HHS Public Access

Author manuscript

Surv Ophthalmol. Author manuscript; available in PMC 2023 July 01.

Published in final edited form as:

Surv Ophthalmol. 2022 ; 67(4): 1031–1047. doi:10.1016/j.survophthal.2021.12.008.

Review of Evidence for Environmental Causes of Uveal Coloboma

Evan B Selzer, MS[1], **Delphine Blain, ScM, MBA**[1], **Robert B. Hufnagel, MD, PhD**[1], **Philip J. Lupo, PhD**[2], **Laura E. Mitchell, PhD**[3], **Brian P. Brooks, MD, PhD**[4]

[1]Ophthalmic Genetics & Visual Function Branch, National Eye Institute, National Institutes of Health, Bethesda, MD

[2]Department of Pediatrics, Section of Hematology-Oncology, Baylor College of Medicine, Houston, TX

[3]Department of Epidemiology, Human Genetics and Environmental Sciences, UTHealth School of Public Health, Houston, TX

[4]To whom correspondence should be addressed

Abstract

Uveal coloboma is a condition defined by missing ocular tissues and is a significant cause of childhood blindness. It occurs from a failure of the optic fissure to close during embryonic development, and may lead to missing parts of the iris, ciliary body, retina, choroid, and optic nerve. Because there is no treatment for coloboma, efforts have focused on prevention. While several genetic causes of coloboma have been identified, little definitive research exists regarding the environmental causes of this condition. We review the current literature on environmental factors associated with coloboma in an effort to guide future research and preventative counseling related to this condition.

Keywords

Coloboma; Uveal Coloboma; Microphthalmia; Anophthalmia; Developmental Eye Defects; Environmental Causes; Ocular Teratogens

1. Introduction

Uveal coloboma results when the optic fissure fails to appropriately close during weeks 5–7 of fetal development. The result is a gap in tissue that may affect the iris, ciliary body, retina, and/or retina/choroid up to and including the optic nerve. The prevalence of this condition is estimated to be between 2 and 14 per 100,000 births,[126] with unilateral cases occurring approximately 50% of the time[98]. The genetic causes of uveal coloboma have been well reviewed[17, 155, 1, 159]. Despite significant effort, the yield of current molecular genetic testing of coloboma patients is low, estimated to be about 8%[108], suggesting environmental

Address: 10 Center Drive, 10CRC/Room 3-2531, Bethesda, MD 20892.

causes may contribute to the etiology of this condition[70, 108]. The purpose of this article is to review epidemiologic and basic research evidence for possible environmental contributors to coloboma. The data detailed in this text are summarized in the accompanying Table.

2. Nutritional Deficiencies/Excess

A. Vitamin A and its derivatives

Vitamin A signaling is known to be important in a variety of embryologic processes. Retinoic acid (RA), the active metabolite of vitamin A, acts via nuclear RA receptors (RARα/β/γ) and retinoid X receptors (RXRα/β/γ) to regulate gene expression[139]. RA concentration gradients are found throughout the developing embryo and are a major driver of the spatial organization of various organs. In the eye, mouse studies have shown RA signaling in the optic vesicle, surface ectoderm, the prospective neuroretina and RPE of the optic cup, and the periocular mesenchyme at specific times during embryonic development[25]. Additional studies have shown that RA signaling is impacted by several mechanisms including the differential expression of various RAR and RXR receptors, differential expression of enzymes responsible for RA synthesis and degradation, and differential expression of retinol-, retinaldehyde- and RA-binding proteins[25]. This signaling is thought to be essential for the formation of the optic cup and the anterior segment[36].

The role of RA in optic cup development is particularly important with regard to coloboma. RA has been determined to be essential in mediating the closure of the choroid fissure, a key event in the pathogenesis of coloboma. Zebrafish experiments demonstrated coloboma in 75% of embryos treated with AGN194310, a small molecule inhibitor of all RARs[86]. This same group of experiments was able to link these events to RAR-regulated genes in both the ventral retina/optic stalk and the periocular mesenchyme and show that genes in both of these regions are independently important in mediating optic fissure closure[86]. Further supporting these findings are several studies that have reported coloboma in both humans and animals associated with mutations in various RA signaling genes[70, 86, 66, 91, 90, 131, 130].

In addition to the strong genetic evidence implicating disruption in vitamin A signaling in the pathogenesis of coloboma, there is also evidence to suggest vitamin A deficiency is associated with increased risk of coloboma. A case report described a child born to a mother with abetalipoproteinemia known to be vitamin A deficient and noncompliant with supplementation during pregnancy[43]. The child was born with bilateral iris and choroidal coloboma. Interestingly, the mother was compliant with supplementation for her second pregnancy and delivered a healthy baby with no ocular findings[43]. Another report described a family with compound heterozygous missense mutations in the serum retinol binding protein 4, encoded by the *RBP4* gene. Two affected female children had one sixth the level of normal retinol levels, and ocular exam revealed a “discrete iris coloboma” in one sister[124]. Mutations in *RBP4* have been associated with coloboma in other reports as well. Two siblings with mutations in this gene presented primarily with a rod-cone degeneration phenotype, but one sibling was also noted to have anterior and posterior segment coloboma[23]. While these reports describe loss of function mutations, a third study describes a family with an autosomal dominant *RBP4* mutation that also results in anophthalmia, microphthalmia, and coloboma[19]. This variant affects vitamin A

signaling by increasing RBP (the product of *RBP4*) binding to its receptor, but preventing it activation. Interestingly, the pedigree of this affected family displayed a much higher maternal penetrance compared to paternal penetrance, suggesting that this mutation's impact on maternal-fetal vitamin A metabolism drives the phenotype[19]. A larger, descriptive study based on 110 probands with coloboma and 83 family interviews found that, of the 83 families interviewed, 11 mothers (13%) reported having symptoms of night blindness, suggesting a vitamin A deficiency during the third trimester of pregnancy[64].

Further evidence is provided by studies that examined pregnant rats that were fed a vitamin A deficient diet and observed frequent colobomas as a result[156, 149]. One of these studies supplemented different experimental groups with therapeutic vitamin A doses at various time points[156]. Supplementation with vitamin A on days 10–13 of pregnancy (E10-E13) had a strong protective effect that almost eliminated the number of colobomas seen, while supplementation on the 14th and 15th day of gestation had a weaker, but still observable, protective effect compared to no supplementation[156]. A more recent study went even further in detailing the timing of supplementation relative to optic fissure closure in vitamin A deficient rats[123]. The rat optic fissure closes on embryonic day (E) 13, and while retinol supplementation in vitamin A deficient rats on E11.5 was sufficient for optic fissure closure to occur in 100% of rats, delay of supplementation to E12.5 led to coloboma in 17% of rats[123]. Further delay of supplementation to E13.5 led to coloboma in 100%[123]. Laminin staining at various timepoints revealed that in vitamin A deficient eyes, the basal lamina failed to dissolve, despite close approximation of the optic fissure margins[123], suggesting this essential step in optic fissure closure is vitamin A dependent.

Excess retinoic acid is a known ocular teratogen, though there are no reported cases of it causing coloboma in humans. One study did examine its effects on ocular development in mice[106]. In this study five pregnant mice were given a single intra-peritoneal injection of 12.5 mg/kg retinoic acid on day 7 of pregnancy, before the onset of early eye morphogenesis. The mice were then sacrificed on day 18 of pregnancy, and the fetuses were compared to those of five control mice dosed with corn oil, also sacrificed on day 18 of pregnancy. The authors noted gross malformations in 95.5% of the RA treated group compared to just 6.7% in the control group. They observed faulty closure of the embryonic fissure in 36.4% of the RA treated group compared to 3.3% in the control group[106].

B. Folate

Folates, a group of water-soluble B vitamins, are essential coenzymes in one-carbon transfer reactions. In the human body these reactions add carbon molecules to pathways responsible for purine and pyrimidine synthesis--as well as methionine synthesis, serine and glycine interconversion, and histidine catabolism[85]. Despite the essential nature of folate, it cannot be synthesized *in vivo*, and therefore must be consumed from dietary sources. Maternal folate deficiency is implicated in the development of neural tube defects including spina bifida and anencephaly as well as neurocristopathies, congenital heart defects, and congenital urinary tract defects[4]. Multiple studies show preconception folic acid supplementation to be protective against these birth defects[27, 99, 29, 28, 26, 13, 151]. Closure of the neural tube and the optic fissure are similar in that they both involve the meeting

and fusion of two neuroepithelial sheets during early development. An important difference, however, is that, where the fusion occurs between apical sides of the neuroepithelium in neural tube closure, it is between the basal sides of cells in optic fissure closure.

Folate appears to play a role in ocular development. Folate binding protein 1 (Fbp1), a protein required for folate transport into cells, has been shown to be expressed early in the developing eye[119]. Saitsu and coworkers showed Fbp1 to be expressed in the neural folds of mouse embryos preceding closure of the neural tube. While this observation does not provide direct evidence of the mechanistic role of folate in neural tube closure, it is certainly consistent with the importance of folate in this process. Similarly, after neural tube closure, the authors of this study observed Fbp1 expression in the optic vesicle starting on embryonic day 10.5 and in the choroid plexus starting on embryonic day 12.5[119]. Notably, optic fissure closure in mice occurs between embryonic days 11 and 13[58], meaning the timing of Fbp1 expression in the optic vesicle just before optic fissure closure is analogous to its expression in the neural folds just prior to neural tube closure. Despite these intriguing associations, more research must be conducted regarding the mechanism of Fbp1 and folate and the closure of the optic fissure before any definitive conclusions can be made.

The literature on folate deficiency causing ocular defects is mainly limited to animal studies. Multiple studies giving rodents a folate-restricted diet reported abnormalities related to optic fissure closure. Nelson and coworkers reported coloboma to be among the abnormalities present when feeding pregnant rats a diet deficient in folate[100]. Armstrong and Monie similarly reported anophthalmia and microphthalmia after feeding pregnant rats a folate deficient diet on days 7–9 of pregnancy and found retinal coloboma to be associated with a folate deficient diet between days 9 and 11 of pregnancy[8]. While a similar study in mice also found a folate deficient diet in the weeks preceding pregnancy to be associated with anophthalmia and microphthalmia, the authors do not mention coloboma to be among the abnormalities observed[88]. In humans, one case-control study interviewed 89 women who gave birth to children with microphthalmia or anophthalmia about nutrient intake prior to and during pregnancy compared to 4143 controls. This study found no association between anophthalmia or microphthalmia and either folate supplementation or deficiency. Coloboma specifically was not studied[127].

C. Nickel excess

Nickel is known to be both toxic and carcinogenic in humans. It is commonly used in a variety of industries and can lead to contamination of surrounding food and water sources. Nickel is also known to cross the placenta, and a variety of studies in multiple species have reported congenital malformations in animals birthed to mothers exposed to nickel[83]. While several animal studies cover the topic of nickel teratogenicity, only one contains information regarding coloboma. Pregnant frogs were exposed to Ni2+ as nickel chloride, and at Ni2+ concentrations at and above 4.5umol/L, 100% of tadpoles were born with ocular malformations. The authors reported microphthalmia, focal hypopigmentation, hernias or cysts of the choroid and retina, and iris colobomas as the most common malformations[57].

