrum reflects the rich carotenoid content, compared to transitional and mature milk.

The amount of VA that neonates receive from colostrum and milk depends significantly on the mother's AV nutritional status. VA levels in breast milk reflect the mother's recent diet or supplementation status more than her long-term stores (HOMBALI et al, 2019). The fat content of breast milk can be a useful vehicle to improve the bioaccessibility and bioavailability of carotenoids (MESQUITA et al, 2021). β-carotene is a normal component of human colostrum and mature milk, contributing to the antioxidant defenses of the newborn (NICHHD, 2022).

VITAMIN A IN THE EARLY STAGES OF LIFE

The beginning of life is a window of opportunities for special professional attention, with a focus on ensuring the child's present and future health (ALMEIDA et al, 2022). Recently, the Brazilian Association of Nutrology recommended extending this window from 1,000 to 2,200 days, encompassing 100 days in preconception and from the first to the fifth year of life (ALMEIDA et al, 2022). Adequate nutritional intervention is essential in care during this moment of life, especially in relation to the nutritional status of AV, in view of the increase in its demand, but for this it is necessary to consider the particularities of each phase of early life in relation to this micronutrient (ALMEIDA et al, 2022; CRUZ et al, 2017b).

PRECONCEPTION PHASE

The proper development of the embryo influences the health of the offspring in the long term, being dependent on the good quality of the gametes, which is directly related to the health condition of the parents. A series of health situations and/or behaviors of women in the preconception period have been shown to be associated with a worse prognosis for the health of their offspring, including psychological factors, stress, smoking, alcoholism, and especially poor food quality and exaggerated energy intake, in addition to obesity and malnutrition (ALMEIDA et al, 2022).

AV is essential in the process of female germ cell development. The maternal status of this micronutrient at the time of conception influences the reproductive outcome. VAD in women of reproductive age can impair the processes of fertilization, implantation, and fetal formation, impairing health, pregnancy outcomes, and the growth and development of offspring, in addition to favoring the intergenerational transmission of this condition in the long term (CLAGET-DAME et al, 2011)

FETAL PHASE

The literature has consolidated that maternal behavior during pregnancy influences the baby's health through the provision of an adequate intrauterine environment for fetal development, which favors birth conditions. (ALMEIDA et al, 2022; NEVES et al, 2015). Pregnancy is a unique period of the life cycle in which cell differentiation occurs rapidly, the presence of retinol, is essential for proper fetal growth and development and maternal metabolism, playing an important role in full-term pregnancy and birth weight (MEZZANO et al, 2022; CARAZO et al, 2021; NEVES et al, 2020; THOENE et al, 2020).

During the gestational period, there is an increase of about 40% in the daily requirements of the vitamin for the maintenance of the placenta and fetal development (CRUZ et al, 2018). During this period, the concentration of retinol in maternal plasma decreases during the first trimester and slowly increases again, again reaching normal values before delivery (CARAZO et al, 2021).

There are specific recommendations on the need to assess the nutritional status of AV of all pregnant women during prenatal care (CRUZ et al, 2018). Serum retinol concentrations tend to decrease during the trimesters of pregnancy and serum levels are intensely needed in the last trimesters when compared to the first trimester (CRUZ et al, 2017b). In pregnant women, AV may decrease more intensely in the third trimester, a period considered to have greater transfer of this vitamin to the fetus, which may be aggravated by reduced stores, gestational hemodilution, and the inability of the fetus to synthesize AV (CRUZ et al, 2018; MACHADO et al, 2016)

Nutritional intervention is one of the five axes of intervention recommended by the WHO for prenatal care (ALMEIDA et al, 2022; WHO, 2016). However, few women have access to this follow-up (HOLAND et al, 2021).

NEONATAL PHASE

The neonatal period comprises the day of birth to the first month of life of the newborn (ALMEIDA et al, 2022). Most childhood deaths are concentrated in the first year of life, especially in the first month (WHO, 2024; BUGELLI et al, 2021; FRANÇA et al., 2017). AV has been shown to be important in preventing a variety of neonatal diseases (HUANG et al, 2021).

