Muhammad Zia-Ul-Haq
Saikat Dewanjee
Muhammad Riaz *Editors*

Carotenoids: Structure and Function in the Human Body

Springer

Carotenoids: Structure and Function in the Human Body

Muhammad Zia-Ul-Haq
Saikat Dewanjee • Muhammad Riaz
Editors

Carotenoids: Structure and Function in the Human Body

Springer

Editors
Muhammad Zia-Ul-Haq
Lahore College for Women University
Lahore, Pakistan

Saikat Dewanjee
Jadavpur University
Kolkata, India

Muhammad Riaz
Shaheed Benazir Bhutto University
Sheringal Dir Upper, Pakistan

ISBN 978-3-030-46458-5 ISBN 978-3-030-46459-2 (eBook)
https://doi.org/10.1007/978-3-030-46459-2

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Chapter 25
Carotenoids in Women and Infant Health

Suaad S. Alwakeel, May Bin-Jumah, Khansa Imam, Marius Moga, and Nicu Bigiu

25.1 Introduction

Nutritional requirements escalate during pregnancy and lactation and inadequate supply of nutrients during these crucial life stages impacts negatively impact on the mother and developing child. It is well-known that young, pregnant and breastfeeding women are at risk of having shortage of essential nutrients including carotenoids and vitamin A. The inadequate supply of carotenoids and vitamin A is a risk factor for pregnant and lactating women. The intake of both carotenoids and vitamin A should be increased to 1/3rd times during pregnancy and breastfeeding tenure. Nutrition during pregnancy is essential for development of fetus, pregnancy outcomes, and child and mother health before and after birth [1]. Carotenoids are a key player in outcome of pregnancy and in inhibition of various problems during pregnancy caused by increased oxidative stress [2–4]. Carotenoids assist in sustaining good health during childhood as these are involved in the development and maintenance mechanisms of cognition and vision. One group says that enhanced demand can be met from a balanced diet and maternal reserves of a well-nourished mother. Infant and developing fetus totally depend on mother intake of carotenoids for provitamin A requirements. However, there is limited research except suggestions of provitamin A supplementation in pregnancy and lactation. Encouraging consumption of carotenoid rich foods during pregnancy and breastfeeding should continue

S. S. Alwakeel (✉) · M. Bin-Jumah
College of Sciences, Department of Biology, Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia
e-mail: ssalwakeel@pnu.edu.sa

K. Imam
Department of Education, University of Education, Jauharabad Campus, Jauharabad, Pakistan

M. Moga · N. Bigiu
Faculty of Medicine, Transilvania University of Brasov, Brasov, Romania

M. Zia-Ul-Haq et al. (eds.), *Carotenoids: Structure and Function in the Human Body*, https://doi.org/10.1007/978-3-030-46459-2_25

simultaneously with further research explaining the significance of them during these critical life periods.

25.2 Prevention of Pregnancy Complication by Carotenoids

Hormonal concentrations and energy metabolism change during pregnancy. The placenta becomes operative leading to an increased level of Reactive Oxygen Species (ROS). Increased ROS generation, inappropriate development of placenta and inadequate antioxidant defense leads to oxidative stress. Increased ROS levels damage cells and tissues structurally and functionally, thereby acting as pro-inflammatory agents. This may cause pregnancy abnormalities and complication. Carotenoids protect humans from oxidative stress and resulting complications [1, 2].

Carotenoids intake in pregnant women varies from country to country. It is well established now that oxidative stress increases the risk of pregnancy-initiated hypertension, impulsive abortion, preeclampsia, gestational diabetes mellitus (GDM), and preterm birth [2, 5]. The shielding effects of carotenoids against preeclampsia have been well-studied [6, 92]. Preeclampsia affected pregnant women suffer from increased stress and inflammation and decreased level of carotenoids [7–9]. Risk of incidence of preeclampsia decreases with increased lutein plasma concentration [10]. Higher blood concentration of β-carotene is linked with decreased risk of pre-eclampsia up to 50% in Zimbabwe pregnant women (n = 359) [11].

Out of 3 clinical studies in Indian women regarding influence of lycopene intake (@2 mg/day) up to 2nd trimester of pregnancy, I study indicated very small decrease risk of development of preeclampsia [12], while remaining 2 studies did not show any link between the two [13, 14].

Oxidative stress is also linked with GDM [15]. Antioxidant potential of plasma in GDM-women is very less as compared to healthy pregnant women [16]. An intervention study suggested that intake of carotenoid supplements did not decrease the hydroperoxide concentration in pregnant women serum [17]. However, a substantial difference in oxidative stress in a 24 women group (12 suffering from GDM) values between newborn to untreated mothers at 2 h of life and newborns to mothers treated with lutein which disappeared after 48 h. The women had taken lutein supplements (10 mg) and zeaxanthin (2 mg), however since no placebo or randomization was used and due to lack of anthropometric and demographic data of participating women, the strength of results are not strong enough for convincing [17]. Mortality and morbidity ate increases due to preterm birth. Increased oxidative stress has been observed in premature births [18]. Premature rupture of membranes (PROM) leads to about 30–40% preterm birth .Further, increased status of oxidative stress biomarkers have been observed in amniotic fluid during the development of such pregnancy [19]. Mothers who give birth to premature newborns, have decreased carotenoid serum concentrations. Increased concentration of lycopene, β-cryptoxanthin and α- and β-carotene decrease risk of preterm births [20]. Preterm birth risk depends upon the dietary pattern of pregnant mothers. Lower intake of

α- and β-carotene are associated with increased risk of premature births in USA [21, 22]. Subjects fed lycopene supplements (@2 mg/day) in a randomized controlled trial from the first gestation trimester indicated a weak but substantial continuation of gestation period in subjects [12]. A diet containing carotenoids prevents preterm births in women [23].

Infants who are small for gestational age (SGA) are mostly hyotrophic and few of them are born form pregnancies with problems of intrauterine growth rate (IUGR). Low antioxidant potential and higher oxidative stress biomarkers are characteristics of both IUGAR and SGA [24, 25]. Risk of birth of SGA babies decreases in mothers having increased plasma concentration of α- and β-cryptoxanthin, lutein, zeaxanthin and β-carotene [26]. Decreased levels of carotenoids have been detected in breast milk and serum of mothers giving birth to babies having IUGR [27]. Another study revealed that lycopene intake (@2 mg/day during 16–20 Hbd) lowers the incidence of happening of IUGR [12].Study has revealed that maternal carotenoids level or their concentration in cord blood did not influence the birth parameters of newborn babies [25]. These results were also confirmed in an intervention study (randomized placebo-controlled trial) involving β-carotene intake from first gestation trimester to 3rd month post-birth [28]. However, minor negative impact of β-carotene intake on birth weight needs further investigation [28]. Similarly opposing result of lycopene intake on prevalence of low birth weight was observed in another study although it was a weak study [13]. A positive correlation was found between β-carotene intake in 4th month of pregnancy and head perimeter at time of birth however no association was detected between seasonal differences in nutrients supplementation and birth characteristics [29].

