

## Review

# Impact of Fetal Alcohol Exposure on Body Systems: A Systematic Review

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Review of published manuscripts on fetal alcohol exposure on several body systems. Method: Articles in this review were found online using databases such as Medline, Medline Complete, PubMed, and Health Source: Nursing/Academic Edition. The following terms were searched: fetal alcohol spectrum disorders, fetal alcohol syndrome, prenatal alcohol exposure, and alcohol related birth defects. Results: Thirteen articles were gathered, five original investigations and eight reviews. This review identified several abnormalities in the body systems discussed and their associations to fetal alcohol syndrome. Conclusions: Evidence shows that the brain was the most severely impacted organ of the body systems discussed. However, prenatal alcohol exposure

causes several abnormalities within the heart, kidney, liver, gastrointestinal tract, and the endocrine systems. In addition, preventative measures need to be taken by mothers during pregnancy.

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**Key words:** fetal alcohol spectrum disorders; fetal alcohol syndrome; prenatal alcohol exposure; alcohol-related birth defects

## Introduction

Fetal alcohol syndrome (FAS) is a condition that results from moderate to excessive alcohol exposure during the mother's pregnancy. The symptoms can present themselves *in utero* through early childhood. There are a wide variety of developmental defects that result from alcohol exposure, including brain abnormalities, central nervous system dysfunctions, and growth deficiencies of developing organs and body systems. These adverse effects on the developing fetus are known collectively as fetal alcohol spectrum disorders (FASD). FAS causes dysfunctions in learning, emotion, cognition, motor performance, and can lead to behavioral as well as social problems. For diagnoses with FAS, an individual must meet the following criteria: growth impairments with neuro-cognitive delays (mental retardation, developmental delays, or attention deficit hyperactivity disorder-ADHD), at least two facial features (thin vermilion, short palpebral fissures, or smooth philtrum), and prenatal alcohol exposure. These individuals have significant cognitive and behavioral impairments that impact their daily lives (Hoyme et al., 2005; Klingenberg et al., 2010). There is no treatment to reverse alcohol-induced damage to the central nervous system (CNS). FAS is not a genetic disorder, and therefore earlier intervention on the fetus *in utero* in alcohol abusing mothers is key in preventing the severity of FAS (Young

et al., 2014). Although the negative consequences of drinking during pregnancy and the effects of fetal alcohol syndrome are well known, pregnant women continue to consume alcohol during pregnancy. Of the four million annual pregnancies in the United States, ~40% of women drink alcohol during pregnancy, and 3–5% of women drink heavily throughout pregnancy (Floyd and Sidhu, 2004).

This article used a systematic review of published literature on birth defects of the different organ systems, including the brain, heart, kidney, liver, gastrointestinal tract, and endocrine system, and their association to FAS. Although recent reviews have shown the association between FAS and central nervous system abnormalities, neuropsychiatric impairments, and congenital heart defects, no reviews have covered the combination of all the different organ systems with their association on FAS and birth defects.

## BRAIN

Of the various organ systems affected by FAS, the brain is the most severely impacted. Until more recently, in order to study the structural brain damage in young children with prenatal alcohol exposure, autopsy studies had to be performed, limiting the subjects to children who were so severely affected, that they died during infancy (Jones and Smith, 1973; Clarren et al., 1978; Peiffer et al., 1979). More recently, magnetic resonance imaging (MRI), a noninvasive technique, has made studying the brain, brain development, and brain abnormalities possible by allowing for *in vivo* measurements (Lebel et al., 2011). MRI allows for larger studies to take place, including individuals who may be less severely affected than others. The aim of the MRI studies was to examine brain structures and regions, and reveal the nature of brain abnormalities associated with prenatal alcohol exposure. A very typical finding was that individuals who were exposed to alcohol *in utero*

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were observed to have small brain volumes, including smaller volumes of white and gray matter within the brain (Mattson et al., 1992, 1994; Archibald et al., 2001; Sowell et al., 2001; Lebel et al., 2008; Bjorkquist et al., 2010; Nardelli et al., 2011; Roussotte et al., 2011). More subtle abnormalities need to be observed to further understand the effects of prenatal alcohol exposure itself, and its relationship with brain structure.

The most common findings include reduced brain volume and malformations of the corpus callosum (Jones and Smith, 1973; Clarren et al., 1978; Peiffer et al., 1979). Although not as common, there are also effects to the vasculature development within the brain. Alcohol negatively impacts vasculogenesis and angiogenesis in the brain. These events establish the formation of the vascular network in the embryo, responsible for providing crucial oxygen and nutrients for the growth of neural cells. Vascular endothelial growth factor (VEGF) A is a powerful regulator of blood vessel formation and a single inactivation of one of its alleles results in the death of an embryo (Carmeliet et al., 1996; Ferrara et al., 1996). Exposure to alcohol prenatally affects the expression of several genes in the VEGF family. A case study was conducted with eighteen human fetal brains that were used to compare the cortical vascular network to human fetuses with FAS, in different developmental stages human fetal brains that were free of any macroscopical or microscopical abnormalities. The other eleven brains were obtained as FAS specimens after spontaneous death *in utero*. The results showed that alcohol exposure during angiogenesis affected the generation of collaterals, which are side branches of blood vessels. A loss of radial organization in the microvascular network was also observed, specifically from week 30 of gestation to week 38 (Jegou et al., 2012).

