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# Mechanisms of Prenatal Ethanol Exposure on Causing Developmental Defects Associated with Fetal Alcohol Syndrome Disorders

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Development in humans is a long and complex process that begins at fertilization and proceeds for many years into an individual's life. The period of gestation is an important and sensitive period regarding the growth and development of the embryo and eventually the fetus. Any errors in this gradual process can result in major birth defects.<sup>1</sup> Major birth defects are found in about 1 in 33 children.<sup>1</sup> One study found that in cases of known etiology, the main cause of birth defects was due to chromosomal/genetic abnormalities (94%).<sup>1</sup> On the other hand, this study showed that environmental teratogens only caused 4% of the birth defects. Despite these numbers, environmental teratogens can be much more significant without maternal awareness of avoiding them whenever possible.<sup>1</sup>

One example of a harmful environmental teratogen is alcohol. Alcohol is known to be a very dangerous substance to people of all ages. However, it can be especially dangerous to the development of a fetus if the mother consumes it prenatally.<sup>2</sup> The broad range of abnormalities and developmental defects that can be caused by prenatal exposure to alcohol are categorized into fetal alcohol spectrum disorders (FASD).<sup>2</sup> This range of disorders can be categorized into a few different subsections, which includes fetal alcohol syndrome, partial fetal alcohol syndrome, alcohol-related birth defects, alcohol-related neurobehavioral disorder, and alcohol-related neurodevelopmental disorder.<sup>2</sup>

The negative effects of prenatal ethanol exposure (PrEE) were noticed by many, even as early as the 1700s.<sup>3</sup> Various researchers and physicians across the world made claims against the consumption of alcohol during pregnancy during the 1900s.<sup>3</sup> However, it wasn't until the 1970s when two American doctors, David Smith and Kenneth Jones, finally officially recognized the disorder and established a guide to diagnosing it.<sup>3</sup> This led to the United States Food and Drug Administration advising pregnant women to consume no more than 2 drinks per day.<sup>3</sup> The advisement today says that there is no known safe amount of alcohol to consume while pregnant.<sup>3</sup> This speaks strongly to the extent of research that has been

done since the 1970s which has found the horrific effects that prenatal alcohol exposure can cause.

There are many abnormalities and developmental defects that result from fetal alcohol syndrome disorders.<sup>4</sup> The most severely impacted organ in the body is the brain.<sup>4</sup> Consumption of alcohol at almost any time during pregnancy can damage the brain because it is continually developing.<sup>4</sup> First, those with fetal alcohol syndrome have smaller brains in terms of size and volume.<sup>4</sup> Specifically their brains consist of less gray and white matter.<sup>4</sup> The developmental problems with the brain can have many long-term impacts including seizures/seizure disorders, delayed development/mental retardation, and other behavioral or psychological issues.<sup>4</sup> Also, facial dysmorphism and growth deficits are very commonly seen.<sup>4</sup> The brain and the central nervous system are highly affected, but many other problems can arise from this disorder.<sup>4</sup>

The cardiovascular system is the second most affected system. Many children born with FAS have defects in their atrioventricular valves, which negatively affects blood flow through the heart.<sup>4</sup> Atrium and ventricle abnormalities are common.<sup>4</sup> There are also inconclusive studies examining how fetal alcohol syndrome affects the kidney, liver, and gastrointestinal system.<sup>4</sup> Recent studies show results that consist of underdeveloped kidneys and chronic intestinal pseudo-obstruction resulting from this disorder.<sup>4</sup> Lastly, many believe that the endocrine system is negatively impacted.<sup>4</sup>

Despite the many known effects of fetal alcohol syndrome disorders, the mechanisms that cause these abnormalities are still being studied. It is known that the ethanol enters through the placenta that is formed around the twelfth week of pregnancy.<sup>5</sup> After going through the placenta and entering the fetus, ethanol has a much slower elimination rate compared to its mother and tends to accumulate in the amniotic fluid.<sup>5</sup> In addition, the metabolic enzymes that are typically used on alcohol like CYP2E1 and ADH are significantly reduced in a fetus compared to a grown adult.<sup>5</sup> These enzymes increase as the fetus develops, but

maximum levels are not achieved until after the growing child is born.<sup>5</sup> These reasons contribute to the enhanced consequences of alcohol on a growing fetus.<sup>5</sup>

