YALE JOURNAL OF BIOLOGY AND MEDICINE 97 (2024), pp.41-48. doi: 10.59249/RRMM8911

REVIEW

YALE JOURNAL OF BIOLOGY AND MEDICINE
YJBM

External Disruption of Ocular Development *in Utero*

Hyun Sue Kim[a,b], Soshian Sarrafpour[b], Christopher C. Teng[b], and Ji Liu[b,*]

[a]*Virginia Tech Carilion School of Medicine, Roanoke, VA, USA;* [b]*Department of Ophthalmology and Visual Science, Yale School of Medicine, New Haven, CT, USA*

The intricate steps of human ocular embryology are impacted by cellular and genetic signaling pathways and a myriad of external elements that can affect pregnancy, such as environmental, metabolic, hormonal factors, medications, and intrauterine infections. This review focuses on presenting some of these factors to recognize the multifactorial nature of ocular development and highlight their clinical significance. This review is based on English-language articles sourced from PubMed, Web of Science, and Google Scholar; keywords searched included "ocular development in pregnancy," "ocular embryology," "maternal nutrition," "ophthalmic change," and "visual system development." While some animal models show the disruption of ocular embryology from these external factors, there are limited post-birth assessments in human studies. Much remains unknown about the precise mechanisms of how these external factors can disrupt normal ocular development *in utero*, and more significant research is needed to understand the pathophysiology of these disruptive effects further. Findings in this review emphasize the importance of additional research in understanding the dynamic association between factors impacting gestation and neonatal ocular development, particularly in the setting of limited resources.

INTRODUCTION

Fetal ocular development commences during early embryogenesis and continues progressing even in the postnatal period [1]. Human eye embryogenesis *in utero* is governed by a sequence of biological processes that begin during the third week of gestation with gastrulation, marked by the differentiation of the single-layered blastocyst into multi-layers encompassing the ectoderm, mesoderm, and endoderm [1,2]. These three distinct germinal layers continue to give rise to different eye structures.

The invagination of the neuroectoderm during neurulation leads to the formation of the neural tube [3]. The protrusions on the side of the neural tube give rise to optic vesicles, which consist of both proximal and distal components [2]. Subsequently, the proximal vesicle differentiates into the optic nerve, and the distal vesicle differentiates into the optic cup, which consists of the retina, ciliary body, and iris [1,2].

The intricate steps of human ocular embryology are impacted by cellular and genetic signaling pathways and a myriad of external elements that can affect pregnancy,

*To whom all correspondence should be addressed: Ji Liu, Yale Eye Center, New Haven, CT, 06510; Email: liu.ji@yale.edu.

Abbreviations: CMV, Cytomegalovirus; DHA, Docosahexaenoic Acid; IGF-1, Insulin-like Growth Factor-1; IOP, Intraocular Pressure; MMP-2, Matrix Metalloproteinase-2; RAE, Retinol Activity Equivalents; ROP, Retinopathy of Prematurity; STGD, Stargardt's disease; VEGF, Vascular Endothelial Growth Factor; WASH, Water, Sanitation, and Hygiene; TORCH, *Toxoplasma gondii*, rubella virus, cytomegalovirus (CMV), herpes simplex virus, and others such as Zika, Syphilis, and HIV.

Keywords: Ocular development, eye, gestation, pregnancy, embryology, ocular malformations, maternal nutrition, ophthalmic change, visual change, visual system

Author Contributions: HK, SS, CT, and JL all contributed equally to the creation of this manuscript.

such as environmental, metabolic, and hormonal factors, as well as intrauterine infections that transplacentally affect the fetus. The blood-placental barrier plays a significant role in preventing maternal transmission of infections and serves as a defense mechanism in conjunction with the maternal immune system [4]. Similarly, the blood-brain barrier has efflux transporters that protect the developing brain from toxins [5]. Despite these physical barriers, some infections, such as the Zika virus, may traverse them and lead to disruptions in ocular development [6].

This literature review will focus on presenting some of the external factors to recognize the multifactorial nature of human ocular development and highlight their clinical significance. Intrinsic factors, including genetics, also play a role in the embryologic development of the eyes, though these are out of the scope of this review. This review is based on English-language articles sourced from PubMed, Web of Science, and Google Scholar; keywords searched included: "ocular development in pregnancy," "ocular embryology," "maternal nutrition," "ophthalmic change," and "visual system development."

TOPICS

Metabolic Factors

Comprehensive maternal nutrition with essential nutrients, such as choline, folic acid, vitamin A, and omega-3 fatty acids, supports the healthy development of the fetus during pregnancy [7].

Choline was shown to be necessary for the development of neural progenitor cells in mice models [8]. Accordingly, mothers who supplemented their diet with excess choline had children who reported better visual outcomes than the children of mothers without dietary supplementation [9,10]. Conversely, low levels of choline have been associated with abnormal ocular development, specifically, the retina [8,11].