Birth, by itself, represents an oxidative stress to the newborn. The transition from an intrauterine environment, which is relatively oxygen-poor, to the extrauterine one, which is significantly richer in oxygen, is a toxic transition and exposes the infant to increased free

radical production, leading to an imbalance in the antioxidant system (SOUZA et al, 2015). Thus, the importance of the antioxidant function of AV is highlighted.

The role of AV as an anti-inflammatory and in the immune system are also fundamental in this age group, since newborns have an immature immune system and, consequently, their functional impairment, in addition to having antigenic inexperience, which favors microbial invasion, making this group highly susceptible to infection and reinfection (SOUZA et al, 2015). In newborns, VAD increases the risk of death from infectious and respiratory diseases (GURGEL et al, 2018).

The nutritional status of the newborn is closely linked to the intake of breast milk during the first week of life (SOUZA et al, 2015). Therefore, the importance of adequate nutrition for mother-infant dyads at all times between preconception and postpartum is highlighted (THOENE et al, 2020). There is currently no consensus in the scientific literature on the cutoff value for adequate retinol concentration for newborns, or whether adult values should be chosen for this age group (DEMINICE et al, 2018).

PRESCHOOL PHASE

Globally, preschool-aged children are the population groups most at risk for VAD. The population in this group is at risk for xerophthalmia due to relatively high growth requirements and relatively low body storage. The general picture of food consumption patterns in this population is a monotonous cereal-based diet, devoid of the necessary amount of AV sources (LIMA et al, 2018; DALLAZEN et al, 2018).

In this period, the outcomes of VAD to be highlighted are dry eyes, night blindness, impaired immune system, anemia and increased mortality in children suffering from infectious diseases such as measles or diarrhea. Another important factor to note is the marginal deficiency of AV, which is usually ignored, but has a higher prevalence than VAD in this population, leading to an inadequate level of AV, which can cause anemia, respiratory and digestive tract infections, in addition to affecting the growth and development of children (CHEN et al, 2021).

Evidence shows that the chances of survival of preschool children increase when VA status improves, reducing the risk of all-cause mortality by 23-34% (YISAK et al, 2020). High levels of prevalence of VAD were also found in preschool children, especially those under three years of age, in addition to high rates of marginal VAD, which were shown to increase with age (CHEN et al, 2021; YISAK et al, 2020).

VITAMIN A DEFICIENCY PREVENTIVE STRATEGIES

With the worldwide effort to reduce the problem of VAD, strategies have been developed to prevent and treat it in populations. Among the adopted conducts are encouraging increased AR intake, industrial and homemade food fortification, and periodic supplementation of high doses with AV capsules or tablets (FAYE et al, 2021; HOMBALI et al, 2019).

BREASTFEEDING

Souza et al. point out that the hepatic concentration of retinol in newborns may be sufficient to meet daily requirements only during the first days of life, since it is a period of increased nutritional demands (SOUZA et al, 2015). Breast milk is considered the most important AV source to increase the hepatic reserves of the newborn (NEVES et al, 2015), favoring rapid growth and acting as an antioxidant and immune barrier; however, many factors modulate the composition of this nutrient in breast milk, such as diet, economic situation, and maternal nutritional status (MESQUITA et al, 2021; GURGEL et al, 2018).

The WHO recommends six months of exclusive breastfeeding and partial breastfeeding up to two years or more (MINISTRY OF HEALTH, 2019). According to the *National Study of Child Food and Nutrition (ENANI-2019).* Breastfeeding rates have been growing in Brazil, however, we are still far from the WHO goals (ENANI, 2021).

