Chapter

# Vitamin E for the Children: From Neonates to Adolescents

Jaydeb Ray1,[[1]](#footnote-1)\*, Shrilaxmi Bagali2 and Surupa Basu1,2

1Department of Pediatric Medicine,

2Department of Biochemistry, Institute of Child Health, Kolkata, India

3Laboratory of Vascular Physiology and Medicine,   
Department of Physiology, BLDE (Deemed to be University)   
Shri B.M.Patil Medical College, Hospital and Research Centre, Vijayapur, Karnataka, India

## Abstract

Early childhood is the most rapid period of growth and a properly balanced diet is essential to ensure optimal development. Similarly, adolescence is another critical period of growth, during which the requirements for vitamins, minerals and trace elements increase substantially. Nutrition in preschool age also plays an important role in influencing growth and development, as well as future risk of diet-related diseases. Vitamin E is a collective term to include compounds either naturally occurring or synthetic analogues that exhibit biological activity of vitamin E. Naturally occurring homologues of vitamin E are α, β, γ, δ tocopherols and α, β, γ, δ tocotrienols. Vitamin E is micronutrient, a fat-soluble vitamin which has an important role in human beings, especially in children. It has been reported that vitamin E probably influences neonatal hyperbilirubinemia. It is vital for the health and well-being of preterm neonates. It has been observed that mothers who have given birth prematurely have higher levels of vitamin E in the breast milk and probably may have a beneficial role in preventing or limiting some of the health conditions associated with preterm birth like anaemia due to haemorrhaging. It is present at higher than usual levels in the breast milk of mothers who have given birth prematurely and may be able to prevent or limit some of the health problems associated with preterm birth, such as anaemia due to haemorrhaging. It has been thought that deficiency of vitamin E is at least partly responsible for the anaemia which often occurs 4 to 6 wk after premature birth, hence routine dietary supplementation with vitamin E is frequently recommended. Interestingly it was further observed that additional supplementation of Vitamin E to preterm infants may also enhance the risk infections, such as sepsis which may be fatal for life. The recommended intakes of vitamin E are as following: for healthy breastfeeding infants of 0-6 months old is 4 mg/d (6 IU); for infants of 7-12 months old is 5 mg/d (7.5 IU); for children of 1-3 years old is 6 mg/d (9 IU); for those of 4-8 years old is 7 mg/d (10.5 IU); for those of 9-13 years old, 11 mg/d (16.5 IU); for those over 14 or pregnant women of any age it is 15 mg/d (22.5 IU); and for lactating women of any age, 19 mg/d (28.5 IU). In preterm and very low birth weight infants supplementation with 10-25 mg/kg/d intramuscular (i.m) has been recommended within 8-24 hours of birth and continued up to 30 days. These doses may be accompanied by doses of 15-20 mg/kg administered intravenously, subsequently, 15-200 mg/d orally started after at least three days of life. One must note that treatment with vitamin E should be under medical supervision. Adolescence is the transitional stage of development between childhood and adulthood and it is associated with marked physical growth, reproductive maturation, and cognitive transformation. It has been observed that vitamin E as a micronutrient is needed around 15 mg/d (22.5 IU/day) for adolescents of both sexes to support the growth and developmental changes of adolescence. Despite the seldom occurrence of true vitamin E deficiency in children, it has been observed in cases of severe malnutrition, genetic defects affecting the α-tocopherol transfer protein, and fat malabsorption syndrome. Vitamin E an important antioxidant is genuinely needed for protection against complex stress mechanism of cells.

## 1. Introduction

Reactive oxygen species (ROS) are a by-product of normal cellular metabolism. They are also generated following exposure to certain environmental factors like air pollution, cigarette smoking, heavy metals, ionizing radiation etc. Although at low to moderate concentrations, ROS produced endogenously take part in some of the physiological processes like intracellular differentiation and cell progression, the arrest of growth, apoptosis, immunity and defence against microorganisms (Kurutas et al., 2005), at high concentrations poses a significant threat. Being highly reactive, at high concentrations, they damage cell structures like lipids, proteins, nucleic acids, carbohydrates and alter their functions (Birben et al., 2012). To counteract the ROS, the human body is equipped with an antioxidant defence that scavenges the ROS. The endogenous antioxidants include superoxide dismutase (SOD), catalase, glutathione peroxidase (GSH-Px), glutathione reductase, heme oxygenase-1 and redox proteins like thioredoxins, peroxiredoxins, glutaredoxins, flavonoids, bilirubin, uric acid, melatonin, thiols, reduced coenzyme Q, alpha lipoic acid, endogenous organic selenium, and the metal binding proteins transferrin, ferritin, lactoferrin, ceruloplasmin and albumin. Vitamin C, vitamin E, β-carotene, stilbene antioxidants, phenolic acids, flavonoids, oil lecithins, acetylcysteine, exogenous selenium, zinc, magnesium, copper are some of the exogenous antioxidants (Sen and Chakraborty, 2011).

Oxidative stress results when there is increased production of reactive oxygen species and/or depletion of antioxidant defence (Jesenak et al., 2017). Oxidative stress has been implicated in the pathophysiology of several diseases including cancer, atherosclerosis, hypertension, ischemia/perfusion, diabetes, acute respiratory distress syndrome, idiopathic pulmonary fibrosis, chronic pulmonary diseases, asthma (Birben et al., 2012).

Vitamin E is an essential micronutrient, a fat-soluble vitamin and a potent non-enzymatic antioxidant. Vitamin E is a collective term to include compounds either naturally occurring or synthetic analogues that exhibit biological activity of vitamin E. Naturally occurring homologues of vitamin E are α, β, γ, δ tocopherols and α, β, γ, δ tocotrienols. Among the naturally occurring homologues of vitamin E, α- tocopherol is biologically the most active form and also the most abundant form found in the human tissues and blood (Traber and Kayden, 1989) (WHO and FAO, 2004). In blood, about 90% of vitamin E is α- tocopherol and the rest 10% is γ – tocopherol. In the tissues, α- tocopherol is present at a higher concentration (about 10 times higher) than the γ – tocopherol (Dror and Allen, 2011). In the diet, vitamin E is present as tocopherol and tocopheryl esters. The most common dietary tocopherols are α and γ – tocopherol, γ – tocopherol being the predominant form (Dror and Allen, 2011).