One of the most crucial regional abnormalities observed within a brain prenatally exposed to alcohol, is the corpus callosum. MRI imagining has shown complete and partial agenesis, failure of the organ to fully develop, as well as callosal thinning (Jones and Smith 1973; Clarren et al., 1978; Peiffer et al., 1979; Kinney et al., 1980; Wisniewski et al., 1983; Ronen and Andrews 1991; Couller et al., 1993). The most severely affected region within the corpus callosum appeared to be the splenium, which functions to connect and communicate the parietal and temporal lobes of the brain, linking visual areas (Lebel et al., 2011). This region was also displaced inferiorly and anteriorly. Also, the more severe the displacement was in the anterior direction, the more negatively it affected the verbal learning ability (Sowell et al., 2001a).

Neuropsychological studies have established that almost every cognitive domain that has been evaluated is affected by prenatal alcohol exposure and the effects lead to FAS (Nunez et al., 2011). The most common effect of antenatal alcohol exposure is the dysfunction of the central nervous system (Mattson et al., 2011; Riley et al., 2011). Alcohol

exposure causes dysfunctions in learning, emotion, cognition, motor performance, perception, and behavioral difficulties (Kelly et al., 2000; Riley and McGee, 2005; Mattson et al., 2011). One way to examine antenatal neurobehavioral function is through habituation response of the fetus (Leader, 1995; Hepper and Leader, 1996; Krasnegor et al., 1998; Dirix et al., 2009). Normal habituation is a learning process that requires intact and integrated CNS (Thompson and Spencer, 1966; Jeffrey and Cohen, 1971). It is the decline of physiological response to a frequently repeated stimulus. A prospective cohort study examined habituation in the human fetus in relation to moderate and high levels of maternal alcohol consumption exposure, and compared the effects between mothers who binge drink with those who drank more moderately. A series of stimuli was presented to the fetus by the stimulator until there was no fetal response observed on five consecutive stimuli. The fetus responded if it made observable movement of its arms, head, or upper body. Results showed that heavy binge drinking, which was self reported, increased the number of trials required to habituate, and decreased the functional stability of the brain. It also affected the fundamental brain function (Hepper et al., 2012).

Researchers also reported that there are differences in volume and thickness within the cerebral cortex (Archibald et al., 2001). The frontal lobes are affected, which leads to impairments in attention and working memory. There were decreased volumes predominantly in the left hemisphere of the ventral frontal lobe, but increased cortical thickness in the right ventral frontal lobe (Sowell et al., 2001b). The parietal lobes, which are associated with visuospatial functions and attention, are also affected. Young children with FAS have observable white matter reduction with bilateral increased parietal lobe thickness (Sowell et al., 2008b). This suggests that there is an overwhelming amount of gray matter, either because the white matter is less myelinated or there is an incomplete pruning of neurons (Sowell et al., 2004; Toga et al., 2006). The temporal lobes, which are associated with formation of memories, auditory processing, and language comprehension, are impacted the same way as the parietal lobes (Archibald et al., 2001). Research has indicated that there is significantly less activation in the left medial and posterior temporal regions in individuals with FAS (Sowell et al., 2008b).

The subcortical region, which is just below the cerebral cortex, is also heavily impaired. Structures such as the basal nuclei, and more specifically the caudate nucleus within the basal nuclei, are smaller (Mattson et al., 1996; Archibald et al., 2001). This leads to insufficient motor control, learning abilities, and behavioral inhibition (Cortese et al., 2006). The diencephalon, which includes the thalamus and hypothalamus, also show reduced volumes (Mattson et al., 1996). The only subcortical structure that seemed to be spared was the hippocampus (Archibald et al., 2001). The cerebellum, which is associated with

executive functions, attention, and movement, also showed abnormalities (Strick et al., 2009). Specifically in the vermis, there were size and location abnormalities in individuals with FAS. The anterior portion of the vermis appeared to shift inferiorly and posteriorly, leading to insufficient verbal learning performances (O'Hare et al., 2005).