While VA stores during pregnancy are important for fetal development, healthy breast milk production needs a greater boost from diet or liver stores. Increased uptake of retinoids by the mammary gland is necessary for its production (MESQUITA et al, 2021; CRUZ et al, 2017a). The literature indicates a significant increase of approximately 90% in the need for AV during lactation (CRUZ et al, 2017a). Breastfeeding women can quickly deplete their stores of the vitamin if dietary intake is not increased during this time (TANUMIHARDJO et al, 2021; CARAZO et al, 2021).

The Dietary Reference Intake specifies the value of 4.6 IU of daily retinol for the infant in the first months of life as the amount necessary for the child to meet daily requirements, accumulate liver stores and prevent the development of clinical symptoms of deficiency (CRUZ et al, 2017a; IOM, 2001). It has been found that if maternal VA concentrations are not adequate, the mature milk of infants may not reach the adequate amount of this nutrient and they may develop VAD (CRUZ et al, 2017a).

The WHO classifies VAD as a public health issue for mothers and babies as mild (equal to or less than 10% of the population), moderate (10 to 25% of the population) and severe (equal to or greater than 25% of the population), according to the concentration of

VA in breast milk. In populations with adequate concentrations of VA, the average concentration of this vitamin in breast milk is 1.75–2.45 mol/L, while the average values are below 1.4 mol/L in populations with deficiency (SOUZA et al, 2015). The inadequacy of AV in milk can result in the maintenance of low hepatic reserves in the infant, increasing their susceptibility to severe respiratory infections, pneumonia, and diarrhea, which contributes to increased rates of infant morbidity and mortality (SOUZA et al, 2015).

Newborns rely on breast milk, infant formula, or other external sources of retinol to meet essential needs after birth. Therefore, adequate dietary intake also remains important during pregnancy to prevent deficiency in early lactation. The recommended dietary intake for maternal intake of RAE increases from 770 to 1300 µg/day from pregnancy to lactation to support the transfer of retinol through the human milk supply. Retinol stores are expected to be further depleted during lactation for retinol-deficient or under-retaining mothers with persistently inadequate dietary intake. Similarly, mothers with lower serum retinol concentrations produce milk with lower retinol content for their babies, which increases the risk of infant deficiency (THOENE et al, 2020; DEMINICE et al, 2018).

FOOD INTRODUCTION

Adequate food introduction is one of the most important factors in early life, as at this stage the individual's eating habits are established (MINISTRY OF HEALTH, 2019). After six months, breastfeeding is no longer exclusive and water and fresh food sources must be added, adapting the amount and consistency according to age, from one year onwards the child's diet is already similar to the rest of the family (MINISTRY OF HEALTH, 2019; 2014).

At this time, all the foods necessary to maintain the child's nutritional status should be introduced, including the foods that are the source of VA (MINISTRY OF HEALTH, 2019). Important factors related to eating behavior are also stimulated, such as a sense of satiety and adaptation of the food reward system, which will influence eating throughout life (MINISTRY OF HEALTH, 2019; 2014).

The child's taste is influenced by the mother's diet at the time of lactation (MINISTRY OF HEALTH, 2019; 2005). The consumption of complementary food together with breastfeeding improves the absorption of AV. Children whose mothers have adequate concentrations of AV in their breast milk reach, with relative ease, the daily requirements of the vitamin through adequate complementary foods (MINISTRY OF HEALTH., 2005).

However, an unfavorable complementary feeding pattern is observed in Brazilian children . Feeding is introduced early and in a monotonous way, the use of bottles is very frequent, even among breastfed children, complementary foods do not meet the needs of

VA, especially for low-income families. There are still many beliefs and taboos related to young children's diet, which contribute to the infrequent use of sources of vitamins and minerals, even when they are available and consumed in the family (ENANI, 2021; MINISTRY OF HEALTH, 2005).

MATERNAL AND CHILD VITAMIN A SUPPLEMENTATION

WHO and PAHO classify some countries as having severe subclinical disability and an AV supplementation program targeting children aged 6 to 59 months has been implemented since 1983. In 2005, this program was extended to postpartum women and residents in higher-risk areas, consisting of the administration of a single dose of AV with 200,000 IU orally in the immediate postpartum period (MESQUITA et al, 2021; MIRANDA et al, 2018; CRUZ et al, 2017a).