25.2.1 Maternal-Fetal Transfer of Carotenoids

Fetal development in terms of its vitamin A needs greatly dependent on mother intake during pregnancy, as the liver store of the child only lasts for a few days and can be speedily emptied due to abrupt strains for the development. Furthermore, the insufficient intake of vitamin A by the mother during pregnancy can also influence the postpartum supply of the child through breast milk.

Absorption and transportation of carotenoids is analogous to that of fats in human body. Carotenoids when absorbed from small intestine initially circulate through the lymphatic system, and then make a complex with the chylomicron offcuts in the blood system and finally transported to the liver. In liver, this combination of carotenoid and chylomicron remnants is modified, can be stored storage, or may be conveyed back to the blood circulation along with lipoproteins. Xanthophyll transportation is assisted mostly by high-density lipoprotein (HDL) and to a smaller extent by very low-density lipoprotein (VLDL) while carotenes are carried by low-density lipoprotein (LDL). Association of various types of lipoproteins to carotenoids and the quantity and shares between their receptors in several tissues regulate

the changes in saturation level of various organs in carotenoids. For this reason, testes, liver and adrenal glands contain the largest quantity of carotene since LDL receptor is mainly located at these 3 places. Since central nervous system (CNS) and nervous tissue of eye retina are hub of HDL, therefore, xanthophylls are preferably transported there [22, 30, 31]. Carotenoids transportation take place by various proteins like lactoglobulin and albumin [32–34].The mode of transfer, metabolism and exploitation of carotenoids in fetus development is still unclear. Increased concentration of maternal lipoproteins during pregnancy helps uptake of carotenoids by placenta. Cord blood contains lipoprotein fractions in order of HDL > LDL > VLDL.

Unlike in adults, the HDL of cord blood is involved in β-carotene transport more than LDL (55% vs. 45%) [32–35] Animal model study suggested that administration of β-carotene controlled transcription, MTP activity and apoB thus increasing β-carotene transfer to placenta [36]. Vitamin A shortage reduces carotenoid levels in placenta which may be due to their reduced translocation to placenta [37].Optimum concentration of carotenoids (276 ng) and total albumin (1.42 mg) was found nearly 20–22 Hbd in tissues of vitreous body of aborted fetuses. Carotenoids and albumin levels were highest during weeks 16–17 and 17 correspondingly of prenatal progress. Carotenoid quantity reduced slowly after that and by 31 week of gestation, was lower than detection threshold [33].

25.2.2 Carotenoid Status in the Newborn

Carotenoid concentration in mother serum and cord blood is the key biomarker of carotenoid status. Majority of studies suggest that carotenoid level in newborn directly relies on their concentration in mother which is mostly many times lower. Carotenoid level in mother blood is many times higher than carotenoid quantity in carotenoid blood [25–27, 38–43]. Minor differences between polar carotenoids level in mother blood and cord blood were noted .The reason is that HDL is the major lipoprotein fraction in initial lifespan of fetus till 1st week post-birth of newborn [41]. Variation in carotenoid levels especially β-carotene and other pro-vitamin A carotenoids between fetus and mother cannot be ascribed to restrictions in placental transport of carotenoids. Inadequate β-carotene storage capacity, transformation of β-carotene to retinol and storage of retinol esters in liver and intensive fetal metabolism may be potential causes of it [44, 45].

It was observed that plasma zeaxanthin of newborn and mother was linked with macular pigment optical density (MPOD) in infants. However, no such correlation existed for the main macular pigment lutein. Transformation of lutein to mesozeaxanthin detected in macula of retina by an immature enzyme system is reasonable for it thus highlighting importance of zeaxanthin in macular pigment development in infants [27].The newborn nutritional rank relies upon the delivery week of newborn. It may be associated with dynamics and mechanism of fetus growth which is maximum during pregnancy third trimester. Examination of lutein and metabolite 3′-oxolutein quantity in cord blood of full-term and preterm

neonates suggested that lutein level peaks at start of third trimester and starts decreasing from 37 Hbd attaining its minimum level at 41–42 Hbd [46]. Lutein quantity in male newborns and newborns delivered from numerous pregnancies was found less [47]. Another element that reduces carotenoids concentration especially β-carotene in cord blood is smoking during pregnancy [38, 48, 49].

It is well-known that oxidative stress increases during child delivery. Child birth through planned cesarean section is associated with elevated oxidative stress although this experiment results are considered poor [50, 51]. No differences were observed in β-carotene level with regard to type of child birth [38] however declined lutein level was observed in cord blood of newborns delivered by cesarean section [46].

Since infant's eye lens is more transparent than adult, therefore their eyes are more vulnerable to blue light damage. Enhanced zeaxanthin and lutein consumption defends human eye by antioxidant and blue light filtration capacity of these carotenoids. β-carotene intake reduced weights of newborns in A study conducted among 450 women from a New Zealand clinic [29]. More than 30 carotenoids in various forms have been reported in breast milk [52], However, 6 carotenoids including lutein, lycopene,α- and β-carotene, Zeaxanthin, and β-cryptoxanthin have been more frequently reported and detected.

Global Exploration of Human Milk study was conducted in China, USA and Mexico (n = 240 samples, n = 60 donors). Milk collected longitudinally in 2,4,13 and 26 weeks postpartum from 20 women. Results indicated that β-carotene, lutein, lycopene and β-cryptoxanthin contents of milk are substantially linked with maternal and neonatal plasma carotenoids level. Provitamin A potential of β-cryptoxanthin, α- and β-carotene and to some extent α-cryptoxanthin play a significant role for mom and neonate. Since vitamin A is needed for immune and visual development for which provitamin A carotenoids are key source in developing tissues. Lack of standardized protocols for determination of carotenoids in milk as well as reference values of carotenoids for each country are 2 major problems [53].

Milk composition is best guide for appraisal of infant carotenoid requirement. Levels of carotenoids and tocopherols were assessed in milk of 509 healthy mothers. Lactation phase, regional variations and socio-economic factors were linked with human milk contents in health Chinese mothers [54].

25.2.3 Carotenoids in Breast Milk

It is well-established fact that breast milk composition varies depending upon phase of time of day, rate of breastfeeding during the year, lactation period and time of single breastfeeding. It also varies from person to person, gestation week, birth week and rate of breast emptying. Dietary practices of lactating women influences nutrient concentration of breast milk including carotenoids [55–59].