Vitamin E is a major membrane-bound phenolic antioxidant, localized on the hydrophobic site of the phospholipid bilayer of the cell and subcellular membranes, at a concentration of one molecule for every 2000 phospholipid molecules (Kagan VE, 1998) (WHO and FAO, 2004). It acts as a chain breaking, free radical trapping antioxidant in the cellular membrane. It also protects the plasma lipoproteins against oxidation. Vitamin E donates an electron to peroxyl radical produced during lipid peroxidation to form relatively unreactive tocopheroxyl radical. The tocopheroxyl radical is reduced back to tocopherol by reaction with vitamin C or glutathione ((Dror and Allen, 2011). It thus protects the PUFA and other components of the cell membrane and plasma lipoproteins from oxidative damage by free radicals (Murray et al., 2006; Rizvi et al., 2014).

In addition to its role as a potent antioxidant, it plays an important role in development and functioning of the immune system, acts as a redox sensor, regulates signal transduction, gene expression, plays a role in cellular trafficking, control of inflammation. α- tocopherol maintains cardiovascular health by inhibiting platelet aggregation, smooth muscle proliferation and by maintaining endothelial function. α- tocopherol affects cognitive development and physical performance (Dror and Allen, 2011). α- tocopherol also has a role in improving the repair of the cell membrane, in particular, the muscle membrane which is exposed to constant physical stress by lipid peroxidation (Raederstorff et al., 2015).

Deficiency of vitamin E: The diet usually contains sufficient vitamin E to satisfy the nutritional requirements and hence the possibility of dietary deficiency of vitamin E is rare (WHO and FAO, 2004). The deficiency of vitamin E is commonly observed in preterm infants due to low stores, in infants and adults with fat malabsorption secondary to cystic fibrosis, cholestatic liver disease, abetalipoproteinemia, homozygous hypobetalipoproteinemia, celiac disease, chronic pancreatitis, intestinal resection, individuals with genetic anomalies in α- tocopherol transport protein (α- TTP) or lipoprotein synthesis (Kalra et al., 2001). Vitamin E deficiency is also observed at two extremes of nutrition i.e., severe malnutrition and obesity as reported in several studies (Kalra et al., 2001). Inadequate dietary intake of fat, proteins and calories are associated with low circulating α-tocopherol levels since they have a role in the absorption of vitamin E and its lipoprotein transport (Traber, 2014). In their prospective therapeutic intervention study, Kalra et al., reported reduced serum alpha-tocopherol levels and presence of neurological signs of vitamin E deficiency in children with protein-energy malnutrition (PEM) and also made an interesting observation of improvement in serum alpha-tocopherol levels and neurological signs following administration aqueous oral vitamin E supplementation for 6 weeks (Kalra et al., 2001). In developing countries, malaria and HIV infection are other causes of vitamin E deficiency in children in addition to protein-energy malnutrition (Dror and Allen LH, 2011). Deficiency of vitamin E is characterized by a progressive neurological disorder, spinocerebellar ataxia due to dying of peripheral nerves in particular sensory neurons. With continued vitamin E deficiency, the neurologic disorder becomes more severe ultimately leading to ataxia and onset of muscle deterioration specifically involving cardiomyocytes. Vitamin E deficiency ultimately causes death. Children with vitamin E deficiency can be supplemented with vitamin E at a dose of about 1000 mg/day. Vitamin E supplementation stops the progression of neurologic disorders and in some patients may even reverse the symptoms (Traber, 2014).

### 1.1. Neonates - A Pediatricians View

The period of childbirth is a crucial phase not only for the mother but also for the infant as it involves a transition from a relatively hypoxic intrauterine environment with a PO2 of 20-25 mmHg to a normoxic extrauterine environment with a PO2 of 100 mm Hg inducing the generation of excess ROS (Friel et al., 2004). Added to this is the immature antioxidant defence, susceptibility to infection or inflammation, excess free iron that enhances the production of highly toxic hydroxyl radicals via Fenton reaction (Perrone et al., 2010). All the above-mentioned factors make the newborn susceptible to oxidative stress, especially preterm infants. The mode of delivery i.e., vaginal delivery or caesarean section does not seem to affect the degree of fetal oxidative stress (Wilinska et al., 2015). Oxidative stress may be involved in the pathogenesis of several disease states in the newborn. Different organs are affected often simultaneously and the manifestations vary according to organ most affected. In 1988 Saugstad introduced the term ‘oxygen radical diseases of neonatology’ to include all conditions with a possible oxidative stress aetiology. The term includes bronchopulmonary dysplasia (BPD)/chronic lung disease (CLD), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), periventricular leukomalacia (PVL), patent ductus arteriosus (PDA), respiratory distress syndrome (RDS) (Gitto Eloisa et al., 2012) (Ozsurekci and Aykac, 2016).

## 2. Neonate to Adolescence: Respiratory, Cardiovascular and Neural Physiology

The respiratory system is one organ that is continuously exposed to high oxygen tension owing to its function of gaseous exchange. It is also exposed to various environmental pollutants like cigarette smoke, diesel exhaust, O3 generating free radicals. Free radicals are also generated as a consequence of lung diseases and infections. The generated free radicals cause oxidative damage of the cellular proteins, lipids, carbohydrates and DNA of the lining epithelium of the respiratory tract thereby impairing the cell functions and enhancing the inflammatory reactions thus setting a vicious cycle. The respiratory system suffers more oxidative stress in comparison to other tissues in the body. To counteract the enhanced generation of free radicals the respiratory lining epithelium is lined by a thin, highly complex and heterogenous layer of fluid called the respiratory tract lining fluid (RTLF) that provides the antioxidant defence. The RTLF contains high concentrations of antioxidants like vitamin E, vitamin C, urate, reduced glutathione (GSH), and extracellular superoxide dismutase (SOD), catalase, glutathione peroxidase. Additional antioxidants include mucopolypeptide glycoproteins, ceruloplasmin, iron-binding proteins (e.g., lactoferrin and transferrin) and small molecules such as bilirubin. Marked interindividual differences in the composition and size of the RTLF antioxidant pool exist (Kelly, 2005).