Postnatal supplementation is performed to minimize reversible damage to the newborn and partially recover the maternal state of AV before lactation, being an emergency measure, not the resolution of the central problem (GURGEL et al, 2018). Despite significantly increasing the VA in colostrum, concentrations seem to decrease in mature milk, reaching insufficiency 30 days after calving. There is still contradiction in the literature regarding the ideal dose of postnatal supplementation (CRUZ et al, 2017a).

In 2011, the WHO began to recommend supplementation with daily or weekly doses with daily or weekly doses for pregnant women from vulnerable groups in areas with endemic deficiency, due to the benefits achieved in this population group, a recommendation reaffirmed in 2013 (CRUZ et al, 2017a; NEVES et al, 2015). The recommended dose is 10,000 IU daily or 25,000 IU weekly for four to eight weeks for prevention and treatment of gestational night blindness, without risk of teratogenicity (SOUZA et al, 2015; NEVES et al, 2015).

Despite having lower serum retinol levels compared to adult populations, the WHO currently does not recommend VA supplementation for infants aged one to five months, stating that supplementation offers no benefit in reducing infant morbidity and mortality (THOENE et al, 2020). However, the literature points to AV supplementation as a way to increase AV stores in the newborn and improve infant survival (CHOOBDAR et al, 2023). A review in 2021 indicated a positive effect on oral supplementation of newborns, without adverse effects such as Hypervitaminosis or increased intracranial pressure (HUANG et al, 2021).

AV supplementation has been implemented in some regions and countries, but full implementation of periodic high-dose interventions is difficult in countries with large

populations; thus, the coverage rate remains low (ZHAO et al, 2022). Despite its importance, there are a small number of studies available on AV supplementation during the gestational period, mainly studies on the reduction and prevention of maternal-neonatal morbidity and mortality (CRUZ et al, 2017a).

FOOD ENRICHMENT

Fortification, enrichment or simply addition is a process in which one or more nutrients, whether or not naturally contained in it, are added to the food, within the legal parameters, with the aim of reinforcing its nutritional value and preventing or correcting any nutritional deficiencies presented by the general population or groups of individuals. Food fortification has been used as a low-cost strategy to prevent nutritional deficiencies in many countries, both developed and developing (HOMBALI et al, 2019).

It is proposed that food fortification with VA works by increasing daily intake and absorption of the vitamin to sufficiently high levels, aiming to close the existing intake gap and significantly increase liver stores to correct VAD and its implications on health and survival (HOMBALI et al, 2019). Staple food vehicles potentially suitable for AV fortification in public health programs include refined or crude sugar, edible vegetable oils, fats, and cereal grains (rice); wheat flour, corn flour or corn flour; condiments and seasonings; and powdered or liquid milk (WHO, 2006).

Some countries have implemented mandatory programs at the national level to fortify staple foods with VA. A global review concluded that fortifying staple foods with VA and other micronutrients may not improve vitamin status. However, for children and adolescents in low- and middle-income populations, this conduct may lead to a lower risk of subclinical AV deficiency (HOMBALI et al, 2019).

VITAMIN A AND CAUSES OF INFANT DEATH

PREMATURITY

Prematurity is the leading cause of death and disability in children under five years of age worldwide (YE et al, 2022). The AV plays a vital role in full-term pregnancy, providing fetal reserves and maintaining maternal metabolism during pregnancy, in addition to its role in the immune system (MEZZANO et al, 2022; SOUZA et al, 2015). Preterm infants represent a population that inspires concern about AV, as the vitamin is transmitted primarily from the mother through the placenta to the fetus in the third trimester. Therefore, VAD is prevalent in preterm infants (YE et al, 2022; SUN et al, 2022; DING et al, 2021; TAO et al, 2016). As a result, it is expected that preterm birth will reflect negatively on the nutritional

status of this vitamin, causing low concentrations of serum retinol and retinol-binding protein (RBP), in addition to low hepatic reserve (SUN et al, 2022; SOUZA et al, 2015).