Changes occur very frequently in breast milk fat and single breastfeeding phase and lactation phase are mainly responsible for it. Fat contents of mature milk and

colostrum are 4.1 g/100 mL and 2.6 g/100 mL respectively [55, 56, 58, 60]. Lutein, α- and β-carotene, β-cryptoxanthin, lycopene and zeaxanthin are major carotenoids of breast milk [53, 60–65]. Average contents of carotenoids, i.e. lycopene, β-cryptoxanthin, β-carotene and lutein in breast milk were 33.7, 33.8, 49.4 and 114.4 nmol/L respectively [53]. Provitamin A carotenoids contents were 62% while other carotenoids accounted for less quantity [61]. The results differences of various studies may be due to different protocols for milk fat extraction and different units of milk fat expression, variations in seasons of breast milk collection and dietary pattern of females [53, 64, 66]. Just like fat contents, foremilk contains less carotenoids (by 25%) than hind milk [64]. Breast milk composition even varies within the same day at various times [63, 64]. Carotenoids contents decreases with duration of breastfeeding. Variations in carotenoids level can be between 82.7–91.3% (for lycopene) and 32.5–52.0% for zeaxanthin [53, 60, 65, 79, 85, 115]. Carotenoid concentration greatly decreases between 2nd and 4th week of breastfeeding but remains same between 4th and 16th week of breastfeeding [53, 67]. Non-provitamin A carotenoids (lutein and lycopene) [53] and less polar carotenes are extra prone to variations [60].

Dietary practices of mother greatly influences carotenoid contents of breast milk. Variation in breast milk composition noted in numerous studies may be due to various dietary practices of populations scrutinized [53, 61, 17, 79]. Milk carotenoid concentration changes easily with dietary intake patterns.

A 3-day intervention study with intake of tomato paste or carrot paste containing 15 mg β-carotene and lycopene respectively by 26 women led to enhanced concentration of both carotenoids in milk even after first day of intervention. Optimum β-carotene and lycopene contents comprising 200% and 130% of initial value was observed in subjects after 2nd and 4th day of intervention respectively [68]. Lutein, β-carotene and zeaxanthin contents increased 2.6X,1.7X and 2.7X after intake of chlorella supplements during 16–20 Hbd [69].The carotenoids content in breast milk is 10 or sometimes even 20 times less than their plasma level and degree of association between two varies depending upon carotenoid or population investigated. Differences also exist in proportion of milk carotenoids to their plasma concentration. A randomized placebo-controlled trial suggested that a 6 week lutein intake (6 or 12 mg/day) enhanced in its serum level by about 170% and 250% and in breast milk by 140% and 250% correspondingly. Lutein serum level amplified by 180% and 330% in case of 6 mg/day and 12 mg/day after lutein consumption [70]. Serum and breast milk carotenoid ratio is variable and amounts to 560–600% for β-cryptoxanthin, 270–300 for α- and β-carotene and 133% for lutein. Intensive turnover and uptake by newborn tissues may be the reason for decreased lutein value [53]. Serum carotenoids contents and their composition in plasma lipoprotein is also observed. Variations in ratio of breast milk carotenoid to serum carotenoid with regard to polarity indicates that a unique mechanism operates for carotenoids transfer to milk which is different from fat transfer mechanism [60]. Breast milk components can be secreted by 5 different mechanism, including 1 para-cellular mechanism with assistance of tight-junction connections and 4 trans-cellular pathways (milk fat transport, intracellular vesicle transport, membrane pathway and transport through

Golgi apparatus and milk secretion via secretive cells through exocytosis) [53, 71]. Carotenoids transfer to breast milk may consist of preferred uptake by lipoproteins and intracellular transport. All kinds of lipoproteins are found in breast tissue but mammary alveolar epithelium cells prefer HDL fraction [53, 65, 72].

25.2.4 Infant Feeding Method and Infant carotenoid Status

Carotenoids cannot be produced de novo in humans. Further carotenoids occur in traces in infant formulas, hence method of infant feeding plays a major role in determination of carotenoid level in infant [27, 67, 73]. Totally breastfed Infants possess superior nutritional status than mixed or artificially fed infants. Carotenoid contents of artificially fed infants after many months are many times less than vales noticed in breastfed infants and sometimes even less than detection threshold [8, 45, 70, 73–76]. It highlights the significance of fortifying infant formulas with carotenoids especially lutein to boost the nutritional status of artificially fed newborn infants. Lutein enriched infant formulas are well-tolerated by neonates and enhance their dietetic level [77]. Experimental studies have established that rhesus macaques fed with a mixture of carotenoids-supplemented foods not only enhances the saturation level of lutein in brain tissue but also elevates zeaxanthin, lycopene and β-carotene from negligible and below detection level to substantial level thus highlighting the importance of lutein for developing brain increases the saturation degree [78]. It is important to increase lutein level 4–5 times than its level in breast milk because of limited bio-accessibility of lutein from infant formulations [73, 77, 79].

25.2.5 Carotenoids and Infant Health and Development

Lot of studies suggest importance of carotenoids in infant health and growth due to their well-accepted health benefits and preferred uptake by breast milk and fetus [31, 80]. These health benefits in infants are due to their antioxidant potential and their role in cognitive and visual development [80, 81].

25.2.6 Visual Development

Macular pigment consist of lutein, zeaxanthin, meso-zeaxanthin, isomers of zeaxanthin and lutein derivatives [82]. Eye carotenoid contents are not equally distributed. Carotenoid optimum quantity is detected in central foveal region and they decline with growing space from fovea being 100 times less in peripheral area. Carotenoid contents are present in different ratios in various retinal regions eg.in

central foveal region zeaxanthin dominates while in peripheral region lutein dominates [83–85].

Age also affects macular pigment structure and density. Infants have very less or undetectable mezzo-zeananthin contents and contradictory lutein:zeaxnanthin ratio until 2 years of age. It may be due to immaturity of enzymes responsible for transformation of lutein to mezzo-zeaxnathin [27, 83–85]. Further premature infants have undetectable MPOD and depleted carotenoids due to decreased parental development [86]. Infant MPOD depends upon mom carotenoid level and after birth, baby feeding method is important for maintaining carotenoid concentration [27]. Breastfed neonates have increased MPOD than artificially fed infants. Recent research indicates that early carotenoid exposition can be a major indicator of MPOD in adulthood [87, 88]. Oxidative damage is a potential threat for eye retina due to extreme metabolic activity, extensive vascularity and increase LC PUFA concentration [89]. Newborns suffer more risk of damage due to undeveloped autoregulation of blood flow within the choroid and their extra permeable lens that permits to pass increased quantities of energetic short-wave light [90, 91].

Premature newborns are extra prone to oxidative stress which may cause progress of premature retinopathy [92]. Macular carotenoids shield retina by: (1) absorption of 40–90% of incident blue light which defends retia from photo-injuries [93]; (2) antioxidant potential i.e. a combination of zeaxanthin, lutein and mezo-zeaxanthin may extinguish more singlet oxygen than separate carotenoids [94]; (3) neuroprotective capacity [95] and (4) anti-apoptotic and anti-inflammatory capacity of carotenoids [96]. Zeaxanthin and lutein also help in transfer and managing of visual information by: (1) increasing the gap junctional communication between neurons and glia [97, 98],(2) stabilizing microtubules in cytoskeleton [99]; uplifting visual parameters including light scattering and scoptopic noise [100]; and (4) involvement in oxygen consumption from foveal region [76, 101].Studies also confirm important part of macular carotenoids in appropriate visual and eye development [89]. Animal studies suggest the carotenoids importance for appropriate retina development [102, 103].Proper cognitive development depends upon appropriate visual development of infants [80, 104]. Further lutein status in retina is associated with brain lutein contents in humans [105], primates [106] and to cognitive functioning in children and old age population [107].