Folic acid is another necessary nutrient for mothers and is widely known for its role in preventing neural tube defects [7,12,13]. Folic acid plays a fundamental role in cellular division as a DNA and RNA synthesis cofactor [13]. In the US, the Centers for Disease Control and Prevention (CDC) recommends that women of reproductive age prophylactically supplement their diet with 400 mcg of folic acid daily [14]. In the eye, folate receptors exist predominantly in the retina, including the Müller cells, ganglion cells, outer limiting membrane, and the outer plexiform layer, but also in the lens and other parts of the eye [12,13,15]. Low levels of folate have presented with sequelae, including amblyopia, central scotomas, and optic neuropathy [12]. During embryonic development in mice, maternal folic acid deficiency led to smaller eyes and morphological changes to the lens and the retina [16]. However, one report estimated that only 25% of neural tube defects are being prevented globally due to barriers to accessing supplements or fortified foods [17,18].

In addition, both folic acid and choline participate in the remethylation process that converts homocysteine to methionine (Figure 1). Folate is a universal methyl donor for methylation reactions [19]. Betaine, a metabolite of choline, also act as a methyl-group donor in the alternative pathway [20]. Folic acid deficiency may lead to abnormally elevated levels of homocysteine [21]. Increased homocysteine levels in the retina upregulate pro-inflammatory cytokines and microglia activation, inducing systemic and local retinal inflammation [22]. Elevated homocysteine levels induce retinal neuron death, disrupting the inner and outer retinal and ganglion cell layers [23]. Homocystinuria is a rare autosomal recessive metabolic disease with raised body homocysteine secondary to cystathionine beta-synthase deficiency. Approximately 90% of patients with homocystinuria may develop natural crystalline lens subluxation or displacement, namely, ectopia lentis. It has been hypothesized that elevated serum homocysteine interferes with the cross-linking process in lens zonular proteins, causing impairment of zonular integrity and lens instability and dislocation [24]. Interestingly, an animal study also showed exogenously elevated levels of homocysteine in embryonic development can lead to lens dislocation and abnormal retinal development due to changes in neural crest cell migration [25].

Vitamin A supplementation is vital for early ocular development, organogenesis, and maintaining a robust immune system [26]. Its active form and derivatives, such as retinoic acid, play an integral role in developing the retina's photoreceptors, such as the rods and the cones [26]. Xerophthalmia encompasses the ocular manifestations of vitamin A deficiency and characteristically can present with night blindness and, chronically, with corneal ulcerations and scarring [27,28].

While vitamin A deficiency continues to present significant morbidity and burden among afflicted infants and children, excess vitamin A has also been associated with teratogenic effects in newborns [29]. Vitamin A toxicity is rare but can result from the overconsumption of supplements or overutilization of pharmacologic agents, such as isotretinoin, indicated in severe cystic acne treatment [30-32]. Affected infants have been shown to present with characteristic retinoic acid embryopathy that encompasses neural tube defects and craniofacial defects [31]. It is hypothesized that high vitamin A concentrations are highly toxic to neural crest cells and mediate homeobox gene regulation, thus negatively impacting neural development [31].

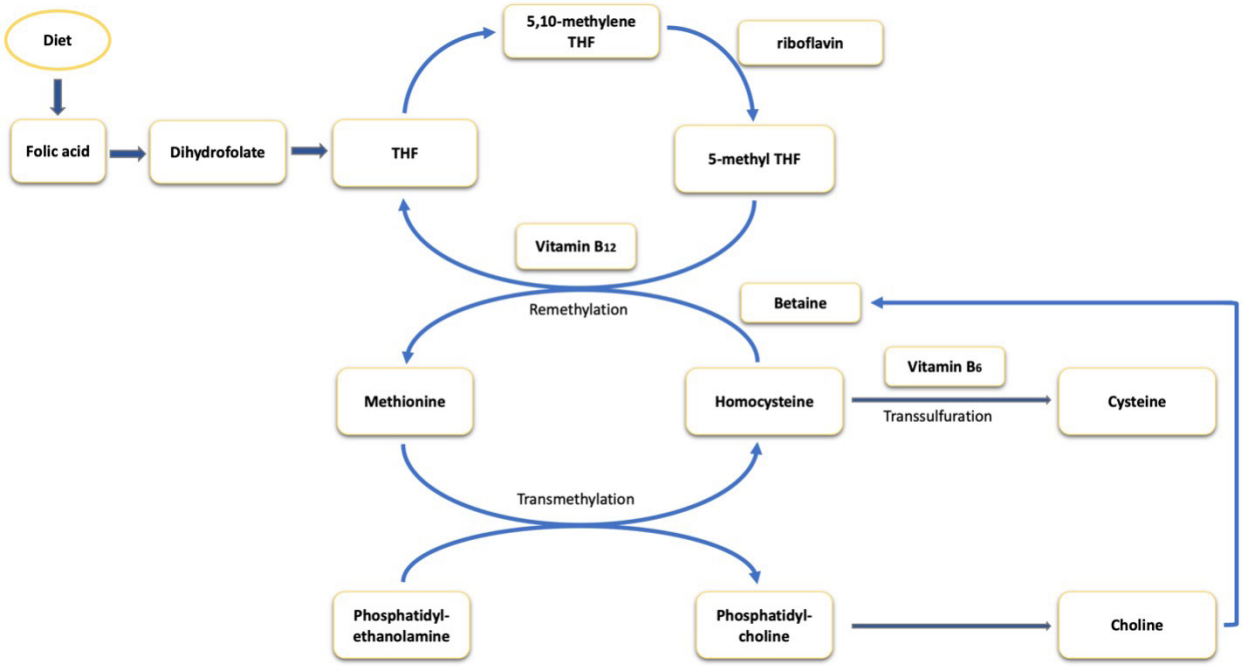

Figure 1. **Schematic representation of folate, choline, and homocysteine metabolism**. THF, tetrahydrofolate.