D. Vitamin E

Vitamin E is an essential, fat-soluble compound with both antioxidant and immunomodulatory effects. Vitamin E deficiency is rare, and though decreased vitamin E intake is the most common cause in developing countries, in the developed world it typically only occurs secondary to a variety of conditions resulting in fat-malabsorption, including cystic fibrosis, abetalipoproteinemia, and Crohn disease. It can also occur secondary to genetic diseases that affect vitamin E transport proteins[71, 9]. The syndrome of vitamin E deficiency manifests with primarily neurologic symptoms. Its presentation can involve ataxia, hyporeflexia, decreased night vision, and decreased vibratory sensations and the most severe forms can progress to blindness, arrythmias, and altered cognition[71, 9].

Research on the impact of vitamin E levels on pregnancy outcomes is limited and will require further study for definitive conclusions to be made. Researchers showed that vitamin E levels vary throughout pregnancy in humans with the levels at their lowest early in pregnancy and then increasing throughout[18]; however, this study did not comment on clinical outcomes associated with this observation. Other studies have found decreased vitamin E levels in pregnancy to be associated with increased incidence of hypertensive diseases of pregnancy[116, 118, 148, 11]. A large case-control study using data from the National Birth Defects Prevention Study found associations between the third quartile of vitamin E intake and both congenital heart defects and anorectal atresia as well as the fourth quartile of vitamin E intake with hypospadias[46]; however, further study is needed to corroborate their findings.

Only one study makes mention of an association between vitamin E deficiency and coloboma. A case report from New Zealand reported a white rabbit born with a head tilt that was found to have left microphthalmia along with iris and choroidal coloboma[102]. When the rabbit colony was examined, vitamin E concentrations in the feed were found to be at 25.1mg/kg compared to 40mg/kg recommended, and no vitamin E was detectable in the livers of other rabbits tested in the colony. Normal vitamin A and selenium concentrations were found in testing of both feed and liver samples. Because this is only one report, any association between coloboma and vitamin E deficiency would need to be confirmed with further study, which the authors acknowledge. No report of this phenomenon exists in other animals or in humans.

3. Parental factors

A. Maternal thyroid disease

Thyroid hormones act via intranuclear receptors that can form either co-activator or co-repressor complexes that regulate gene transcription[55]. There are several known effects of hypothyroidism on the developing human fetus. Severe hypothyroidism can lead to congenital hypothyroidism, the features of which include poor growth, hair loss, thick skin, protuberant abdomen, a large tongue, and intellectual disability[80]; however, even mild hypothyroidism has been associated with neurologial deficits[48]. Additionally, congenital hypothyroidism is associated with an increased risk of congenital malformations[104, 78]. While little is known about the role of thyroid hormone in early ocular development,

studies in zebrafish have shown that disruption of normal thyroid hormone signaling leads to abnormal ocular and visual development[114, 12]. Later in development, thyroid hormone signaling has been shown to be essential in retinal cone opsin expression in model systems[87].

A study using the population-based Hungarian Case-Control Surveillance of Congenital Abnormalities data set reported an association between maternal hypothyroidism and coloboma. Among the mothers of 46 cases of coloboma, two (4.4%) had hypothyroidism, which was markedly higher than the proportion of mothers with hypothyroidism in both population (0.4%) and matched patient (0.3%) controls[146]. While these differences were statistically significant, they are based on very small numbers and are yet to be confirmed in independent studies.

B. Maternal diabetes

Maternal diabetes, including both gestational and pre-gestational diabetes, is a common complication of pregnancy. Pregnancy naturally leads to decreased insulin sensitivity, and maternal diabetes results when the body cannot produce enough insulin to overcome this. Gestational diabetes is estimated to affect around 8% of pregnancies in the United States[161]. While pregestational diabetes is less prevalent, it does create a greater risk to neonatal morbidity[41]. Congenital anomalies are among the numerous complications associated with maternal diabetes, with the National Birth Defects Prevention Study reporting an association between many malformations and pre-gestational diabetes[140]. *In utero* exposure to high glucose levels is thought to result in increased oxidative stress via the production of reactive oxygen species, which in turn leads to an increase in the risk of congenital anomalies[110].

A few reports in the literature have described cases of coloboma in children born to diabetic mothers. A 1958 study from the University of Helsinki performed ophthalmologic examinations on 49 children born to diabetic mothers and found five children with pathologic findings. One of these five children was a 2-year-old boy born via an uncomplicated pregnancy to a mother noted to have poor control of her diabetes whose only abnormality was a right uveal coloboma[75]. Notably, this presentation was in contrast to the other four cases, which all described children exhibiting varying combinations of mental deficits, strabismus, and cataracts, among other findings[75]. Another study retrospectively reviewed 156 cases of children born to diabetic mothers and reported one of these children born with a coloboma of unspecified type[50]. Lastly, a third study reviewed 31 cases from infants born to diabetic mothers where at least one malformation was observed and found 14 cases where multiple malformations were present[51]. One of these cases was born with numerous malformations including small ear, cleft palate multiple cardiac defects, absent right and dysplastic left kidneys, skeletal anomalies, agenesis of the corpus callosum, and an iris coloboma[51]. Two other cases noted ocular malformations. One presented with bilateral microphthalmia and another with bilateral optic atrophy[51].

C. Assisted Reproductive Technologies

During *in vitro* fertilization (IVF), mothers, oocytes, and developing fetuses are exposed to altered environments at various stages in the process, most notably, supraphysiologic

hormone levels. Changes in hormone levels are known to alter transcription factor expression leading to “altered placentation”[82, 89]. Reports conflict regarding the existence and relevance of epigenetic changes, namely DNA methylation, seen following IVF[111]. Other research has noted increased incidence of both chromosomal aberrations and congenital anomalies following IVF. One meta-analysis examined 21 cohort studies and reported a higher risk of chromosomal defects, urogenital malformations, and circulatory system abnormalities in children born following IVF or intracytoplasmic sperm injection compared to those naturally conceived[160]; however, they found no significant difference in malformations in all other systems analyzed, including in the eye[160], although coloboma was not specifically evaluated.

While an increase in ocular malformations following IVF has not been definitively reported, one case series describing 47 children referred for ophthalmologic evaluation following IVF has suggested an association[3]. The authors observed major ocular malformations in 12 (26%) of these children including uveal coloboma with microphthalmos in two[3]. Though this series suggests an increased risk of coloboma in children born following IVF, the evidence is not strong enough to draw definitive conclusions. It does however suggest further study is worthwhile.

It is becoming clear that paternal factors may also have significant epigenetic implications[84, 61], and therefore become important when considering environmental causes of congenital malformations. This is particularly relevant given the increasing prevalence of intracytoplasmic sperm injection, which similarly subjects oocytes to foreign environments.

4. Toxicity and Exposures

A. Alcohol

Maternal alcohol consumption during pregnancy is associated with a range of both physical and neuropsychologic deficits, called fetal alcohol spectrum disorder. Altered neurologic development is most associated with this disorder, and though they are less common, growth retardation and characteristic facial abnormalities, including smooth philtrum, thin upper lip, and shortened palpebral fissures, can also be present[121, 158]. Children with this disorder can therefore present with a wide variety of findings ranging from mild cognitive impairment to significant physical and neurologic impairment. The timing and dose of *in utero* alcohol exposure is thought to contribute significantly to the malformations present. Animal studies have shown that exposing rodents to alcohol during gastrulation results in the characteristic facial anomalies, while exposure during neurulation leads to a different set of facial anomalies[107, 158]. Though exposure later in development produces fewer craniofacial abnormalities, it continues to affect brain development[107, 158]. The pathophysiology of these abnormalities is thought to be related to alcohol’s toxic effects on neural crest cells, which contribute to the craniofacial abnormalities[37] and neural stem cells, which contribute to neurologic deficits[115].

In addition to the facial malformations classically associated with fetal alcohol exposure, the eye is frequently affected in cases of fetal alcohol syndrome[134]. Ocular malformations seen include strabismus, microphthalmos, anterior segment anomalies, and fundus changes,

mainly optic nerve hypoplasia and tortuous retinal vessels[134]. Few studies have suggested an association between alcohol exposure and coloboma. A prospective observational study followed 25 children diagnosed with fetal alcohol syndrome referred for ophthalmologic examination starting at median age of 1 year old with a median follow up time of 11 years. Of the 25 patients followed, 24 had ocular anomalies, and 23 had fundus abnormalities (primarily optic nerve hypoplasia)[132]. One patient presented with bilateral iris and uveal coloboma, optic nerve hypoplasia, exotropia, nystagmus, and poor vision[132]. This clinical observation is strengthened by evidence from a study that gave intraperitoneal alcohol injections to pregnant mice. The study found a significant increase in congenital anomalies after alcohol treatment on days 8, 9, or 10 of gestation, and iris coloboma was one of the two most frequently observed anomalies[77].

Despite limited clinical evidence, recent studies involving the role of neural crest cells on ocular development provide a potential link between fetal alcohol exposure and coloboma. Neural crest cells have been shown to play a critical role in ocular development and are thought to control appropriate optic cup development through non-cell autonomous mechanisms, including the secretion of nidogen, an extracellular matrix protein[150]. Two separate populations of neural crest, one defined by expression of the transcription factor Sox10 and the other by expression of Foxd3 enter the eye at different time points[37, 150]. While the different roles these populations play is yet to be elucidated, the Foxd3 expressing population is known to primarily contribute to the formation of the anterior segment of the eye, specifically the lens, iris and corneal stroma, and aqueous outflow channels[37]. The majority of Sox10 expressing neural crest is found in jaw and pharyngeal arches, but a small population enters the eye for a short period early in ocular development[37]. Interestingly, the Sox10 expressing neural crest population in the jaw and pharyngeal arches was found to be more susceptible to the toxic effects of alcohol compared to the Foxd3 expressing population in the eye, and this is thought to explain how fetal alcohol syndrome leads to primarily craniofacial abnormalities, with anterior ocular malformations being more rare[37]. Given their increased susceptibility to alcohol, pursuing the exact role of the small ocular Sox10 expressing neural crest cell population would be interesting in exploring a mechanistic link between prenatal alcohol exposure and coloboma.

B. Methimazole

The prevalence of hyperthyroidism in pregnancy is estimated to be between 0.1 and 1%, and it is associated with fetal complications when untreated[94]. Antithyroid treatment, typically with either methimazole or propylthiouracil, is therefore recommended to avoid these complications; however, a “CHARGE-like” syndrome with defects including choanal atresia, nipple hypoplasia, facial anomalies, and developmental delay has been defined in association with prenatal exposure to methimazole[20]. More recently, anti-thyroid drugs have been associated with an increased risk of major congenital anomalies, though sub-group analysis for malformations of the eye, ear, face, and neck did not reach statistical significance[125].