25.2.7 Brain and Cognitive Development

Nervous tissues capture carotenoids especially with lutein constituting 59% of all carotenoids in infants while its share in adults is only 31% [78]. In brain, carotenoids are carotenoids are concentrated in frontal and occipital cortex, hippocampus and areas linked with cognitive process. Optimum lutein contents are detected in cellular membranes and axon terminals of neurons, and structure of neurons's cell membranes and amonal axonal projections rely upon brain areas in which they are present [99].Lutein functions in nervous tissue by (1) increasing intracellular

communications [97, 108];(2) neuroprotective potential [109]; (3) modifying cell membranes including their stability, fluidity, ion exchange, and oxygen diffusion [108];and (4) contribution in metabolic pathways of brain [110]. However another study did not endorse the effect of infant breastfeeding method on carotenoids contents in brains of full term neonates [111]. The brains of pre-term newborns have decreased carotenoids level than full-term newborns [107, 111]. Studies suggest the importance of carotenoids in cognitive functions and their intake enhances cognitive functioning in adults and elderly people [107].Current study held among 55 exclusively breastfed infants from USA suggested that increased lutein contents in breastmilk of 3 months can enhance cognitive performance in infants at 6 months of life [112].The relationship observed can be due to lutein transport to brain through high density lipo-proteins (HDL) [113].

25.2.8 Preterm Infants

Infants are extra prone to oxidative stress due to increased oxygen intrauterine environment and extreme metabolic activity [81]. Undeveloped antioxidant defense mechanism, allied disorders and extensive medical mechanism make preterm newborns even more susceptible to oxidative damage [81]. Lutein supplementation in infants @ 0.28 mg at 6 and 36 h of life suggested that it can protect against oxidative stress by enhancing biological antioxidant system and diminishing oxidative stress [114]. Lutein intake is well-accepted by preterm neonates and can decrease the danger of occurrence of diseases linked with pre-term birth e.g. necrotizing enterocolitis (NEC),retinopathy of prematurity (ROP) and bronchopulmonary dysplasia (BPA) [115].

25.2.9 Long-Term Studies in Infants and Children

Carotenoids supplementation during pregnancy can have long lasting effects on infants. Study performed among moms of babies suffering from sporadic retinoblastoma and health controls suggested that insufficient intake of fruits and vegetables and zeaxanthin and lutein derived from them can enhance the possibility of sporadic retinoblastoma in children [116]. Carotenoids particularly provitamin A can change the various parameters in progressing immune system including natural killer cell functions or T-cell proliferation [117]. Supplementation of mothers by zeaxanthin and lutein decreased the possibility of respiratory infections in 2 years old kids [118]. A study involving 763 mother-infants dyads in Japan suggested that β-carotene intake during pregnancy reduced possibility of infantile eczema but not wheeze [119]. A cross-sectional study was conducted well-fed, healthy kids aged 5.75 years living in Vancouver, Canada probing lutein supplementation. Results did not endorse lutein importance in cognitive performance evaluated by Peabody

Picture Vocabulary Test (PPVT) and Kaufman Assessment Battery (KABCC-II) [120]. The absence of impact of lutein on cognitive function can be due to inclusion of well-nourished population while principal functional impact of lutein can be critical for those with comparative insufficiency; choice of weak biomarker (plasma contents) for lutein in brain and improper choice of cognitive assessments for computing diet impact on brain growth [121]. Another study on 2044 healthy Dutch children did not confirm the supposition that lutein supplementation in initial life of 1 year has positive effects on later anthropometrics, body measures and cardiometabolic health at age of 6 years [122].

25.2.10 Safety of Carotenoids and the Intake Recommendations for Pregnant Women and Infants

Although carotenoids act as antioxidant however their antioxidant potential declines when oxygen pressure mounts probably because of auto-oxidative processes [123]. This characteristic may be potential reason of reports of adverse health effects of increased carotenoid intake. ABTS clinical trial performed in male smokers of Finland indicated that increased duration (5–8 years) intake of β-carotene (@20 mg/day) led to 18% enhancement of lung cancer incidence and an overall 8% increased mortality [124]. Another study indicated that this intake augmented post-trial of a first nonfatal myocardial infraction [125]. Some studies involving non-smokers however did not suggest any relationship between carotenoid intake (β-carotene @ 50 mg/day) and increased possibility of cardiovascular mortality or morbidity [126]. β-carotene oxidation by cigarette smoke can be responsible for carotenoid adverse health effects which supported formation of toxic β-carotene oxidation products [127]. Carotenodermia having specific yellow discoloration of skin may also occur due to more lutein uptake [128]. Only 1 study suggested adverse health effects of lycopene intake (2 mg/day since 15.7 Hbd). No other study reveals adverse health effects of carotenoid consumption in pregnant women, newborns and infants although these studies were not long-term or used low doses of carotenoids. Since carotenoids are not essential nutrients so there is not any recommended dietary intake for any population group. However, it is being increasingly suggested that dietary intake recommendations should be fixed for zeaxanthin and lutein. Optimal lutein intake for eye health is supposed to be 6 mg/day and no toxic symptoms appeared in clinical trial even when intake was 3 times more than 6 mg [80]. No recommended intake of lutein exists for breastfeeding women or infants, however EFSA confirmed that lutein @ 250 μg/L is safe in infants' formulas [128]. Diet rich in fruits and vegetables being carotenoid source should be suggested to pregnant and lactating women and infants as they have good effects on health and no toxic effects have been reported [30]. Complete breast-feeding upto 6 months should be recommended for infants and overall breastfeeding period should be at least 2 years

as breast milk is better carotenoid source than formula and it leads to numerous health results [129].

25.3 Conclusions

Epidemiological, interventional, clinical, animal and human studies strongly suggest relationship between sufficient carotenoid intake, from fruits and vegetables or from supplements and formulas and decreased chances of age-related decline of cognitive performance and chronic disease. However, no strong relationship has yet been confirmed between carotenoid intake and decrease risk of pregnancy and allied disorders. Even studies exist which suggest inverse relationship between beneficial effects of carotenoid intake and pregnancy problems. Since most of RCT studies were small and biased therefore further research is needed in this area. Lutein is one of most-researched carotenoid for its beneficial effects. Its sufficient intake during neonatal period is of vital importance due to its antioxidant and anti-inflammatory activities and its role in development of nervous and vision system. In initial life phases, visual stimuli are necessary factors for brain development cognitive processes of child. As most infant formulas lack carotenoids, therefore carotenoid level of newborns and infants relies upon the nutritional status of mother and her breastfeeding method. Zeaxanthin and lutein role in development of visual and nervous systems has been observed only in animal models. Further studies are required to establish role of carotenoid in newborn, infant, child and pregnant women health.

Funding This research was funded by the Deanship of Scientific Research at Princess Nourah bint Abdurrahman University through the Fast-track Research Funding Program.