Immediately following birth the first challenge the newborn faces is to initiate breathing and gaseous exchange for its survival. With the first few breaths, the alveoli expand and the respiratory system undergoes major changes. At birth, the respiratory rate is usually high about 30-40 breaths/min and decreasing gradually to 20-25 breaths/min at 5-12 years of age (Moini J, 2013). The growth of the lung continues with the number of alveoli increasing and growth of the airways throughout childhood into adulthood (Kelly, 2005), (Moini J, 2013). In addition to initiating a gaseous exchange, the lung in the newborn must be capable of resisting the oxidative stress to which it is exposed immediately on birth on encountering a relatively high atmospheric oxygen tension compared to an intrauterine hypoxic environment. A fully developed lung with well equipped antioxidant defence is a prerequisite for the immediate survival following birth in term infants. However, the problem arises in premature infants where the lungs are not sufficiently developed structurally and functionally, necessitating supplemental O2 therapy. Poor antioxidant defence in preterm infants and supplemental oxygen therapy leads to oxygen-related lung injury progressing to bronchopulmonary dysplasia. Hence supplementation with antioxidant could possibly minimise the lung injury in premature babies (Kelly, 2005).

The antioxidant vitamin plays an important role in maintaining the health of lung throughout the lifespan. Inadequate intake of antioxidant vitamins during periods of growth and development during childhood may affect lung functions as an adult. Studies have demonstrated that adequate intake of fruits and antioxidant vitamins like vitamin C, vitamin A and vitamin E protect the lung from damage and low dietary intake is associated with obstructive airways conditions and reduction in pulmonary functions particularly forced expiratory volume in 1 sec and forced vital capacity. It has been observed that low intake of antioxidant vitamins may have untoward effects on pulmonary functions in children of school age. Association has been observed between low dietary intake of vitamin E and deficits in FEF 25-75%, a measure of small airway flow since vitamin E plays a vital role in maintaining functions of the small airway (Gilliland et al., 2003).

Immune cells owing to their metabolic activity and polyunsaturated fatty acid content are susceptible to oxidative damage. Vitamin E plays a vital role in protecting the immune cells from oxidative damage. It has been observed that serum vitamin E levels along with serum vitamin A and vitamin D levels were lower in children with recurrent respiratory tract infections. Hence intake of adequate vitamin E and normal serum vitamin E levels may prevent the occurrence of recurrent respiratory tract infections in children (Zhang et al., 2016). Graham Devereux et al., in their longitudinal cohort study observed a negative association between maternal vitamin E intake during pregnancy assessed at 32 weeks of gestation and wheezing and asthma outcomes in children at 5 years of age. Low maternal intake of vitamin E during pregnancy is associated with increased probability of wheezing and asthma in 5-year-old children and with persistent asthma and persistent wheezing phenotype during first five years of life (Devereux et al., 2006). This could be probably due to modulation of fetal airway development by maternal vitamin E intake. In addition to the above observation, it has been reported in rat models of fetal hypoplastic lung growth that maternal vitamin E supplementation promotes the growth of hypoplastic lung increasing lung complexity, surface area and bud count (Islam et al., 1999).

The cardiovascular system undergoes major changes following birth. The fetal shunts (foramen ovale and ductus arteriosus) begin to close. The relative size of the heart is large at birth and the right ventricle is stronger than the left ventricle. During the first year of life, the heart increases in size and weight and almost becomes double the size and the left ventricle becomes stronger. The heart rate which is high at birth begins to slow down and the systolic blood pressure begins to increase with age (Moini J, 2013).

Atherosclerosis is the initiating event in the majority of cardiovascular diseases. The primary event in atherosclerosis is the oxidation of lipoproteins particularly of the LDL to form oxidised LDL (Ox-LDL) in the vessel wall. The sources of oxidants being endothelial cells, smooth muscle cells and macrophages. The Ox-LDL is transported across the endothelium into the arterial wall at sites of endothelial damage caused by a number of factors (physical or chemical forces, infection) including Ox LDL itself (Madamanchi Nageshwara et al., 2005). Fatty streaks in the aorta, an early sign in atherosclerosis may be detected in childhood and is related to fat mass, blood pressure, plasma cholesterol and triacylglycerol levels (Mishra et al., 2003). Fatty streaks are the precursors for the development of fibrous plaque and other complex lesions that cause angina pectoris and myocardial infarction (Institute of Medicine (US) Panel on Dietary Antioxidants and Related Compounds). Therefore it can be concluded that atherosclerosis begins as early as in childhood and continues into adolescence and adulthood and is influenced by the presence of cardiometabolic risk factors like glucose intolerance, obesity, high blood pressure, high levels of total and low density lipoprotein (LDL) cholesterol and low levels of high density lipoproteins (HDL) cholesterol (Funtikova et al., 2015). Cardiovascular disease in adulthood is not just a result of risk factors present during midlife but a consequence of risk factors present during childhood tracking into adulthood. Several studies have demonstrated the influence of diet during childhood and adulthood on cardiovascular disease risk. Diet with low saturated fat, plenty of fruits and vegetables and fish and rich in antioxidants are associated with reduced risk of cardiovascular disease (Ness et al., 2005). Also, there is evidence in support of the role of antioxidants like α-tocopherol in modifying cardiovascular disease (CVD) risk. Since vitamin E is a potent lipid phase antioxidant, it protects against LDL oxidation. Additionally, it activates the nitric oxide pathway in the endothelial cells to reduce vasoconstriction. Adequate intake of vitamin E during childhood ensures optimal development of vascular responsiveness and compliance with protection being conferred by sustained intake during adulthood (Mishra et al., 2003).