Along with the brain, the spinal cord is also impacted by FAS. In a recent prospective cohort study (Smith et al., 2014), researchers compared the children of 101 pregnant women who were considered nondrinkers during pregnancy, and women who reported alcohol consumption during pregnancy. It was found that functional CNS abnormalities were found in 44% of the exposed children (Streissguth et al., 2004), and that ethanol persists in the amniotic fluid which adversely affects the neural crest development. Induction, proliferation, apoptosis, migration, and differentiation processes are all negatively impacted (Smith et al., 2014). In the early head fold of the neural crest, exposure to ethanol instigates the mobilization of intracellular calcium stores. This then activates the calcium/calmodulin-dependent protein kinase II (CaMKII) enzyme which phosphorylates and destabilizes active  $\beta$ -catenin. This in turn causes apoptosis within the neural crest and impairments in the neural crest migration. This leads to cytoskeletal rearrangements that destabilize focal adhesions, impairing interactions between cells (Flentke et al., 2014a). Of these CNS impairments, language problems and attention deficits were most common (Smith et al., 2014).

#### HEART

Although extensive research has been done on the effect of maternal alcohol consumption on congenital heart defects (CHD), conclusions are still inconsistent regarding this association, including the CHD subtypes. Congenital heart defects are structural anomalies of the heart that are present at birth and can disturb the normal blood flow through the heart or surrounding vessels. It is the most prevalent congenital abnormality accounting for thirty percent of major congenital anomalies (Dolk et al., 2011). A recent meta-analysis of 20 studies investigated the association between prenatal alcohol exposure and the risks of CHD and its subtypes (Henderson et al., 2007a). The analysis concluded that prenatal alcohol exposure was only significantly associated with the conotruncal defects (CTDs) subtypes. Conotruncal defects are malformations in the outflow tract of the heart from developmental damage to the branchial arch and arteries. In addition, prenatal alcohol exposure was significantly associated with d-transposition of the great arteries (dTGA), a subtype of CTDs, which causes the aorta and the pulmonary arteries that carry blood away from the heart to become reversed. Consequently, these structures are connected to the wrong chambers, where the aorta is connected to the right ventricle and the pulmonary arteries are connected to the left

ventricle, leading oxygenated blood to flow into the lungs and deoxygenated blood to flow into the body. dTGA causes a lack of oxygen throughout the body, resulting in severe damage to the muscles of the heart. Statistically, mothers who drink while pregnant were found 1.64 times more likely to have a newborn with dTGA. Overall, the evidence shows that both prenatal heavy drinking and binge drinking were strongly associated with the overall congenital heart defects risk (Yang et al., 2015).

#### KIDNEY, LIVER, AND GASTROINTESTINAL

The association between FASD and birth defects of the kidney, liver, and gastrointestinal tract are inconclusive. A recent systematic review article investigated the birth defects among these organ systems in subjects with FASD. They found nonspecific abnormalities associated with FASD in the three organ systems. Kidney anomalies consisted of hypoplasia, which is the underdevelopment of the organ, agenesis, which is when the kidney is absent, and hydronephrosis, when the kidney swells due to abnormal drainage. Liver showed the abnormality of hyperbilirubinemia, which is an over-production of the pigment bilirubin in the blood, causing newborns to have jaundice (Hofer and Burd, 2008). Lastly, *in utero* neurotoxicity of alcohol can cause an enteric neuropathy that presents itself in infancy as chronic intestinal pseudo-obstruction. This is a condition where the intestines are unable to contract to push food, stool, or air through the tract. This causes abdominal pain and constipation (Uc et al., 1997).

#### ENDOCRINE SYSTEM

Many studies have been performed to identify the long-term neurodevelopmental effects in children who were prenatally exposed to alcohol. A recent case study aimed to identify the effects of prenatal alcohol exposure on the limbic-hypothalamic-pituitary-adrenal axis. The main focus of the study was to examine the association of prenatal alcohol exposure and cortisol response. It also determined whether or not cortisol response was moderated by the sex of the child or testosterone levels (Ouellet-Morin et al., 2010). Cortisol is the stress hormone that regulates the changes that occur in the body in response to stress such as immune responses, and blood sugar levels (Goodyear et al., 2001). The results of this study indicated that prenatal alcohol exposure was associated with disrupted cortisol activity. This study also showed that there was an altered sensitivity to the inhibitory effects of testosterone in male participants (Ouellet-Morin et al., 2010).

Another case study was performed in 2010 to study the effects of prenatal alcohol exposure on the insulin-like growth factor (IGF) and leptin during infancy, considering that exposed children may exhibit pre- and postnatal growth retardation. Pre- and postnatal growth retardation is one of the main characteristics of fetal alcohol syndrome (Stratton et al., 1996). Researchers wanted to study the

effects of alcohol exposure during pregnancy on insulin-like growth factors and insulin-like growth factor binding-proteins concentrations. Analysis of IGF-II levels revealed several noteworthy points. Serum IGF-II levels increased with age in both groups, but was significantly higher in the ethanol-exposed group, as compared to the unexposed group. Fluctuation of IGF-II levels in the exposed groups was also significantly different than the unexposed group. Initially the exposed group had lower levels, but overtime their levels increased. In addition, serum IGF-I levels were significantly higher in the ethanol-exposed group, compared to the unexposed group. Lastly, leptin levels were significantly lower in the exposed group. Although this study only showed differences in the levels of IGF-I, IGF-II, and leptin between the exposed and unexposed groups, it suggested that IGF-II concentrations can now be a marker to prenatal alcohol exposure (Aros et al., 2010).