References

1. Berti C, Cetin I, Agostoni C, Desoye G, Devlieger R, Emmett P et al (2016) Pregnancy and infants' outcome: nutritional and metabolic implications. Crit Rev Food Sci Nutr 56(1):82–91
2. Agarwal A, Aponte-Mellado A, Premkumar BJ, Shaman A, Gupta S (2012) The effects of oxidative stress on female reproduction: a review. Reprod Biol Endocrinol 10(1):49
3. Al-Gubory KH, Fowler PA, Garrel C (2010) The roles of cellular reactive oxygen species, oxidative stress and antioxidants in pregnancy outcomes. Int J Biochem Cell Biol 42(10):1634–1650
4. Thorne-Lyman AL, Fawzi WW (2012) Vitamin A and carotenoids during pregnancy and maternal, neonatal and infant health outcomes: a systematic review and meta-analysis. Paediatr Perinat Epidemiol 26:36–54
5. Pereira AC, Martel F (2014) Oxidative stress in pregnancy and fertility pathologies. Cell Biol Toxicol 30(5):301–312
6. Mol BW, Roberts CT, Thangaratinam S, Magee LA, De Groot CJ, Hofmeyr GJ (2016) Pre-eclampsia. Lancet 387(10022):999–1011

7. Barden A, Beilin LJ, Ritchie J, Croft KD, Walters BN, Michael CA (1996) Plasma and urinary 8-iso-prostane as an indicator of lipid peroxidation in pre-eclampsia and normal pregnancy. Clin Sci 91(6):711–718
8. Staff AC, Halvorsen B, Ranheim T, Henriksen T (1999) Elevated level of free 8-iso-prostaglandin F2α in the decidua basalis of women with preeclampsia. Am J Obstet Gynecol 181(5):1211–1215
9. Mert I, Sargın Oruc A, Yuksel S, Cakar ES, Buyukkagnıcı U, Karaer A et al (2012) Role of oxidative stress in preeclampsia and intrauterine growth restriction. J Obstet Gynaecol Res 38(4):658–664
10. Cohen JM, Kramer MS, Platt RW, Basso O, Evans RW, Kahn SR (2015) The association between maternal antioxidant levels in midpregnancy and preeclampsia. Am J Obstet Gynecol 213(5):695.e1–695.e13
11. Williams MA, Woelk GB, King IB, Jenkins L, Mahomed K (2003) Plasma carotenoids, retinol, tocopherols, and lipoproteins in preeclamptic and normotensive pregnant Zimbabwean women. Am J Hypertens 16(8):665–672
12. Sharma J, Kumar A, Kumar A, Malhotra M, Arora R, Prasad S et al (2003) Effect of lycopene on pre-eclampsia and intra-uterine growth retardation in primigravidas. Int J Gynecol Obstet 81(3):257–262
13. Banerjee S, Jeyaseelan S, Guleria R (2009) Trial of lycopene to prevent pre-eclampsia in healthy primigravidas: results show some adverse effects. J Obstet Gynaecol Res 35(3):477–482
14. Antartani R, Ashok K (2011) Effect of lycopene in prevention of preeclampsia in high risk pregnant women. J Turkish Ger Gynecol Assoc 12(1):35
15. Lappas M, Hiden U, Desoye G, Froehlich J, SH-d M, Jawerbaum A (2011) The role of oxidative stress in the pathophysiology of gestational diabetes mellitus. Antioxid Redox Signal 15(12):3061–3100
16. Grissa O, Atègbo J-M, Yessoufou A, Tabka Z, Miled A, Jerbi M et al (2007) Antioxidant status and circulating lipids are altered in human gestational diabetes and macrosomia. Transl Res 150(3):164–171
17. Lorenzoni F, Giampietri M, Ferri G, Lunardi S, Madrigali V, Battini L et al (2013) Lutein administration to pregnant women with gestational diabetes mellitus is associated to a decrease of oxidative stress in newborns. Gynecol Endocrinol 29(10):901–903
18. Clerici G, Slavescu C, Fiengo S, Kanninen T, Romanelli M, Biondi R et al (2012) Oxidative stress in pathological pregnancies. J Obstet Gynaecol 32(2):124–127
19. Longini M, Perrone S, Vezzosi P, Marzocchi B, Kenanidis A, Centini G et al (2007) Association between oxidative stress in pregnancy and preterm premature rupture of membranes. Clin Biochem 40(11):793–797
20. Kramer MS, Kahn SR, Platt RW, Genest J, Rozen R, Chen MF et al (2009) Antioxidant vitamins, long-chain fatty acids, and spontaneous preterm birth. Epidemiology 20:707–713
21. Huber JC, Brender JD, Zheng Q, Sharkey JR, Vuong AM, Shinde MU et al (2013) Maternal dietary intake of nitrates, nitrites and nitrosamines and selected birth defects in offspring: a case-control study. Nutr J 12(1):34
22. Kotake-Nara E, Nagao A (2011) Absorption and metabolism of xanthophylls. Mar Drugs 9(6):1024–1037
23. Englund-Ögge L, Brantsæter AL, Sengpiel V, Haugen M, Birgisdottir BE, Myhre R et al (2014) Maternal dietary patterns and preterm delivery: results from large prospective cohort study. BMJ 348:g1446
24. Saker M, Mokhtari NS, Merzouk SA, Merzouk H, Belarbi B, Narce M (2008) Oxidant and antioxidant status in mothers and their newborns according to birthweight. Eur J Obstet Gynecol Reprod Biol 141(2):95–99
25. Weber D, Stuetz W, Bernhard W, Franz A, Raith M, Grune T et al (2014) Oxidative stress markers and micronutrients in maternal and cord blood in relation to neonatal outcome. Eur J Clin Nutr 68(2):215–222