The development of the brain is a complex process beginning in the intrauterine life and continuing into adolescence and even beyond. From birth till 2 years of age significant brain growth with peak synaptic development takes place. The synaptic density reaches adult levels by preschool age. However, myelination of some regions of the brain particularly those that are involved in the control of higher cognitive functions like frontal lobe continues until adolescence. The development of grey matter is almost complete by the age of 7-11 years while the development of white matter continues beyond 20 years of age. During childhood, there is the development of specific cognitive functions like language, reading and memory as specific areas of the brain that are involved in these functions mature. Development of higher cognitive functions controlled by frontal lobes like planning, sequencing and self-regulation occurs at the time of growth spurts during first 2 years of age and then between 7-9 years and also around 15 years of age. The development of some subcortical structures like basal ganglia, amygdala, and hippocampus mediating other higher cognitive functions like memory, executive functions and emotions also continues until late adolescence. Besides the predominant role of genetic factors in brain development several environmental factors also contribute to its development notably nutrition. Nutrition makes a very significant contribution to cognitive development by influencing genetic expression. The first 2 years of life is very crucial for brain development since the majority of brain growth and development occurs during this period with the brain attaining 80% of the adult weight. In addition, adolescence is also an important stage for the structural reorganization and maturation of the brain especially the prefrontal cortex. Hence adequate nutrition must be ensured during these stages for complete brain development (Nyaradi et al., 2013).

The brain is susceptible to oxidative damage due to its high metabolic activity and abundance of oxidizable material such as polyunsaturated fatty acids forming the plasma membrane of neural cells. Decreasing serum levels of vitamin E are associated with poor memory supporting its role in cognitive functions. Although the mechanism by which vitamin E affects cognition is not clear, it may be probably related to its antioxidant property. Vitamin E protects the synaptic membrane from oxidation and supports synaptic plasticity (Gomez Pinillia, 2008). Vitamin E deficiency causes irreversible brain damage and severe cognitive impairment due to the destruction of neuronal membranes by oxidative stress. It has been observed that children with normal blood vitamin E concentrations have better cognitive skills when compared to children with low vitamin E concentration (Leray Claude, 2016). Mental development in extremely low birth weight children supplemented with alpha-tocopherol for more than 6 months was assessed and was found to have better mental development in particular performance IQ at school age (Kitajima et al., 2015).

## 3. Oxidative Stress in Children

Reactive oxygen species are generated as a result of aerobic respiration and substrate oxidation. Normally they produced in small amounts and serve several biological processes like intracellular differentiation and cell progression, the arrest of growth, apoptosis, immunity and defence against microorganisms. Oxidative stress results when there is increased production of reactive oxygen species and/or depletion of antioxidant defence causing damage to biological membranes (Kurutas et al., 2005). Oxidative stress in children can be observed during periods of rapid growth due to decreased resistance to stress and increased oxidative damage. The rate of living free radical theory predicts that increased metabolism required for rapid growth enhances ROS production at the cellular level and generates oxidative stress (Kim et al., 2013). Environmental factors like exposure to pollutants like air pollutants cause oxidative stress contributing to respiratory and cardiovascular diseases (Bae et al., 2009). Passive parental smoking is also one of the important factors which alter the plasma oxidant and antioxidant balance and contributes to oxidative stress in children (Yildirim et al., 2011). The occurrence of infections like malaria, HIV infections are also some of the other causes of oxidative stress in children in developing countries (Dror and Allen, 2011). Oxidative stress has also been observed in response to mental stress (Sen and Chakraborty, 2011). Severe life stress (SLS) in contrast to everyday trivial life stress is defined as a severe psychosocial event which has the potential to cause considerable psychological trauma. Maternal separation, sleep deprivation, survivors of war, child abuse, divorce, social isolation, post-traumatic stress etc are some of the examples of SLS. SLS by altering the hypothalamohypophyseal axis may probably induce ROS generation (Schiavone et al., 2013). Several diseases are associated with oxidative stress as reflected by increased MDA levels which is a lipid peroxidation product. Urinary tract infections are known to occur in all age groups from neonates to adults and elderly. Kurutas et al assessed oxidative stress by quantitatively measuring urinary MDA levels and antioxidant enzymes like catalase (CAT) and superoxide dismutase (SOD) in patients with urinary tract infection (UTI). Overproduction of ROS in UTI caused oxidative stress, enhanced lipid peroxidation levels and insufficient antioxidant enzymes. Urinary MDA levels may also be increased in some other disease conditions like thalassemia, acute renal diseases and pancreatic diseases (Kurutas et al., 2005). Garlet TR et al assessed systemic oxidative stress in children and teenagers with Down’s syndrome (DS) and observed a systemic pro-oxidant status evidenced by increased activity of antioxidant enzymes like catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR), glutathione transferase (GST), decreased reduced glutathione (GSH), and elevated plasma uric acid levels (UA) to compensate for the redox imbalance. DS is caused by chromosomal aberration involving partial or total trisomy of chromosome 21. The distal region of chromosome 21, the 21q22 band is known as the critical region. The gene for SOD 1 is located in this region and since this region is tripled the activity of SOD 1 is increased. SOD1 catalyzes the conversion of superoxide anion into hydrogen peroxide (H2O2). CAT and GPx catalyze the conversion of H2O2 into the water and molecular oxygen. H2O2 is produced in excess due to increased activity of SOD1 without a concomitant increase in CAT and GPx. The accumulated H2O2 generates other deleterious ROS through the Haber-Weiss-Fenton reactions. These ROS oxidize biomolecules like amino acid residues, proteins, lipids and DNA damaging vital cellular components (Garlet et al., 2013).

## 4. Child Nutrition

‘Today’s children are tomorrow’s citizens.’ Healthy children will grow up as healthy adults. Optimal physical growth, mental development, performance, productivity, health and wellbeing of a child depend on adequate nutrition influenced by genetic potential, secure environment, social interaction and stimulation. Nutrition should be taken care of across entire lifespan from the earliest stages of foetal development, at birth, through infancy, childhood, adolescence and on into adulthood (Ekweagwu et al., 2008).

