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# Binge alcohol administration on pregnant rats results in decreasing of insulin like growth factor-1 and aldehyde dehydrogenase, increasing apoptosis index, and fetal alcohol syndrome in offsprings



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## ABSTRACT

**Background:** Addiction of alcoholic beverage by early pregnancy women results in fetal alcohol syndrome of her baby. This study aims to investigate fetal alcoholic syndrome due to binge alcoholic drinking by the early pregnant of wistar rat.

**Methods:** This is an experimental study applying posttest only control group design. Wistar Rats were in preconditioning for pregnancy and divided into two groups, i.e. one group was fed with normal feeding and the other group was fed with normal feeding and 40% of ethanol. The offspring then were observed and divided into three groups, i.e. normal fetal, normal fetal from the mother fed with ethanol, and fetal alcoholic syndrome. Insulin like growth factor (IGF-1), aldehyde dehydrogenase (ALDH), apoptosis index, pathology of their brain and heart were observed. The different of all these parameters were then compared by applying one way anova, and considered significant at  $p < 0.05$ .

**Results:** In this study we found that there were fetals alcoholic syndrome (FAS) due to the mother of the Wistar Rat fed with ethanol during their pregnancy. There were also a significant different of IGF-1, ALDH, apoptosis index between these three groups ( $p < 0.05$ ), i.e. normal baby, normal fed with ethanol, and FAS. IGF-1 for these three groups were  $56.59 \pm 0.52$  ng/ml,  $55.17 \pm 2.41$  ng/ml, and  $36.64 \pm 4.86$  ng/ml, respectively. ALDH for the groups were  $21.41 \pm 2.38$  ng/ml,  $21.16 \pm 4.77$  ng/ml, and  $17.05 \pm 2.68$  ng/ml, respectively. Their brain apoptosis indexes were  $4.56 \pm 0.78$ ,  $4.58 \pm 1.17$ , and  $7.86 \pm 1.31$ , respectively. Heart apoptosis indexes were found  $2.81 \pm 1.18$ ,  $5.36 \pm 1.37$ , and  $7.50 \pm 1.43$ , respectively.

**Conclusion:** Binge alcohol drinking during pregnancy of Wistar Rat results in FAS and identified by decrease of IGF-1, ALDH and increase of brain apoptosis index and heart apoptosis index of the off spring.

**Keywords:** addiction; alcoholic; drinking; apoptosis, index.

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## INTRODUCTION

The concept of fetal alcohol syndrome (FAS) refers to a set of birth defects that occur in children born to mothers who abused alcohol during pregnancy. The alcohol-induced defects include pre- and post-natal growth deficiencies, minor facial abnormalities, and damage to development of central nervous system (CNS). FAS is the most serious condition physicians group under the heading of Fetal Alcohol Spectrum Disorders, which also includes Alcohol-Related Birth Defects, like alcohol-induced congenital cardiac defects that are unrelated to a diagnosis of FAS, and Alcohol-Related Neuro-developmental disorders, which occur in the absence of any facial birth defects or growth delays. The severity of birth defects associated with FAS can vary depending on the intensity, duration, and frequency of exposure to alcohol during gestation. In addition to these dose-related concerns, maternal factors such as the mother's genetics or how quickly she metabolizes alcohol, and the timing of exposure during prenatal

development also impact alcohol-induced abnormalities. As birth defects and anomalies can arise when pregnant women consume alcohol, alcohol is a teratogen, an environmental agent that negatively impacts the course of normal embryonic or fetal development.<sup>1</sup>

Groups of French and American researchers concurrently observed the defects specific to FAS in the late 1960s and early 1970s. In 1968, Paul Lemoine and colleagues in Nantes, France, examined 127 children from 69 families that had at least one parent with chronic alcoholism. Among these children, researchers observed facial abnormalities and cognitive defects that manifested as low Intelligence Quotient (IQ) scores, hyperactivity, and developmental delays in motor coordination and language skills. Medical communities abroad largely dismissed the initial reports, indicating that many viewed alcohol as a benign agent into the late 1960s. Five years later US researchers observed a similar set of birth defects,

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and researchers recognized the potential of alcohol as a teratogen, legitimizing FAS.<sup>2-4</sup>

This study aims to investigate fetal alcoholic syndrome due to binge alcoholic drinking by the early pregnant of wistar rat. IGF-1, ALDH, and apoptosis index of brain and heart of the off springs were also observed.