26. Cohen J, Kahn S, Platt R, Basso O, Evans R, Kramer M (2015) Small-for-gestational-age birth and maternal plasma antioxidant levels in mid-gestation: a nested case–control study. BJOG Int J Obstet Gynaecol 122(10):1313–1321
27. Henriksen BS, Chan G, Hoffman RO, Sharifzadeh M, Ermakov IV, Gellermann W et al (2013) Interrelationships between maternal carotenoid status and newborn infant macular pigment optical density and carotenoid status. Invest Ophthalmol Vis Sci 54(8):5568–5578
28. Christian P, Klemm R, Shamim AA, Ali H, Rashid M, Shaikh S et al (2013) Effects of vitamin A and β-carotene supplementation on birth size and length of gestation in rural Bangladesh: a cluster-randomized trial. Am J Clin Nutr 97(1):188–194
29. Watson P, McDonald B (2007) Seasonal variation of nutrient intake in pregnancy: effects on infant measures and possible influence on diseases related to season of birth. Eur J Clin Nutr 61(11):1271–1280
30. Krinsky NI, Johnson EJ (2005) Carotenoid actions and their relation to health and disease. Mol Asp Med 26(6):459–516
31. Fiedor J, Burda K (2014) Potential role of carotenoids as antioxidants in human health and disease. Nutrients 6(2):466–488
32. Herrera E, Amusquivar E, Lopez-Soldado I, Ortega H (2006) Maternal lipid metabolism and placental lipid transfer. Horm Res Paediatr 65.(Suppl. 3:59–64
33. Panova I, Tatikolov A, Sukhikh G (2007) Correlation between the content of albumin and carotenoids in human vitreous body during prenatal development. Bull Exp Biol Med 144(5):681–683
34. Bhattacharya N, Stubblefield PG (2016) Human fetal growth and development: first and second trimesters. Springer, Cham
35. Mango M, Tamai H, Ogihara T, Mino M (1992) Distribution of circulating β-carotene in human plasma lipoproteins. J Nutr Sci Vitaminol 38(5):405–414
36. Costabile BK, Kim Y-K, Iqbal J, Zuccaro MV, Wassef L, Narayanasamy S et al (2016) β-Apo-10′-carotenoids modulate placental microsomal triglyceride transfer protein expression and function to optimize transport of intact β-carotene to the embryo. J Biol Chem 291(35):18525–18535
37. Gomes MM, Saunders C, Ramalho A (2010) Placenta: a possible predictor of vitamin A deficiency. Br J Nutr 103(9):1340–1344
38. Scaife AR, McNeill G, Campbell DM, Martindale S, Devereux G, Seaton A (2006) Maternal intake of antioxidant vitamins in pregnancy in relation to maternal and fetal plasma levels at delivery. Br J Nutr 95(4):771–778
39. Masters ET, Jedrychowski W, Schleicher RL, Tsai W-Y, Tu Y-H, Camann D et al (2007) Relation between prenatal lipid-soluble micronutrient status, environmental pollutant exposure, and birth outcomes. Am J Clin Nutr 86(4):1139–1145
40. Karakilcik AZ, Aksakal M, Baydas G, Sozen R, Ayata A, Simsek M (1996) Plasma -carotene concentrations in pregnancies, new born infants and their mothers. J Pak Med Assoc 46:77–79
41. Yeum K-J, Ferland G, Patry J, Russell RM (1998) Relationship of plasma carotenoids, retinol and tocopherols in mothers and newborn infants. J Am Coll Nutr 17(5):442–447
42. Kiely M, Cogan P, Kearney P, Morrissey P (1999) Concentrations of tocopherols and carotenoids in maternal and cord blood plasma. Eur J Clin Nutr 53(9):711–715
43. Franke A, Lai J, Morrison C, Pagano I, Li X, Halm B et al (2013) Coenzyme Q10, carotenoid, tocopherol, and retinol levels in cord plasma from multiethnic subjects in Hawaii. Free Radic Res 47(9):757–768
44. Goldberg JS (2012) Monitoring maternal beta carotene and retinol consumption may decrease the incidence of neurodevelopmental disorders in offspring. Clin Med Insights Reprod Health 6:CMRH. S8372
45. Spiegler E, Kim Y-K, Wassef L, Shete V, Quadro L (2012) Maternal–fetal transfer and metabolism of vitamin A and its precursor β-carotene in the developing tissues. Biochim Biophys Acta (BBA)-Mol Cell Biol Lipids 1821(1):88–98

46. Picone S, Ritieni A, Fabiano A, Troise AD, Graziani G, Paolillo P et al (2012) Arterial cord blood lutein levels in preterm and term healthy newborns are sex and gestational age dependent. Clin Biochem 45(18):1558–1563
47. Schulz C, Engel U, Kreienberg R, Biesalski HK (2007) Vitamin A and β-carotene supply of women with gemini or short birth intervals. Eur J Nutr 46(1):12
48. Chelchowska M, Ambroszkiewicz J, Gajewska J, Laskowska-Klita T, Leibschang J (2011) The effect of tobacco smoking during pregnancy on plasma oxidant and antioxidant status in mother and newborn. Eur J Obstet Gynecol Reprod Biol 155(2):132–136
49. de Barros Silva SS, de Carvalho Rondó PH, Erzinger GS (2005) β-Carotene concentrations in maternal and cord blood of smokers and non-smokers. Early Hum Dev 81(4):313–317
50. Hung T-H, Chen S-F, Lo L-M, Li M-J, Yeh Y-L (2011) The associations between labor and delivery mode and maternal and placental oxidative stress. Reprod Toxicol 31(2):144–150
51. Noh EJ, Kim YH, Cho MK, Kim JW, Kim JW, Byun YJ et al (2014) Comparison of oxidative stress markers in umbilical cord blood after vaginal and cesarean delivery. Obstet Gynecol Sci 57(2):109–114
52. Khachik F, Spangler CJ, Smith JC, Canfield LM, Steck A, Pfander H (1997) Identification, quantification, and relative concentrations of carotenoids and their metabolites in human milk and serum. Anal Chem 69(10):1873–1881
53. Lipkie TE, Morrow AL, Jouni ZE, McMahon RJ, Ferruzzi MG (2015) Longitudinal survey of carotenoids in human milk from urban cohorts in China, Mexico, and the USA. PLoS One 10(6):e0127729
54. Xue Y, Campos-Giménez E, Redeuil KM, Lévèques A, Actis-Goretta L, Vinyes-Pares G et al (2017) Concentrations of carotenoids and tocopherols in breast milk from urban Chinese mothers and their associations with maternal characteristics: a cross-sectional study. Nutrients 9(11):1229
55. Ballard O, Morrow AL (2013) Human milk composition: nutrients and bioactive factors. Pediatr Clin 60(1):49–74
56. Gidrewicz DA, Fenton TR (2014) A systematic review and meta-analysis of the nutrient content of preterm and term breast milk. BMC Pediatr 14(1):216
57. Kent JC, Mitoulas LR, Cregan MD, Ramsay DT, Doherty DA, Hartmann PE (2006) Volume and frequency of breastfeedings and fat content of breast milk throughout the day. Pediatrics 117(3):e387–ee95
58. Khan S, Hepworth AR, Prime DK, Lai CT, Trengove NJ, Hartmann PE (2013) Variation in fat, lactose, and protein composition in breast milk over 24 hours: associations with infant feeding patterns. J Hum Lact 29(1):81–89
59. Mitoulas LR, Kent JC, Cox DB, Owens RA, Sherriff JL, Hartmann PE (2002) Variation in fat, lactose and protein in human milk over 24h and throughout the first year of lactation. Br J Nutr 88(1):29–37
60. Macias C, Schweigert FJ (2001) Changes in the concentration of carotenoids, vitamin A, alpha-tocopherol and total lipids in human milk throughout early lactation. Ann Nutr Metab 45(2):82–85
61. Canfield LM, Clandinin MT, Davies DP, Fernandez MC, Jackson J, Hawkes J et al (2003) Multinational study of major breast milk carotenoids of healthy mothers. Eur J Nutr 42(3):133–141
62. de Azeredo VB, Trugo NM (2008) Retinol, carotenoids, and tocopherols in the milk of lactating adolescents and relationships with plasma concentrations. Nutrition 24(2):133–139
63. Giuliano AR, Neilson EM, Yap H-H, Baier M, Canfield LM (1994) Quantitation of and inter/intra-individual variability in major carotenoids of mature human milk. J Nutr Biochem 5(11):551–556
64. Jackson JG, Lien EL, White SJ, Bruns NJ, Kuhlman CF (1998) Major carotenoids in mature human milk: longitudinal and diurnal patterns. J Nutr Biochem 9(1):2–7

