Developmental Timeline of Alcohol-Induced Birth Defects [1]

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Maternal consumption of alcohol (ethanol) during pregnancy [5] can result in a continuum of embryonic developmental abnormalities that vary depending on the severity, duration, and frequency of exposure of ethanol during gestation [6]. Alcohol is a teratogen, an environmental agent that impacts the normal development of an embryo or fetus [7]. In addition to dose-related concerns, factors such as maternal genetics and metabolism and the timing of alcohol exposure during prenatal development also impact alcohol-related birth defects [8].

Fetal Alcohol Syndrome [9] (FAS) is the most severe collection of alcohol-related birth defects [8], and is defined by pre- and post-natal growth retardation [10], minor facial abnormalities, and deficiencies in the central nervous system [11] (CNS). The effects of alcohol on prenatal development can include much more than those defining criteria, however, and prenatal exposure to alcohol can potentially impact normal development at almost any point in the pregnancy [5], from embryonic through fetal development.

Prenatal development has into two stages, the embryonic stage that comprises the first eight weeks of development after fertilization [12], and the fetal stage that encompasses the remainder of development. The embryonic stage is the period when body plans are laid out, and the precursors of what will become organ systems are determined. Alcohol introduced at this stage can have significant repercussions depending on the population of cells negatively affected. Those developmental deviations can result in a range of birth defects [9] or may completely arrest the pregnancy [5] if malformations are particularly severe. During the fetal stage, prenatal alcohol exposure still has the potential to negatively impact development, but much less than the massive developmental defects that can result from exposure during the embryonic stage.

In the first two weeks following fertilization [12], excessive alcohol consumption does not generally have a negative effect on the zygote [13] and emerging blastocyst [14] (pre-embryo). Maternal consumption of alcohol during this time can prevent proper implantation [15] of the blastocyst [14] in the uterus [16], resulting in an increased rate of resorption or early termination of the pregnancy [5], generally before a woman realizes she is pregnant. The potential for the cells in the blastocyst [14] to become any cell lineage [17] in the body generally confers protection against the negative effects that alcohol has on specific cellular populations.

It is in the third week after fertilization [12] that specific alcohol-induced birth defects [8] begin to affect the developing embryo. At this point in the developmental timeline, gastrulation [18] commences and the three embryonic germ layers [19] (ectoderm [20], mesoderm [21], and endoderm [22]) are set. Between this point and the sixth week after fertilization [19], when neurulation [23] occurs, the cranial neural crest [24] cell population is vulnerable to alcohol-induced damages. The cranial neural crest cells [25] compose the frontal process of the developing embryo, which interacts with the ectoderm [20] to differentiate into facial features. Damage to this cellular progenitor pool can result in the minor midline facial abnormalities characteristic of FAS.

Precursor cells that give rise to the heart also begin to differentiate shortly after the third week and by the fourth week of development, the embryonic heart is already beating. During this rapid period of cardiac development, alcohol can impede the proliferation, migration, and specification of cardiac progenitor cells by prompting either a deficient or toxic levels of retinol (vitamin A) in the developing embryo. Defects that result from those impediments can include atrial and ventricular abnormalities, issues with valve formation, and a potential increase in the risk of heart disease later in adulthood.

The neural plate [26] forms in the third week, the anterior portion of which gives rise to neuroectoderm, tissues fated to form the tissues of the central nervous system [11] (CNS). From this point through the third trimester [27], the cellular progenitor pools, called radial glia [28], that will give rise to the CNS become vulnerable to the effects of alcohol. The radial glia [28] signals the creation and migration of neurons and their support cells (glia [29]) during development. Damage to this cellular pool can result in morphological abnormalities and an overall reduction [30] in white matter [31] within the brain. Alcohol also impacts the mechanisms and signaling pathways responsible for the creation of those brain cells, impeding cellular proliferation, differentiation [32], and survival.

During the third week of gestation [6], ocular development begins and tissues of the eye are the first component of the central nervous system [11] compromised by the prenatal introduction of alcohol. During this time and continuing forward, the retina becomes vulnerable to the effects of alcohol. At about four weeks after fertilization [12], the neuroectoderm begins to interact with the surface ectoderm [20] to create tissues that later give rise to the lens and cornea of the eye. In the fifth week following fertilization [19], the mesoderm [21] surrounding the developing eye begins to give rise to the uvea (iris and other associated
abnormalities that vary depending on the severity, duration, and frequency of exposure of ethanol during gestation. Alcohol is a factor in a wide range of birth defects, including microcephaly, ventriculomegaly, and cardiac malformations. Maternal consumption of alcohol (ethanol) during pregnancy can result in a continuum of embryonic developmental abnormalities that vary depending on the severity, duration, and frequency of exposure to ethanol during gestation. Alcohol is a factor in a wide range of birth defects, including microcephaly, ventriculomegaly, and cardiac malformations.

Sources

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