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Relationship between Ocular Morbidity and Infant Nutrition

Erdinc Bozkurt and Hayrunisa Bekis Bozkurt

Abstract

The nutrition of the constantly growing and developing infant even after birth has an undeniable contribution to the development of eyes, which can be considered as the extension of the brain. Therefore, the elucidation of these physiological developments is valuable in terms of preventing pathological conditions. During the first six months of an infant's life, nutrition is provided through breast milk or infant formula, and after the sixth month, there is a transition to additional food. Breast milk is, thus, considered as 'miracle food', with a growing body of research being undertaken to investigate its relationship with orbital diseases and reporting that breast milk reduces ocular morbidity. Breast milk is an accessible, economical and important nutrition source for eye development and infant health. The developments in recent years have resulted in the content of formula being closer to that of breast milk, which can positively affect the neurovisional development of babies that cannot be fed with breast milk.

Keywords: breastfeeding, formula, infant, visual development, refractive disorders, retinal disease

1. Nutrition in the first year of life and orbital development

Orbital development begins in fourth to sixth weeks of the intrauterine period. The eye develops from the surface ectoderm, neural ectoderm, and mesoderm. The optic nerve is also seen as an extension of the brain [1]. There is a significant relationship between the mother's diet during pregnancy and the orbital development of the infant. In recent years, the concept of the "first 1000" days emerged to refer to the process during pregnancy and the first two years after birth. The first 1000 days play a key role in many stages of life [2], and this period is also important in terms of healthy eye development and the prevention of orbital diseases, comorbid conditions, and complications.

The mother's diet during pregnancy is very valuable in terms of providing essential fatty acids and amino acids, which are necessary for the development of the orbital tissues of the infant. Studies have shown this developmental process is positively affected by a diet rich in phospholipids (PL), phosphatidylcholine (PC), phosphatidylethanolamine (PE), N-acylphosphatidylethanolamine (NAPE), phosphatidylinositol (PI), and phosphatidylserine (PS) [3]. Similarly, the mother's malnutrition during breastfeeding in the first year after birth negatively affects the orbital and brain development of the infant. In the complex process of orbital and visual development, tissues and cells need many minerals, vitamins and nutrients to continue their functions [4]. For example, in this process, vitamin A plays a vital

role for photoreceptors, vitamin C is important for the development of the aqueous humor, and fatty acids are essential for the development of the optic nerve and myelin sheath [5]. In recent years, with the development of technology, premature infants now live longer, and the nutrition and supportive treatments for premature newborns have become even more important. In these infants, retinopathy of prematurity (ROP), which can cause blindness when not treated early, is seen very often due to hyperoxia, long stay in mechanical ventilation, infection, prematurity, low birth weight, and low-calorie maternal diet [6]. A diet rich in vitamins A and E, and longer duration of breastfeeding decreases the requirement of surgery to treat ROP [7, 8].

The nutrition of the constantly growing and developing infant even after birth has an undeniable contribution to the development of eyes, which can be considered as the extension of the brain. Therefore, the elucidation of these physiological developments is valuable in terms of preventing pathological conditions [9]. During the first six months of an infant's life, nutrition is provided through breast milk or infant formula, and after the sixth month, there is a transition to additional food. In this chapter, we discuss breast milk, infant formula, and their relationship with ocular morbidity.

2. Breast milk: the best nutrition for orbital development

After the baby is born, breastfeeding especially in the first six months is considered as a fundamental right by WHO and necessary actions are taken to ensure this for every child [10]. Breast milk is the most suitable food for a newborn in terms of the balance of nutrients it contains [11]. Studies have shown that breast milk protects the infant against many diseases, malignancies, obesity, and malnutrition [12]. Degeneration occurs in retinal ganglion cells and photoreceptors, especially when the infant's diet is deficient in taurine found at high levels in breast milk [13]. Many bioactive compounds, such as α -lactalbumin, lactoferrin and immunoglobulins, which have antioxidant properties, are known to be important for brain and orbital development, as well as immunomodulatory functions [14]. Being rich in glial cell-line derived neurotrophic factor (GDNF) and oligosaccharides, breast milk acts as an important stimulator for healthy development [15]. The presence of many growth factors and the importance of the baby being in proper osmolarity and balance for the full development of the intestines and kidneys further increase the value of breast milk [16]. Breast milk is, thus, considered as 'miracle food', with a growing body of research being undertaken to investigate its relationship with orbital diseases and reporting that breast milk reduces ocular morbidity [17].