There is limited data suggesting vitamin D and E affect ocular embryology in post-birth assessments in human studies, but some animal studies show an association. Vitamin D deficiency is associated with various ocular diseases, including diabetic retinopathy and dry eye syndrome, by impacting signaling in human ocular barrier cells [33,34]. In Zebrafish embryos, vitamin D has been found playing an important role in regulating ocular angiogenesis [35]. Vitamin E-free diets in a rodent study led to significant retinal photoreceptor damage and retinal pigment epithelial cell disfunction [36]. Vitamin E deficiency in Zebrafish embryos is hypothesized to impact lipid peroxidation and affect ocular development, but further research is needed to understand the exact mechanism [37].

Docosahexaenoic acid (DHA) is an omega-3 fatty acid highly concentrated in the retina and plays a significant role in maintaining myelin and synaptic terminals [7]. While there is equivocal evidence to ascertain the importance of taking DHA prenatally or postnatally, one study showed that DHA intake during the third trimester was significantly associated with improvement in infants' visual acuity [38-41]. DHA intake can support patients into adulthood; supplementation of DHA was shown to protect against retinal diseases [42]. Among adult patients, DHA was shown to be decreased in adult patients with retinal diseases, such as age-related macular degeneration and retinitis pigmentosa [43-46].

Medications

Polysubstance use during pregnancy can affect newborns with significant congenital disabilities and developmental disorders that impact their growth and development into adulthood [47]. Despite these known risks, it is estimated that approximately 5% to 10% of women use substances during pregnancy [47,48].

Alcohol use during pregnancy notably presents with fetal alcohol syndrome, characterized by fetal growth restrictions, distinctive physical features, and ocular abnormalities, including shortened palpebral fissures, ocular hypertelorism, and epicanthic folds [29,49]. Infants with fetal alcohol syndrome also may present with strabismus, microphthalmia, and decreased visual acuity [49-51]. Fundus exams have shown optic nerve hypoplasia and tortuous retinal vessels among affected infants [50,51]. It is hypothesized that ethanol impacts the survival of glial cells, leading to decreased optic nerve myelination [51,52]. Concurrently, some animal models have shown decreased retinal thickness and ganglion cell loss in animals who were exposed to ethanol. Zebrafish models showed a dose-dependent and temporal relationship between ethanol exposure and photoreceptor changes, with more dramatic changes seen with chronic and higher doses [51].

One study estimated that approximately over 40% of women who used alcohol during pregnancy reported using additional substances [47,53]. Similarly to alcohol, fetal exposure to cocaine has also been associated with

fetal growth restrictions and delays [53]. Infants exposed to cocaine were shown to present with signs of palpebral edema, structural ocular abnormalities, and strabismus [29,53-55]. However, it is unclear whether these abnormalities were attributable solely to the effects of cocaine, given the shared nature of polysubstance use among mothers [53].

The use of certain anticonvulsants, such as valproic acid, carbamazepine, and phenytoin, has been associated with teratogenic effects on neural tubes [29]. Infants exposed to valproic acid were shown to present with ocular abnormalities, most commonly with early-onset myopia and strabismus [56]. It is hypothesized that valproic acid can decrease the amount of type 2 collagen in the vitreous, leading to vitreous degeneration and high myopia [29].

Thalidomide is an immunomodulator indicated for the treatment of multiple myeloma, graft versus host disease, leprosy, HIV, Crohn's disease, and other cancers [57]. Historically, thalidomide was available over the counter in the 1950s as an antiemetic to treat morning sickness in pregnant women in Europe and Australia [57,58]. In 1961, there were over 10,000 reported cases of thalidomide-induced severe congenital disabilities in newborns, and the drug was subsequently withdrawn from the market [58]. Thalidomide is a potent angiogenic inhibitor with rapid hydrolysis [59]. It is theorized to cause teratogenic damage by disrupting embryonic angiogenesis and can affect a wide array of organs and tissues in the body [58]. In the UK, reported ocular malformations of thalidomide embryopathy encompassed colobomas, external ophthalmoplegia, anophthalmos, and microphthalmos [60,61]. One study in Sweden reported incomitant strabismus as the most common ocular anomaly, followed by aberrant lacrimation [59]. Maternal thalidomide use led to devastating malformations in affected children, and to this day, the medication still carries significant contraindications [57].

Infections

Maternal intrauterine infections can impact fetal development primarily through hematogenous vertical transmission, where the infection is transmitted transplacentally from the mother to the fetus, but also by ascending infections [62]. The delivery process and method can also expose infants to a plethora of microbiomes.

TORCH infections, comprised of *toxoplasma gondii*, rubella virus, cytomegalovirus (CMV), herpes simplex virus, and others such as Zika, Syphilis, and HIV, manifest in a constellation of characteristic ocular sequelae for affected infants [62-64]. The development of cataracts, microphthalmos, and chorioretinitis are common ocular complications of TORCH infections but can present significant variability in presentation [29]. Notably, the rubella virus has been associated with congenital glaucoma, strabismus, and uveitis [65]. *Toxoplasma gondii* infection can present with a characteristic pigmented retinal scar representative of retinochoroiditis [63].