**MATERIALS AND METHODS**

This is an experimental study applying post only control group design. Wistar Rats were in preconditioning for pregnancy and divided into two groups, i.e. one group was fed with normal feeding and the other group was fed with normal feeding and 40% of ethanol. The off spring then were observed and divided into three groups, i.e. normal fetal, normal fetal from the mother fed with ethanol, and fetal alcoholic syndrome. Insulin like growth factor (IGF-1), aldehyde dehydrogenase (ALDH), apoptosis index, pathology of their brain and heart were observed. The different of all these

parameters were then compared by applying one way anova, and considered significant at  $p < 0.05$

**RESULTS**

**Characteristics of Wistar Rats**

In this study, of 4 Wistar rats that were not given the alcohol produced as many as 29 normal pup rats. Further, Wistar rats were given alcohol produce 9 normal pup rats and 20 FAS pup rats (68.97%) Thoroughly characteristic data of Wistar rats used are presented in Table 1 and 2.

**Fetal Alcohol Syndrome (FAS) Defects**

The occurrence of defects in pup Wistar rats undergoing FAS can be seen morphologically. FAS are wrinkled skin abnormalities compared to the normal ones.

**Insulin-like Growth Factor-1 (IGF-I)**

Data of IGF-1 levels for FAS and normal offsprings were presented in Table 3.



**Figure 1** Morphological defects of pup rats with FAS A. Normal pup rats; B. Pup rats with FAS

**Table 1** Characteristics of Wistar Rats

No	Initial rat weight(g)	Weight during pregnancy (g)		Number of pups		
		without alcohol	with alcohol	Normal without alcohol	Normal with alcohol	FAS with alcohol
1	265.36	289.77		7		
2	266.78	283.56		7		
3	271.44	281.08		8		
4	270.11	281.73		7		
5	269.82	295.76		2	5	
6	268.69		289.37		2	5
7	270.07		299.61		2	5
8	266.89		290.35		3	5
Mean	268.65	284.04	293.77			
SD	268.65	284.04	293.77			

FAS = fetal alcohol syndrome  
SD = standard deviation

**Table 2** Body Weight of Pup Wistar Rats

No	Body Weight of Wistar Rats (g)		
	Normal without alcohol	Normal with alcohol	FAS with
1	10.83	9.93	9.06
2	11.67	8.93	8.99
3	11.29	9.08	8.27
4	10.66	9.21	8.79
5	9.82	8.76	9.11
6	10.61	8.93	8.85
7	9.73	8.81	8.93
8	10.62	9.18	9.17
9	11.36	9.38	8.88
Mean	10.37	9.13	8.89
SD	0.66	0.36	0.27

FAS = fetal alcohol syndrome  
SD = standard deviation

**Table 3** Level of IGF-1 in Normal Pup Wistar Rats, Normal with alcohol, and FAS

No	Level of IGF-1 (ng/ml)				
	Normal	Normal with Alcohol	FAS	F	p*
Mean (SD)	56.59 (0.51)	55.17 (2.41)	36.64 (4.86)	112.95	0.001

FAS = Fetal Alcohol Syndrome  
SD = standard deviation  
\*Significant at  $p < 0.05$

**Table 4** Level of ALDH in Normal Pup Wistar Rats, Normal with alcohol, and FAS

No	ALDH level (ng/ml)			F	p*
	Normal	Normal Alcohol	FAS		
Mean (SD)	21.41 (2.38)	21.16 (4.77)	17.05 (2.68)	4.55	0.021