3. New formulas enriched with vitamin and minerals

In circumstances where breast milk is insufficient or contraindicated, the use of formula approaching breast milk in terms of content has increased in recent years. Infant formula can be divided into three groups as soy-based, cow milk-based and hypoallergic or amino acid-based special foods produced for special conditions, such as metabolic diseases [18]. However, there have been discussions of safety for formula in terms of infant health since its first use [19]. Due to the high levels of renal solute load of the foods used in the first year of life, infant formula still lags behind breast milk, and there are only limited scientific studies on the relationship between infant formula and highly critical molecules for brain and eye development. Considering the positive impact of breast milk on the immune system, the

food given to the infant in case of breast milk deficiency or contraindication should be “closest” to breast milk [20]. With the latest technologies, the enrichment of formula foods with prebiotics, probiotics, oligosaccharides, and various vitamins and minerals has made significant contributions to infant nutrition [21]. In particular, molecules which take part in the development of visual functions, such as docosahexaenoic acid (DHA), vitamin A, and vitamin E have started to be added to infant formula. In a study on baby rhesus monkeys, it was observed that formula enriched with carotenoid increased the amount of lutein in the brain and tissues and positively affected their development, but not to the extent of the positive effect of breast milk [22].

A healthy and balanced nutrition in childhood is very important for not only growth and development and but also prevention of diseases. In terms of eye health, it is important to ensure that the infant receives age-appropriate nutrition with breast milk and foods close to breast milk in content and quality, which will protect her/him against malnutrition and obesity and an adequate intake of vitamins and minerals.

4. Breastfeeding and ocular disease

4.1 Breastfeeding and visual development

Breast milk contains an average of 1.1% protein, 4.2% fat, and 7.0% carbohydrates, and is a miraculous nutrient in which every 100 g contains 72 kcal energy [23]. Breast milk also has vitamins E and C, as well as enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase with strong antioxidant properties. In this way, it protects the infant from eye damage that may be caused by oxidative stress [24]. Generally, breast milk has been found to be inadequate in certain vitamins and minerals, such as vitamin D, iodine, iron, and vitamin K. Since the deficiency of these vitamins and minerals can affect the infant systematically, going beyond eye diseases, they are usually added to the infant's diet as supplements [25].

Breast milk supports the infant's growth and development through its content of long-chain polyunsaturated essential fatty acids, such as arachidonic acid, long chain polyunsaturated fatty acids (LC-PUFAs) (20: 4n-6) and DHA (22: 6n-3), linoleic (LA; 18: 2n-6) and alpha-linolenic (18: 3n-3) acid [26]. DHA and arachidonic acid (AA) in the membrane lipids of the brain and retina are critical for visual and neuronal functions. Taking these substances with diet in the first year of life is important for the visual development of infants [27].

The retina (and the crystalline lens to a lesser extent) has reduced light-sourced oxidative damage by vitamin E and C, and carotenoids (lutein and zeaxanthin), which are intensely present in the macular region. Vitamins E and C and lutein cannot be synthesized by the infant, and therefore should be taken in through the diet [28]. Dietary carotenoid, lutein and zeoxanthin are known to be protective against some eye diseases, such as macular degenerations [29]. It was observed that the serum lutein level of infants fed with breast milk was higher than that of infants fed with formula [30]. This indicates that infants fed with breast milk may be resistant to many eye diseases caused by oxidative damage due to its higher antioxidant levels than formula. Vitamin A is an important vitamin used by photoreceptors in visual physiology. Adequate intake of vitamin A, which is found in breast milk and formula foods, has been shown to reduce the severity of ROP through vascular endothelial growth factor (VEGF-A). In addition, preterm infants fed with breast milk have higher serum insulin-like growth factor-1 (IGF-1) levels than those who

feed with formula [31]. A high IGF-1 level decreases the severity of ROP by ensuring the normal development of retinal vascularization [32].