The pathogenesis of ocular abnormalities associated with TORCH infections is poorly understood; however, it is hypothesized that TORCH infections disrupt ocular development with cell division inhibition [63]. Rubella virus is thought to impact actin filaments, leading to actin depolymerization [63]. CMV and HSV prevent neural stem cells from further differentiation, inducing apoptosis [63]. Increased placental inflammation occurring after infection is also thought to impact neurodevelopment. As an intracellular parasite, *Toxoplasma gondii* can produce tissue cysts in the retina and cause inflammation, eventually leading to tissue necrosis [63].

The sequelae of these infections can be devastating; TORCH infections remain one of the leading causes of congenital blindness [63,66,67]. Prenatal maternal screening and medical management have alleviated some of the burden in developed countries, but this concern remains in particularly resource-limited settings [64].

Zika virus is transmitted with a bite of the Aedes mosquito and can be vertically transmitted to the fetus *in utero* [68]. From 2007, there was a series of Zika virus outbreaks around the world, predominantly in tropical areas, that eventually led to the 2015-2016 Zika virus epidemic [68,69]. Congenital Zika infection can lead to the collection of characteristics known as Congenital Zika Syndrome, which encompasses microcephaly with a partially collapsed skull, decreased brain tissue with brain damage, damage to the posterior eye, limited joint movement, and hypertonia after birth [68,70]. Cases of fetuses with congenital Zika syndrome showed ocular abnormalities in various tissues, including the pupillary membranes and immature anterior chamber angle [71]. Posteriorly, there were losses of retinal pigment epithelium, undifferentiated retinal nuclear layers, choroidal thinning, and optic nerve atrophy [71,72].

Most recently, maternal infection with the SARS-CoV-2 virus, introduced to the population during the COVID-19 pandemic, has yet to be associated with ocular malformations among infants [73]. However, further research may be needed to identify any long-term sequelae associated with the aftermath of the COVID-19 pandemic.

Environmental Factors

Amniotic fluid provides the fetus with essential nutrients and components of the immune system, protecting the vulnerable fetus from harmful pathogens [74]. The unique cellular profile of amniotic fluid can also be utilized to detect and progress ocular conditions [75]. Infants with retinopathy of prematurity (ROP) were as-

sociated with having significantly higher levels of matrix metalloproteinase-2 (MMP-2) but lower levels of IL-10 and TNF-α compared to infants without ROP [75]. ROP occurs due to the development of signaling proteins, such as vascular endothelial growth factor (VEGF) and insulin-like growth factor-1 (IGF-1), leading to abnormal vascular disruptions in the retina [75,76]. MMP-2 is known to play a role in destroying collagen crucial for vasculature, and its presence has been associated with abnormal angiogenesis [75,77]. It is suggested that high amounts of MMP-2 in the immature retina are associated with ROP [75]. In contrast, IL-10 and TNF-α are anti-inflammatory cytokines; thus, their suppression promotes ongoing inflammation [75,78]. There may be an opportunity for future research to identify earlier detection of ROP with amniotic fluid sampling prenatally.

The mode of delivery was shown to affect intraocular pressure (IOP) among newborns. Infants who were born via expected vaginal delivery presented with higher IOP measured 5 minutes after birth, compared to infants born via cesarean section [79,80]. It is hypothesized that the varying levels of hormones, such as adrenaline, noradrenaline, and cortisol, that are activated with the sympathoadrenal system at expected vaginal delivery and differences in anesthesia can impact IOP after delivery [80]. However, it was uncertain whether the postpartum differences seen with IOP are transient or have implications for future development.

Inadequate water, sanitation, and hygiene (WASH) access in resource-limited settings is strongly associated with adverse maternal and infant outcomes [81]. Adequate access to WASH during pregnancy is crucial for preventing maternal and congenital infections that affect eye health [81,82]. There is a need to assess further the role and impact of WASH on ocular outcomes and to strategize globally for ways to obtain universal access for the safety and health of mothers and children worldwide.

There is limited data suggesting heavy metal toxicity affects embryology in both animal models and postbirth assessments in human studies, though the exact mechanism requires further study. Lead reduces tight junctions in the blood-brain barriers, and the increased hyperpermeability can lead to severe outcomes in early development [83,84]. In Zebrafish embryos, there was an observed dose-dependent relationship between the level of lead exposure and the severity of neurotoxicity [85]. In newborns, higher levels of lead exposure in late pregnancy were associated with lower visual acuity due to changes in sensory system myelination [83]. Other heavy metals, such as cadmium, were associated with reduced retinal ganglion cells in Zebrafish embryos [84]. Prenatal exposure to mercury-induced free radical formation in newborns and was related to degenerative changes in the retina and the optic nerve [86]. Similarly, other heavy metals, such as molybdenum, have been found to impact visual acuity in infants, though this association requires further research [87].

Radiation exposure from X-rays during pregnancy can lead to significant changes during organogenesis due to radiation-induced cell death; common manifestations include microcephaly and microphthalmia [88,89]. In Zebrafish embryos, exposure to higher doses of radiation impacted the diameter of the eye and the inner nuclear cell layer and resulted in lens opacification [90,91]. Even exposure to low doses of radiation has been shown to interrupt human retinal ganglion cell development [92]. Limited studies in humans report similar findings, such as microphthalmia and increased risk of refractive errors [93].