Two case reports describe birth defects in mothers taking methimazole that include iris/retinal coloboma. The first was in a 4-year-old girl whose mother took methimazole

during the first two months of pregnancy. She presented with choanal atresia, iris and retinal coloboma, and facial anomalies[54]. The second report described a mother who was taking 20mg/day of methimazole throughout her first trimester and switched to 5mg/day during her third trimester. Her child was born with hypoplastic nipples, microcornea, and a right iris coloboma along with other abnormalities[6]. Of 72 cases that reported congenital defects after prenatal exposure to either methimazole or carbimazole (a precursor that is metabolized to methimazole in the liver), these two cases were the only ones that described coloboma to be among the defects[16]. In addition, a study that dosed zebrafish embryos with varying amounts of methimazole found “hypoplastic brain and spinal cord, pharyngeal and esophageal narrowing, and retinal disruption” in fish that had been exposed[74]. These data further support prenatal methimazole exposure as the cause of this syndrome[125]. It should be noted that, given the associations between coloboma and maternal thyroid disease discussed above, it is unclear whether the observations in these case studies are secondary to the drugs or the underlying thyroid disorders being treated.

C. Hydroxyethylrutoside

Hydroxyethylrutoside (HER) is a semisynthetic form of rutoside, a flavonoid derivative found in a variety of plant species. It is thought to reduce microvascular permeability and erythrocyte aggregation and is therefore used in the treatment of chronic venous insufficiency and hemorrhoids, as well as prophylaxis of venous microangiopathy and edema. While studies have shown that HER may be effective in reducing symptoms of vascular complications in pregnancy, namely varicose veins and hemorrhoids[113, 10], concerns about its safety prevent it from being commonly used.

With regard to coloboma specifically, a Hungarian case-control study on 46 cases of isolated ocular coloboma identified higher HER usage among pregnant mothers whose children were born with coloboma compared to mothers of matched, population, and patient (affected with nonocular congenital anomalies) controls[146]. A follow-up case-control study compared a group of 22,843 cases with congenital abnormalities to 38,151 controls without anomalies[112]. There were four children born with coloboma and one born with bilateral microphthalmia among these 22,843 cases. In all five of these cases, the mothers had exposure to HER treatment during pregnancy. The mothers of three of the coloboma cases received HER treatment from month one of pregnancy until delivery, the mother of the fourth case received HER treatment from month 4 of pregnancy, and the mother of the microphthalmia case received HER treatment from month 3 of pregnancy. Analysis of this data revealed an association of unilateral ocular coloboma with HER treatment during the second and/or third month of pregnancy[112].

D. Anticonvulsants

The teratogenic effects of anticonvulsants are well known and complicate the treatment of mothers with epileptic disorders during pregnancy. The highest risk of major malformations from these drugs come during the first trimester, but use throughout pregnancy is thought to impact growth and neurodevelopment of the fetus[142]. A Cochrane systematic review of the literature and a network meta-analysis both calculated the risk of major congenital malformations in children born to mothers on various antiepileptics compared

to those born to mothers without epilepsy and found statistically significant increased risk from many commonly used antiepileptics[153, 145]. Valproate demonstrated the highest risk of malformations, with the Cochrane review reporting a 10.93% prevalence of major malformations in babies born to mothers using the drug[153, 145]. Carbamazepine and phenytoin both demonstrated an increased risk of malformations in both studies, with the Cochrane review reporting risk ratio of 2.01 and 2.38 respectively compared to unexposed children born to mothers without epilepsy[153] and the network meta-analysis reporting comparable odds ratios of 1.37 and 1.67 respectively compared to controls[145].

Fetal growth restriction, craniofacial and limb anomalies, and neural tube defects are among the typical malformations that can be seen following fetal exposure to carbamazepine[68]. Two studies have reported on the association between coloboma and fetal exposure to carbamazepine. The first is a case series that described four patients with ocular malformations seen following first trimester exposure to the drug. One child was born with bilateral anophthalmia and low birth weight, two were born with severe, bilateral microphthalmia, and the last was born with a unilateral optic nerve coloboma[136]. The mother of this fourth case was taking 600mg of carbamazepine three times per day throughout pregnancy. The second study retrospectively reviewed 77 cases of anophthalmia, microphthalmia, and coloboma to follow up on the initial report by Sutcliffe. Carbamazepine exposure was not reported in any of these cases and a subsequent literature review found no association between coloboma and carbamazepine use[76].

A combination of growth restriction, microcephaly, limb, craniofacial, and cardiac defects following fetal exposure to phenytoin defines fetal hydantoin syndrome[38]. Though reports have also suggested an increase in both periocular and ocular anomalies in this syndrome[147, 157], the evidence linking fetal hydantoin exposure to coloboma is limited to a single case report. It describes a child exposed to Dilantin (phenytoin), phenobarbital, and primidone born with a constellation of malformations including hirsutism, cranial and facial deformities, limb abnormalities, and scoliosis--along with a microphthalmic left eye with an inferior iris and choroidal coloboma[56].

E. Lysergic acid diethylamide (LSD)

One case reported on a child born to a mother who used lysergic acid diethylamide (LSD) both before and during pregnancy. The child was born with a wide variety of limb, craniofacial, organ, and ocular malformations that included a small iris coloboma[5]. While other cases reporting ocular malformations other than coloboma as a result of LSD usage have been published[93], this one report does not provide strong enough evidence to confirm an association between coloboma and maternal LSD usage.

F. Radiation

In utero exposure to ionizing radiation is known to have harmful effects on developing fetuses, but ethical considerations limit research that can be done in this population. Radiation has been described as having teratogenic, carcinogenic, and mutagenic effects on developing fetuses, and while exposure to any dose of radiation confers a risk, the timing and dose of ionizing radiation can have a large impact on resulting malformations,

with exposure during weeks 2 to 7 of gestation having the most significant effect[35, 154]. Additionally, studies that examined decedents of residents of the Marshall Islands during the mid-20th century nuclear tests[101] as well as the survivors of the Chernobyl[152] and Fukushima[42] nuclear disasters have reported on the effects of radiation exposure. Specifically, increases in rates of congenital cataracts and truncus arteriosus were noted in decendents of Marshall Islands residents,[101] with higher rates of microcephaly, neural tube defects, and microphthalmia observed in areas of Ukraine affected by the Chernobyl disaster when compared to adjacent, less affected regions[152]. This phenomenon has also been observed in rodents with a study that dosed pregnant rats with varying levels of radiation on day nine of gestation and performed ocular examinations during postnatal week 5 finding iris and choroidal coloboma, microphthalmia, and anophthalmia in groups dosed with 3.2, 6.3 and 12.6 Gy along with additional ocular malformations in the 12.6Gy group[79]. Further investigation of these observations performed transcriptional analysis on irradiated mice, and linked the structural ocular defects observed to changes in RPE melanogenesis[22]. These studies collectively provide observational and experimental data from both humans and rodents that links radiation exposure to structural ocular defects.

G. Saccharine

The literature linking maternal saccharine consumption to coloboma is limited to one French study. Rats were fed diets containing varying concentrations and purities of saccharine produced by two different synthesis methods. Microphthalmia, anophthalmia, and coloboma were commonly seen malformations. The authors concluded that the contaminants of saccharine synthesis, ortho-sulfobenzoic acid, para-sulfobenzoic acid, para-sulfamolybenzoic acid, and para-toluenesulfonamide are responsible for the observed teratogenic effects and that sufficient purification of commercial saccharine is necessary to mitigate these risks[21].

H. Mycophenolate mofetil

A new embryopathy has been defined related to *in utero* exposure to mycophenolate mofetil (MMF). MMF is a potent immunosuppressant that inhibits inosine 5'-monophosphate dehydrogenase (IMPDH), the rate-limiting enzyme in *de novo* guanine synthesis. It is therefore able to selectively inhibit lymphocyte proliferation, as these cells are unable to utilize the guanine salvage pathway and are therefore dependent on *de novo* synthesis. Because of both its potent immunosuppressive effects and minimal side effect profile, MMF has quickly become one of the primary immunosuppressants for prevention of allograft rejection after solid organ transplant since its approval by the FDA in 1995. Additionally, it is commonly used in immunosuppressive regimens for the treatment of autoimmune diseases.

Starting in the early 2000s, several reports were published documenting congenital malformations in babies born to mothers who had undergone renal transplants and were on immunosuppressive regimens that included MMF[7, 81, 128, 141]. These included cleft lip and palate, microtia, external auditory canal atresia, micrognathia, and hypertelorism along with other varied malformations. In 2007, a similar case was reported[109] with similar malformations of the face, palate, ears, and jaw as well as bilateral chorioretinal colobomas.

Following this case report, several other individual case reports and case series have been published on babies with in-utero exposure to MMF. Two of these reports noted colobomas among the malformations present[2, 122]. A 2012 prospective study of 57 women who were exposed to MMF during pregnancy found 8 fetuses/infants with major malformations[62]. One of these cases was noted to have coloboma.

Perez and coworkers reviewed published cases of MMF embryopathy. In their analysis they found that 34% of the reported cases of MMF embryopathy reported ocular anomalies including chorioretinal coloboma, iris coloboma, or microphthalmia. They also note that, though 20% of cases revealed chorioretinal coloboma, not every patient received a funduscopic exam, and this may underrepresent the incidence of this malformation[109]. Also of note, the authors draw attention to the fact that in every case that reported features typical of MMF embryopathy with the exception of one case, where the fetus was exposed until 7 weeks gestation[2], exposure to MMF occurred until at least the 8th week of gestation. This suggests a “critical period” of MMF exposure in the first trimester. Optic fissure closure is known to occur between weeks 5 and 7 of fetal life, and failure of this process results in uveal coloboma.

Similar malformations have also been seen in *in vitro* rat models. A 2013 study of mycophenolic acid (MPA), the active ingredient in MMF, in whole-embryo rat cultures found that exposure to MPA resulted in comparable malformations including truncated torsos, deformed and fused brachial arches, and missing optic and otic vesicles[120]. While the exact mechanism of the teratogenicity of MMF is unknown, the authors of this study suggest that it could be related to the inhibition of IMPDH, as they measured IMPDH activity in embryonic tissues throughout the period that they were cultured[120]. Further study is needed to investigate this mechanism further.

I. Thiourea

Thiourea, though structurally similar to urea, contains a sulfur atom in place of an oxygen atom. In addition to use in industrial applications, the antithyroid drugs methimazole and propylthiouracil are structural derivatives of thiourea, which exhibits an antithyroid effect on its own[15]. It is known to be teratogenic, causing neural tube and growth defects in rodents[73]. Additionally, one study dosing fetal rats for the first 14 days of development with a 0.2% aqueous solution of 2’-thiourea observed colobomas along with other abnormalities[72]. Given the possible association of coloboma with maternal hypothyroidism and antithyroid drugs, and the antithyroid properties of thiourea, a common mechanism could be explored.

