**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 [6], 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 [13], when neurulation [23] occurs, the cranial neural crest [24] cell population is vulnerable to alcohol-induced damages. The cranial neural crest cells [24] 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 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, the neuroectoderm begins to interact with the surface ectoderm to create tissues that later give rise to the lens and cornea of the eye. In the fifth week following fertilization, the mesoderm surrounding the developing eye begins to give rise to the uvea (iris and other associated muscles), sclera (protective sheath surrounding the eye) and eyelids. The most common defects, microphthalmia and optic nerve hypoplasia, arise when prenatal alcohol exposure compromises this developmental cycle.

Specific damage to the brain can continue in the sixth and seventh week following fertilization, after the brain has begun to divide into vesicles. At that point, the corpus callosum, a midline structure responsible for the communication between the left and right hemispheres of the brain, becomes vulnerable to alcohol. Prenatal alcohol exposure can result in the underdevelopment or complete agenesis of that structure, which is composed primarily of myelinated axons, and is therefore extremely vulnerable to ethanol’s impact on radial glia progenitor pools.

The eighth week after fertilization is the end of the embryonic stage and the beginning of the fetal stage of pregnancy. Prenatal alcohol exposure still has the potential to negatively impact normal development, but as the majority of organ systems have been determined by this point in time, organ-specific birth defects are not normally expected. The developing central nervous system remains vulnerable to the prenatal exposure of alcohol, particularly in the formation of the cerebellum, and the fetus remains vulnerable in terms of prenatal growth restrictions.

The cerebellum 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 in the cerebellum occur in the third trimester, 24 weeks after fertilization through birth. This period of intense neuronal creation, organization and connectivity is called the brain growth spurt. While the radial glia progenitor pool has already been established by this point in time, alcohol can still impact neural migration and synaptogenesis.

The fetus is not as sensitive to the effects of alcohol as is the embryo, and in the third trimester the fetus begins to self-regulate and redirect resources to cope with environmental damages. Self-regulation 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, or consistently throughout the entire pregnancy, then the growth deficiencies will be symmetric and observed across all parts of the developing fetus. 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 the fetus 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 correlates with exposure to alcohol in the embryonic stage rather than the fetal stage. FAS and related alcohol-induced birth defects are an example of what can happen when a mother heavily imbibes alcohol during the course of the pregnancy. In the United States, the Surgeons General caution women against drinking while pregnant and require warnings be displayed on all alcoholic products.

Sources

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