At the same time, the nutritional needs of AV in a premature infant are higher than at any other time in life. This is due to the intense catabolism during the first few weeks after birth with the low supply of retinol in the liver at birth, the low concentrations of plasma retinol, and the low concentrations of RBPs, compared to full-term infants (SOUZA et al, 2015).

In addition, hepatic storage of VA is not as efficient in extremely preterm infants, which contributes to low plasma retinol concentrations (SUN et al, 2022). Studies show that the lower the gestational age, the lower the weight and the more severe the VAD (HUANG et al., 2021; DING et al, 2021). VAD in premature infants can cause retinopathy due to prematurity, in addition to making them predisposed to the development of various diseases (YE et al., 2022; SUN et al, 2022).

However, the milk of breastfeeding women who had preterm delivery tends to be inadequate from a quantitative point of view, since fetal needs were not fully met with the interruption of maternal-fetal transfer. In case of absence of breast milk, the baby can stay for several weeks on enteral feeding, whose composition does not meet its needs adequately (SUN et al, 2022; MESQUITA et al, 2021; SOUZA et al, 2015). Thus, low VA level in preterm infants at birth can last throughout childhood (TAO et al, 2016).

If the hepatic reserves of the newborn remain low, it can favor the installation, maintenance and/or worsening of OLD, forming a vicious cycle of infection/OLD/infection, in addition to the occurrence of long-term episodes (SOUZA et al, 2015). The risks of developing diseases related to AV status that are of most concern to premature infants are respiratory distress syndrome, chronic lung disease, retinopathy of prematurity, necrotizing enterocolitis, patent ductus arteriosus, and infections in general (TAO et al, 2016).

Due to the fragility of this population, when it comes to premature babies, not only the effectiveness but also the safety of the intervention must be considered. Despite the need for deeper checks, the use of clinical VA has been shown to be safe for premature infants, free from adverse reactions such as pain and sepsis (DING et al, 2021). There is still a lack of evidence to determine the most appropriate AV treatment method for premature infants (DING et al, 2021; TAO et al, 2016)

CONGENITAL ANMALIES

The composition of the maternal diet during pregnancy has metabolic importance for the health of the offspring, even before conception, and can permanently program their

offspring (MESQUITA et al, 2021). Once VA is deficient, it will not only affect the normal growth and development of the embryo, but it can also cause congenital diseases, including pulmonary hypoplasia, central nervous system malformations, and bone deformity of the fetus (MA et al, 2021). VAD predisposes pregnant women to miscarriage, as well as brain, macular, renal, and vascular congenital defects (MESQUITA et al, 2021).

Two periods during pregnancy are more critical and should be treated with the utmost care, the first trimester of pregnancy (up to 14 weeks), when the vital parts of the body are formed and the end of pregnancy, when the maturation of the hypothalamic-pituitary axis occurs (MESQUITA et al, 2021). Unfortunately, the initial window of development occurs before many women can be aware of pregnancy, and VAD is chronic among women of childbearing age, which is compounded by the increased demand of this critical period (Gilbert et al., 2023; IBGE, 2020; MICHIKAWA et al, 2019).

The relationship between maternal nutrition and fetal programming is informed through endocrine signals, epigenetics, and oxidative stress. During pregnancy, carotenoids play an important role in promoting communication between cells (gap junctions), regulating hormonal imbalances, and increasing the immune response, which prevents gestational complications. The fetal and neonatal periods have considerable epigenetic plasticity. Altering VA signaling through dietary and genetic disruptions can create birth defects (Gilbert et al., 2023; MESQUITA et al, 2021)element. Findings in the literature suggest a crucial role of pro-AV carotenoids and preformed AV in the epigenetic programming of offspring, possibly influencing the phenotype and the development of diseases in adulthood. It has been suggested that the performance of carotenoids as antioxidants can reduce oxidative stress, infection, inflammation, and damage to the placenta during pregnancy, thus conferring a healthy life to the offspring (MESQUITA et al, 2021). The type of congenital anomaly most associated with AV in the literature are those of bone origin (ROCKE et al, 2022; MICHIKAWA et al, 2019).