J. Hyperthermia

In animals, experiments across multiple species have demonstrated teratogenic effects from even 1.5–2.5 °C elevations in body temperature in certain species[39]. Hyperthermia has been shown to primarily affect the central nervous system, especially if it occurs during critical periods of embryonic development[39]. Epidemiologic studies in humans have also demonstrated an increased prevalence in neural tube defects associated with maternal fevers, hot tub, and sauna use[95, 96]. Though human studies have not examined the potential of hyperthermia to cause coloboma, animal studies have described coloboma after maternal

hyperthermia in chicks[103] and guinea pigs[49]. Given the ability of high temperatures to disrupt neural tube closure, it is plausible to hypothesize that exposure to high temperature during the embryonic period of optic fissure closure could result in coloboma, but this would have to be confirmed experimentally.

K. Synthetic Cannabinoids

Synthetic cannabinoids are laboratory derived compounds designed to interact with the cannabinoid receptor and are commonly abused as recreational substances[53]. Usageis associated with a variety of harmful effects, including aggressive behavior, anxiety, paranoia, and memory problems[92]. Studies on the teratogenic effects of natural cannabinoids have linked marijuana use to growth, limb, and behavioral defects in humans[44, 59], and administration of high doses of Δ9-THC, the active ingredient in marijuana, to pregnant mice led to fetal malformations[69]. Given that synthetic cannabinoids are associated with more toxic effects than naturally occurring cannabinoids and are often stronger agonists of the cannabinoid receptors than naturally occurring cannabis[138], Gilbert and coworkers tested the teratogenicity of the synthetic cannabinoid CP-55,940 in mice by administering it on day 8 of pregnancy[45]. Theyobserved craniofacial and ocular malformations in all drug-treated groups, which increased in frequency with increasing dose. Ocular malformations commonly observed included microphthalmia, coloboma, and anophthalmia.

L. Thalidomide

Thalidomide, a drug originally released in the 1950s to treat morning sickness in pregnant women, is now infamous for the birth defects it caused. Thalidomide embryopathy can affect almost any organ in the body and is most severe when the developing embryo is exposed during the “critical period” between days 20 and days 36 after fertilization[144]. Several studies have reported on the association between thalidomide exposure and coloboma. Multiple case series from the 1960s describe cases of coloboma in thalidomide babies, with one describing colobomatous defects in 5 out of 20 with ocular defects[47] and another detailing 3 cases in a series of 12 children with defects resulting from thalidomide[24]. Another larger series reported findings related to the examination of 154 children with thalidomide-induced defects and reported coloboma in 5 of these children[129]. In addition to these retrospective reports, a prospective study performed ophthalmologic exams on 86 Swedes with confirmed thalidomide embryopathy and found ocular finding in 46, 3 of which were coloboma[133]. Despite the rarity of coloboma among the numerous defects seen as a result of thalidomide exposure, this combination of retrospective and prospective data makes thalidomide a likely candidate as a cause of this malformation.

5. Infection

A. Cytomegalovirus (CMV)

Around 10% of babies born with congenital cytomegalovirus (CMV) present with various problems at birth[65]. These can include petechial rash, jaundice hepatosplenomegaly, microcephaly, restricted growth, sensorineural hearing loss, and chorioretinitis, and, as a result, infants born with this infection are at risk for debilitating long-term disabilities[65, 14]. Congenital CMV infection has been linked to coloboma through one case report that

presented four patients born with congenital CMV and optic nerve abnormalities[60]. Of these 4 patients, one was noted to have a unilateral partial optic nerve coloboma discovered at 20 weeks of agealong with other abnormalities, and a second presented with a complete unilateral optic nerve coloboma and microphthalmia. A retrospective analysis of 28 children with optic nerve hypoplasia and 10 children with coloboma attempted to find any association between these conditions and environmental exposures and noted no exposure to CMV in any of the 10 coloboma cases[40]; however, the small sample size of these studies prevents any definitive conclusions from being made regarding CMV infection and coloboma.

B. Toxoplasmosis

The classic congenital infection caused by *Toxoplasma gondii*, a protozoan parasite, causes a triad of chorioretinitis, hydrocephalus, and intracranial calcifications[137]. The connection between congenital toxoplasmosis and coloboma has been suggested many times. The original description of ocular toxoplasmosis described an infant with hydrocephalous, microphthalmia, and a “colobomatous area” in the macula, which may not be a true optic fissure closure defect[105, 67]. Another report on ocular toxoplasmosis specifically highlighted the similarities in appearance between a toxoplasma infection scar and a coloboma[117], which calls into question what was being referred to in the original report. A case of a congenital coloboma discovered in a 25-year-old with congenital toxoplasmosis has also been observed[30]. A descriptive retrospective cohort study of 173 cases of ocular toxoplasmosis in Indonesia aimed to more definitively define the clinical features and risk factors of ocular toxoplasma infection, but reported no cases of coloboma[135]. Despite coloboma being considered a feature of ocular toxoplasmosis, the published evidence linking the two is limited to two individual cases.

C. Zika virus

Zika virus, a primarily mosquito-borne arbovirus, is known to cause a group of congenital anomalies known as congenital zika syndrome that includes microcephaly, thinned cortices and subcortical calcifications in the brain, macular scarring and focal pigmentary retinal mottling in the eye, contractures, and hypertonia[97]. Notably, the eye can be affected in 29–70% of cases[32]. While other ocular findings are more common, numerous studies have reported coloboma associated with congenital zika syndrome[33, 31, 162, 63, 52]. Two studies performed ocular exams on patients with congenital microcephaly secondary to zika infection, and reported coloboma in 9.7% of 62 patients examined[143] and 41.7% of 12 eyes examined[34]. Infection during the first trimester of pregnancy is associated with higher rates of fundus abnormalities, suggesting infection during a “critical period” is important in the development of malformations[32].

6. Conclusion

Despite a large number of studies linking various environmental exposures to coloboma, the vast majority are either single case reports or deal in numbers too small to provide strong evidence. Studying this condition in humans is made particularly difficult both by its rarity and the potential for under ascertainment, especially if it arises as an isolated and relatively asymptomatic defect however, there is compelling evidence for the role of some

environmental exposures on the development of coloboma including vitamin A deficiency, folate deficiency, maternal hypothyroidism, maternal alcohol use, fetal mycophenolate mofetil exposure, and congenital zika virus infection. These findings are supported by experimental animal data, epidemiologic evidence, and plausible mechanisms, which point to the need for additional studies integrating more comprehensive methods. Other exposures, for example radiation and hyperthermia, may not be specific to coloboma, but may occur if the insult arises during a specific critical period in optic fissure closure; however, more purposeful epidemiologic and experimental studies will need to be performed to identify and eliminate environmental causes of coloboma.

7. Methods of Literature Search

The citations for this article were obtained from PubMed searches covering the years 1966–2021 using the search terms “coloboma,” “environmental causes,” and “teratogen.” Studies that provided evidence of coloboma linked to environmental causes were included, while studies that either did not include coloboma, or linked coloboma to genetic causes were excluded. Additional references were obtained from Chang 2006 to capture relevant references that were not found with these search terms, included older references. Each environmental cause described in Chang’s review was searched in PubMed along with the terms “coloboma” and “teratogen” to capture more recent publications. Again, references that specifically described the environmental cause and coloboma were included. English translations of the abstracts of non-English publications were used. While there are limitations to this approach, the authors felt this was preferable to excluding the evidence provided by these sources entirely.

Funding Sources

This work was supported by the intramural program of the National Eye Institute, National Institutes of Health, project EY000469 (2020) The Genetics of Uveal Coloboma and National Institutes of Health project 1U01EY032403. Additionally, this research was made possible through the NIH Medical Research Scholars Program, a public-private partnership supported jointly by the NIH and contributions to the Foundation for the NIH from the Doris Duke Charitable Foundation, Genentech, the American Association for Dental Research, and the Colgate-Palmolive Company.

References

1. Al Somiry AS, Gregory-Evans CY, Gregory-Evans K. An update on the genetics of ocular coloboma. Hum Genet. 2019;138(8–9):865–880. [PubMed: 31073883]
2. Ang GS, Simpson SA, Reddy AR. Mycophenolate mofetil embryopathy may be dose and timing dependent. Am J Med Genet A. 2008;146A(15):1963–1966. [PubMed: 18570296]
3. Anteby I, Cohen E, Anteby E, BenEzra D. Ocular manifestations in children born after in vitro fertilization. Arch Ophthalmol. 2001; 119:1525–1529. [PubMed: 11594955]
4. Antony AC. In utero physiology: role of folic acid in nutrient delivery and fetal development. Am J Clin Nutr. 2007;85(2):598S–603S. [PubMed: 17284762]
5. Apple DJ, Bennett TO. Multiple systemic and ocular malformations associated with maternal LSD usage. Arch Ophthalmol. 1974; 92:301–303. [PubMed: 4213259]
6. Aramaki M, Hokuto I, Matsumoto T, et al. Iridic and retinal coloboma associated with prenatal methimazole exposure. Am J Med Genet A. 2005; 139:156–158.

7. Armenti VT, Radomski JS, Moritz MJ, et al. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. Clin Transpl. 2004:103–14. [PubMed: 16704142]
8. Armstrong RC, Monie I (1966) Congenital eye defects in rats following maternal folic-acid deficiency during pregnancy. Development. 16;531–542.
9. Azzi A. Many tocopherols, one vitamin E. Mol Aspects Med. 2018;61:92–103. [PubMed: 28624327]
10. Bamigboye AA, Smyth R. Interventions for varicose veins and leg oedema in pregnancy. Cochrane Database Syst Rev 2007;(1): CD001066. [PubMed: 17253454]
11. Banerjee S, Chambers AE, Campbell S. Vitamin C and vitamin E in pregnant women at risk of pre-eclampsia. Lancet. 2006;368:199.
12. Baumann L, Ros A, Rehberger K, Neuhauss SC, Segner H. Thyroid disruption in zebrafish (Danio rerio) larvae: Different molecular response patterns lead to impaired eye development and visual functions. Aquat Toxicol. 2016;172:44–55. [PubMed: 26765085]
13. Berry RJ, Li Z, Erickson JD, et al. Prevention of neural-tube defects with folic acid in China: China-US Collaborative Project for Neural Tube Defect Prevention. N Engl J Med 1999;341:1485–1490. [PubMed: 10559448]
14. Boppana SB, Ross SA, Fowler KB. Congenital cytomegalovirus infection: clinical outcome. Clin Infect Dis. 2013;57. [PubMed: 23532474]
15. Capen CC. Mechanisms of chemical injury of thyroid gland. Prog Clin Biol Res. 1994;387:173–91. [PubMed: 7526405]
16. Cassina M, Dona M, Di Gianantonio E, Clementi M. 2012. Pharmacologic treatment of hyperthyroidism during pregnancy. Birth Defects Res A 94:612–619.
17. Chang L, Blain D, Bertuzzi S, Brooks BP. Uveal coloboma: clinical and basic science update. Curr Opin Ophthalmol. 2006 Oct;17(5):447–70. [PubMed: 16932062]
18. Chen H, Qian N, Yan L, Jiang H. Role of serum vitamin A and E in pregnancy. Exp Ther Med. 2018;16(6):5185–5189. [PubMed: 30542475]
19. Chou CM, Nelson C, Tarlé SA, et al. Biochemical Basis for Dominant Inheritance, Variable Penetrance, and Maternal Effects in RBP4 Congenital Eye Disease. Cell. 2015 Apr 23;161(3):634–646. [PubMed: 25910211]
20. Clementi M, Di Gianantonio E, Pelo E, et al. Methimazole embryopathy: delineation of the phenotype. Am J Med Genet. 1999 Mar 5;83(1):43–6. [PubMed: 10076883]
21. Colson A, Lederer J, Michiels J. Ocular lesions induced by saccharin and its pollutants in the rat fetus. J Fr Ophtalmol. 1984; 7:399–410. [PubMed: 6438215]
22. Craenen K, Verslegers M, Craeghs L, et al. Abnormal retinal pigment epithelium melanogenesis as a major determinant for radiation-induced congenital eye defects. Reprod Toxicol. 2020;91:59–73. [PubMed: 31705956]
23. Cukras C, Gaasterland T, Lee P, et al. Exome analysis identified a novel mutation in the RBP4 gene in a consanguineous pedigree with retinal dystrophy and developmental abnormalities. PLoS One. 2012;7(11):e50205. [PubMed: 23189188]
24. Cullen JF. Ocular defects in thalidomide babies. Brit J Ophthal. 1964;48:151–153. [PubMed: 14193669]
25. Cvekl A, Wang WL. Retinoic acid signaling in mammalian eye development. Exp Eye Res. 2009;89(3):280–291. doi:10.1016/j.exer.2009.04.012 [PubMed: 19427305]
26. Czeizel AE, Dobó M, Vargha P: Hungarian cohort controlled trial of periconceptional multivitamin supplementation shows a reduction in certain congenital abnormalities. Birth Defects Res A Clin Mol Teratol. 2004;70:853–861. [PubMed: 15523663]
27. Czeizel AE, Dudás I, Paput L, Bánhidy F. Prevention of neural-tube defects with periconceptional folic acid, methylfolate, or multivitamins? Ann Nutr Metab. 2011 Oct;58(4):263–71.
28. Czeizel AE, Dudás I: Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. N Engl J Med 1992;327:1832–1835. [PubMed: 1307234]
29. Czeizel AE: Ten years of experience in the periconceptional care. Eur J Obstet Gynecol Reprod Biol. 1999;89:43–49.

