

Effects of Prenatal Alcohol Exposure on Ocular Development ^[1]

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Maternal consumption of alcohol (ethanol) can result in a range of alcohol-induced developmental defects. In [humans](#) ^[5], those collective [birth defects](#) ^[6] are called Fetal Alcohol Spectrum Disorders, with the most severe manifestation being [Fetal Alcohol Syndrome](#) ^[7] (FAS). FAS is defined by pre- and post-natal growth [retardation](#) ^[8], minor facial abnormalities, and deficiencies in the [central nervous system](#) ^[9] (CNS). The eye and ocular system development is particularly susceptible to the effects of prenatal alcohol exposure and can result in visual impairment or blindness.

The ocular defects of prenatal ethanol exposure include overall growth deficiencies, retinal defects, and optic nerve [hypoplasia](#) ^[10] (underdevelopment). Those defects, which are all part of the developing CNS, have been well catalogued in children clinically diagnosed with FAS. Developmental pathways for how those defects occur have been proposed and examined in [mouse](#) ^[11], [rat](#) ^[12], [chick](#) ^[13], and zebrafish model systems. The effects of ethanol on embryonic development are largely conserved across species, and animal models provide important information for how alcohol affects ocular development in children with FAS.

Externally, ocular defects are reflected primarily by smaller eyes, a distinct characteristic of ethanol-induced facial abnormalities. Those minor facial defects in the area of the eye consist of smaller eye openings bounded by upper and lower eyelid (palpebral fissures) and skin folds (epicanthal folds) at the corner of the eyes that stretch the upper lid taut to create a more almond shape. Other facial abnormalities can occur that affect the eyes, but are not considered criteria for diagnosis and can include: a drastic increase in the distance between eyes (telecanthus), drooping of the eyelids (blepharoptosis), and crossed or lazy eyes (strabismus).

Those minor facial abnormalities can result if prenatal ethanol exposure occurs after [gastrulation](#) ^[14], when the three embryonic [germ layers](#) ^[15] are set, but before [neurulation](#) ^[16], when the [neural tube](#) ^[17] is formed. In [humans](#) ^[5], that vulnerable developmental period corresponds to between three and six weeks after [fertilization](#) ^[18]. During that time, ethanol damages the cranial [neural crest cells](#) ^[19] which later differentiate into facial features. Prenatal ethanol exposure results in a marked decrease in cranial [neural crest](#) ^[20] cell proliferation and survival, primarily due to impaired migration and faulty programmed cell death ([apoptosis](#) ^[21]).

Prenatal ethanol exposure can also cause direct damage to the developing eyes, which are formed from three embryonic tissues: neuroectoderm, surface [ectoderm](#) ^[22] and [mesoderm](#) ^[23]. The human eye precursor population begins to differentiate three weeks after [fertilization](#) ^[18], when the [neural plate](#) ^[24] begins to form. The anterior portion of the [neural plate](#) ^[24] gives rise to neuroectoderm, tissues fated to form the CNS, including the retina of the eye. The retina is the interior cavity of the eye lined by photoreceptor cells which receive visual information and communicate with the brain through the optic nerve. About four weeks after [fertilization](#) ^[18], the neuroectoderm begins to interact with the surface [ectoderm](#) ^[22] to create tissues that will later give rise to the lens and cornea of the eye. The [mesoderm](#) ^[23] that surrounds the developing eye begins to interact in this developmental process as early as week five, giving rise to the iris and other associated muscles (uvea), protective sheath surrounding the eye (sclera), and eyelids. The effects of ethanol on that complex developmental process often result in microphthalmia and optic nerve [hypoplasia](#) ^[10] in individuals with FAS.

Upwards of 90 percent of children diagnosed with FAS are affected by microphthalmia, abnormally small eyes, due to the teratogenic effect of ethanol on normal embryonic development. In [chick](#) ^[13] and zebrafish embryos, microphthalmia occurs when prenatal ethanol exposure coincides with retinal neurogenesis. As the optic cup that forms the retina is the first ocular feature to appear, a smaller retina decreases the size of the eye. Ethanol exposure during the development of the optic cup results in an overall decrease in the [differentiation](#) ^[25] of retinal cells. Ethanol affects ten distinct layers of retinal cells in a dose-dependent manner. That can result in much smaller [retinas](#) ^[26] that lack the well-organized cellular structure characteristic of non-affected [retinas](#) ^[26]. The [reduction](#) ^[27] in retinal cells is most pronounced in the layer of photoreceptors lining the eye, a defect that can result in visual impairment or blindness.

Prenatal ethanol exposure can cause optic nerve [hypoplasia](#) ^[10], one of the leading causes of developmental blindness in children. Hypoplasia occurs when fewer optic nerve axons are developed and maintained, as a result of premature [apoptosis](#) ^[21] or as a decrease in the number of glial support cells. A decrease in glial cell formation and subsequent myelination occur as a result of damages to the neural stem cell progenitor pools, such as [radial glia](#) ^[28], that give rise to neurons and [glia](#) ^[29] in the CNS. Glia are essential for the myelination of neuronal axons that compose the optic nerve, so if fewer [glia](#) ^[29] are present during development, then fewer functional optic nerve axons result. Additionally, the myelin sheaths surrounding the optic nerves

in ethanol-affected individuals are generally thinner and exhibit disorganization. Optic nerve [hypoplasia](#)^[10] can result in visual impairment and occurs in a dose-dependent manner, whereby a higher and more lasting exposure to ethanol results in greater damage to the optic nerve.

That dose-dependency is a common factor to all ethanol-induced defects. During ocular development, a greater exposure to ethanol will result in more severe facial abnormalities, microphthalmic growth defects, and optic nerve [hypoplasia](#)^[10]. Those defects range from mild facial abnormalities to severe and lasting damage to the visual system that can compromise vision and lead to blindness. Understanding the developmental mechanisms behind those defects could impact future research into FAS, which may lead to a better understanding of how to develop treatment plans for those prenatally exposed to alcohol.

Sources

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Maternal consumption of alcohol (ethanol) can result in a range of alcohol-induced developmental defects. In humans, those collective birth defects are called Fetal Alcohol Spectrum Disorders, with the most severe manifestation being Fetal Alcohol Syndrome (FAS). FAS is defined by pre- and post-natal growth retardation, minor facial abnormalities, and deficiencies in the central nervous system (CNS). The eye and ocular system development is particularly susceptible to the effects of prenatal alcohol exposure and can result in visual impairment or blindness.

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