FAS = Fetal Alcohol Syndrome

SD = standard deviation

\*Significant at  $p < 0.05$ **Table 5** Apoptosis index of liver and brain in Normal Pup Wistar Rats, Normal with alcohol, and FAS

No	Apoptosis Index			F	p*
	Normal	Normal Alcohol	FAS		
Liver Mean (SD)	4.56 (0.78)	4.58 (1.17)	7.86 (1.31)	26.35	0.001
Brain Mean (SD)	2.81 (1.18)	5.36 (1.37)	7.50 (1.43)	27.84	0.001

FAS = Fetal Alcohol Syndrome

SD = standard deviation

\*Significant at  $p < 0.05$ 

### Aldehyde Dehydrogenase (ALDH)

Data of ALDH levels for FAS and normal offsprings were presented in [Table 4](#).

### Apoptosis Index

Data of apoptosis index for FAS and normal offsprings on liver and brain were presented in [Table 5](#).

## DISCUSSION

### Characteristics of Pup Wistar Rats

This study examined the occurrence of defects in FAS pup Wistar rats whose mothers were given binge alcohol during pregnancy. As for the case in humans, those who used to drink alcohol during pregnancy have clearly resulted in infants with FAS.<sup>5</sup> From these results, it was found that, of 4 mother Wistar rats which were not given alcohol during pregnancy gave birth to as many as 29 normal pup rats, a rat on the average gave birth to 7 pup rats (see [Table 1](#)). From the same table it can be seen that of 4 mother Wistar rats which were given binge alcohol during pregnancy gave birth to 9 normal pup Wistar rats and 20 FAS pup Wistar rats (68.97%). Furthermore, of the pup Wistar rats, 9 normal ones were taken without being given alcohol, 9 normal pup Wistar rats were from the mothers which were given alcohol, and 9 FAS pup Wistar rats came from the mothers which were given alcohol.

Furthermore, from the data in [Table 2](#), it can be seen that the pups due to the fact that FAS mother Wistar rats were given binge alcohol, they have the smallest weight, the average weight ( $8.89 \pm 0.27$ ) g,

compared to normal without alcohol ( $10.37 \pm 0.66$ ) g, and that is normal with alcohol ( $9.13 \pm 0.36$ ) g. These results are consistent with the findings of Hamzelou (2010) who found that pup rats of the mothers which consumed alcohol also had the symptoms of FAS as in the human fetus, i.e. low body weight. It is recommended that in order for FAS to occur in pup Wistar rats further in-depth studies are needed to find new biomarkers.<sup>6</sup>

### Fetal Alcohol Syndrome (FAS) Defects

As already mentioned above, there occurs a defect of weight loss in FAS pup Wistar rats compared with normal pup rats born to mothers which no alcohol during pregnancy and those from mothers who were given binge alcohol. Morphological picture obtained in this study also supports the occurrence of defects in FAS pup Wistar rats. Referring to Alcohol Related Birth Defects from IOM (1996), defects are due to the administration of binge alcohol to the pregnant mother Wistar rats which produce FAS pup Wistar rats with defects, such as low body weight (growth deficits), small head size (microcephaly), hydrocephalus, spina bifida, abnormalities of the face (facial dysmorphism), and drooping eyelids (ptosis).<sup>7-12</sup>

### Insulin-like Growth Factor-1 (IGF-I)

This study found differences in the levels of IGF-1 in pup Wistar rats which experienced FAS compared to the normal ones without alcohol and the normal ones whose mothers were given alcohol. Data IGF-1 in each group of pup Wistar rats are:  $36.64 \pm 4.86$  ng / ml for FAS pup Wistar rats,  $55.17 \pm 02.41$  ng / ml for normal pup Wistar rats from mothers given binge alcohol during pregnancy, and  $56.59 \pm 0.51$  ng / ml for normal pup Wistar rats from the mothers who abstained from alcohol. Interestingly, it was found that there was no significant difference between the levels of IGF-1 in pups of normal rats from the mother Wistar rats which were not given alcohol and normal pup Wistar rats from the mother Wistar rats which were given alcohol. Significant differences were found in the levels of IGF-1 of FAS pup Wistar rats with normal IGF-1 levels without alcohol or normal with alcohol.