30. de Jong PT. Ocular toxoplasmosis; common and rare symptoms and signs. Int Ophthalmol. 1989;13(6):391–7. [PubMed: 2697705]
31. de Oliveira Dias JR, Ventura CV, Borba PD, et al. Infants with congenital zika syndrome and ocular findings from Sao Paulo, Brazil: Spread of infection. Retin Cases Brief Rep. 2018;12(4):382–386. [PubMed: 28060137]
32. de Oliveira Dias JR, Ventura CV, de Paula Freitas B, et al. Zika Virus Study Group. Zika and the Eye: Pieces of a Puzzle. Prog Retin Eye Res. 2018;66:85–106. [PubMed: 29698814]
33. de Paula Freitas B, de Oliveira Dias JR, Prazeres J, et al. Ocular findings in infants with microcephaly associated with presumed zika virus congenital infection in Salvador, Brazil. JAMA Ophthalmol. 2016;134(5):529–535. [PubMed: 26865554]
34. de Paula Freitas B, Zin A, Ko A, et al. Anterior-segment ocular findings and microphthalmia in congenital zika syndrome. Ophthalmology. 2017;124(12):1876–1878. [PubMed: 28676282]
35. De Santis M, Cesari E, Nobili E, et al. Radiation effects on development. Birth Defects Res C Embryo Today. 2007;81(3):177–82. [PubMed: 17963274]
36. Duester G. Retinoic acid synthesis and signaling during early organogenesis. Cell. 2008;134(6):921–931. [PubMed: 18805086]
37. Eason J, Williams AL, Chawla B, Apsey C, Bohnsack BL. Differences in neural crest sensitivity to ethanol account for the infrequency of anterior segment defects in the eye compared with craniofacial anomalies in a zebrafish model of fetal alcohol syndrome. Birth Defects Res. 2017;109(15):1212–1227. [PubMed: 28681995]
38. Easton JD. “Potential hazards of hydantoin use”. Ann Intern Med. 1972; 77 (6): 998–9. [PubMed: 4644176]
39. Edwards MJ. Hyperthermia as a teratogen: a review of experimental studies and their clinical significance. Teratog Carcinog Mutagen. 1986;6(6):563–82. [PubMed: 2881371]
40. Fahnehjelm KT, Jacobson L, Hellström A, Lewensohn-Fuchs I, Ygge J. Visually impaired children with posterior ocular malformations: pre- and neonatal data and visual functions. Acta Ophthalmol Scand. 2003;81(4):361–72. [PubMed: 12859263]
41. Fong A, Serra A, Herrero T, Pan D, Ogunyemi D. Pre-gestational versus gestational diabetes: a population based study on clinical and demographic differences. J Diabetes Complicat. 2014;28(1): 29–34.
42. Fujimori K, Kyozuka H, Yasuda S, et al. Pregnancy and Birth Survey Group of the Fukushima Health Management Survey. Pregnancy and birth survey after the Great East Japan Earthquake and Fukushima Daiichi Nuclear Power Plant accident in Fukushima prefecture. Fukushima J Med Sci. 2014;60(1):75–81. [PubMed: 25030719]
43. Gaudet LM, MacKenzie J, Smith GN. Fat-soluble vitamin deficiency in pregnancy: a case report and review of abetalipoproteinemia. J Obstet Gynaecol Can. 2006 Aug;28(8):716–719. [PubMed: 17022912]
44. Gibson GT, Baghurst PA, Colley DP, Aust NZJ. Maternal alcohol, tobacco and cannabis consumption and the outcome of pregnancy. Obstet Gynaecol. 1983; 23(1):15–9.
45. Gilbert MT, Sulik KK, Fish EW, et al. Dose-dependent teratogenicity of the synthetic cannabinoid CP-55,940 in mice. Neurotoxicol Teratol. 2016;58:15–22. [PubMed: 26708672]
46. Gilboa SM, Lee KA, Cogswell ME, et al. Maternal intake of vitamin E and birth defects, national birth defects prevention study, 1997 to 2005. Birth Defects Res A Clin Mol Teratol. 2014;100(9):647–657. [PubMed: 24740457]
47. Gilkes MJ, Strode M. Ministry of Health: CENSUS OF THALIDOMIDE BABIES. Brit. med. J 1962;2:1176. [PubMed: 20789542]
48. Glinoer D. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. Endocr Rev. 1997;18:404–433. [PubMed: 9183570]
49. Graham JM Jr. Marshall J. Edwards: discoverer of maternal hyperthermia as a human teratogen. Birth Defects Res A Clin Mol Teratol. 2005;73(11):857–64. [PubMed: 16265640]
50. Grenet P, de PF, Badoual J, et al. Newborn infant of the diabetic mother. Arch Fr Pediatr 1972; 29:925–933. [PubMed: 4661880]
51. Grix A Jr. Malformations in infants of diabetic mothers. Am J Med Genet 1982; 13:131–137 [PubMed: 7137227]

52. Guevara JG, Agarwal-Sinha S. Ocular abnormalities in congenital zika syndrome: a case report, and review of the literature. J Med Case Rep. 2018;12(1):161. [PubMed: 29884243]
53. Gunderson EW, Haughey HM, Ait-Daoud N, Joshi AS, Hart CL. Synthetic cannabinoids: a new frontier of designer drugs. Subst Abus. 2014; 35(2):184–9. [PubMed: 24821356]
54. Hall BD. Methimazole as a teratogenic etiology of choanal atresia/multiple congenital anomaly syndrome. Am J Hum Genet 1997;(Suppl)61:A100.
55. Hammes SR, Davis PJ. Overlapping nongenomic and genomic actions of thyroid hormone and steroids. Best Pract Res Clin Endocrinol Metab. 2015;29(4):581–593. [PubMed: 26303085]
56. Hampton GR, Krepostman JI. Ocular manifestations of the fetal hydantoin syndrome. Clin Pediatr (Phila). 1981; 20:475–478. [PubMed: 6786811]
57. Hauptman O, Albert DM, Plowman MC, et al. Ocular malformations of Xenopus laevis exposed to nickel during embryogenesis. Ann Clin Lab Sc.i 1993; 23:397–406.
58. Hero I. Optic fissure closure in the normal cinnamon mouse. An ultrastructural study. Invest Ophthalmol Vis Sci. 1990;31(1):197–216. [PubMed: 2298539]
59. Hingson R, Alpert JJ, Day N, et al. Effects of maternal drinking and marijuana use on fetal growth and development. Pediatrics. 1982; 70(4):539–46. [PubMed: 6981792]
60. Hittner HM, Desmond MM, Montgomery JR. Optic nerve manifestations of human congenital cytomegalovirus infection. Am J Ophthalmol. 1976;81(5):661–5. [PubMed: 179325]
61. Hoek J, Steegers-Theunissen RPM, Willemsen SP, Schoenmakers S. Paternal Folate Status and Sperm Quality, Pregnancy Outcomes, and Epigenetics: A Systematic Review and Meta-Analysis. Mol Nutr Food Res. 2020;64(9):1–14.
62. Hoeltzenbein M, Elefant E, Vial T, et al. Teratogenicity of myciphenolate confirmed in a porspective study of the European network of Teratology Information Service. Am. J. Med. Genet 2012; 158A(3):588–96. [PubMed: 22319001]
63. Honein MA, Dawson AL, Petersen EE, et al. US zika pregnancy registry collaboration. Birth defects among fetuses and infants of US women with evidence of possible zika virus infection during pregnancy. JAMA. 2017;317(1):59–68. [PubMed: 27960197]
64. Hornby SJ, Ward SJ, Gilbert CE, et al. Environmental risk factors in congenital malformations of the eye. Ann Trop Paediatr 2002; 22:67–77. [PubMed: 11926054]
65. Istas AS, Demmler GJ, Dobbins JG, Stewart JA. Surveillance for congenital cytomegalovirus disease: a report from the National Congenital Cytomegalovirus Disease Registry. Clin Infect Dis. 1995;20(3):665–70. [PubMed: 7756493]
66. Jakubiuk-Tomaszuk A, Murcia Pienkowski V, Zietkiewicz S, et al. (2019). Syndromic chorioretinal coloboma associated with heterozygous de novo RARA mutation affecting an amino acid critical for retinoic acid interaction. Clinical Genetics, 96(4), 371–375. [PubMed: 31343737]
67. Janku J. Pathogenesa a patologicka anatomie tak nazvaneho vrozeneho kolobomu zlute skvrny v oku normalne velikem a microphthalmickem s nalezem parasitu v sitnici. Cas Lek Ces 1923; 62: 1021, 1054, 1081, 1111, 1138.
68. Jentink J, Dolk H, Loane MA, et al. EUROCAT Antiepileptic study working group. Intrauterine exposure to carbamazepine and specific congenital malformations: systematic review and case-control study. BMJ. 2010;341:c6581. [PubMed: 21127116]
69. Joneja MG. A study of teratological effects of intravenous, subcutaneous, and intragastric administration of delta9-tetrahydrocannabinol in mice. Toxicol Appl Pharmacol. 1976; 36(1):151–62. [PubMed: 1273835]
70. Kalaskar VK, Alur RP, Li LK, et al. High-throughput custom capture sequencing identifies novel mutations in coloboma-associated genes: Mutation in DNA-binding domain of retinoic acid receptor beta affects nuclear localization causing ocular coloboma. Hum Mutat. 2020;41(3):678–695. [PubMed: 31816153]
71. Kemnic TR, Coleman M. Vitamin E Deficiency, in: StatPearls [Internet]. Florida, StatPearls Publishing; 2020.
72. Kern M, Tatár-Kiss Z, Kertai P, Földes I. Teratogenic effect of 2'-thiourea in the rat. Acta Morphol Acad Sci Hung. 1980;28(3):259–67. [PubMed: 6778083]
73. Khera KS. Ethylenethiourea: teratogenicity study in rats and rabbits. Teratology. 1973;7(3):243–52. [PubMed: 4807127]

