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 postnatal 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 [8] 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 [8], 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 [12], when neurulation [23] occurs, the cranial neural crest [24] cell population is vulnerable to alcohol-induced damages. The cranial neural crest cells [22] compose the frontonasal 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 retardation [25], and may completely arrest the pregnancy [5] if malformations are particularly severe. During this time, the neuroectoderm begins to interact with 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
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The cerebellum [35] is one of the last structures of the brain to differentiate during development, with the majority of structures in the
brain having begun development earlier. Most cellular proliferation, migration, and synaptic regulation [36] in the cerebellum [35]
occurs in the third trimester [27], 24 weeks after fertilization [12] through birth. This period of intense neuronal creation, organization
[37] and connectivity is called the brain growth spurt [38]. While the radial glia [28] progenitor pool has already been established by
this point in time, alcohol can still impact neural migration and synaptogenesis [39].

The fetus [7] is not as sensitive to the effects of alcohol as is the embryo, and in the third trimester [27] the fetus [7] begins to self-
regulate and redirect resources to cope with environmental damages. Self-regulation [36] is observed in the pre-natal growth
deficiencies that accompany FAS, which fall into two broad categories, symmetric or asymmetric intrauterine growth restrictions.
If alcohol impacts cellular proliferation in the first and second trimester [27], or consistently throughout the entire pregnancy [5],
then the growth deficiencies will be symmetric and observed across all parts of the developing fetus [7]. Asymmetric growth
restrictions, which result in a normal-sized head but smaller than normal abdominal cavity, may result in the third semester. The
head is a normal size because in the third trimester [27] the fetus [7] can redistribute cardiac resources to the command centers of the
body, like the brain and heart, at the expense of other less vital processes like digestion.

There is no point during development when prenatal alcohol exposure lacks consequences, the occurrence of the more severe
birth defects [8] correlates with exposure to alcohol in the embryonic stage rather than the fetal stage. FAS and related alcohol-
induced birth defects [8] are an example of what can happen when a mother heavily imbibles alcohol during the course of the
pregnancy [9]. In the United States, the Surgeons General caution women against drinking while pregnant and require warnings
be displayed on all alcoholic products.

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