The results are consistent with the findings of Hallak *et al.* (2001) which finds that insulin and IGF-1 signaling pathways is an important target of neurotoxicity of alcohol.<sup>13</sup> It plays a role in the nervous system resulting in immature neuronal loss. In fetuses exposed to alcohol in part are due to the constraints of alcohol on survival mechanisms that are stimulated by insulin / IGF-I. Hallak *et al* use experimental rats which are given chronic alcohol during pregnancy, the pups showed Hypoplasia of

cerebellum, reducing the function of mitochondria and increases neuronal apoptosis.<sup>13</sup>

Research by Resnickoff *et al.*, 1993 found that ethanol in low concentrations clearly inhibits IGF-I receptor autophosphorylation and IGF-I-mediated cell growth.<sup>14</sup> IGF-1 is a potential mitogenic growth factor belonging to the family of Insulin-like Growth Factor (IGF) of a signaling molecule that plays an important role in energy metabolism in cells, growth and development, especially prenatal growth. IGF-1 works to facilitate the activity of Growth Hormone (GH) during the post-birth. IGF-1 is also known as somatomedin C secreted by the liver into the blood circulation in a process that is regulated by the Pituitary Growth Hormone (PGH).<sup>15</sup> In the developing embryo IGF-I is mainly expressed by cells derived from mesenchym. After birth the expression of IGF-11 in most extrahepatic tissues decreases and hepatic expression of IGF-1 is regulated by GH. IGF-1 Expression outside the liver is regulated by various mechanisms depending on the type of the specific tissues.<sup>15</sup>

### Aldehyde Dehydrogenase (ALDH)

This study found no significant difference of ALDH levels between FAS pup Wistar rats and normal pup Wistar rats without alcohol as well as normal pup rats whose mothers were given binge alcohol. The average levels of ALDH in each group were  $17.25 \pm 2.68$  ng/l for FAS pup Wistar rats,  $21.41 \pm 2.38$  ng/ml for normal pup Wistar rats from the mothers without being given alcohol during pregnancy, and  $21.16 \pm 4.77$  ng/ml for normal pup Wistar rats from the mothers given binge alcohol.

The results show a decrease in ALDH levels in FAS pup rats compared to normal pup rats whose mothers are not given alcohol or are given alcohol. The reduction obtained is statistically significant at 4.36ng/ml between FAS pup Wistar rats and normal pup rats whose mothers are not given alcohol and at 4.11ng/ml to normal pup Wistar rats whose mothers drank binge alcohol.

The results of this study are in line with the results of research conducted by Messiha and Varma (1983).<sup>16</sup> Both researchers report that indeed there is an increase in the level of ALDH in mother rats which are given alcohol, while the pups are found to have undergone decreased levels of ALDH. Elimination of alcohol in the body occurs through different metabolic mechanisms. Enzyme Alcohol Dehydrogenase (ADH), aldehyde dehydrogenase (ALDH), Cytochrome P450 (CYP2E1) and catalase play an important role in the metabolism process. The consequence of this alcohol metabolism is that there is a decline in oxygen (hypoxia) in the liver, interactions between by-products of the alcohol metabolism and components of other cells

that lead to the formation of harmful compounds, such as the formation of compounds containing reactive oxygen (ROS) that can damage components of other cells. Likewise, changes occur in the ratio of NADH to NAD<sup>+</sup> ratio (i.e. the Redox state of cells); tissue damage; fetal damage; other metabolic processes disorders and cancer.