74. Komoike Y, Matsuoka M, Kosaki K. Potential teratogenicity of methimazole: exposure of zebrafish embryos to methimazole causes similar developmental anomalies to human methimazole embryopathy. Birth Defects Res B Dev Reprod Toxicol. 2013;98(3):222–9. [PubMed: 23630110]
75. Koskenoja M. Eye findings in children born to diabetic mothers. Acta Ophthalmol (Copenh). 1958; 36:559–564. [PubMed: 13594364]
76. Kroes HY, Reefhuis J, Cornel MC. Is there an association between maternal carbamazepine use during pregnancy and eye malformations in the child? Epilepsia. 2002; 43:929–931. [PubMed: 12181014]
77. Kronick JB. Teratogenic effects of ethyl alcohol administered to pregnant mice. Am J Obstet Gynecol. 1976; 124:676–680. [PubMed: 1258925]
78. Kumar J, Gordillo R, Kaskel FJ, Druschel CM, Woroniecki RP. Increased prevalence of renal and urinary tract anomalies in children with congenital hypothyroidism. J Pediatr. 2009;154(2):263–266. [PubMed: 18823909]
79. Kuno H, Kemi M, Akimoto M, et al. Effects of soft X-ray irradiation on ocular development in Sprague–Dawley rats. Jikken Dobutsu. 1993; 42:443–449. [PubMed: 8354368]
80. LaFranchi SH, Murphey WH, Foley TP Jr, Larsen PR, Buist NR. Neonatal hypothyroidism detected by the Northwest Regional Screening Program. Pediatrics. 1979;63(2):180–91. [PubMed: 108659]
81. Le Ray C, Coulomb A, Elefant E, Frydman R, Audibert F. Mycophenolate mofetil in pregnancy after renal transplantation: A case of major fetal malformations. Obstet Gynecol. 2004; 103:1091–1094. [PubMed: 15121619]
82. Lee B, Kroener LL, Xu N, et al. Function and hormonal regulation of GATA3 in human first trimester placentation. Biol Reprod. 2016;95(5):113. [PubMed: 27733378]
83. Léonard A, Gerber GB, Jacquet P. “Carcinogenicity, Mutagenicity and Teratogenicity of Nickel.” Mutation research. Reviews in genetic toxicology 1981;87(1): 1–15.
84. Lucas ES, Watkins AJ. The Long-Term Effects of the Periconceptional Period on Embryo Epigenetic Profile and Phenotype; The Paternal Role and His Contribution, and How Males Can Affect Offspring’s Phenotype/Epigenetic Profile. Adv Exp Med Biol. 2017;1014:137–154. [PubMed: 28864989]
85. Lucock M. Folic acid: nutritional biochemistry, molecular biology, and role in disease processes. Mol Genet Metab. 2000;71(1–2):121–38. [PubMed: 11001804]
86. Lupo G, Gestri G, O’Brien M, et al. Retinoic acid receptor signaling regulates choroid fissure closure through independent mechanisms in the ventral optic cup and periocular mesenchyme. Proc Natl Acad Sci U S A. 2011;108(21):8698–8703. [PubMed: 21555593]
87. Ma H, Ding XQ. Thyroid Hormone Signaling and Cone Photoreceptor Viability. Adv Exp Med Biol. 2016;854:613–8. [PubMed: 26427466]
88. Maestro-de-las-Casas C, Pérez-Miguelsanz J, López-Gordillo Y, et al. Maternal folic acid-deficient diet causes congenital malformations in the mouse eye. Birth Defects Res A Clin Mol Teratol. 2013;97(9):587–96. [PubMed: 24078476]
89. Mainigi MA, Sapienza C, Butts S, Coutifaris C. A molecular perspective on procedures and outcomes with assisted reproductive technologies. Cold Spring Harb Perspect Med. 2016;6(4):a023416. [PubMed: 26747835]
90. Matt N, Ghyselinck NB, Pellerin I, Dupé V. Impairing retinoic acid signalling in the neural crest cells is sufficient to alter entire eye morphogenesis. Dev Biol. 2008;320(1):140–148. [PubMed: 18539269]
91. Matt N, Dupe V, Garnier JM, et al. Retinoic acid-dependent eye morphogenesis is orchestrated by neural crest cells. Development. 2005;132(21), 4789–4800. [PubMed: 16207763]
92. McGuinness TM, Newell DJ. Risky recreation: synthetic cannabinoids have dangerous effects. Psychosoc Nurs Ment Health Serv. 2012; 50(8):16–8.
93. McLane NJ, Carroll DM. Ocular manifestations of drug abuse. Surv Ophthalmol. 1986;30(5):298–313. [PubMed: 2872731]
94. Mestman JH. Hyperthyroidism in pregnancy. Best Pract Res Clin Endocrinol Metab. 2004;18:267–288. [PubMed: 15157840]

95. Miller P, Smith DW, Shepard T. Maternal hyperthermia as a possible cause of anencephaly. Lancet. 1978;1(8063):519–21. [PubMed: 76068]
96. Milunsky A, Ulcickas M, Rothman KJ, et al. Maternal heat exposure and neural tube defects. JAMA. 1992;268(7):882–5. [PubMed: 1640616]
97. Moore CA, Staples JE, Dobyns WB, et al. Characterizing the pattern of anomalies in congenital Zika syndrome for pediatric clinicians. JAMA Pediatr. 2017;171(3):288–295. doi:10.1001/jamapediatrics.2016.3982. [PubMed: 27812690]
98. Morrison D, FitzPatrick D, Hanson I, et al. National study of microphthalmia, anophthalmia, and coloboma (MAC) in Scotland: investigation of genetic aetiology. J Med Genet. 2002 Jan;39(1):16–22. [PubMed: 11826019]
99. MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. Lancet 1991;338:131–137. [PubMed: 1677062]
100. Nelson MM, Wright HV, Asling CW, Evans HM. Multiple congenital abnormalities resulting from transitory deficiency of pteroylglutamic acid during gestation in the rat. J Nutr 1955; 56:349–369. [PubMed: 13243148]
101. Nembhard WN, McElfish PA, Ayers B, et al. Nuclear radiation and prevalence of structural birth defects among infants born to women from the Marshall Islands. Birth Defects Res. 2019;111(16):1192–1204. [PubMed: 31313527]
102. Nielsen JN, Carlton WW. 1995. Colobomatous microphthalmos in a New Zealand white rabbit, arising from a colony with suspected vitamin E deficiency. Lab Anim Sci. 1995;45(3):320–2. [PubMed: 7650909]
103. Nilsen NO. Eye malformations in chick embryos exposed to elevated incubation temperatures. Acta Ophthalmol (Copenh). 1968;46(3):322–8. [PubMed: 4974455]
104. Olivieri A, Stazi MA, Mastroiacovo P, et al. Study Group for Congenital Hypothyroidism. A population-based study on the frequency of additional congenital malformations in infants with congenital hypothyroidism: data from the Italian Registry for Congenital Hypothyroidism (1991–1998). J Clin Endocrinol Metab. 2002;87(2):557–62. [PubMed: 11836285]
105. Orefice F. Toxoplasmosis. In: Foster CS, Vitale AT, (eds). Diagnosis and treatment of uveitis. Second Edition. New Delhi; London: Jaypee Highlights, 2013:543–44.
106. Ozeki H, Shirai S. Developmental eye abnormalities in mouse fetuses induced by retinoic acid. Jpn J Ophthalmol 1998; 42:162–167. [PubMed: 9690892]
107. Parnell SE, Riley EP, Warren KR, Mitchell KT, Charness ME. The contributions of Dr. Kathleen K. Sulik to fetal alcohol spectrum disorders research and prevention. Alcohol. 2018;69:15–24. [PubMed: 29571046]
108. Patel A, Hayward JD, Tailor V, et al. The Oculome Panel Test: Next-Generation Sequencing to Diagnose a Diverse Range of Genetic Developmental Eye Disorders. Ophthalmology. 2019;126(6):888–907. [PubMed: 30653986]
109. Perez-Aytes A, Marin-Reina P, Boso V, et al. Mycophenolate mofetil embryopathy: A newly recognized teratogenic syndrome. Eur J Med Genet. 2017;60(1):16–21. [PubMed: 27639443]
110. Peters S, Andrews C, Sen S. Care of Infants Born to Women with Diabetes. Curr Diab Rep. 2020;20(8):39. [PubMed: 32699971]
111. Pisarska MD, Chan JL, Lawrenson K, Gonzalez TL, Wang ET. Genetics and Epigenetics of Infertility and Treatments on Outcomes. J Clin Endocrinol Metab. 2019;104(6):1871–1886. [PubMed: 30561694]
112. Pósfai E, Bánhidy F, Czeizel AE. Teratogenic effect of hydroxyethylrutoside, a flavonoid derivate drug--a population-based case-control study. J Matern Fetal Neonatal Med. 2014;27(11):1093–8. [PubMed: 24087950]
113. Quijano CE, Abalos E. Conservative management of symptomatic and/or complicated haemorrhoids in pregnancy and the puerperium. Cochrane Database Syst Rev. 2005; (3):CD004077. [PubMed: 16034920]
114. Reider M, Connaughton VP. Effects of low-dose embryonic thyroid disruption and rearing temperature on the development of the eye and retina in zebrafish. Birth Defects Res B Dev Reprod Toxicol. 2014;101(5):347–54. [PubMed: 25250784]