RESPIRATORY DISEASES

Respiratory tract infections (RTIs) are the most widespread infectious diseases in children, promoting high morbidity and mortality. Preschool children who have experienced more than eight episodes of airway infections per year are considered to have recurrent respiratory tract infections (IRTRs) (ZHANG et al, 2024; ABDELKADER et al, 2022; SUN et al, 2022; WANG et al, 2021). Respiratory diseases such as asthma, pneumonia, and bronchiolitis are the most common reasons for hospitalization in the pediatric population (GOTH et al, 2022; WANG et al, 2021). Infection from TRRIs can, over the course of

occurrences, migrate to other organs, in addition to harming the child's physical and mental health in the long term, and increasing health care expenses (ZHANG et al, 2024; HURWITZ et al, 2017)

The mechanisms by which AV aids in the prevention of respiratory diseases include: regulation and promotion of the proliferation and differentiation of various lung cells, thereby maintaining the integrity of the airway epithelium; improvement of immune function, further enhancing resistance to disease and damage; promotion of the synthesis of active substances on the lung surface; antioxidant effect; and promotion of repair after lung injury (WEI et al, 2024; HUANG et al, 2021). VA can regulate the content of mRNAs and reduce the expression of fatty acid synthase genes, affecting the synthesis of phospholipid precursors. Thus, protein synthesis of phospholipids and pulmonary surfactants is increased, promoting lung development and maturity. (DING et al, 2021). Pulmonary surfactant is essential for maintaining alveolar stability and reducing surface tension during breathing (WEI et al, 2024). In addition, the vitamin promotes antioxidant protection and the functioning of repair mechanisms after lung injury (DING et al, 2021).

AV is recognized for its role in lung maturation and function during pregnancy and lactation (CRUZ et al, 2017a) and is required in the fetal lung for cell differentiation and surfactant synthesis (SUN et al, 2022). Studies in animal models have observed that it can improve alveolar formation and alveolar hair growth, reduce the expression of elastin messenger ribonucleotides from the lung parenchyma and the accumulation of elastic fibers, and promote better gas exchange (DING et al, 2021). VA consumption is exceptionally high as the lungs grow and develop during the last trimester and shortly after birth due to its role in lung maturation (GOTH et al, 2022; SUN et al, 2022). In addition, free radicals produced by oxidative stress from childbirth increase vitamin requirement and have been associated with damage to the respiratory system (SOUZA et al, 2015).

In preterm infants, this issue is even more concerning due to the immaturity of antioxidant systems and inadequate AV reserves (SOUZA et al, 2015). In animal experiments, lower plasma concentrations and hepatic retinol reserve were found in preterm infants who developed bronchopulmonary disease, compared to those who did not, corroborating the hypothesis that VAD contributes to the development of chronic lung disease and/or respiratory tract infections in this type of population (SUN et al, 2022). Wei et al. studied the relationship between cord blood AV and neonatal lung diseases, cord blood VAD and preterm birth were independent risk factors for neonatal lung diseases, and the lower the level of AV in umbilical cord blood, the more susceptible newborns were to neonatal respiratory infections (WEI et al, 2024).

Childhood-acquired lung function predicts adult lung function, so maternal and neonatal AV levels are predictive of future lung function and respiratory morbidity (GOTH et al., 2022). It was found that administering VA supplementation before and during pregnancy and postpartum in women with VAD had an influence on their children's lung function in the long term. This benefit is likely due to the effects of in utero supplementation (CRUZ et al, 2017a).