Metabolism of alcohol passes the stomach and liver, as well as through a tissue that does not contain ADH extra hepatic tissues such as brain via Cytochrome P450 enzymes and Catalase. Metabolism of alcohol could be through oxidative pathway that adds oxygen or remove hydrogen (via pathway involving the enzymes ADH, Cytochrome P450 and Catalase). ADH, Cytochrome P450 (CYP2E1), and Catalase contribute to the oxidative metabolism of ethanol being converted into acetaldehyde. This reaction involves an intermediate carrier of electrons, Nicotinamide adenine dinucleotide (NAD<sup>+</sup>), which is reduced by 2 electrons to NADH.

Some ALDH isoenzymes have been identified, but only ALDH1 cytosolic and Mitochondrial ALDH2 that metabolize Acetaldehyde. There is important genetic polymorphism namely the ALDH2 gene, where there are 2 variant alleles namely ALDH2 \* 1 and ALDH2 \* 2 which are virtually inactive. ALDH2 \* 2 is found in 50% of the people of Taiwan, Han Chinese, and Japanese, and virtually no acetaldehyde metabolism shows activity in vitro.<sup>17</sup> People with one (heterozygous) or especially 2 (homozygous) copies of the ALDH2 \* 2 allele show increased levels of Acetaldehyde after alcohol consumption and they therefore experience physiological response which is negative to alcohol.<sup>18-19</sup>

ALDH oxidizes Acetaldehyde into acetic acid and can be analyzed in mitochondria and cytosol. This is promising to us, i.e. the researchers are now looking for an analogy of the ALDH2 enzyme activator that can cure, slow down or even prevent the disease. Such a drug or patent will improve the quality of life or prolong the life-span of patients. This of course would be very interesting both for basic research and for the potential development in the field of pharmacy.<sup>20</sup>

### Apoptosis Index

Apoptosis index data in this study was obtained from liver and brain of FAS pup Wistar rats, normal ones without alcohol, and normal ones from the mothers who were given binge alcohol. As shown in [Table 5](#) average liver apoptotic index in all three groups of Wistar rats was  $7.86 \pm 1.31$  for FAS pup Wistar rats,  $4.58 \pm 1.17$  for normal pup Wistar rats whose mothers were given binge alcohol during pregnancy, and  $4.56 \pm 0.78$  for the normal Wistar

rats without alcohol. Likewise, the average index of apoptosis of pup Wistar rats's brain can be seen from the same table, namely,  $7.50 \pm 1.43$  for FAS pup Wistar rats,  $5.36 \pm 1.37$  for normal pup Wistar rats whose mothers were given binge alcohol during pregnancy, and  $2.81 \pm 1.18$  for normal pup Wistar rats without alcohol.

This study found that there was an increase in apoptotic index in FAS pup Wistar rats compared with of normal pup Wistar rats who were given alcohol or not. The data of the increase in apoptotic index in liver and brain of pup Wistar rats can be seen in Table 5. Increased liver apoptosis index of 3.31 for FAS pup rats was compared with normal pup rats without alcohol and index of 3.28 for FAS pup Wistar rats compared with normal pup Wistar rats whose mothers were given binge alcohol during pregnancy.

Liver apoptosis index between normal pup Wistar rats without alcohol was found insignificantly different compared with the apoptotic index of normal pup Wistar rats whose mothers were given binge alcohol during pregnancy. The similar situation was also found in the apoptotic index in the brain. Significant increase in the apoptotic index was found in the brain amounting to 4.69 in FAS pup Wistar rats compared with pups of normal Wistar rats from the mothers which abstained from alcohol during pregnancy. Likewise, there was a significant increase in apoptotic index by 2.14 to FAS pup Wistar rats compared with pup Wistar rats originating from the mothers who were given binge alcohol during pregnancy.

The interesting thing is the occurrence of a significant increase in the apoptotic index of 2.55 in the brain of normal pup Wistar rats whose mothers were not given alcohol during pregnancy compared to pups of normal Wistar rats from the mothers who were given binge alcohol.