115. Riar AK, Narasimhan M, Rathinam ML, Henderson GI, Mahimainathan L. Ethanol induces cytostasis of cortical basal progenitors. J Biomed Sci. 2016;23:6. [PubMed: 26786850]
116. Roberts JM, Myatt L, Spong CY, et al. Vitamins C and E to prevent complications of pregnancy-associated hypertension. N Engl J Med. 2010;362(14):1282–1291. [PubMed: 20375405]
117. Rothova A. Ocular involvement in toxoplasmosis. Br J Ophthalmol. 1993;77(6):371–377. [PubMed: 8318486]
118. Rumbold AR, Maats FH, Crowther CA. Dietary intake of vitamin C and vitamin E and the development of hypertensive disorders of pregnancy. Eur J Obstet Gynecol Reprod Biol. 2005;119:67–71. [PubMed: 15734087]
119. Saitsu H, Ishibashi M, Nakano H, Shiota K. Spatial and temporal expression of folate-binding protein 1 (Fbp1) is closely associated with anterior neural tube closure in mice. Dev Dyn. 2003;226:112–117. [PubMed: 12508232]
120. Schmidt F, Eckardt K, Shakibaei M, Glander P, Stahlmann R. Effects of mycophenolic acid alone and in combination with its metabolite mycophenolic acid glucuronide on rat embryos in vitro. ArchToxicol. 2013; 87(2):361–70.
121. Schölin L, Mukherjee RAS, Aiton N, et al. UK FASD Research Collaboration. Fetal alcohol spectrum disorders: an overview of current evidence and activities in the UK. Arch Dis Child. 2021 :archdischild-2020–320435. Epub ahead of print..
122. Schoner K, Steinhard J, Figiel J, Rehder H. Severe facial clefts in acrofacial dysostosis: a consequence of prenatal exposure to mycophenolate mofetil? Obstet Gynecol. 2008;111(2 Pt 2):483–486. [PubMed: 18238994]
123. See AW, Clagett-Dame M. The temporal requirement for vitamin A in the developing eye: mechanism of action in optic fissure closure and new roles for the vitamin in regulating cell proliferation and adhesion in the embryonic retina. Dev Biol. 2009;325(1):94–105. [PubMed: 18955041]
124. Seeliger MW, Biesalski HK, Wissinger B, et al. Phenotype in retinal deficiency due to a hereditary defect in retinol binding protein synthesis. Invest Ophthalmol Vis Sci 1999;40(1):3–11. [PubMed: 9888420]
125. Seo GH, Kim TH, Chung JH. Antithyroid drugs and congenital malformations: A nationwide Korean cohort study. Ann Intern Med. 2018;168(6):405–413. [PubMed: 29357398]
126. Shah SP, Taylor AE, Sowden JC, et al. Surveillance of Eye Anomalies (SEA-UK) Special Interest Group. Anophthalmos, microphthalmos, and typical coloboma in the United Kingdom: a prospective study of incidence and risk. Invest Ophthalmol Vis Sci. 2011 Feb 1;52(1):558–64. [PubMed: 20574025]
127. Shaw GM, Carmichael SL, Laurent C, et al. National Birth Defects Prevention Study. Nutrient intakes in women and risks of anophthalmia and microphthalmia in their offspring. Birth Defects Res A Clin Mol Teratol. 2007;79(10):708–13. [PubMed: 17847120]
128. Sifontis NM, Coscia LA, Constantinescu S, et al. Pregnancy outcomes in solid organ trasplant recipients with exposure to mycophenolate mofetil or sirolimus. Transplantation. 2006; 82:1698–1702. [PubMed: 17198262]
129. Smithells RW. Defects and disabilities of thalidomide children. Br Med J. 1973; 1:269–272. [PubMed: 4631040]
130. Srour M, Caron V, Pearson T, et al. Gain-of-Function Mutations in RARB Cause Intellectual Disability with Progressive Motor Impairment. Hum Mutat. 2016;37(8):786–793. [PubMed: 27120018]
131. Srour M, Chitayat D, Caron V, et al. Recessive and dominant mutations in retinoic acid receptor beta in cases with microphthalmia and diaphragmatic hernia. Am J Hum Genet. 2013;93(4):765–772. [PubMed: 24075189]
132. Stromland K, Hellstrom A. Fetal alcohol syndrome: an ophthalmological and socioeducational prospective study. Pediatrics. 1996; 97:845–850. [PubMed: 8657525]
133. Stromland K, Miller MT. Thalidomide embryopathy: revisited 27 years later. Acta Ophthalmol (Copenh). 1993; 71:238–245. [PubMed: 8333272]
134. Stromland K, Pinazo-Duran MD. Ophthalmic involvement in the fetal alcohol syndrome: clinical and animal model studies. Alcohol. 2002; 37:2–8.

135. Suhardjo, Utomo PT, Agni AN. Clinical manifestations of ocular toxoplasmosis in Yogyakarta, Indonesia: a clinical review of 173 cases. Southeast Asian J Trop Med Public Health. 2003;34(2):291–7. [PubMed: 12971552]
136. Sutcliffe AG, Jones RB, Woodruff G. Eye malformations associated with treatment with carbamazepine during pregnancy. Ophthalmic Genet. 1998; 19:59–62. [PubMed: 9695086]
137. Tamma P. Toxoplasmosis. Pediatr Rev. 2007;28(12):470–1. [PubMed: 18055648]
138. Thomas BF, Compton DR, Martin BR. Characterization of the lipophilicity of natural and synthetic analogs of delta 9-tetrahydrocannabinol and its relationship to pharmacological potency. Pharmacol Exp Ther. 1990; 255(2):624–30.
139. Thompson B, Katsanis N, Apostolopoulos N, et al. Genetics and functions of the retinoic acid pathway, with special emphasis on the eye. Hum Genomics. 2019;13(1):61. [PubMed: 31796115]
140. Tinker SC, Gilboa SM, Moore CA, et al. National Birth Defects Prevention Study. Specific birth defects in pregnancies of women with diabetes: National Birth Defects Prevention Study, 1997–2011. Am J Obstet Gynecol. 2020;222(2):176.e1–176.e11. [PubMed: 31454511]
141. Tjeertes IFA, Bastiaans DET, van Ganzewinkel CJML, Zegers SHJ. Neonatal anemia and hydrops fetalis after maternal mycophenolate mofetil use. J Perinatol. 2007; 27:62–64. [PubMed: 17180133]
142. Tomson T, Battino D, Perucca E. Teratogenicity of antiepileptic drugs. Curr Opin Neurol. 2019;32(2):246–252. [PubMed: 30664067]
143. Valadares M, Pedroso ACLO, Santana A, et al. Ocular findings in infants with microcephaly caused by presumed congenital infection by zika virus in Sergipe. J Ophthalmol. 2020; 2020(34):1–5.
144. Vargesson N. Thalidomide-induced teratogenesis: history and mechanisms. Birth Defects Res C Embryo Today. 2015;105(2):140–56. [PubMed: 26043938]
145. Veroniki AA, Cogo E, Rios P, et al. Comparative safety of antiepileptic drugs during pregnancy: a systematic review and network meta-analysis of congenital malformations and prenatal outcomes. BMC Med. 2017;15:95. [PubMed: 28472982]
146. Vogt G, Puho E, Czeizel AE. A population-based case-control study of isolated ocular coloboma. Ophthalmic Epidemiol 2005; 12:191–197. [PubMed: 16036478]
147. Waller PH, Genstler DE, George CC. Multiple systemic and periocular malformations associated with the fetal hydantoin syndrome. Ann Ophthalmol. 1978; 10(11):1568–72. [PubMed: 103474]
148. Wangkheimayum S, Kumar S, Suri V. Effect of vitamin E on sP-selectin levels in pre-eclampsia. Indian J Clin Biochem. 2011;26:169–171. [PubMed: 22468044]
149. Warkany J, Schraffenberger E. Congenital malformations induced in rats by maternal vitamin A deficiency; defects of the eye. Arch Ophthal. 1946;35:150–69.
150. Weigele J, Bohnsack BL. Genetics underlying the interactions between neural crest cells and eye development. J Dev Biol. 2020;8(4):26.
151. Werler MM, Hayes C, Louik C, Shapiro S, Mitchell AA. Multivitamin supplementation and risk of birth defects. Am J Epidemiol 1999;150: 675–82. [PubMed: 10512421]
152. Wertelecki W, Chambers CD, Yevtushok L, et al. Chornobyl 30 years later: Radiation, pregnancies, and developmental anomalies in Rivne, Ukraine. Eur J Med Genet. 2017;60(1):2–11. [PubMed: 27697599]
153. Weston J, Bromley R, Jackson CF, et al. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database Syst Rev 2016; 11:CD010224.
154. Williams PM, Fletcher S. Health effects of prenatal radiation exposure. Am Fam Physician. 2010;82(5):488–93. [PubMed: 20822083]
155. Williamson KA, FitzPatrick DR. The genetic architecture of microphthalmia, anophthalmia and coloboma. Eur J Med Genet. 2014 Aug;57(8):369–80. [PubMed: 24859618]
156. Wilson JG, Roth CB, Warkany J. An analysis of the syndrome of malformations induced by maternal vitamin A deficiency: effects of restoration of vitamin A at various times during gestation. Am J Anat 1953; 92:189–217. [PubMed: 13030424]

157. Wilson RS, Smead W, Char F: DPH teratogenicity: ocular manifestations and related deformities. J Pediatr Ophthalmol Strabismus. 1978;15(3):137–40. [PubMed: 105119]

158. Wozniak JR, Riley EP, Charness ME. Clinical presentation, diagnosis, and management of fetal alcohol spectrum disorder. Lancet Neurol. 2019;18(8):760–770. [PubMed: 31160204]

159. Yoon KH, Fox SC, Dicipulo R, Lehmann OJ, Waskiewicz AJ. Ocular coloboma: Genetic variants reveal a dynamic model of eye development. Am J Med Genet C Semin Med Genet. 2020;184(3):590–610. [PubMed: 32852110]

160. Zheng Z, Chen L, Yang T, et al. Multiple pregnancies achieved with IVF/ICSI and risk of specific congenital malformations: a meta-analysis of cohort studies. Reprod Biomed Online. 2018;36(4):472–482. [PubMed: 29609768]

161. Zhou TAO, Sun D, Li X, et al. Prevalence and trends in gestational diabetes mellitus among women in the United States, 2006–2016. Diabetes. 2018;67(Supplement 1):121–OR.

162. Zin AA, Tsui I, Rossetto J, et al. Screening criteria for ophthalmic manifestations of congenital zika virus infection. JAMA Pediatr. 2017;171(9):847–854. [PubMed: 28715527]

Table:

Summary of reports implicating an environmental cause of uveal coloboma with major conclusions, reference and level of evidence.