Growth depends on nutrition. Marked growth is observed during the first 1000 days of life or period from conception to 2 years of life. Therefore any damage to physical growth and cognitive development during the first two years of life is largely irreversible. From a nutritional point of view this period involves a phase when the child is entirely dependent on the mother for its nutritional requirements with the maternal health and nutrition directly impacting the child's health and a transition period that involves the initiation of complementary feeding and finally when a child is ready to make its own nutritional choices. WHO and UNICEF in Global Strategy have recommended exclusive breastfeeding for first 6 months (180 days) of life with starting of nutritionally adequate and safe complementary feeding initiated from 6 months of age with continued breastfeeding for up to 2 years of age or beyond. *Exclusive breastfeeding* means that an infant is fed only with breast milk from the mother or a wet nurse, or expressed breast milk, barring other liquids or solids, including water, however oral rehydration solution, drops or syrups consisting of vitamins, minerals supplements or medicines may be administered as and when required (WHO/UNICEF/USAID, 2008). When breast milk is no longer sufficient to meet the nutritional requirements of infants, other foods and liquids are fed along with breast milk. This is called complementary feeding. The target range for complementary feeding is generally taken to be 6 to 23 months of age, even though breastfeeding may continue beyond two years (PAHO/WHO, 2002). Here comes the role of the family to inculcate good nutritional habits in the growing child. Diet of the child should be a balanced one with a combination of macronutrients (carbohydrates, proteins, fats) micronutrients and fibre. Micronutrients, as defined by UNICEF, are nutrients that are needed by the body in minute amounts. Some of the important micronutrients include vitamins A, E, C, D, B2, B6, folate, zinc, selenium, iodine, iron and copper (Ekweagwu et al., 2008).

Nutritional deficiency is one of the common causes of deaths in children contributing to two-thirds of all deaths worldwide. Nutritional deficiency includes protein-energy malnutrition and micronutrient deficiency (Caballero, 2002). Protein-energy malnutrition and subclinical deficiency of micronutrients are common among growing children because of the increased demands for energy and nutrients. Children with nutritional deficiencies often succumb to common diseases such as acute gastroenteritis, pneumonia and measles etc setting up a vicious cycle of undernutrition and recurrent infections (Singh, 2004). Kalra et al. observed that children with PEM demonstrated neurological signs of vitamin E deficiency and serum α- tocopherol levels were significantly reduced in such children. They studied the effect of supplementation with aqueous oral vitamin E for 6 weeks to children with moderate PEM and reported improvement in neurological functions (Kalra et al., 2001).

Malnutrition during first two years of life causes developmental delays, increased susceptibility to disease, stunted growth with the average height that is attained during adulthood being several centimetres less compared to his/her potential height (Martorell et al., 1994). Adults who were undernourished as children are at risk of developing long term disease conditions like cardiovascular diseases, obesity and diabetes during adulthood in addition to certain short term health consequences (Martins et al., 2011).

Inappropriate nutrition in children can result in childhood obesity which is a rapidly growing public health problem. Several studies have demonstrated normal plasma alpha-tocopherol levels in obese children. Obese children have elevated circulating cholesterol and triglyceride concentrations and on correction for circulating lipids, the alpha-tocopherol: lipid ratios were notably lower than those in non-obese control. Children who are obese are also prone to oxidative stress due to chronic inflammation secondary to obesity. Obese children consume inadequate amounts of antioxidants and supplementation with vitamin E reduces oxidative stress in them (Traber, 2014).

## 5. Vitamin E for Newborn

Growth and development begin from the time of conception progress through embryo, foetus, infant, child and adult. Vitamin E is a potent antioxidant that is extremely important during every stage of life including from the time of conception to postnatal development of the infant, deficiency of which may lead to serious health consequences during intrauterine development as well as after birth. Vitamin E protects the newborn against oxidative stress by its ability to scavenge free radicals in addition to stimulating the development of the immune system. Plasma vitamin E levels at birth are low (2.5 mg/L) requiring an adequate intake of vitamin E soon after birth. Low plasma vitamin E levels at birth can be attributed to limited transplacental transfer. The placental transfer remains so even if the dietary intake of the vitamin is increased in gestating mother thereby increasing her serum levels (Debier and Larondelle, 2005). Colostrum and human milk have adequate vitamin E levels and appropriate vitamin E to polyunsaturated fatty acid ratios (PUFA) constituting an invaluable source of vitamin E to the newborn. In particular, colostrum has approximately 2-3 times higher vitamin E concentration in comparison to mature milk emphasising the importance of feeding colostrum to the newborn baby. Unlike the placental transfer, the concentration of vitamin E in the milk is influenced by maternal ingestion of vitamin E (Debier and Larondelle, 2005). Human milk contains 0.32 mg α- tocopherol/100 ml of milk, the rationale for the formula milk to contain no less than 0.3 mg α- tocopherol/100ml of the feed and 0.4mg α- tocopherol/g of PUFA (WHO and FAO, 2004). Term infants fed with human milk achieve adult serum vitamin E levels in a few days to a few weeks (Debier and Larondelle, 2005). In addition, human milk not formula milk contains antioxidant enzymes like glutathione peroxidase, catalase, superoxide dismutase which provide antioxidant defence not only in the GIT but can also easily pass across the neonatal intestine that is porous. Infants fed with human milk have a higher resistance to oxidative stress in contrast to formula-fed infants (Friel et al., 2004). Human milk is always superior in every aspect to formula feed and it should be the first choice to feed newborns and infants.

## 6. Premature Infants

Premature Infantshave 15% lower plasma vitamin E levels at birth compared to healthy term newborn babies since foetus accumulate vitamin E mainly throughout the last trimester of pregnancy (Debier and Larondelle, 2005). By day 8 the levels further decrease to about 9% but in term infants’ vitamin E concentration increases during the first week (Kolleck et al., 2002). Newborns particularly preterm experience increased oxidative stress due to low vitamin E levels and reduced activities of antioxidant enzymes. The occurrence of haemolytic anaemia as a result of enhanced lipid peroxidation of the erythrocyte membrane is an early indicator of oxidative stress in preterm babies (Debier and Larondelle, 2005). Deficiency of vitamin E in preterm infants results in oedema, haemolytic anemia, thrombocytosis and spinocerebellar degeneration. The deficiency is further enhanced by iron supplementation and administration of formula milk containing a high concentration of PUFA (Brion et al., 2003). Assessment of vitamin E deficiency in preterm infants is complicated because serum tocopherol levels may not reflect tissue levels and are influenced by serum lipid levels. Hence a lipid standardised vitamin E concentration should be considered. A tocopherol/lipid ratio of greater than 0.8mg/g has been recommended as an indicator of vitamin E sufficiency (Johnson, 1998). Although human milk is the preferred nutritional source in enteral feeding in preterm infants, the concentration of vitamin E in the human milk may not be sufficient to meet high recommended intake (Henriksen et al., 2006). Hence preterm infants require supplementation for a longer duration to replenish the serum levels. Administration of vitamin E in preterm babies prevents occurrence/severity of retinopathy of prematurity, intraventricular haemorrhage and bronchopulmonary dysplasia all known to occur due to increased oxidative stress. However such babies should be carefully monitored for the occurrence of sepsis which is a potentially toxic side effect of supplementation with vitamin E (Henriksen et al., 2006).