Apoptosis is a cascade or simultaneous process of programmed cell death in multicellular organisms. Although apoptosis can run very fast, once it has been started but its onset can be delayed for some time after the toxic incident; at least it can be seen in some cases, apoptotic cell death is seen to include the activation of gene-directed program for self-destruction of the cell itself.<sup>21,22</sup>

Various molecular signals can initiate apoptosis, the activation of caspases is an important step towards cell death. Therefore, specific inhibitors of caspases have been proven to prevent apoptotic cell death in several experimental models. DNA becomes broken and phosphatidyl serine is transferred out of the cell membrane. Apoptosis plays an important role in physiological events and the occurrence of disease. Biochemical events also occur resulting in a change in the typical cell morphology and death.

These changes include relaxation of the cell membrane, shrinkage, and fragmentation of nuclei, chromatin condensation and chromosome DNA fragmentation.<sup>23</sup> Research of apoptosis has developed substantially since the beginning of 1990. As it is known that apoptosis is a normal part of the development program. Signs that enhances or inhibits the apoptotic event of neuron cells play an important role in the formation of the correct relationship between neurons and follow accurately the development program that has been well- organized.<sup>24</sup>

Alcohol is known as an antagonist of NMDA glutamate receptors and as an agonist of substances that activate GABAA receptors, therefore, it can provide a strong apoptotic response when induced by the latter substance.<sup>25</sup> Covering apoptosis pattern made by NMDA antagonist with substances GABA-ergic would give the combined pattern that is very similar to what is induced by ethanol. Recent studies indicate that blockage/resistance at the NMDA glutamate receptors resulted in very extensive apoptotic neuro-degeneration in the brains of fetal rats.<sup>26</sup>

Subsequent studies investigated the effects of ethanol during developing brain of pup rats is i.e. during the synaptogenesis period (i.e. the embryonic period between the nineteenth day and the post-birth, the fourteenth day. The percentage of apoptotic cells was obtained in 15 different brain regions studied in rats at the time of day-8 post-birth.<sup>27</sup> But the frequency of apoptosis in brain regions in animals with ethanol treatment was found to increase 1-2 times greater. The increase in apoptotic index was stimulated only when blood alcohol levels were maintained above the toxic threshold i.e. approximately 0.2% (200 mg/dL) for at least 4 consecutive hours.

In all cases, the sensitivity of apoptosis is associated with synaptogenesis. The alcohol exposure during synaptogenesis can destroy millions of neurons during brain development. Various populations of neurons can be exposed, depending on the period of its exposure. Therefore, the toxicity of ethanol can contribute to a variety of neurobehavioral disorders. Besides this very important biological phenomenon, the wrong process of apoptosis is allegedly associated with a variety of diseases.

There is a tendency of apoptosis index differences in liver and brain in this study as described above, where the index of apoptosis in the brain was found to differ significantly between pups of normal Wistar rats and normal pup Wistar rats coming from the mothers who were given binge alcohol while this is not the case for apoptosis index in the liver. This proves that alcohol has inhibitory effects on insulin/IGF signaling pathway in the

developing brain and immature neurons. In addition, alcohol also has a neurotoxic and teratogenic effect by increasing oxidative stress and damage the insulin/IGF signaling pathway in a developing brain.<sup>28-30</sup>

Alcohol also interferes with the signaling pathways associated with several neurotrophic and growth factors that control important processes in cells such as proliferation, differentiation, and death during brain development.<sup>31</sup>

## CONCLUSION

There was a decrease in IGF-1 in pups of FAS rats after their mothers drank binge alcohol during pregnancy. There was a decrease in the enzyme Aldehyde Dehydrogenase (ALDH) in the blood of the pups of FAS rats after their mother drank binge alcohol during pregnancy. There was an increase in Apoptosis indices in the pups of FAS rats after their mothers were given binge alcohol. There was a Fetal Alcohol Syndrome (FAS) defect on the pups of Wistar rats after the mothers was given binge alcohol.

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