

INVESTIGATING THE FETAL AND POSTNATAL EFFECTS OF PATERNAL ALCOHOL EXPOSURE IN MOUSE OFFSPRING: A REVIEW

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ABSTRACT

To further elucidate the possible effects of paternal alcohol exposure on fetal and post-natal development, Lee et al. conducted an experimental animal study from which potential transgenerational consequences of paternal alcohol exposure on mouse offspring were explored. The authors concluded that paternal alcohol consumption likely poses some risk to those developing offspring.

However, the authors' analysis of the incidence of fetal abnormalities may be misleading. The incidence of abnormality for each treatment group was calculated by dividing the number of abnormalities by the total number of dams. This approach to presenting the data is misrepresentative, because if a dam were carrying one abnormally developed fetus out of a litter of, say, 16, the entire litter would be captured as an "abnormality" in the calculation of incidence.

Key Words: *Paternal alcohol exposure, fetal effects, post-natal effects, transgenerational effects*

While the possible teratogenic effects of maternal drinking in pregnancy are widely documented and understood, the potential effects (if any) of paternal alcohol use prior to conception on the developing fetus or child are comparatively poorly elucidated in the existing literature. The mechanisms by which paternal exposure to alcohol can theoretically affect the developing fetus have not been clearly established, however, they might exist at the level of sperm DNA.¹ Emerging literature suggests an epigenetic mechanism of inheritance, whereby environmental factors can alter phenotype, which can be transmitted in subsequent generations. Epigenetic changes to sperm DNA induced by alcohol exposure may be responsible for the transgenerational effects of paternal alcohol use.¹ A number of studies have shown that paternal alcohol exposure prior to conception can lead to developmental^{2,3} and behavioural abnormalities^{4,5}, however, there are disparities in their findings.

In order to further examine the possible effects of paternal alcohol exposure on fetal and post-natal development, Lee et al. conducted an experimental animal study to explore the transgenerational consequences of paternal alcohol exposure on mouse offspring.⁶ Following

a seven-week exposure to one of five treatment groups (saline or 0.5, 1, 2, 4 g/kg of alcohol), male mice were mated to alcohol-naïve female mice. Fetal development was assessed at gestational day 16.5 and post-natal growth and organ weights were examined at post-natal days 35 and 56. The primary findings of the study were that the incidence of developmental abnormalities (agenesis and skull malformation) in the 4 g/kg alcohol treatment group was statistically different from the control group (saline) and that the major organ weights of postnatal offspring were affected by paternal alcohol exposure. The authors concluded that paternal alcohol consumption poses a potential risk to the developing offspring. In this review, we will address aspects of the study that limit the interpretation of its findings.

The novelty of this research article lies in the fact that it examined both fetal and post-natal effects of paternal alcohol exposure within one study. The authors were thorough in their examination of fetal development, capturing the average number of fetuses per dam and average fetus weight in each treatment group, along with macroscopically observed abnormalities.

However, the analysis of the incidence of fetal abnormalities may be misleading. The

incidence of abnormality for each treatment group was calculated by dividing the number of abnormalities by the total number of litters. This approach to presenting the data is misrepresentative, because if a dam were carrying one abnormally developed fetus out of a litter of, say, 16, the entire litter would be captured as an “abnormality” in the calculation of incidence. In other words, if every dam within a particular treatment group were carrying only one abnormally developed fetus, the incidence of abnormality would be 100%, despite the fact that the vast majority of fetuses are normally developed within each litter. A more informative approach to presenting the data would have been to compare the number of abnormal fetuses divided by the total number of fetuses for each treatment group. Had the authors chosen this approach, the data would reveal relatively similar incidences of abnormality between the treatment groups: 0/93, 1/120, 2/65, 0/101 and 3/63 for the control, 0.5, 1.0, 2.0 and 4.0 g/kg groups, respectively. The data should be interpreted in light of the fact that there is a baseline risk for defects that exist in every pregnancy, and that the species of mice used in this study (CD1) are known to be particularly sensitive to the effects of alcohol exposure.⁷ Hence, the evidence does not support the conclusion that paternal alcohol consumption prior to conception represents a potential risk to fetal development.

In the assessment of post-natal effects of paternal alcohol consumption, analysis of major organ weights revealed that the lung weights of F1 males were decreased at post-natal day 35, when exposed to 1 and 4 g/kg of alcohol, compared to control. These differences were no longer seen at post-natal day 56. On the basis of these results, the authors concluded that paternal alcohol exposure affected major organ weights of post-natal offspring.

These results should be interpreted with caution for several reasons. First, the authors, without explanation, conducted multiple comparisons without correction (i.e. Bonferroni). Second, the effects were seen at 1 g/kg, but not at double the dose - 2 g/kg. The authors should have clarified the factors that could have contributed to this result. Third, the differences in lung weights

appear to be transient, suggesting that if there are in fact post-natal effects of paternal alcohol consumption prior to conception, they appear to be temporary. The authors should consider other factors that mediate lung development in post-natal offspring. Although this study uniquely focuses on the effects of paternal alcohol exposure in both fetal and post-natal stages of development, the results should be interpreted with caution given the points addressed in this review.

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REFERENCES

1. Knezovich JG, Ramsay M. The effect of preconception paternal alcohol exposure on epigenetic remodeling of the h19 and rasgrf1 imprinting control regions in mouse offspring. *Front Genet* 2012;3:1-10.
2. Abel EL. Rat offspring sired by males treated with alcohol. *Alcohol* 1993;10:237-242.
3. Tanaka H, Suzuki N, Arima M. Experimental studies on the influence of male alcoholism on fetal development. *Brain Dev* 1982;4:1-6.
4. Abel EL. Paternal alcohol consumption affects grooming response in rat offspring. *Alcohol* 1991;8:21-23.
5. Ledig M, Misslin R, Vogel E, et al. Paternal alcohol exposure: developmental and behavioral effects on the offspring of rats. *Neuropharmacology* 1998;37:57-66.
6. Lee HJ, Ryu J-S, Choi NY, et al. Transgenerational effects of paternal alcohol exposure in mouse offspring. *Anim Cells Syst* 2013;17:429-434.
7. Houchi H, Warnault V, Barbier E, et al. Involvement of A2A receptors in anxiolytic, locomotor and motivational properties of ethanol in mice. *Genes Brain Behav* 2008;7:887-898.