There are many mechanisms that have been studied and proposed over the years to cause FASD, but the complete connection and relationship between the mechanisms are not fully known.<sup>6</sup> In 2012 Bosco and Diaz examined several years of research and came to an important connection between fetal alcohol exposure and placental hypoxia.<sup>6</sup> Hypoxia, resulting from lack of needed oxygen supply, has a severe effect on the development of the fetus and its central nervous system.<sup>6</sup> Oxidative stress, a possible result of hypoxia, was believed by many to contribute to fetal alcohol syndrome disorders for years, but the exact mechanism was not understood.<sup>6</sup>

A study performed on mice in 2014 shed more light on reactive oxygen species and their impact on fetal alcohol syndrome disorders.<sup>7</sup> The goal was to determine if increased nicotinamide adenine dinucleotide phosphate oxidase (NOX) played a role in the high amounts of reactive oxygen species forming due to prenatal ethanol exposure.<sup>7</sup> The NOX system functions by complex mechanisms that allow reactive oxygen species to be limited in quantity and duration of their function.<sup>7</sup> The study concluded that mRNA expression of components within the NOX family were increased due to prenatal ethanol exposure in the mice studied.<sup>7</sup> Their results demonstrated that NOX as an enzyme contributes to high amounts of oxidative stress due to in utero ethanol exposure.<sup>7</sup> Furthermore, this study agreed with the idea that this increased oxidative stress contributes to FASD and cognitive defects.<sup>7</sup> The exact mechanism of reactive oxygen species having teratogenic effects is not definitively known, but it has been hypothesized to involve altered signal transduction or oxidative damage to macromolecules in the cells.<sup>8</sup>

Another proposed mechanism associated with fetal alcohol syndrome disorder is reduced retinoic acid signaling.<sup>9</sup> Retinoic acid is involved in regulating many different developmental processes.<sup>9</sup> This includes anterior-posterior axis formation and development of specific tissue types and formation of organs.<sup>9</sup> It is believed that reduced retinoic acid signaling has a role in causing some of the abnormalities associated with FASD.<sup>9</sup> Retinoic acid can be made from three different precursor sources in vertebrates: vitamin A, retinyl esters, and B-carotene.<sup>9</sup> Retinoic acid in its simplest form is made by two sequential oxidations that are similar to how ethanol is cleared from the body.<sup>9</sup> The similarity between ethanol clearance from the body and the biosynthesis of retinoic acid led to the belief that fetal alcohol syndrome could be caused by an inhibitory effect of alcohol on the biosynthesis of retinoic acid.<sup>9</sup>

Reduced retinoic acid concentrations have been linked to a variety of disorders that have similar effects to fetal alcohol syndrome disorder.<sup>9</sup> This includes Vitamin A Deficiency Syndrome, Matthew-Wood Syndrome, and Smith-Magenis syndrome.<sup>9</sup> All of these disorders and others have been linked to reduced retinoic acid signaling in individuals.<sup>9</sup> They also all have contrasting mechanisms that cause the reduced retinoic acid levels.<sup>9</sup> These disorders cause developmental malformations that closely resemble some of the same abnormalities caused by various fetal alcohol syndrome disorders.<sup>9</sup>

Another study done in 2018 suggested the correlation between fetal alcohol syndrome disorders and reduced Wnt signaling in the peripheral ciliary marginal zone.<sup>10</sup> Wnt signaling is crucial in the developmental process including having functions in cell polarity, cell migration, cell fate determination, and organogenesis.<sup>10</sup> In addition, Notch signaling was reduced as well.<sup>10</sup> Notch signaling has many important functions as well including the promotion of proliferative signaling during neurogenesis.<sup>10</sup> Zebrafish were used and exposed to ethanol during the developmental period that corresponded to the first trimester in the human gestation period.<sup>10</sup>

The results were clear with reduced Wnt activity, which was believed to lead to reduced downstream signaling pathway activation which includes Notch signaling.<sup>10</sup> This idea was reinforced by several rescue experiments performed by the same team on the zebrafish.<sup>10</sup> One rescue experiment involved supplementing the zebrafish with both retinoic acid and folic acid in addition to ethanol.<sup>10</sup> The findings from this demonstrated reactivated Wnt signaling and supported the theory that ethanol was the probable cause behind the reduced Wnt and Notch signaling.<sup>10</sup>

Another study that had similar findings was performed in 2013 on rats.<sup>11</sup> Rats subject to prenatal alcohol exposure had cerebellar motor abnormalities that were believed to be caused by Wnt and insulin/IGF-1 signaling impairments.<sup>11</sup> This study had many interesting findings from post-experiment observations on the rats.<sup>11</sup> First, the mean brain weight to bodyweight ratio was significantly lower in rats exposed to ethanol prenatally.<sup>11</sup> Next, the rats were given a variety of rotarod tests which varied in difficulty.<sup>11</sup> The rats exposed to ethanol performed worse on average compared to the control group and performed especially inferior in the most difficult trials.<sup>11</sup>