## 7. Adolescence and Vitamin E

The span of life between 10-19 years constitutes adolescence (according to WHO) and is a phase of transition from childhood to adulthood. Adolescence is characterized by marked growth spurt second only to the one occurring around the first year of life. This spurt in growth involves marked physical growth, cognitive development, emotional changes and the accompanying hormonal changes. Early adolescence a period from 10-15 years is crucial as about 80% of the adult height and weight is attained during this period. In girls, the growth spurt begins at 12 years of age and attains her full adult height at around the age of 16 years. In boys, the growth spurt begins around 12 years of age and adult height is reached somewhere around the age of 18 years (World Health Organization, ‎2006)‎.

The marked growth spurt that characterizes adolescence should be supported by adequate nutrition with an ample supply of proteins, energy, minerals and micronutrients. Nutrition during adolescence should also provide adequate stores of energy for illness and pregnancy in females and to prevent adult-onset nutritional diseases (Story and Stang, 2005; World Health Organization, ‎2006).

Nutrition during adolescence is affected by the quality and quantity of the available food, ability to digest, absorb and utilize the food. The level of education of the parents and the family income also influence the nutrition in adolescence. Of special concern is the social discrimination faced by girls with respect to the availability and the quality of food particularly observed in rural areas and in lower socioeconomic status. In some regions, the marriage of adolescent girls and pregnancy during adolescence is still common. Malnourished adolescent girls give birth to low birth weight babies resulting in the intergenerational cycle of malnutrition (World Health Organization, ‎2006).

The rising prevalence of overweight and obesity among adolescents is of growing concern as it heralds the onset of obesity during adulthood. The most common causes are faulty dietary practices that include consumption of high fat, low fibre diet, decreased intake of fruits and vegetables, sedentary lifestyle and lower physical activity due to television viewing and computer games to add to the list is the addiction to mobile phones. Lack of knowledge and awareness regarding health, growth and development and their nutritional requirements may also contribute to the nutritional problems. Obesity has been associated with decreased vitamin E levels due to its sequestration in adipose tissue. Hence adolescents are vulnerable to micronutrient deficiencies including vitamin E due to increased requirements and decreased intake and to add to this is the occurrence of infections that increase the oxidative stress.

Table 1. Adequate intake (AI\*) of vitamin E, Ages 0-12 months

|  |  |
| --- | --- |
| Age | AI (mg/day) |
| 0-6 months | 4 mg/day of α- tocopherol (0.6 mg /Kg) |
| 7-12 months | 5 mg/day of α- tocopherol (0.6 mg /Kg) |

Source: Data from reports from the Institute of Medicine, Food and Nutrition Board, Standing Committee on the Scientific Evaluation of Dietary Reference Intakes: Vitamin C, Vitamin E, Selenium and Carotenoids.

\*Adequate Intake – is a calculated mean value of vitamin E intake of infants fed exclusively with human milk.

Table 2. Recommended Dietary Allowance (RDA) of Vitamin E in children and adolescents

|  |  |  |
| --- | --- | --- |
| Age | RDA | |
| 1-3 years | 6 mg/day of α- tocopherol | |
| 4-8 years | 7 mg/day of α- tocopherol | |
|  | Girls | Boys |
| 9-13 years | 11 mg/day of α- tocopherol | 11 mg/day of α- tocopherol |
| 14-18 years | 15 mg/day of α- tocopherol | 15 mg/day of α- tocopherol |
| 19-30 years | 15 mg/day of α- tocopherol | 15 mg/day of α- tocopherol |
| Pregnancy  14-18 years  19-30 years | 15 mg/day of α- tocopherol  15 mg/day of α- tocopherol |  |
| Lactation  14 – 18 years  19-30 years | 19 mg/day of α- tocopherol  19 mg/day of α- tocopherol |  |

Source: Data from reports from the Institute of Medicine, Food and Nutrition Board, Standing Committee on the Scientific Evaluation of Dietary Reference Intakes: Vitamin C, Vitamin E, Selenium and Carotenoids.

## Conclusion

The period from birth till adolescence is a crucial phase of life marked by rapid physical growth, mental development and a transition phase from childhood to adulthood. Proper nutrition should be ensured during this period to support growth and development. Oxidative stress which is essential for cell function is also deleterious to its survival if it’s beyond the body’s defence mechanisms. Vitamin E is one such micronutrient, a potent antioxidant. By virtue of its free radical trapping activity, it prevents lipid peroxidation and contributes to the integrity of the cell membrane. It has diverse and multiple actions from regulating the gene expression, immune function, respiratory, neural and cardiovascular health and many more from intrauterine life, birth, childhood, adolescence and adulthood and old age. Healthy children will grow up as healthy adults. So proper nutrition during childhood must be ensured with ample intake of antioxidants. Also, supplementation of vitamin E in newborn particularly preterm babies has been demonstrated to be beneficial but still one needs to be cautious and under observation since there are reports of the adverse effects like the occurrence of neonatal sepsis. Although the role oxidative stress in the pathophysiology of several diseases has been proved, there are still conflicts in the role of antioxidants in disease progression and prevention. Further research should be undertaken to clarify the role of oxidative stress in the pathophysiology of diseases and to provide concrete evidence to substantiate the role of antioxidants in disease prevention and progression.