SEPTICEMIA

Sepsis is the dysfunction of one or more organs resulting from the host's dysregulated response to an infection, severe or not, that has not been treated correctly. The inflammatory response originates in one organ and can extend and affect others, causing inflammation in different parts of the body, endothelial and mitochondrial vascular dysfunction, and life-threatening (DOLIN et al, 2023; LOU et al, 2023; FIOCRUZ, 2021; ZHANG et al, 2019; CHERUKURI et al, 2019). The intrinsic factors of sepsis refer to the immaturity of the immune system and the barrier functions of the skin, mucous membranes, and gastrointestinal tract. (FIOCRUZ, 2021; SOUZA et al, 2015).

With a mortality rate of more than 25%, sepsis represents a significant burden on public health resources. A steady increase in the incidence of severe sepsis has been reported in recent decades (LOU et al, 2023; ZHANG et al, 2019; CHERUKURI et al, 2019).

Notably, sepsis is a common cause of death in children (CHOOBDAR et al, 2023; ZHANG et al, 2019). Mortality from severe sepsis has been reported to be as high as 34.6% in children. It was revealed that more than 50% of deaths in preschool children were due to serious infectious diseases that can result in sepsis (ZHANG et al, 2019).

Newborn patients and those with immunosuppression are among the most affected by sepsis. In this age group, the risk of developing the disease is inversely proportional to gestational age (FIOCRUZ, 2021; SOUZA et al, 2015), and the lack of specific symptoms hinders early diagnosis, which is essential for survival (CHOOBDAR et al, 2023; FIOCRUZ, 2021. In developing countries, neonatal sepsis is a leading cause of death and morbidity in infants, accounting for 44% of all deaths. Lower levels of VA in newborns and their mothers have been associated with increased risk of sepsis (CHOOBDAR et al,2023).

AV is an immunomodulator and its deficiency can cause an imbalance between pro- and anti-inflammatory factors and impaired immune function, which are found in sepsis. VAD is also associated with a worsening of the inflammatory response, generating an unfavorable situation for patients with sepsis in the early stages (CHOOBDAR et al, 2023; ZHANG et al, 2019). In addition, sepsis is known to increase urinary retinol loss by more

than five times the reference dietary intake, contributing to deficiency of this micronutrient and greater fragility to recurrent infections (CHERUKURI et al, 2019). Lower incidence of sepsis in children can be attributed to improved immune function after VA administration (CHOOBDAR et al, 2023; CHERUKURI et al, 2019). It has been suggested that RA may aid in the treatment of sepsis through the activation of RAR/RXR by promoting the expression of mitogen-activated protein kinase phosphatase 1 (MKP-1), which reduces inflammation by inhibiting the production of pro-inflammatory cytokines by phosphorylation of the mediators p65 and JNK (DOLIN et al, 2023). VAD may play another role in sepsis by dysregulating the total platelet count, in addition to playing a specific role in the post-disease period through immune system dysfunction and the epithelial barriers that cover the digestive, respiratory, and urinary tracts, leading to a higher risk of clearance of bacteria in the blood and overlapping infection (ZHANG et al, 2019).

MENINGOENCEPHALIC DISEASES

Meningoencephalitis, inflammation of the brain and the membranes that surround it (meninges), is usually caused by a viral, bacterial or fungal infection (MARFIN et al, 1994). Children under five years of age are among the most vulnerable population for these diseases, in which the prevalence of the infectious agent is associated with previous immune status. Among the main symptoms are nausea, vomiting and food refusal, thus highlighting the importance of nutritional status in the occurrence, duration and outcome of meningoencephalitis (MINISTRY OF HEALTH, 2017). There are few studies on AV and meningoencephalic diseases. It has been suggested that VA supplementation may contribute to reducing the severity and mortality associated with certain meningoencephalic diseases (MARFIN et al, 1994). AV supplementation has been shown to be effective in the treatment of measles-induced encephalitis. A dose of 200,000 IU per day for two days can lead to reduced inflammation and reduced mortality from the disease in children (DIWAN et al, 2022; AL-QAYOUDHI et al, 2016)

DISEASES OF THE DIGESTIVE TRACT

Intestinal inflammatory disorders have been recognized to stimulate the production of tumor necrosis factor-alpha (TNF-α), a key etiological mediator of intestinal barrier dysfunction. Reduced numbers of regulatory T cells (Tregs) in the intestinal mucosa of patients with this pathology have been associated with disrupted epithelial junctions. The strong exposure linked to the high susceptibility to infections characteristic of this age group makes it a crucial moment of intervention for these diseases (MEDEIROS et al, 2018).