These results of course were expected due to the teratogenic nature of ethanol.<sup>11</sup> However, the results also showed reduced IRS-1 proteins (insulin receptor substrate), reduced levels of IGF-1 receptors, and reduced levels of receptor tyrosine phosphorylation due to prenatal ethanol exposure.<sup>11</sup> The evidence from the study

pointed to the cerebral motor impairments being caused by increased levels of insulin/IGF-1 receptor expression and reduced levels of receptor tyrosine phosphorylation.<sup>11</sup> This insulin/IGF-1 resistance of the brain would lead to continual cell loss due to impaired survival mechanisms, deficits in the function of cholinergic receptors, and even increased oxidative stress.<sup>11</sup> Also, the insulin/IGF-1 resistance increased GSK-3 $\beta$  activity and reduced Axt.<sup>11</sup> They believed the combination of reduced Akt and increased insulin/IGF-1 resistance accounted for the functional and structural abnormalities in the ethanol exposed rat cerebella.<sup>11</sup> In addition, the deleterious effects of insulin/IGF-1 resistance on metabolism, cell survival, and growth were worsened by the increased activity of GSK-3 $\beta$  and increased oxidative stress.<sup>11</sup> This study showed some indication that Wnt signaling was reduced as well, but not much was definitely observed regarding the mechanism.<sup>11</sup> The mechanism was built on and explained years later in the aforementioned study using zebrafish.<sup>10</sup>

The next mechanism with a substantial amount of research to support it is epigenetic modifications. One study published in 2019 in mouse models highlighted the epigenetic changes that occurred due to prenatal ethanol exposure.<sup>12</sup> Western blotting was used to determine the histone acetylation and methylation in the mice.<sup>12</sup> A significant correlation between ethanol consumption levels and H4K5ac levels were found. H4K5ac is an epigenetic modification to histone H4.<sup>12</sup> This increase in histone acetylation causes an open chromatin structure which leads to an active state of gene transcription in the prefrontal cortex.<sup>12</sup>

Also, enzyme levels of HAT and HDAC were recorded. These enzymes regulate the acetylation and deacetylation of histones in the brain of the mice.<sup>12</sup> HAT levels were significantly increased in the mice exposed to ethanol prenatally.<sup>12</sup> This increase suggests that long-term epigenetic alterations due to in utero ethanol exposure might be mediated by a dysregulation of the chromatin-modifying enzymes.<sup>12</sup> However, further research needs to confirm and expand on this mechanism.<sup>12</sup> This study concludes that ethanol exposure prenatally will lead to epigenetic modifications in the brain that have been consistently shown to reduce cognitive function and ability.<sup>12</sup>

Fetal alcohol syndrome disorders have a high comorbidity with autism spectrum disorders.<sup>13</sup> It has been proposed that this is because the two different disorder types have similar epigenetic modifications that contribute to the cognitive impairments that cause each of them.<sup>13</sup> For example, deficiencies of MeCP2 and mutations of MeCP2 are seen in both autism spectrum disorders (ASD) and fetal alcohol syndrome disorders (FASD).<sup>13</sup> It was also

proposed that changes in GABA receptor expression could be due to prenatal alcohol exposure and cause ASD. More definitively, there has been increased apoptosis of neurons, reduced neuronal size compared with normal brain, and decreased number of Purkinje cells found in those with FASD and ASD.<sup>13</sup> The link between FASD and ASD seems evident, but needs to be supported with further research and a clearer method of action.<sup>13</sup>

Another proposed epigenetic change in those with fetal alcohol syndrome disorders is decreased H2A.Z.<sup>14</sup> H2A.Z is involved in many processes like DNA repair, transcriptional control, regulation of centromeric heterochromatin, and many others.<sup>14</sup> This epigenetic modification was found in a study on rats done by Gretzinger et al.<sup>14</sup> This study linked prenatal ethanol exposure to decreases in H2A.Z due to downregulation of H2A.Z-2 isoform gene expression.<sup>14</sup> Their data demonstrated the alteration of this histone variant during the formation of the rat's hippocampus which could contribute to a variety of neurological abnormalities.<sup>14</sup>