## References

1. Bae, S., Pan Xiaochuan, Kim Su-young, Park Kwangsik, Kim Yoon Hee, Kim Ho, Hong Yun-Chul (2009). Air pollution causes oxidative stress in school children. *Epidemiology*, 20(6): pS26.
2. Birben, E., Sahiner, U. M., Sackesen, C., Erzurum, S., Kalayci, O. (2012). Oxidative stress and antioxidant defense. *World Allergy Organ J,* 5(1): 9-19.
3. Brion, L. P., Bell, E. F., Raghuveer, T. S. (2003). Vitamin E supplementation for prevention of morbidity and mortality in preterm infants. *Cochrane* *Database of Systematic Reviews*, Issue 4. Art. No.: CD003665.
4. Caballero, B. (2002). Global patterns of child health: the role of nutrition. *Ann Nutri Metab*., Vol. 46. Suppl. 1: 3-7.
5. Debier, C., Larondelle, Y. (2005). Vitamins A and E: metabolism, roles and transfer to offspring. *British Journal of Nutrition*, 93: 153-174.
6. Devereux, G., Turner, S. W., Craig, C. A. L., McNeill, G., Martindale, S., Harbour, P. J., et al. (2006). Low Maternal Vitamin E Intake during Pregnancy is associated with Asthma in 5-year-Old Children. *American Journal of Respiratory and Critical Care Medicine, 174(5): 499-507*.
7. Dror, D. K., Allen, L. H. (2011). Vitamin E deficiency in developing countries. *Food Nutr Bull*, 32(2):124-43.
8. Ekweagwu, E., Agwu, A. E., Madukwe, E. (2008). The role of micronutrients in child health: A review of the literature. *African Journal of Biotechnology*, 7(21): 3804-3810.
9. Friel, J. K., Friesen, R. W., Harding, S. V., Robert, J. L. (2004). Evidence of Oxidative Stress in Full-Term Healthy Infants. *Paediatric Research*, 56:878-882.
10. Funtikova, A. N., Navarro, E., Bawaked, R. A., Fito, M., Schroder, H. (2015). Impact of diet on cardiometabolic health in children and adolescents. *Nutrition Journal,* 14: 118.
11. Garlet, T. R., Parisotto, E. B., de Medeiros Gda, S., Pereira, L. C., Moreira, E. A., Dalmarco, E. M., Dalmarco, J. B., Wilhelm, Filho. D. (2013). Systemic oxidative stress in children and teenagers with Down syndrome. *Life Sci*., 93(16): 558-63.
12. Gilliland, F. D., Berhane, K.T., Li, Y. F., Ganderman, W. J., McConnell, R., Peters, J. (2003). Children’s lung function and antioxidant vitamin, fruit, juice and vegetable intake. *American journal of epidemiology*, 158(6):576-584.
13. Gitto Eloisa, Cusumano Erika, D’Angelo Gabriella, Reiter Russel J. Oxidative Stress of Newborn, Complementary Pediatrics. *Dr Oner Ozdemir* (Ed). Intech publishers. 2012. DOI: 10.5772/32062.
14. Gomez-Pinillia, F. (2008). Brain foods: the effects of nutrients on brain function. *Nature reviews Neuroscience*, 9(7): 568-578.
15. Henriksen, C., Helland, I. B., Ronnestad, A., Gronn, M., Iversen, P. O., Drevon, C. A. (2006). Fat – soluble vitamins in breast-fed preterm and term infants. *European Journal of Clinical Nutrition*, 60: 756-762.
16. Institute of Medicine (US) *Panel on Dietary Antioxidants and Related Compounds.* Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. Washington (DC): National Academies Press (US); 2000. Pg 47. Available from: [https://www.  
    ncbi.nlm.nih.gov/books/NBK225483/](https://www.ncbi.nlm.nih.gov/books/NBK225483/) doi: 10.17226/9810.
17. Institute of Medicine, Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Subcommittee on Upper Reference Levels of Nutrients and Interpretation and Uses of DRIs, Panel on Dietary Antioxidants and Related Compounds. *Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids.* Washington, DC: National Academy Press; 2000. Pg 230-241.
18. Islam, S., Narra, V., Cote, G. M., Manganaro, T.F., Donahoe, P. K., Schnitzer, J. J. (1999). Prenatal Vitamin E treatment improves lung growth in fetal rats with congenital diaphragmatic hernia. *J Pediatr Surg.,*34: 172-176.
19. Jesenak, M., Zelieskova, M., Babusikova, E. (2017). Oxidative Stress and Bronchial Asthma in Children – Causes or Consequences? *Frontiers in Paediatrics,* 5: 162.
20. Johnson, L. Vitamin E nutrition in the fetus and newborn. In: Polin RA, Fox WW editor(s). *Fetal and Neonatal Physiology. 2nd Edition*. Philadelphia: WB Saunders, 1998:425-42.
21. Kagan VE. Recycling and redox cycling of phenolic antioxidants. *Annals of the New York Academy of Sciences* 1998; 854:425–434.
22. Kalra, V., Grover, J.K., Ahuja, G.K., Rathi, S., Gulati, S., Kalra, N. (2001). Vitamin E administration and reversal of neurological deficits in protein-energy malnutrition. *J Trop Pediatr*., 47(1):39-45.
23. Kelly, F.J. (2005). Vitamins and respiratory disease: antioxidant micronutrients in pulmonary health and disease. *Proceedings of the Nutrition Society,* 64(4): 510-526.
24. Kim, S. Y., Noguera, J. C., Tato, A., Velando, A. (2013). Vitamins, stress and growth: the availability of antioxidant in early life influence the expression of cryptic genetic variation. *J Evol Biol.,* 26: 1341-1352.
25. Kitajima, H., Kanazawa, T., Mori, R., Hirano, S., Ogihara, T., Fujimura, M. (2015). Long-term alpha-tocopherol supplements may improve mental development in extremely low birth weight infants. *Acta Paediatr.,* 104(2):e82-9.
26. Kolleck, I., Sinha, P., Rustow, B. (2002). Vitamin E as an antioxidant of the lung: mechanisms of vitamin E delivery to alveolar type II cells. *Am J Respir Crit Care Med.*, 166(12 Pt 2): S62-6.