65. Schweigert FJ, Bathe K, Chen F, Büscher U, Dudenhausen JW (2004) Effect of the stage of lactation in humans on carotenoid levels in milk, blood plasma and plasma lipoprotein fractions. Eur J Nutr 43(1):39–44
66. Jackson JG, Zimmer JP (2007) Lutein and zeaxanthin in human milk independently and significantly differ among women from Japan, Mexico, and the United Kingdom. Nutr Res 27(8):449–453
67. Jewell V, Mayes C, Tubman T, Northrop-Clewes C, Thurnham D (2004) A comparison of lutein and zeaxanthin concentrations in formula and human milk samples from Northern Ireland mothers. Eur J Clin Nutr 58(1):90–97
68. Haftel L, Berkovich Z, Reifen R (2015) Elevated milk β-carotene and lycopene after carrot and tomato paste supplementation. Nutrition 31(3):443–445
69. Nagayama J, Noda K, Uchikawa T, Maruyama I, Shimomura H, Miyahara M (2014) Effect of maternal Chlorella supplementation on carotenoid concentration in breast milk at early lactation. Int J Food Sci Nutr 65(5):573–576
70. Sherry CL, Oliver JS, Renzi LM, Marriage BJ (2014) Lutein supplementation increases breast milk and plasma lutein concentrations in lactating women and infant plasma concentrations but does not affect other carotenoids. J Nutr 144(8):1256–1263
71. Shennan D, Peaker M (2000) Transport of milk constituents by the mammary gland. Physiol Rev 80(3):925–951
72. Schweigert F (1990) Effect of gestation and lactation on lipoprotein pattern and composition in dairy cows 1. J Anim Physiol Anim Nutr 63(1–5):75–83
73. Bettler J, Zimmer JP, Neuringer M, DeRusso PA (2010) Serum lutein concentrations in healthy term infants fed human milk or infant formula with lutein. Eur J Nutr 49(1):45–51
74. Chan GM, Chan MM, Gellermann W, Ermakov I, Ermakova M, Bhosale P et al (2013) Resonance Raman spectroscopy and the preterm infant carotenoid status. J Pediatr Gastroenterol Nutr 56(5):556
75. Sommerburg O, Meissner K, Nelle M, Lenhartz H, Leichsenring M (2000) Carotenoid supply in breast-fed and formula-fed neonates. Eur J Pediatr 159(1–2):86–90
76. Zimmer JP, Hammond BR Jr (2007) Possible influences of lutein and zeaxanthin on the developing retina. Clin Ophthalmol 1(1):25
77. Capeding R, Gepanayao CP, Calimon N, Lebumfacil J, Davis AM, Stouffer N et al (2010) Lutein-fortified infant formula fed to healthy term infants: evaluation of growth effects and safety. Nutr J 9(1):22
78. Jeon S, Neuringer M, Johnson EE, Kuchan MJ, Pereira SL, Johnson EJ et al (2017) Effect of carotenoid supplemented formula on carotenoid bioaccumulation in tissues of infant rhesus macaques: a pilot study focused on lutein. Nutrients 9(1):51
79. Lipkie TE, Banavara D, Shah B, Morrow AL, McMahon RJ, Jouni ZE et al (2014) Caco-2 accumulation of lutein is greater from human milk than from infant formula despite similar bioaccessibility. Mol Nutr Food Res 58(10):2014–2022
80. Johnson EJ (2014) Role of lutein and zeaxanthin in visual and cognitive function throughout the lifespan. Nutr Rev 72(9):605–612
81. Perrone S, Longini M, Marzocchi B, Picardi A, Bellieni CV, Proietti F et al (2010) Effects of lutein on oxidative stress in the term newborn: a pilot study. Neonatology 97(1):36–40
82. Loskutova E, Nolan J, Howard A, Beatty S (2013) Macular pigment and its contribution to vision. Nutrients 5(6):1962–1969
83. Bernstein PS, Khachik F, Carvalho LS, Muir GJ, Zhao D-Y, Katz NB (2001) Identification and quantitation of carotenoids and their metabolites in the tissues of the human eye. Exp Eye Res 72(3):215–223
84. Bone R, Landrum J, Fernandez L, Tarsis S (1988) Analysis of the macular pigment by HPLC: retinal distribution and age study. Invest Ophthalmol Vis Sci 29(6):843–849
85. Bone RA, Landrum JT, Frides LM, Gomes CM, Kilburn MD, Menenes E et al (1997) Distribution of lutein and zeaxanthin stereoisomers in the human retina. Exp Eye Res 64(2):211–218

86. Hendrickson A, Possin D, Vajzovic L, Toth CA (2012) Histologic development of the human fovea from midgestation to maturity. Am J Ophthalmol 154(5):767–78. e2
87. Liu Z, Meyers KJ, Johnson EJ, Snodderly M, Tinker L, Wallace R et al (2015) Exposure to lutein in infancy via breast milk and later life macular pigment optical density. Invest Ophthalmol Vis Sci 56(7):192
88. Neuringer M, Bone R, Jeffrey B, Bettler J, Zimmer J, Wallace P et al (2009) Lutein in breast-milk and infant formula: effects on serum lutein, macular pigment and visual function. Invest Ophthalmol Vis Sci 50(13):1707
89. Lien EL, Hammond BR (2011) Nutritional influences on visual development and function. Prog Retin Eye Res 30(3):188–203
90. Dillon J, Zheng L, Merriam JC, Gaillard ER (2004) Transmission of light to the aging human retina: possible implications for age related macular degeneration. Exp Eye Res 79(6):753–759
91. Hardy P, Dumont I, Bhattacharya M, Hou X, Lachapelle P, Varma DR et al (2000) Oxidants, nitric oxide and prostanoids in the developing ocular vasculature: a basis for ischemic retinopathy. Cardiovasc Res 47(3):489–509
92. Jewell VC, Northrop-Clewes CA, Tubman R, Thurnham DI (2001) Nutritional factors and visual function in premature infants. Proc Nutr Soc 60(2):171–178
93. Landrum JT, Bone RA, Krinsky N, Mayne S, Sies H (2004) Mechanistic evidence for eye diseases and carotenoids. Oxid Stress Dis 13:445–472
94. Li B, Ahmed F, Bernstein PS (2010) Studies on the singlet oxygen scavenging mechanism of human macular pigment. Arch Biochem Biophys 504(1):56–60
95. Ozawa Y, Sasaki M, Takahashi N, Kamoshita M, Miyake S, Tsubota K (2012) Neuroprotective effects of lutein in the retina. Curr Pharm Des 18(1):51–56
96. Li S-Y, Fung FK, Fu ZJ, Wong D, Chan HH, Lo AC (2012) Anti-inflammatory effects of lutein in retinal ischemic/hypoxic injury: in vivo and in vitro studies. Invest Ophthalmol Vis Sci 53(10):5976–5984
97. Bernstein PS, Balashov NA, Tsong ED, Rando RR (1997) Retinal tubulin binds macular carotenoids. Invest Ophthalmol Vis Sci 38(1):167–175
98. Stahl W, Nicolai S, Briviba K, Hanusch M, Broszeit G, Peters M et al (1997) Biological activities of natural and synthetic carotenoids: induction of gap junctional communication and singlet oxygen quenching. Carcinogenesis 18(1):89–92
99. Crabtree DV, Ojima I, Geng X, Adler AJ (2001) Tubulins in the primate retina: evidence that xanthophylls may be endogenous ligands for the paclitaxel-binding site. Bioorg Med Chem 9(8):1967–1976
100. Hammond BR Jr (2008) Possible role for dietary lutein and zeaxanthin in visual development. Nutr Rev 66(12):695–702
101. Liew SM, Gilbert CE, Spector TD, Mellerio J, Van Kuijk FJ, Beatty S et al (2006) Central retinal thickness is positively correlated with macular pigment optical density. Exp Eye Res 82(5):915–920
102. Leung IY-F, Sandstrom MM, Zucker CL, Neuringer M, Snodderly DM (2004) Nutritional manipulation of primate retinas, II: effects of age, n–3 fatty acids, lutein, and zeaxanthin on retinal pigment epithelium. Invest Ophthalmol Vis Sci 45(9):3244–3256
103. Malinow M, Feeney-Burns L, Peterson LH, Klein ML, Neuringer M (1980) Diet-related macular anomalies in monkeys. Invest Ophthalmol Vis Sci 19(8):857–863
104. Knickmeyer RC, Gouttard S, Kang C, Evans D, Wilber K, Smith JK et al (2008) A structural MRI study of human brain development from birth to 2 years. J Neurosci 28(47):12176–12182
105. Vishwanathan R, Schalch W, Johnson EJ (2016) Macular pigment carotenoids in the retina and occipital cortex are related in humans. Nutr Neurosci 19(3):95–101
106. Vishwanathan R, Neuringer M, Snodderly DM, Schalch W, Johnson EJ (2013) Macular lutein and zeaxanthin are related to brain lutein and zeaxanthin in primates. Nutr Neurosci 16(1):21–29