The wide range of studies done on epigenetic changes due to PrEE have shown a clear connection between epigenetic differences and characteristics and physiological similarities of fetal alcohol syndrome disorder.<sup>15</sup> However, clear patterns or trends in all of the research done still needs to be elucidated further.<sup>15</sup> Many of these studies use various levels of ethanol exposure and different timing of providing it.<sup>15</sup> There can be some broad conclusive patterns found in the wide variety of studies done, though.<sup>15</sup>

First, there seems to be a clear increase in epigenetic modification to histone H3 with increases in H3K9ac.<sup>15</sup> It is believed that this is the result of increased HAT activity which is also commonly seen across many studies.<sup>15</sup> Also, changes in histone modification are evident, but the mechanism is still being continually explored.<sup>15</sup> The best evidence seems to be the changes in the euchromatic histone-lysine N-methyltransferase 2 (EHMT2) also known as G9a.<sup>15</sup> G9a catalyzes histone modifications that are critical in early development and synapse remodeling.<sup>15</sup> Studies have found increases in G9a due to PrEE which appeared to be related to neuronal degeneration.<sup>15</sup> Increases in G9a increase catalyzation of closed-chromatin H3K9me2 modifications.<sup>15</sup> This change in H3K9me2 has been found to be very consistent with levels of those exposed to prenatal ethanol.<sup>15</sup>

Many observations from different studies have resulted in conflicting data on levels of methylation.<sup>15</sup> Some studies have found consistent increases in methylation while other studies have seen consistent decreases.<sup>15</sup> It is believed that this is due to differences in ethanol exposure timing and other factors at play.<sup>15</sup> For example, oxidative stress has been seen to decrease methyl donors which has

caused decreasing methylation in some studies.<sup>15</sup> Increases in HAT activity, altered G9a, and increases in H3K9ac and H3K9me2 are common epigenetic trends, but further research needs to be performed to completely understand their correlation and their mechanistic effects.<sup>15</sup>

Alterations in microRNAs(miRNA) have also been hypothesized to contribute to the mechanisms of obtaining FASD.<sup>16</sup> The miRNA changes are greatly dependent on the timing and dosage size of ethanol exposure.<sup>16</sup> One study of zebrafish found decreased miR-9 expression in neural progenitor cells as a result of PrEE.<sup>17</sup> This decrease can cause changes in the effect of miR-9 expression and result in improper formation and maturation of the brain.<sup>17</sup> Also, miR-153 is overexpressed due to PrEE, which is typically correlated with decreased gliogenesis.<sup>17</sup> This change in miR-153 was shown to cause inappropriate cortical development and cause changes in zebrafish behavior.<sup>17</sup>

In addition to neurodevelopmental defects, miR-21 and miR-10 changes due to PrEE have been linked to heart disease.<sup>16</sup> This is because miR-21 acts by inhibiting sprouty homolog 1 (SPRY1) which functions as a regulator for fundamental pathways.<sup>16</sup> MiR-10, on the other hand, is located within the Hox gene domains and appears to regulate Hox expression.<sup>16</sup> MiR-10 targets Hoxa1 which is transiently expressed in cardiac progenitors and mutations in Hoxa1 result in heart defects.<sup>16</sup> These miRNAs are also believed to be involved with pancreas and liver problems caused by prenatal ethanol exposure.<sup>16</sup>

Long non-coding RNAs are beginning to be considered as a causal factor of FASD.<sup>16</sup> One long non-coding RNAs (lncRNAs), H19, has an important role in determining fetal size and is believed to have an impact on prenatal growth restriction that is seen in FASD.<sup>16</sup> H19 can act as an epigenetic factor that binds the protein MBD-1 which recruits histone methyltransferases genes related to growth and development which decreases transcription.<sup>16</sup> Also, H19 can serve as the primary transcript for mi-R675 that targets insulin-like growth factor 1 receptor mRNA.<sup>16</sup> It is believed that reduced methylation and increased transcription related to H19 can be caused by ethanol and lead to reduced prenatal growth.<sup>16</sup> It has even been claimed that excessive paternal drinking prior to conception can cause H19 modifications that result in FASD related abnormalities.<sup>16</sup>