Exposure	Type of Study	Main Conclusions	Level of Evidence	Study
Nutritional Deficiency/Excess				
Vitamin A and its Derivatives	Zebrafish embryos treated with RAR inhibitor AGN194310	Coloboma in 75% of treated embryos	IIa	Lupo et al 2011 [86][b]
	Case report of child born to vitamin A deficient mother	Child born with bilateral colobomas	IIb	Gaudet et al 2006 [43]
	Case report of two sisters with RBP4 mutation and 1/6th normal vitamin A levels	One of two sisters born with coloboma	IIb	Schoner et al 2008 [124]
	Case report and exome analysis of two siblings with RBP4 mutations	One of two siblings with RBP4 mutations born with coloboma	IIb	Cukras et al 2012 [23]
	Genetic analysis of 3 unrelated families with multiple members with MAC	Autosomal dominant RBP4 mutations found to drive MAC by disrupting vit A transport	IIb	Chou et al 2015 [19]
	Descriptive study of 83 mothers of 110 probands with coloboma	13% of mothers reported symptoms of vitamin A deficiency during third trimester of pregnancy	III	Hornby et al 2004 [64]
	Study of rats fed vitamin A deficient diet during pregnancy	Vit A deficiency resulted in babies born with coloboma, but vit A supplementation during days 10–15 of pregnancy significantly reduced number of colobomas seen	IIb	Wilson et al 1953 [156][b]
	Study fed pregnant rats vit A deficient diet	Colobomas observed in offspring	IIb	Warkany and Schraffenberger 1946 [149][b]
	Study supplemented vit A deficient pregnant rats on days 11.5–13.5 of pregnancy	Vitamin A supplementation on day 11.5 of pregnancy was 100% protective of coloboma while supplementation on days 12.5 and 13.5 led to colobomas in 17% and 100% of births respectively	IIa	See and Clagett-Dame 2009 [123][b]
	Study dosed rats with intraperitoneal injections of retinoic acid on day 7 of pregnancy	Congenital malformations observed in 95.5% of rats on day 18 with 36.4% displaying faulty closure of the embryonic fissure	IIa	Ozeki and Shirai 1998 [106][b]
Folate	Pregnant rats were given a diet deficient in folate	Colobomas were among the congenital malformations noted	IIb	Nelson et al 1955 [100][b]
	Rats fed folate deficient diet at various timepoints in pregnancy	Coloboma was associated with a folate deficiency during days 9–11 of pregnancy	IIa	Armstrong and Monie 1966 [8][b]
	Folate deficient diet given to mice in the weeks prior to pregnancy	Associated with anophthalmia and microphthalmia with no mention of coloboma	IIb	Maestro-de-las-Casa et al 2013 [88][b]
	Case control study compared 89 women who gave birth to offspring with anophthalmia or microphthalmia to 4143 controls with regard to nutrient intake during pregnancy	No association was found between either condition and folate supplementation or deficiency	III	Shaw et al 2007 [127]
Nickel Excess	Pregnant frogs exposed to various nickel chloride concentrations	Tadpoles were born with ocular malformations that included coloboma at and above concentrations of 4.5umol/L	IIa	Hauptman et al 1993 [57][b]

Exposure	Type of Study	Main Conclusions	Level of Evidence	Study
Vitamin E	Case report of a white rabbit born with left microphthalmia along with iris and choroidal coloboma	Rabbit was found to have vitamin E deficiency	IV	Nielson and Carlton 1995 [102][b]
Parental Factors				
Maternal Thyroid Disease	Case-control study comparing the mothers of 46 cases of coloboma with the general population	4.4% of coloboma mothers had hypothyroidism, which was markedly higher than the proportion of mothers with hypothyroidism in both population (0.4%) and matched patient (0.3%) controls	III	Vogt et al 2005 [146]
Maternal Diabetes	Prospective study of 49 children born to diabetic mothers	One coloboma was reported	IV	Koskenoja 1958 [75]
	Retrospective review of 156 of cases of children born to diabetic mothers	One coloboma was reported	IV	Grenet et al 1972 [50]
	Retrospective review of 31 cases of infants born to diabetic mothers where at least one malformation was observed	One coloboma was reported	III	Grix 1982 [51]
Assisted Reproductive Technologies	Analysis of 21 cohort studies comparing children born following IVF or intracytoplasmic sperm injection to those naturally conceived	No significant difference in ocular malformations found	IIa	Zheng et al 2018 [160]
	Prospective study of 47 children referred for ophthalmologic evaluation following IVF	Major ocular malformations occurred in 26% of children and included uveal coloboma with microphthalmos in two	III	Anteby et al 2001 [3]
Toxicity and Exposures				
Alcohol	Prospective observational study of 25 children with fetal alcohol syndrome referred for ophthalmologic evaluation	24 children had ocular malformations including one coloboma	III	Stromland Hellstrom 1996 [132]
	Mice given intraperitoneal alcohol injections on days 8, 9, or 10 of gestation	Iris coloboma was one of the most frequently observed malformations	IIb	Kronick 1976 [77][b]
Methimazole	Case report of a 4-year old girl whose mother took methimazole during the first two months of pregnancy	Child presented with choanal atresia, iris and retinal coloboma, and facial anomalies	IV	Hall 1997 [54]
	Case report of a child whose mother was taking methimazole throughout her pregnancy	Child born with a right iris coloboma among other abnormalities	IV	Aramaki et al 2005 [6]
	Review of 72 cases that reported congenital defects after prenatal exposure to either methimazole or carbimazole	2 cases of coloboma noted to be among the defects	IV	Cassina et al 2012 [16]
	Zebrafish embryos dosed with varying concentrations of methimazole	“Retinal disruptions” were among the malformations seen	IIa	Komoike et al 2013 [74][b]
Hydroxyethylrutoside (HER)	Case-control study comparing the mothers of 46 cases of coloboma with the general population	Mothers of cases of isolated ocular coloboma identified had higher HER usage than mothers of matched, population, and patient controls	III	Vogt et al 2005 [146]
	Case-control study of 22,843 cases with congenital abnormalities	4 colobomas and 1 case of microphthalmia were noted along with an association between unilateral ocular coloboma with	III	Pósfai et al 2014 [112]

Exposure	Type of Study	Main Conclusions	Level of Evidence	Study
		HER treatment during the second and/or third month of pregnancy		
Anticonvulsants	Case series of four patients with ocular malformations seen following first trimester exposure to carbamazepine	Malformations included one case of anophthalmia, two microphthalmia, and one coloboma	IV	Sutcliffe et al 1998 [136]
	Retrospective review of 77 cases of anophthalmia, microphthalmia, and coloboma	No instance of carbamazepine exposure found	III	Kroes et al 2002 [76]
	Case report of a child exposed to phenytoin, phenobarbital, and primidone	Child born with a constellation of malformations including inferior iris and choroidal coloboma	IV	Hampton and Krepostman 1981 [56]
Lysergic Acid Diethylamide (LSD)	Report of a child born to a mother who used LSD both before and during pregnancy	Child born with a wide variety of limb, malformations that included a small iris coloboma	IV	Apple and Bennett 1974 [5]
Radiation	Pregnant rats dosed were with radiation on day 9 of pregnancy and examined during postnatal week 5	Iris and choroidal coloboma, microphthalmia, and anophthalmia were observed	IIb	Kuno et al 1993 [79][b]
	Rates of malformations in areas of Ukraine affected by the Chernobyl disaster were compared to adjacent, less affected regions	Higher rates of microphthalmia were among the malformations noted	IIa	Wertelecki et al 2017 [152]
Saccharine	Pregnant rats fed varying concentrations and purities of saccharine	Microphthalmia, anophthalmia, and coloboma were commonly seen malformations and these malformations were attributed to contaminants of saccharine synthesis	IIb	Colson et al 1984 [21][b]
Mycophenolate Mofetil (MMF)	Report of child born following in-utero MMF exposure	Child born with coloboma among other malformations	IV	Ang et al 2008 [2]
	Report of child born following in-utero MMF exposure	Child born with coloboma among other malformations	IV	Schoner et al 2008 [122]
	Prospective study of 57 women who were exposed to MMF during pregnancy	8 fetuses/infants with major malformations, one of which was noted to have a coloboma	IV	Hoeltzenbein et al 2012 [62]
	Literature review of reported cases of MMF embryopathy	20% of cases of MMF embryopathy were noted to have chorioretinal coloboma	III	Perez-Aytes et al 2017 [109]
	Whole embryo rat cultures expsosed to mycophenolic 451 acid (MPA)	Exposure to MPA resulted in malformations including truncated torsos, deformed and fused brachial arches, and missing optic and otic vesicles	IIb	Schmidt et al 2013 [120][b]
Thiourea	Rats dosed for the first 14 days of development with a 0.2% aqueous solution of 2'-thiourea	Rats observed to have colobomas along with other abnormalities	IIb	Kernet al 1980 [72][b]
Hyperthermia	Chicks exposed to hyperthermia during development	Colobomas described among abnormalities	IIb	Nilsen 1968 [103][b]
	Review describing exposure of guinea pig embryos to hyperthermia	Colobomatous malformation noted among malformations seen	IV	Graham 2005 [49][b]
Synthetic Cannabinoids	Mice dosed with the synthetic cannabinoid CP-55 on day 8 of pregnancy	Craniofacial and ocular malformations noted in all drug-treated groups, which included microphthalmia, coloboma, and anophthalmia	IIa	Gilbert et al 2016 [45][b]
Thalidomide	Series of 20 children with ocular defects after thalidomide exposure	Colobomatous defects observed in five children	IV	Gilkes and Strode 1962 [47]

Exposure	Type of Study	Main Conclusions	Level of Evidence	Study
	Series of 12 children with defects resulting from thalidomide	Three cases of coloboma observed	IV	Cullen 1964 [24]
	Examination of 154 children with thalidomide-induced defects	Coloboma reported in 5 children	IV	Smithells 1973 [129]
	Prospective study of 86 Swedes with confirmed thalidomide embryopathy	Ocular findings noted in 46 individuals, 3 of which were coloboma	III	Stromland and Miller1993 [133]
Infection				
Cytomegalovirus (CMV)	Report of four patients born with congenital CMV and optic nerve abnormalities	Two patients born noted to have optic nerve colobomas	IV	60
	Retrospective analysis of 28 children with optic nerve hypoplasia and 10 children with coloboma	No exposure to CMV in any of the 10 coloboma cases	III	40
Toxoplasmosis	Original description of ocular toxoplasmosis	Infant descrived with hydrocephalous, microphthalmia, and a “colobomatous area” in the macula	IV	67
	Case of a 25 year old patient with congenital toxoplasmosis	Patient was noted to have a coloboma	IV	30
	Retrospective cohort study of 173 cases of ocular toxoplasmosis	Study reported no cases of coloboma	IIb	135
Zika Virus	Series of 29 infants with suspected congenital zika infection	Bilateral iris coloboma noted in one patient	IV	33
	Examination of two infants born with seropositive zika infection	One infant noted to have left temporal colobomatous defect	IV	31
	Case series of 112 infants born to mothers with PCR-confirmed zika infection	1 infant noted to have bilateral colobomas	IV	162
	Examination of 442 completed pregnancies in women with laboratory evidence of recent Zika infection	4 infants noted to have eye abnormalities including coloboma	IV	63
	Case report of a 3 day old baby with PCR confirmed zika infection	Infant noted to have severe bilateral colobomatous chorioretinal atrophy	IV	52
	Series of 62 patients with congenital microcephaly secondary to zika infection	Coloboma found in 9.7% of patients	IV	143
	Series of 12 eyes examined in patients with congenital ziika infection	41.7% of found to have coloboma	IV	34

Abbreviations: RAR, retinoic acid receptor; MAC, microphthalmia, anophthalmia, and coloboma.

[a] Using US Agency for Healthcare Research and Quality grading scale for evidence-based reports, level I being the highest rating while level IV is the lowest rating http://www.ahrq.gov/research/findings/evidence-based-reports/index.html

[b] Animal studies.