**Effects of Prenatal Alcohol Exposure on Cardiac Development** [1]

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A variety of developmental defects occur as a result of prenatal exposure to alcohol (ethanol) *in utero*. In *humans* [5], those defects are collectively classified as Fetal Alcohol Spectrum Disorders, with *Fetal Alcohol Syndrome* [6] (FAS) representing the more severe defects. FAS is defined by pre- and post-natal growth retardation [7], minor facial abnormalities, and deficiencies in the central nervous system [8] (CNS). In addition to those defects, prenatal exposure to alcohol impacts cardiogenesis, the developmental stage of heart formation.

Prenatal exposure to alcohol induces a variety of abnormalities in the developing heart which include: atrial and ventricular abnormalities, issues with valve formation, and a potential increase in the risk of heart disease later in adulthood. The specific defects that have been observed from prenatal alcohol exposure include defects to the atrioventricular valves (tricuspid and mitral) that allow blood to flow backward into the atria; ventricular septal defects, commonly known as a “hole in the heart” between the left and right ventricles; enlargement of the left ventricle, the primary pumping chamber in the heart; and an increased risk of developing heart disease later in adult life.

Severe heart defects can be detrimental to the developing embryo and fetus [9] as the heart is the first organ to begin functioning *in utero*. The precursor cells that give rise to the heart begin to differentiate in the third week of gestation [10], following gastrulation [11]. After gastrulation [11], the three embryonic germ layers (ectoderm [12], endoderm [13], and mesoderm [15]) are formed, and the body plan of the organism begins to be determined. From that point forward in embryonic and fetal development, the cellular populations that interact with and give rise to the heart are vulnerable to ethanol. The primordial heart begins to beat during the fourth week of gestation [10] and it precedes the formation of the circulatory system.

The embryonic heart begins developing as two symmetrical tubes of mesoderm [15] that fuse to form a single heart tube at the end of the third week after fertilization [16]. That tubular structure is connected to vitelline veins which will later become the aorta and pulmonary artery. By the fourth week of fertilization [16] the heart begins to beat, and the heart tube undergoes rapid growth until it begins to bulge and fold in a complex process that begins to form the four chambers of the heart.

Several potential mechanisms have been proposed in order to describe how ethanol affects cardiac development and produces those defects. Those mechanisms primarily examine how Vitamin A (retinol) and its derivatives interact with cardiac cells. When retinol is metabolized in the body it forms retinoic acid, a compound that is a critical to early cardiac development. The metabolism of ethanol in the human body produces acetaldehyde as a byproduct and the presence of excess acetaldehyde in the body inhibits the formation of retinoic acid from retinol. Any deviation from the normal amount of retinoic acid in the mother’s body can have...
devastating effects on the embryo's developing heart.

Retinoic acid aids in the specification of cardiac progenitor cells in the developing heart. In particular, retinoic acid determines which cardiac progenitor cells become part of the inflow or outflow portions of the posterior heart tube. Retinoic acid also aids in the proliferation and migration of cardiac progenitor cells. Decreasing the amount of retinoic acid can impact the proliferation and specification of cardiac precursor cells, while an excess of retinoic acid can also impact normal migration and differentiation [17] of those cellular populations. The processes of proliferation, specification, migration, and differentiation [17] are essential for the regular formation of the heart. The cardiac defects, both atrial and septal, observed in individuals affected by prenatal ethanol exposure are often similar to the defects associated with retinol toxicity or deficiency.

Ethanol-induced cardiac abnormalities are serious birth defects [18], and if particularly severe, they have the potential to arrest a pregnancy [19]. Clinical trials examining potential therapeutic solutions to those life threatening birth defects [18] have indicated that folic acid [20] (folate) has the potential to counteract cardiac birth defects [18] if taken from conception [21] and throughout the pregnancy [19]. Although the dosage of folic acid [20] far exceeds the daily value currently recommended to avoid neural tube [22] defects, that treatment represents a promising venue of research to further understand the complex mechanisms of ethanol-induced birth defects [18].

Sources


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Subject