A study done on cynomolgus macaque, a primate species, indicated that PrEE causes widespread apoptosis of neurons in the gray matter regions of developing cynomolgus macaque brains.<sup>18</sup> This study also showed that alcohol can induce widespread apoptosis of glial cells in the oligodendrocyte lineage.<sup>18</sup> However, it is not known

if these apoptotic degenerations result from the same mechanism. It is believed that neuroapoptosis, caused from PrEE, occurs by the blocking of NMDA glutamate receptors and hyperactivation of GABA receptors.<sup>18</sup> The action of removing neurons and glial cells in the oligodendrocyte lineage helps support the idea that apoptosis plays a major role in some of the effects of FASD.<sup>18</sup> Oligodendrocyte myelinate axons that connect neurons throughout the developing brain.<sup>18</sup> Removal of these oligodendrocytes can result in many long term neurobehavioral consequences.<sup>18</sup> This study demonstrated almost 13 times higher apoptosis rates of oligodendrocytes when exposed to prenatal ethanol compared to without this exposure.<sup>18</sup>

The last mechanism this paper will discuss is the altering of neurotransmission. One study performed in 2020 on zebrafish demonstrated how the functionality of glutamatergic neurotransmission is reduced by PrEE.<sup>19</sup> The results clearly demonstrated that the increase in ethanol caused a decrease in glutamatergic neurotransmission.<sup>19</sup> The changes in glutamatergic transmission were believed to be linked to alterations in memory and learning which was due to hippocampus damage.<sup>19</sup> The PrEE that the zebrafish were subject to seemed to cause impairments in the function and structure of presynaptic and postsynaptic compartments.<sup>19</sup> Also, ethanol is believed to cause decreased sodium-potassium ATPase activity.<sup>19</sup> This could be contributing to reduction in glutamate uptake.<sup>19</sup>

The various mechanisms mentioned in this paper are all believed to contribute to the effects displayed in fetal alcohol syndrome disorders. Future research will try to definitively determine the exact causal mechanisms of the birth defects associated with FASD.<sup>20</sup> Despite all of these studies and their findings, a clear causal link between a molecular mechanism and an exact effect of PrEE has not been definitively identified.<sup>20</sup> These studies also need to determine how genetic predisposition and other environmental factors affect the results of prenatal ethanol exposure.<sup>20</sup> One of the most important mechanisms that will direct the future of research of fetal alcohol syndrome disorders seems to be concerning the effects of epigenetics.<sup>21</sup>

Regarding epigenetics, future research needs to prove causation rather than correlation of FASD.<sup>21</sup> Most research done on epigenetics has focused on the similarities of specific epigenetic modifications and has not proved that reversing these changes would change the phenotypic traits associated with FASD.<sup>21</sup> Future research will aim to show clearer evidence of relationships between epigenetic patterns, gene expression profiles, and the specific phenotype.<sup>21</sup> Also, further analysis of tissues in animal models needs to be done before transitioning to

clinical models.<sup>21</sup> This could prove paramount in definitively identifying specific biomarkers of FASD.<sup>21</sup> Lastly, more identification of related epigenetics between FASD and other neurological disorders needs to be found in order to compare possible similar etiologies.<sup>21</sup>

In addition to epigenetics, future research needs to connect several of the other mechanisms referenced in this paper and determine how they cause decreased functioning of the nervous system.<sup>8</sup> It is believed that this decreased functioning is caused by many factors including reduced functions of several transduction signaling pathways.<sup>8</sup> Epigenetics, noncoding RNAs, oxidative stress, and other mechanisms also play a role in the neurological problems derived from FASD.<sup>8</sup> These factors have been shown to cause reduced functioning of the cerebral cortex, hippocampus, cerebellum, and other parts of the brain.<sup>8</sup> Research in the future will focus on finding how these causes are related and also how to connect specific effects to specific causal mechanisms.<sup>20</sup> In addition, this research will continue to attempt to identify more specific details within these individual categories of sources of FASD.<sup>20</sup>

Once the idea of the mechanisms that cause FASD are more clearly understood, then this will open the door to much more influential research that has a more direct effect on families affected by the disorder.<sup>22</sup> First, this will allow more studies to be mechanistically specific and produce a more clear picture of how the timing and amount of alcohol consumption correlates to specific developmental issues.<sup>22</sup> This will lead to physicians providing an earlier diagnosis of FASD which will result in more effective treatment.<sup>22</sup> Second, future research will allow for new intervention methods including nutritional, pharmacological, behavioral, and environmental treatments which will be much more effective for the specific issues one has due to this disorder.<sup>22</sup> Third and finally, research on the specific timing and amount of alcohol needed to affect the growing fetus will result in much clearer guidelines for pregnant mothers to follow.<sup>22</sup> The clear effects of drinking during different periods could help cause reduced cases of fetal alcohol syndrome disorders.<sup>22</sup>

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