107. Vishwanathan R, Iannaccone A, Scott TM, Kritchevsky SB, Jennings BJ, Carboni G et al (2014) Macular pigment optical density is related to cognitive function in older people. Age Ageing 43(2):271–275
108. Stahl W, Sies H (2001) Effects of carotenoids and retinoids on gap junctional communication. Biofactors 15(2–4):95–98
109. Nataraj J, Manivasagam T, Thenmozhi AJ, Essa MM (2016) Lutein protects dopaminergic neurons against MPTP-induced apoptotic death and motor dysfunction by ameliorating mitochondrial disruption and oxidative stress. Nutr Neurosci 19(6):237–246
110. Lieblein-Boff JC, Johnson EJ, Kennedy AD, Lai C-S, Kuchan MJ (2015) Exploratory metabolomic analyses reveal compounds correlated with lutein concentration in frontal cortex, hippocampus, and occipital cortex of human infant brain. PLoS One 10(8):e0136904
111. Vishwanathan R, Kuchan MJ, Sen S, Johnson EJ (2014) Lutein and preterm infants with decreased concentrations of brain carotenoids. J Pediatr Gastroenterol Nutr 59(5):659–665
112. Cheatham CL, Sheppard KW (2015) Synergistic effects of human milk nutrients in the support of infant recognition memory: an observational study. Nutrients 7(11):9079–9095
113. Blusztajn JK, Slack BE, Mellott TJ (2017) Neuroprotective actions of dietary choline. Nutrients 9(8):815
114. Perrone S, Tei M, Longini M, Santacroce A, Turrisi G, Proietti F et al (2014) Lipid and protein oxidation in newborn infants after lutein administration. Oxidative Med Cell Longev 2014:1–7
115. Romagnoli C, Tirone C, Persichilli S, Gervasoni J, Zuppi C, Barone G et al (2010) Lutein absorption in premature infants. Eur J Clin Nutr 64(7):760–761
116. Orjuela MA, Titievsky L, Liu X, Ramirez-Ortiz M, Ponce-Castaneda V, Lecona E et al (2005) Fruit and vegetable intake during pregnancy and risk for development of sporadic retinoblastoma. Cancer Epidemiol Prev Biomarkers 14(6):1433–1440
117. Rühl R (2007) Effects of dietary retinoids and carotenoids on immune development*: symposium on 'nutrition influences on developmental immunology'. Proc Nutr Soc 66(3):458–469
118. Litonjua AA, Rifas-Shiman SL, Ly NP, Tantisira KG, Rich-Edwards JW, Camargo CA Jr et al (2006) Maternal antioxidant intake in pregnancy and wheezing illnesses in children at 2 y of age. Am J Clin Nutr 84(4):903–911
119. Miyake Y, Sasaki S, Tanaka K, Hirota Y (2010) Consumption of vegetables, fruit, and antioxidants during pregnancy and wheeze and eczema in infants. Allergy 65(6):758–765
120. Mulder KA, Innis SM, Rasmussen BF, Wu BT, Richardson KJ, Hasman D (2014) Plasma lutein concentrations are related to dietary intake, but unrelated to dietary saturated fat or cognition in young children. J Nutr Sci 3:e11
121. Hammond BR (2014) Lutein and cognition in children. J Nutr Sci 3:e53
122. Leermakers ET, Kiefte-de Jong JC, Hofman A, Jaddoe VW, Franco OH (2015) Lutein intake at the age of 1 year and cardiometabolic health at the age of 6 years: the generation R study. Br J Nutr 114(6):970–978
123. Eghbaliferiz S, Iranshahi M (2016) Prooxidant activity of polyphenols, flavonoids, anthocyanins and carotenoids: updated review of mechanisms and catalyzing metals. Phytother Res 30(9):1379–1391
124. Group A-TBCCPS (1994) The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. N Engl J Med 330(15):1029–1035
125. Törnwall ME, Virtamo J, Korhonen PA, Virtanen MJ, Taylor PR, Albanes D et al (2004) Effect of α-tocopherol and β-carotene supplementation on coronary heart disease during the 6-year post-trial follow-up in the ATBC study. Eur Heart J 25(13):1171–1178
126. Hennekens CH, Buring JE, Manson JE, Stampfer M, Rosner B, Cook NR et al (1996) Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. N Engl J Med 334(18):1145–1149
127. Rahman A, Bokhari SSI, Waqar MA (2001) Beta-carotene degradation by cigarette smoke in hexane solution in vitro. Nutr Res 21(6):821–829

128. Authority EFS (2008) Safety, bioavailability and suitability of lutein for the particular nutritional use by infants and young children-scientific opinion of the panel on dietetic products, nutrition and allergies. EFSA J 6(11):823
129. Victora CG, Bahl R, Barros AJ, França GV, Horton S, Krasevec J et al (2016) Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. Lancet 387(10017):475–490