CONCLUSION AND OUTLOOK

Human ocular development is a complex process that begins *in utero* during the third week of gestation and continues even in the postnatal period. The regular progress of this development, which relies on an intricate array of cellular and genetic signaling pathways, can be impeded by a various external factors, including maternal medication use, infectious, metabolic, hormonal, and environmental components. It is crucial to learn the mechanisms of ocular development to understand the origination of the various structures that comprise the eye and discern which components are affected during ocular malformations when these pathways are disrupted. Much remains unknown about the precise mechanisms of how these external factors can disrupt normal ocular development *in utero*, and more significant research is needed to understand the pathophysiology of these disruptive effects further.

Future research may also prioritize how the detrimental effects of these external factors on newborn health can be best mitigated in resource-limited settings. As in many domains of health care, pediatric ocular outcomes vary dramatically depending on socioeconomic factors. Achieving societal objectives to alleviate health disparities necessitates both research and clinical efforts to understand these problems and implement solutions.

REFERENCES

1. Ludwig PE, Lopez MJ, Czyz CN. Embryology, Eye Malformations. [Updated 2023 Apr 3]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan.
2. Miesfeld JB, Brown NL. Chapter Ten - Eye organogenesis: A hierarchical view of ocular development. In: Wellik DM, editor. Current Topics in Developmental Biology. 132. Academic Press; 2019. pp. 351–93.
3. Singh R, Munakomi S. Embryology, Neural Tube. [Updated 2023 May 1]. In: StatPearls [Internet]. Treasure Island

(FL): StatPearls Publishing; 2024 Jan.
4. Yong HE, Chan SY, Chakraborty A, Rajaraman G, Ricardo S, Benharouga M, et al. Significance of the placental barrier in antenatal viral infections. Biochim Biophys Acta Mol Basis Dis. 2021 Dec;1867(12):166244.
5. Goasdoué K, Miller SM, Colditz PB, Björkman ST. Review: the blood-brain barrier; protecting the developing fetal brain. Placenta. 2017 Jun;54:111–6.
6. Nelson BR, Roby JA, Dobyns WB, Rajagopal L, Gale M Jr, Adams Waldorf KM. Immune Evasion Strategies Used by Zika Virus to Infect the Fetal Eye and Brain. Viral Immunol. 2020;33(1):22–37.
7. Morse NL. Benefits of docosahexaenoic acid, folic acid, vitamin D and iodine on foetal and infant brain development and function following maternal supplementation during pregnancy and lactation. Nutrients. 2012 Jul;4(7):799–840.
8. Trujillo-Gonzalez I, Friday WB, Munson CA, Bachleda A, Weiss ER, Alam NM, et al. Low availability of choline in utero disrupts development and function of the retina. FASEB J. 2019 Aug;33(8):9194–209.
9. Caudill MA, Strupp BJ, Muscalu L, Nevins JE, Canfield RL. Maternal choline supplementation during the third trimester of pregnancy improves infant information processing speed: a randomized, double-blind, controlled feeding study. FASEB J. 2018 Apr;32(4):2172–80.
10. Boeke CE, Gillman MW, Hughes MD, Rifas-Shiman SL, Villamor E, Oken E. Choline intake during pregnancy and child cognition at age 7 years. Am J Epidemiol. 2013 Jun;177(12):1338–47.
11. Mun JG, Legette LL, Ikonte CJ, Mitmesser SH. Choline and DHA in Maternal and Infant Nutrition: Synergistic Implications in Brain and Eye Health. Nutrients. 2019 May;11(5):1125.
12. Sijilmassi O. Folic acid deficiency and vision: a review. Graefes Arch Clin Exp Ophthalmol. 2019 Aug;257(8):1573–80.
13. Antony AC. In utero physiology: role of folic acid in nutrient delivery and fetal development. Am J Clin Nutr. 2007 Feb;85(2):598S–603S.