Studies have shown that AV is associated with diseases of the gut microbiota and gastrointestinal tract, due to its physical barrier functions (CHENG et al, 2021; LOUNDER et al, 2017). Supplementing with VA helps relieve diarrhea and improves intestinal damage (CHENG et al, 2021). Retinoids are also essential micronutrients to improve malnutrition and enteric diseases and related infant mortality and morbidity (MEDEIROS et al, 2018).

AV modifies intestinal permeability, and is essential for the development of mucosal permeability due to the regulation of lymphocyte traffic to the intestine. AR promotes the secretion of interleukin 22 (IL-22), known to promote the proliferation and healing of epithelial cells, restore tight junctions, and increase the mucus production of goblet cells (MEDEIROS et al, 2018; LOUNDER et al, 2017; LOUNDER et al, 2017).

In addition, gastrointestinal pathologies by themselves are associated with malnutrition, due to their malabsorptive character, impairing the state of AV. Children with diarrheal disease were more malnourished than those without diarrhea, as diarrheal disease disrupted luminal mucosal function and resulted in metabolic dysfunction, malabsorption, and nutrient loss, loss that impaired growth, development, and nutritional status (CHANIE et al, 2021). A double causal relationship was observed between VAD and intestinal villus impairment (HOSSAIN et al, 2016).

Although widely associated with VAD, mortality rates from diarrheal diseases have declined in recent decades, on the other hand, there is increasing morbidity from non-diarrheal environmental enteric dysfunctions, associated with enteric pathogens in early life (MEDEIROS et al, 2018). In this context, studies have addressed the concept of environmental enteropathy, a usually subclinical disorder that usually occurs among residents of low- and middle-income (developing) countries where sanitation is often poor and hygiene practice is inadequate. Persistent contact/exposure to fecal pathogens can trigger inflammation and structural changes in the small intestine, which ultimately result in functional changes. It is manifested by increased intestinal permeability, malabsorption, and inadequate growth in individuals without evident diarrhea (MEDEIROS et al, 2018; HOSSAIN et al, 2016).

Although VAD is associated with a higher risk of occurrence and aggravation of enteric infections, it was pointed out that supplementation may not protect against reinfections, highlighting the need for long-term follow-up. Studies have demonstrated the impact of environmental enteropathy on the maternal and child population. This condition has been linked to impaired intestinal barrier function, leading to malnutrition, impaired intestinal absorption, vaccine response failure, and cognitive deficits in children (MEDEIROS et al, 2018).

CONCLUSION

The metabolism of VA is finely regulated in the body. Absorption, excretion and transport are carried out in order to promote constant serum concentrations, being mediated by the available hepatic reserve and its mobilization into the bloodstream. In view of the important roles played by AV in growth and development, maintenance of the visual cycle, and strengthening of the immune system, as well as the relationship between VAD and increased mortality in children under five years of age due to inflammatory and infectious diseases, the importance of promoting the adequacy of this micronutrient during early life is emphasized in order to improve health in the maternal and child context. In this sense, interventions aimed at improving the status of AV, such as supplementation, nutritional education, and promotion of breastfeeding, can have a positive outcome in the formation and maintenance of infant hepatic reserve, playing an important role in the prevention and management of childhood diseases and in the reduction of mortality. In addition, public health policies that aim to improve access to VA-rich foods and quality health services can have a significant impact on children's health and well-being, especially in vulnerable communities.

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