4.2 Refractive disorders and breastfeeding

Refractive disorders (error) represent a mismatch between the focal and axial lengths of the eye. The 10th revision of the International Classification of Diseases, defines this disorder as blurring in vision as a result of a defect in focusing light on the retina [33]. At birth, the average cycloplegic refractive error for the infant usually ranges from ± 1.50 dioptre (D) to ± 2.50 D, with standard deviations from $+1.00$ to $+2.50$ D [34]. At the age of six to 72 months, the eyes undergo a process of emmetropization in which the average refractive error decreases in both myopic and hypermetropic infants [35].

Refractive disorders are the most common cause of visual impairment and the second most common cause of treatable visual deficiency [36]. The frequency of refractive disorders may vary according to ethnicity, age, and the development level of the country [37]. According to a study carried out in the USA in 2015, the frequency of visual impairment in children between the ages of three and five is estimated to be around 1.5%, which is expected to increase in the near future [38]. Among the most important etiological causes of refractive disorders are genetics and gene-environment interactions [39–41]. In addition, nutrition is considered to have an impact on refractive disorder and orbital health. It is stated that the prevalence of refractive disorders, such as ametropia, anisometropia and astigmatism is high, especially in African societies exposed to malnutrition [37].

Recently, the effect of breast milk intake, which is the most important source of infant nutrition, on refractive disorders has been investigated. It is thought that breastfeeding is important for visual development and orbital growth during the infantile period [42]. In one of these studies, it was shown that breast milk-fed children of mothers with a DHA-rich diet had better stereoscopic vision than the formula-fed children [43].

Refractive disorders can be basically classified as myopia, hyperopia, and astigmatism. Myopia is one of the most common visual impairments and has become an important public health problem due to its increasing prevalence in recent years. While the prevalence of ametropia, anisometropia, and astigmatism is high in Africa, the frequency of myopia is low in developing countries while it is higher in developed societies, such as the United States of America (USA) and the United Kingdom (UK) [44]. This is not a surprising finding considering that myopia is associated with reading and using technological devices, which require looking at objects closely.

In a study carried out in Singapore, high levels of unsaturated fatty acids and cholesterol intake were associated with longer AL, although they could not be directly associated with myopia [45]. In another study undertaken by Liu et al. in China, it was found that feeding the infant with breast milk for the first six months was associated with hyperopic spherical equivalent refraction (SER) and less myopia and was not related to AL [46]. However, in the study of Growing Up in Singapore Towards Healthy Outcomes (GUSTO), infant feeding at the sixth, ninth and 12th months did not affect the myopia levels at the age of 3.5 years [47].

There are also many studies suggesting that breastfeeding has no effect on myopia. In a study on strabismus, amblyopia and refractive disorder (STARS) conducted with 797 children in Singapore, 65.4% of the sample were myopic, of which 8.5% were breastfed. In that study, it was stated that there was no relationship between breast milk and myopia [48]. In another study supporting the STARS study, it was reported that breast milk had no effect on myopia [49]. In a study

which included 311 children in Iran (grades 1–5), the rate of breastfeeding for more than six months was 85% while the frequency of myopia (SE of at least -0.50 D) was 5.2%. It was stated that the breastfeeding of the infant for the first six months had no significant effect on vision level or refractive error [50]. A study undertaken in the UK suggested that other factors, such as parental education status, gender, maternal age, and order of birth were more important for visual development and myopia in early life than the type of infant feeding [49]. The existence of different opinions and findings on this subject indicates that further detailed studies are needed.

Another refractive defect is hypermetropia, which occurs due to either the AL of the eye being shorter than normal or refractive structures such as cornea and lens having less refractive power than normal [51]. In a study investigating the relationship between hyperopia and breastfeeding, it was stated that breastfeeding resulted in a significantly high rate of hyperopia. This increased incidence of hyperopia was associated with various reasons, such as ethnicity, presence of refractive disorder, ethnic and sociocultural structure, and content of the mother's milk [52]. Bozkurt et al. stated that although breastfeeding leads to a hyperopic shift, it has no effect on SER [53].