14. CDC. Folic Acid Recommendations. 2023. Available from: https://www.cdc.gov/ncbddd/folicacid/recommendations.html#:~:text=All%20women%20of%20reproductive%20age,and%20spine%20(spina%20bifida)
15. Muccioli M, Plageman TF. Requirements for cellular folate during lens development. Invest Ophthalmol Vis Sci. 2016;57(12):3062.
16. Sijilmassi O, López-Alonso JM, Del Río Sevilla A, Murillo González J, Barrio Asensio MD. Barrio Asensio MdC. Biometric alterations of mouse embryonic eye structures due to short-term folic acid deficiency. Curr Eye Res. 2019 Apr;44(4):428–35.
17. Flores AL, Vellozzi C, Valencia D, Sniezek J. Global Burden of Neural Tube Defects, Risk Factors, and Prevention. Indian J Community Health. 2014 Nov;26 Suppl 1:3–5.
18. Youngblood ME, Williamson R, Bell KN, Johnson Q, Kancherla V, Oakley GP Jr. 2012 Update on global prevention of folic acid-preventable spina bifida and anencephaly. Birth Defects Res A Clin Mol Teratol. 2013 Oct;97(10):658–63.
19. Mentch SJ, Locasale JW. One-carbon metabolism and epigenetics: understanding the specificity. Ann N Y Acad Sci. 2016 Jan;1363(1):91–8.
20. Zeisel SH. Choline, homocysteine, and pregnancy. Oxford University Press; 2005. pp. 719–20.
21. Blom HJ, Smulders Y. Overview of homocysteine and folate metabolism. With special references to cardiovascular disease and neural tube defects. J Inherit Metab Dis. 2011 Feb;34(1):75–81.
22. Elsherbiny NM, Sharma I, Kira D, Alhusban S, Samra YA, Jadeja R, et al. Homocysteine Induces Inflammation in Retina and Brain. Biomolecules. 2020 Mar;10(3):393.
23. Ganapathy PS, Moister B, Roon P, Mysona BA, Duplantier J, Dun Y, et al. Endogenous elevation of homocysteine induces retinal neuron death in the cystathionine-β-synthase mutant mouse. Invest Ophthalmol Vis Sci. 2009 Sep;50(9):4460–70.
24. Harrison DA, Mullaney PB, Mesfer SA, Awad AH, Dhindsa H. Management of ophthalmic complications of homocystinuria. Ophthalmology. 1998 Oct;105(10):1886–90.
25. Maestro de las Casas C, Epeldegui M, Tudela C, Varela-Moreiras G, Pérez-Miguelsanz J. High exogenous homocysteine modifies eye development in early chick embryos. Birth Defects Res A Clin Mol Teratol. 2003 Jan;67(1):35–40.
26. Bastos Maia S, Rolland Souza AS, Costa Caminha MF, Lins da Silva S, Callou Cruz RS, Carvalho Dos Santos C, et al. Vitamin A and Pregnancy: A Narrative Review. Nutrients. 2019 Mar;11(3):681.
27. Feroze KB, Kaufman EJ. Xerophthalmia. 2023 Apr 17. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan.
28. Gilbert C. The eye signs of vitamin A deficiency. Community Eye Health. 2013;26(84):66–7.
29. Tandon A, Mulvihill A. Ocular teratogens: old acquaintances and new dangers. Eye (Lond). 2009 Jun;23(6):1269–74.
30. Bendich A, Langseth L. Safety of vitamin A. Am J Clin Nutr. 1989 Feb;49(2):358–71.
31. Olson JM, Ameer MA, Goyal A. Vitamin A Toxicity. [Updated 2023 Sep 2]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan.
32. Mondal D, R Shenoy S, Mishra S. Retinoic Acid Embryopathy. Int J Appl Basic Med Res. 2017;7(4):264–5.
33. Alsalem JA, Patel D, Susarla R, Coca-Prados M, Bland R, Walker EA, et al. Characterization of vitamin D production by human ocular barrier cells. Invest Ophthalmol Vis Sci. 2014 Apr;55(4):2140–7.
34. Chan HN, Zhang XJ, Ling XT, Bui CH, Wang YM, Ip P, et al. Vitamin D and Ocular Diseases: A Systematic Review [Internet]. Int J Mol Sci. 2022 Apr;23(8):4226.
35. Merrigan SL, Kennedy BN. Vitamin D receptor agonists regulate ocular developmental angiogenesis and modulate expression of dre-miR-21 and VEGF. Br J Pharmacol. 2017 Aug;174(16):2636–51.
36. Robison WG Jr, Kuwabara T, Bieri JG. Vitamin E deficiency and the retina: photoreceptor and pigment epithelial changes. Invest Ophthalmol Vis Sci. 1979 Jul;18(7):683–90.
37. Traber MG. Vitamin E: necessary nutrient for neural development and cognitive function. Proc Nutr Soc. 2021 Aug;80(3):319–26.