## Method

Articles in this review were found online using databases such as Medline, Medline Complete, PubMed, and Health Source: Nursing/Academic Edition. The search within these databases had the following limitations: human population, publication date between 2009 and 2016, and that were written in English. Keywords were also searched within these databases which include but not limited to; “fetal alcohol spectrum disorders,” OR “fetal alcohol syndrome,” OR “prenatal alcohol exposure,” OR “alcohol-related birth defects.” Any articles that were found to have studied long term effects of FAS in human adolescents or adulthood were excluded.

Thirteen articles were gathered on fetal alcohol syndrome and its association to the organ systems. Of these articles, five were original investigations and eight were reviews. All these articles were gathered by searching computer-based databases, and by cross-referencing the references of previously obtained articles.

## Discussion

In this review, we identified distinctive abnormalities associated with FAS in multiple organ systems. Evidence shows that the most severely impacted organ with nearly every aspect of it being negatively affected by prenatal alcohol exposure is the brain. There were several abnormalities also shown within the heart, kidney, liver, gastrointestinal tract, and endocrine systems. The ability to identify the abnormalities of these organ systems are key in providing the essential knowledge that is needed for possible prevention of FAS.

It has been found that prenatal alcohol exposure is recurrent in families and over multiple generations. Most of the mothers discussed within this review were considered to be nonsmokers, with no recreational drug abuse or medication use. They were classified into moderate,

heavy, or binge drinking groups. One study categorized these groups in grams where one standardized drink was equivalent to 12 g. The moderate group was considered to have  $<24 \text{ g day}^{-1}$  and heavy drinkers were classified in having  $>24 \text{ g day}^{-1}$ . Binge drinking was considered to have 48 g or more on one occasion (Yang et al., 2015). Another study categorized the groups in units of alcohol consumed. One unit was equivalent to 10 ml of ethanol which is the same as 50 ml of wine, a half pint of beer, or 25 ml of liquor. The moderate group was considered to have 5–10 U per week. The heavy drinkers were considered to have over 20 U per week. The binge drinkers were considered to drink moderately or heavy, but on two or three consecutive days (Hepper et al., 2012). Both heavy and binge drinking were found to exert an effect on the stability of organ functions. They both proved to have consequences for the individuals starting *in utero* through early childhood. Because prenatal alcohol exposure is recurrent, identifying women with these alcohol associations during routine clinical care is an opportunity for prevention of FAS. Another prevention plan is for maternal nutrition intervention, which is proven to lessen the effects of FAS.

Although there were strong findings throughout this review, there were also limitations. Because most of the studies used questionnaires or self-reports for data collection, there could be under-reporting and recall biases. The mothers could have underreported because of the negative stigma related to alcohol drinking during pregnancy. The recall bias could occur due to the delay between alcohol consumption and the questionnaire or self-reports. Research on FAS and FASD is strictly limited to self-report and data collection, as it is unethical to host a study in which the methodology includes the knowledge of pregnant women consuming alcohol. Unfortunately, for most studies and reviews addressing maternal drinking and FAS, there are a number of ethical and legal concerns that make progressing knowledge on FAS and FASD very difficult. On the forefront of these challenges for researchers is the conflict of protecting embryonic life, while at the same time retaining the privacy and dignity of the patient contributing to the study.

There are a number of additional unanswered questions. Although prenatal alcohol exposure affects vasculature development during specific gestational periods, results are still inconclusive on the specific gestational period that is most severely affected by FAS. More specific and accurate measures are needed for identifying which newborns have been exposed to alcohol *in utero*, along with a method to determine in which gestational period the alcohol consumption occurred. These advances will allow researchers to be more precise in measuring the impacts of alcohol, and if the time in which alcohol was consumed makes a difference on the severity of FAS.

In addition, as there is no known treatment to reverse alcohol-induced damage to the CNS, finding ways to minimize or reduce the physical and neurological malformations that develop within the fetus will be groundbreaking. A possible preventative plan could be nutrient supplementation, which may play a major role in helping to reduce to damaging effects of FAS. Further research is clearly needed on the specific nutrient supplementation and optimal amount needed to reduce a detrimental effect of FAS on a long-term scale. In combination with prenatal nutritional intervention, it is important that pregnant mothers who are at risk of alcohol consumption are also offered educational materials describing FASD.

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