Another refractive disorder, astigmatism, occurs as a result of the refractive parts of the eye (cornea and lens) not producing an equal amount of refraction on each meridian, leading to images not being focused on a point on the fovea. Generally, the breaking force of the vertical axis of the anterior aspect of the cornea is 0.5 D more than its horizontal axis. This condition, known as physiological astigmatism, is reduced to zero by the cornea posterior face and lens. Lenticular (lens-dependent) astigmatism is rarer. The image of an object being in the form of two separate lines, 90° perpendicular to each other in two planes, is called regular astigmatism, which is the most common type of astigmatism in the clinic [54]. The prevalence of astigmatism can be seen in different countries at different frequencies. While this rate is 2.2% in Nepal, it reaches 82.2% in Singapore [55, 56]. Since there is only limited information in the literature investigating the relationship between breastfeeding and astigmatism, we consider that there is not yet enough data to support the presence of such relationship.

4.3 Breastfeeding and retinal disease

The retina, which is considered an extension of the brain, has two major layers as the outer retinal pigment epithelium and the inner neurosensory layer. The neurosensory layer is formed by a photoreceptor layer, bipolar ganglion, amacrine and horizontal cells, and support cells similar to neuroglia [57]. When the pathologies that may occur with inflammation, trauma, autoimmune or epigenetic mechanisms in each layer are examined, it is seen that they are associated with the deficiency of vitamins and minerals [58, 59].

In addition to except vitamins K and D, breast milk is very rich in other vitamins and minerals that are indispensable elements of a healthy and balanced nutrition. Furthermore, polyunsaturated fatty acids and antioxidants in breast milk play an important role in the development of the eye and neuronal structure in the first months of life [48]. The leading chemical structures that contribute to the development of the brain and retina in breast milk are LA, α -LA, AA, and DHA [60], which are commonly called LC-PUFAs. In animal experiments, DHA deficiency has been shown to cause the impairment of neuronal and retinal functions [61]. It has also been reported that the photoreceptor external segments of monkeys fed with a diet devoid of taurine amino acid are degenerated, and taurine is abundantly found in breast milk [62].

Another important molecule, phosphatidylcholine, is essential for the synthesis of phospholipids, DNA methylation, and the neurodevelopmental process of infants. In an animal experiment study conducted by Surzenko et al., it was shown that a low choline diet during pregnancy affected the retinal development and function in the fetus, and choline provided differentiation and proliferation in retinal progenitor cells [63]. Infants received enough choline and LC-PUFAs from breast milk, which are very important for the brain, retinal and neurovisional development. In another study, it was emphasized that formula foods containing choline and LC-PUFAs were required for growth and development in non-breastfed infants [64].

The thickness of the retinal nerve fiber layer (RNFL) can offer an idea about retinal structures in the early period. Conditions occurring in the retinal layers, such as edema and atrophy can be objectively evaluated using optical coherence tomography. In a study undertaken by Bozkurt et al., stated that the retinal nerve fiber layer was thicker in formula-fed children, than breast-fed infant, which might be related to the content of formula. However, a definitive conclusion could not be reached as to whether the thickening of RNFL in formula-fed infants was a healthy neurotrophs or an adaptive change [53].

Another important eye disease associated with infant nutrition is ROP, which occurs in preterm babies (birth week <37) with an immature retinal structure and not fully developed retinal vasculature. Today, ROP is considered as the most important cause of preventable blindness in childhood in developed and developing countries all over the world [65]. There are many studies showing the relationship between ROP and breast milk intake. For example, Okamoto et al. reported that the content of breast milk could reduce ROP severity and the ingredients in breast milk could protect premature infants from blindness [66]. In another study, Hylander et al. found that antioxidant substances, such as inositol, vitamin E, and beta carotene in breast milk prevented ROP development, and formula-fed infants had a higher ROP frequency than breast-fed infants, especially due to the absence of inositol in standard formula [67]. In another study supporting this study, the supplementation of infant diet with inositol was shown to reduce the incidence of ROP [68]. ROP is the most serious retinal disease that causes the deficiency of vision in the neonatal period, secondary to retinal detachment. According to the literature, breast milk intake should be encouraged to reduce the harm caused by ROP [66, 67].

In conclusion, breast milk is an accessible, economical and important nutrition source for eye development and infant health. The developments in recent years have resulted in the content of formula being closer to that of breast milk, which can positively affect the neurovisional development of babies that cannot be fed with breast milk.

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