38. Basak S, Mallick R, Duttaroy AK. Maternal Docosahexaenoic Acid Status during Pregnancy and Its Impact on Infant Neurodevelopment. Nutrients. 2020 Nov;12(12):3615.
39. Authority EF. DHA and support of the cognitive development of the unborn child and breastfed infant-Scientific substantiation of a health claim related to DHA and support of the cognitive development of the unborn child and breastfed infant pursuant to Article 14 of Regulation (EC) No 1924/2006. EFSA J. 2009;7(4):1007.
40. Colombo J, Gustafson KM, Gajewski BJ, Shaddy DJ, Kerling EH, Thodosoff JM, et al. Prenatal DHA supplementation and infant attention. Pediatr Res. 2016 Nov;80(5):656–62.
41. Rees A, Sirois S, Wearden A. Prenatal maternal docosahexaenoic acid intake and infant information processing at 4.5mo and 9mo: A longitudinal study. PLoS One. 2019 Feb;14(2):e0210984.
42. Dornstauder B, Suh M, Kuny S, Gaillard F, Macdonald IM, Clandinin MT, et al. Dietary docosahexaenoic acid supplementation prevents age-related functional losses and A2E accumulation in the retina. Invest Ophthalmol Vis Sci. 2012 Apr;53(4):2256–65.
43. Sugasini D, Yalagala PC, Subbaiah PV. Efficient Enrichment of Retinal DHA with Dietary Lysophosphatidylcholine-DHA: Potential Application for Retinopathies. Nutrients. 2020 Oct;12(10):3114.
44. Hoffman DR, Hughbanks-Wheaton DK, Spencer R, Fish GE, Pearson NS, Wang YZ, et al. Docosahexaenoic Acid Slows Visual Field Progression in X-Linked Retinitis Pigmentosa: Ancillary Outcomes of the DHAX Trial. Invest Ophthalmol Vis Sci. 2015 Oct;56(11):6646–53.
45. Fan H, Song JT. Potential mechanisms of macular degeneration protection by fatty fish consumption. Curr Opin Pharmacol. 2022 Apr;63:102186.
46. Lawrenson JG, Evans JR. Omega 3 fatty acids for preventing or slowing the progression of age-related macular degeneration. Cochrane Database Syst Rev. 2015 Apr;2015(4):CD010015. https://doi.org/10.1002/14651858.CD010015.pub3.
47. CDC. Polysubstance Use During Pregnancy. 2023. Available from: https://www.cdc.gov/pregnancy/polysubstance-use-in-pregnancy.html
48. Wendell AD. Overview and epidemiology of substance abuse in pregnancy. Clin Obstet Gynecol. 2013;56(1):91–96. doi:10.1097/GRF.0b013e31827feeb9.
49. Abdelrahman A, Conn R. Eye abnormalities in fetal alcohol syndrome. Ulster Med J. 2009 Sep;78(3):164–5.
50. Flanigan EY, Aros S, Bueno MF, Conley M, Troendle JF, Cassorla F, et al. Eye malformations in children with heavy alcohol exposure in utero. J Pediatr. 2008 Sep;153(3):391–5.
51. Matsui JI, Egana AL, Sponholtz TR, Adolph AR, Dowling JE. Effects of ethanol on photoreceptors and visual function in developing zebrafish. Invest Ophthalmol Vis Sci. 2006 Oct;47(10):4589–97.
52. Wilhelm CJ, Guizzetti M. Fetal Alcohol Spectrum Disorders: An Overview from the Glia Perspective. Front Integr Nuerosci. 2016 Jan;9:65.
53. Tsay CH, Partridge JC, Villarreal SF, Good WV, Ferriero DM. Neurologic and ophthalmologic findings in children exposed to cocaine in utero. J Child Neurol. 1996 Jan;11(1):25–30.
54. Block SS, Moore BD, Scharre JE. Visual anomalies in young children exposed to cocaine. Optom Vis Sci. 1997 Jan;74(1):28–36.
55. Dominguez R, Aguirre Vila-Coro A, Slopis JM, Bohan TP. Brain and ocular abnormalities in infants with in utero exposure to cocaine and other street drugs. Am J Dis Child. 1991 Jun;145(6):688–95.
56. Moore SJ, Turnpenny P, Quinn A, Glover S, Lloyd DJ, Montgomery T, et al. A clinical study of 57 children with fetal anticonvulsant syndromes. J Med Genet. 2000 Jul;37(7):489–97.
57. Grogan DP, Winston NR. Thalidomide. [Updated 2023 Jun 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan.
58. Vargesson N. Thalidomide-induced teratogenesis: history and mechanisms. Birth Defects Res C Embryo Today. 2015 Jun;105(2):140–56.
59. Miller MT, Strömland KK. What can we learn from the thalidomide experience: an ophthalmologic perspective. Curr Opin Ophthalmol. 2011 Sep;22(5):356–64.
60. Cullen JF. Ocular defects in thalidomide babies. Br J Ophthalmol. 1964 Mar;48(3):151–3.
61. Smithells RW. Defects and disabilities of thalidomide children. BMJ. 1973 Feb;1(5848):269–72.
62. Megli CJ, Coyne CB. Infections at the maternal-fetal interface: an overview of pathogenesis and defence. Nat Rev Microbiol. 2022 Feb;20(2):67–82.
63. de Campos VS, Calaza KC, Adesse D. Implications of TORCH Diseases in Retinal Development-Special Focus on Congenital Toxoplasmosis. Front Cell Infect Microbiol. 2020 Oct;10:585727.
64. Jaan A, Rajnik M. Torch complex. StatPearls [Internet] StatPearls Publishing; 2023.
65. Armstrong NT. The ocular manifestations of congenital rubella syndrome. Insight. 1992 Apr;17(1):14–6.
66. Amphornphruet A, Rangseechamrat N, Suwansirikul M, Chan RV. Variation of Ophthalmic Manifestations in Congenital TORCH Infection: A 5-Year Review. Invest Ophthalmol Vis Sci. 2017;58(8):3613.
67. Mets MB, Chhabra MS. Eye manifestations of intrauterine infections and their impact on childhood blindness. Surv Ophthalmol. 2008;53(2):95–111.
68. Wolford RW, Schaefer TJ. Zika Virus. [Updated 2023 Aug 7]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan.
69. Gubler DJ, Vasilakis N, Musso D. History and Emergence of Zika Virus. J Infect Dis. 2017 Dec;216 suppl_10:S860–7.
70. CDC. Microcephaly & Other Birth Defects 2019. Available from: https://www.cdc.gov/zika/healtheffects/birth_defects.html
71. Fernandez MP, Parra Saad E, Ospina Martinez M, Corchuelo S, Mercado Reyes M, Herrera MJ, et al. Ocular Histopathologic Features of Congenital Zika Syndrome. JAMA Ophthalmol. 2017 Nov;135(11):1163–9.
72. de Paula Freitas B, de Oliveira Dias JR, Prazeres J, Sacramento GA, Ko AI, Maia M, et al. Ocular Findings in Infants With Microcephaly Associated With Presumed