27. Kurutas, B. E., Ciragil, P., Gul, M., Kilinc, M. (2005). The effects of oxidative stress in urinary tract infection. *Mediators of inflammation*, 4 (2005): 242-244.
28. Leray Claude. Dietary Lipids for Healthy Brain Functions. New York: CRC Press; 2016. *Chapter 2: Brain development*; p. 7-23.
29. Madamanchi, N. R., Vendrov, A., Runge, M. S. (2005). Oxidative stress and vascular disease. *Arterioscler, Thromb Vasc Biol.,* 25(1):29-38.
30. Martins, V. J., Toledo Florêncio, T. M., Grillo, L. P., Franco, M., Martins, P. A. , Clemente, A. P., et al. (2011). Long-Lasting Effects of Undernutrition. *International Journal of Environmental Research and Public Health*, 8(6):1817-1846.
31. Martorell, R., Khan, L. K., Schroeder, D. G. (1994). Reversibility of stunting: epidemiological findings in children from developing countries. *European Journal of Clinical Nutrition*, 58 (Suppl. 1): S45–S57.
32. Mishra, G. D., Mallik, N. S., Paul, A. A., Wadsworth, M. E., Bolton-Smith, C. (2003). Childhood and adult dietary vitamin E intake and cardiovascular risk factor in mid-life in the 1946 British Birth Control. *European Journal of Clinical Nutrition*,57: 1418-1425.
33. Moini, J. *Introduction to pathology for the physical therapist assistant*. Boston: Jones & Bartlett Learning; 2013.
34. Murray RK, Granner DK, Mayes PA, Rodwell VW. *LANGE medical book Harper’s Biochemistry 27th edition* 2006, 494.
35. Ness, A. R., Maynard, M., Frankel, S., Smith, G. D., Frobisher, C., Leary, S. D., Emmett, P. M., Gunnel, D. (2005). Diet in childhood and adult cardiovascular and all-cause mortality: the Boyd Orr cohort. *Heart*, 91: 894-898.
36. Nyaradi, A., Li, J., Hickling, S., Foster, J., Oddy, W. H. (2013). The role of nutrition in children’s neurocognitive development, from pregnancy through childhood. *Frontiers in Human neuroscience,* 7:97.
37. Ozsurekci, Y., Aykac, K. (2016). Oxidative stress related diseases in newborns. *Oxidative Medicine and Cellular Longevity*, 2016:2768365.
38. PAHO/WHO. Guiding principles for complementary feeding of the breastfed child. Washington DC: Pan *American Health Organization/World Health Organization*; 2002.
39. Perrone, S., Negro, S., Tataranno, M.L., Buonocore, G. (2010). Oxidative stress and antioxidant strategies in newborns. *J Matern Fetal Neonatal Med.,*23 Suppl 3: 63-5.
40. Raederstorff, D., Wyss, A., Calder, P. C., Weber, P., Eggersdorfer, M. (2015). Vitamin E function and requirements in relation to PUFA. *The British Journal of Nutrition,* 114(8): 1113-1122.
41. Rizvi, S., Raza, S.T., Ahmed, F., Ahmad, A., Abbas, S., Mahdi, F. (2014). The Role of Vitamin E in Human Health and Some Diseases. *Sultan Qaboos University Medical Journal,* 14(2): e157-e165.
42. Saiket, S., and Chakraborty, R. The Role of antioxidants in human health. In: Silvana Andreescu, Maria Hepel ed(s). Oxidative Stress: Diagnostics, Prevention, and Therapy. American Chemical Society; 2011. 1-37.
43. Schiavone, S., Jaquet, V., Trabace, L., Krause, K.H. (2013). Severe life stress and oxidative stress in the brain: from animal models to human pathology. *Antioxidants and Redox Signaling,* 18(12): 1475-1490.
44. Singh, M. (2004). Role of micronutrients for physical growth and mental development. *Indian J. Pediatr.,* 71(1): 59-62.
45. Stang, J., Story, M. eds. *Guidelines for adolescent nutrition services*. Minneapolis, MN: Center for Leadership, Education and Training in Maternal and Child Nutrition, Division of Epidemiology and Community Health, School of Public Health, University of Minnesota; 2005.
46. Tanyel, M. C., Mancano, L. D. (1997). Neurologic findings in vitamin E deficiency. *Am Fam Physician,* 55(1):197-201.
47. Traber, M. G., Kayden, H. J. (1989). Preferential incorporation of alpha-tocopherol vs. Gamma-tocopherol in human lipoproteins. *American Journal of Clinical Nutrition*, 49(3):517–526.
48. Traber, M. G. (2014). Vitamin E Inadequacy in Humans: Causes and Consequences. *Advances in Nutrition,* 5(5): 503-514.
49. WHO/UNICEF/USAID. *Indicators for assessing infant and young child feeding practices.* Geneva: World Health Organization; 2008.
50. World Health Organization, Regional Office for South-East Asia. (‎2006)‎. Adolescent nutrition: a review of the situation in selected South-East Asian Countries. W*HO Regional Office for South-East Asia*. <http://www.who.int/iris/handle/10665/204764>.
51. Wilinska, M., Borszewska-Kornacka, M. K., Niemiec, T., Jakiel, G. (2015). Oxidative stress and total antioxidant status in term newborns and their mothers. *Annals of Agricultural and Environmental Medicine*., 22(4):736-740.
52. World Health Organization, Food and Agricultural Organization of the United Nations. Vitamin and Mineral Requirements in Human Nutrition. *WHO; 2nd Edition*. 2004. Chapter 5: Vitamin E; 94-104.
53. Yildirim F., Sermetow, K., Aycicek, A., Kocyigit, A., Erel O. (2011). Increased oxidative stress in preschool children exposed to passive smoking. *J Pediatr,* 87 (6): 523-8.
54. Zhang, X., Ding, F., Li, H., et al. (2016). Low serum levels of Vitamins A, D and E are associated with recurrent respiratory tract infections in children living in Northern China: A Case-Control Study. *PLoS ONE*, 11(12):e0167689.

1. \* Corresponding Author: jaydeb\_ray@hotmail.com [↑](#footnote-ref-1)