Zika Virus Congenital Infection in Salvador, Brazil. JAMA Ophthalmol. 2016 May;134(5):529–35.
73. Kiappe OP, Santos da Cruz NF, Rosa PA, Arrais L, Bueno de Moraes NS. Ocular Assessments of a Series of Newborns Gestationally Exposed to Maternal COVID-19 Infection. JAMA Ophthalmol. 2021 Jul;139(7):777–80.
74. Fitzsimmons ED, Bajaj T. Embryology, amniotic fluid. StatPearls [Internet] StatPearls Publishing; 2022.
75. Jang JH, Kim JG, Lee YH, Bae JG, Park JH. The association between amniotic fluid-derived inflammatory mediators and the risk of retinopathy of prematurity. Medicine (Baltimore). 2022 Jul;101(27):e29368.
76. Liegl R, Löfqvist C, Hellström A, Smith LE. IGF-1 in retinopathy of prematurity, a CNS neurovascular disease. Early Hum Dev. 2016 Nov;102:13–9.
77. Ohno-Matsui K, Uetama T, Yoshida T, Hayano M, Itoh T, Morita I, et al. Reduced retinal angiogenesis in MMP-2-deficient mice. Invest Ophthalmol Vis Sci. 2003 Dec;44(12):5370–5.
78. Mirshahi A, Hoehn R, Lorenz K, Kramann C, Baatz H. Anti-tumor necrosis factor alpha for retinal diseases: current knowledge and future concepts. J Ophthalmic Vis Res. 2012 Jan;7(1):39–44.
79. Ozkurt ZG, Balsak S, Balsak B, Guclu H, Sahın M, Yuksel H, et al. The effects of delivery type and gender on intraocular pressure and central corneal thickness in newborns. Arq Bras Oftalmol. 2016 Apr;79(2):92–5.
80. Elbay A, Celik U, Celik B, Ozer OF, Kilic G, Akkan JC, et al. Intraocular pressure in infants and its association with hormonal changes with vaginal birth versus cesarean section. Int Ophthalmol. 2016 Dec;36(6):855–60.
81. Campbell OM, Benova L, Gon G, Afsana K, Cumming O. Getting the basic rights - the role of water, sanitation and hygiene in maternal and reproductive health: a conceptual framework. Trop Med Int Health. 2015 Mar;20(3):252–67.
82. Arowosegbe AO, Ojo DA, Shittu OB, Iwaloye O, Ekpo UF. Water, sanitation, and hygiene (WASH) facilities and infection control/prevention practices in traditional birth homes in Southwest Nigeria. BMC Health Serv Res. 2021 Sep;21(1):912.
83. Silver MK, Li X, Liu Y, Li M, Mai X, Kaciroti N, et al. Low-level prenatal lead exposure and infant sensory function. Environ Health. 2016 Jun;15(1):65.
84. Ebrahimi M, Ebrahimi M, Vergroesen JE, Aschner M, Sillanpää M. Environmental exposures to cadmium and lead as potential causes of eye diseases. J Trace Elem Med Biol. 2024 Mar;82:127358.
85. Curcio V, Macirella R, Sesti S, Ahmed AI, Talarico F, Pizzolotto R, et al. The role of exposure window and dose in determining lead toxicity in developing Zebrafish. Chemosphere. 2022 Nov;307(Pt 4):136095.
86. Pamphlett R, Kum Jew S, Cherepanoff S. Mercury in the retina and optic nerve following prenatal exposure to mercury vapor. PLoS One. 2019 Aug;14(8):e0220859.
87. Wang Z, Dou Y, Guo W, Lin Y, Jiang Y, Jiang T, et al.; China National Birth Cohort (CNBC Study Group). Association between prenatal exposure to trace elements mixture and visual acuity in infants: A prospective birth cohort study. Chemosphere. 2023 Aug;333:138905.
88. Kumar R, De Jesus O. Radiation Effects On The Fetus. 2023 Aug 23. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan.
89. Verma AS, Fitzpatrick DR. Anophthalmia and microphthalmia. Orphanet J Rare Dis. 2007 Nov;2(1):47.
90. Zhou R, Si J, Zhang H, Wang Z, Li J, Zhou X, et al. The effects of x-ray radiation on the eye development of zebrafish. Hum Exp Toxicol. 2014 Oct;33(10):1040–50.
91. Geiger GA, Parker SE, Beothy AP, Tucker JA, Mullins MC, Kao GD. Zebrafish as a "biosensor"? Effects of ionizing radiation and amifostine on embryonic viability and development. Cancer Res. 2006 Aug;66(16):8172–81.
92. Katsura M, Urade Y, Nansai H, Kobayashi M, Taguchi A, Ishikawa Y, et al. Low-dose radiation induces unstable gene expression in developing human iPSC-derived retinal ganglion organoids. Sci Rep. 2023 Aug;13(1):12888.
93. Craenen K, Verslegers M, Callaerts-Vegh Z, Craeghs L, Buset J, Govaerts K, et al. Folic Acid Fortification Prevents Morphological and Behavioral Consequences of X-Ray Exposure During Neurulation. Front Behav Neurosci. 2021 Jan;14:609660.