IOSR Journal Of Pharmacy And Biological Sciences (IOSR-JPBS)
e-ISSN:2278-3008, p-ISSN:2319-7676. Volume 14, Issue 4 Ser. I (Jul – Aug 2019), PP 38-43
www.Iosrjournals.Org

The Maternal pregnancy outcomes following prenatal exposure to varied doses of alcohol in albino rats (*rattusnorvegicus*)

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Abstract: ***Background****- Problems related to ethanol (alcohol) ranks among the global public health concerns andIn-utero exposure to alcohol directly or indirectly perturb maternal organ functions like liver and placental among others. This perturbation has been shown to occurs through different mechanisms including alteration of maternalprotein, carbohydrate and lipid metabolism, as well as placental blood vessel vasoconstriction which in turn may interferes with fetal blood supply and oxygenation hence placing the fetus at risk of weight deficit, congenital defects among others.ThoughMany factors likethe genetic inheritance of mutant genes, nutritional status and many other factors have been shown toinfluence the range and severity of the maternal alcohol outcomes, data on whether the observed maternal alcohol outcomes are dose and time dependent are not well elucidated hence forming the basis of this study.*

Method*: To examine ethanol teratogenesis, 30 expectant dams weighing between 200 to 230 g were used. Simple random sampling was used to assign them into four study groups(A as control group, B –D as low, medium, and high alcohol treatment groups respectively).Each treatment group was further subdivided into first, second and third trimester alcohol treatment subgroup (each n=3) and alcohol was administered throughout the gestation period for trimester 1 subgroups (GD1-GD20), from second trimester for trimester 2 subgroups (GD7-GD20) and from trimester 3 for trimester 3 subgroups (GD14-GD20). Groups A served as Expectant control group and received food and water adlibitum only while Groups B, C and D received 2g/kg, 3.5g/kg and 5g/kg body weight of alcohol respectively once daily via oral gavage. The expectant dams were sacrificed on the 20th day of gestation and the number of fetuses and resorption were counted and recorded whereas, Fetuses were weighed and examined for gross morphological malformations. Fetal data was entered in excel sheet and analyzed using analysis of variance (ANOVA)*

Results*: Fetuses from albino rats exposed to alcohol in-utero had fetal and placental weight deficits, less litter size, increased number of resorbed glands as well as digits and vertebral malformations. Results showed a statistically significant dose and time-dependent decrease in fetal weight especially in treatment groups C and D ($p<0.05$).*

Conclusion*: the present study revealed that alcohol consumption in pregnancy has varying fetal teratogenic effects that are time and dose dependent.*

Alcohol causes varying degrees of injurious effectsto expectant mothers, thereforeshould be completely abstained during pregnancy

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Date of Submission: 29-06-2019 Date of acceptance: 15-07-2019

I. Introduction

Alcohol use by most people is enjoyable, socially accepted but progresses to alcohol abuse or alcoholism(1–3). Women who consume alcohol during pregnancy place themselves and their offspring at risk of a number of injurious effects(4,5), which may rage from placental insufficiency, placental weight deficit, alteration of growth factors, weight deficits among others(6–8). However, the most severematernal alcoholeffects on the developing fetus are diagnosed as fetal alcohol syndrome(FAS), a disordercharacterized by Malformations, intrauterine death, growth deficiency, craniofacial abnormalities and behavioral deficits among others(9–11). Because not all fetuses exposed prenatally to alcohol display the full spectrum of FAS symptoms, the term fetal alcohol spectrum disorders (FASD) has been used to describe the varying degrees of ethanolteratogenesis including FAS(1,10). Though thematernal injurious effectshave widely been studied, if this effects are time or dose dependent when alcohol is administered at varied doses at different gestational periods have not been well established hence the present study was conducted to observe thematernal ethanol effects and determine if they are time or dose dependent by using rats as the experimental model. On the other hand, prenatal effects of alcohol on the developing fetal organs may be associated with many childhood and adult neurodevelopmental and behavioraldeficits witnessed currently all over the world(12). This deficits may includedevelopmental delay, attention deficit, and hyperactivity among others(12,13).Moreover, studies have

shown that genetic differences particularly explain why some offspring of women who consume alcohol during pregnancy are severely affected while others are not(1).Globally,the prevalence of FASD among children has been estimated to be 7.7 per 1000 population of all live births(14), therefore with continued prenatal alcohol consumption, this prevalence may escalatein future hence this guarantees the current study to be carried out and determine if theteratogenic effects are time or dose dependent.

II. Material and Methods

Healthy female nulliparous Albino damsweighing 200 ± 30 gramswere obtained from the Safari Animal house of JKUATfor the experiment. Animals were kept in groups consisting of six rats per cage made of propylene in the animal house. All the animals *were a*cclimatization to laboratory conditions for a period of one week before treatment, received food (rodent pellets) from UNGA meals and water *ad libitum*

Mating and dosing*:* Four females were introducedinto a cage with two males at 2:00 P.M. to 09:00am. The following morning, the males were returned to their separate cages while a vaginal smear was taken from the dams to confirm pregnancy. Observation of large cornified cells, many neutrophils on the smear and scattered epithelial cells with presence of sperm cells confirmed pregnancy. The animal were randomly assigned to either the control or experimental study groups.

Experimental set up: Upon confirmation of pregnancy**,**the animals were randomly assigned into ten subgroups (control, low dose ethanol group trimester I, II, III, medium ethanol group trimester I, II, III and high ethanol group trimester I, II, IIIconsisting of three rats each. The first subgroup was give tap water and designated as control, while the other subgroups were given 30% ethanol solution through oral route using gavage needle. The LEG, MEG and HEG received 2g/kg, 3.5g/kg and 5g/kg body weight of ethanol respectively once daily via gavage needle at different gestational periods. All trimester I animals received ethanol from GD1-GD20, trimester II received from GD7-GD20 while trimester III animals received ethanol from gestational day 14-GD20. On gestation day 20, females were sacrificed; uterine hones were exposed and a count made of live, dead and resorbed fetuses.Fetuses were as well weighed, and examined for gross morphological malformations.

III. Results

The study sought to examine the maternaleffect of *ethanol* on fetusfollowingin-utero exposure to varied doses of ethanol upon sacrifice of the animals on day 20 of gestation .This was determined through count made of live, resorbed embryo as well as determination of the obvious congenital abnormalities.Thematernal and fetal weights were also measured. The data was analyzed using SPSS and Excel statistical software and was expressed as mean ± standard error (SEM). The study compared how the three dose levels (Low, medium and high) and control in the three trimesters (T1, T2 and T3), affected the different maternalpregnancy parameters. This parameters were: number of fetuses, fetal weight, resorbed fetuses and gross abnormalities. To determine the significance, one way analysis of variance with Tukey post hoc test was used and 5% significance level (α = 0.05) was assumed. The results were considered to be significant whenever the probability value is less than 0.05 ($p<0.05$). The results were presented below.

Table 1: Shows inter group comparison of different maternalparameters in the control, low, medium and high dosage groups in the first Trimester

Parameter	Control group	Low alcohol group TM1	Medium alcohol group TM1	High alcohol group TM1	F	P-value
Litter Size	10.33±0.882a	5.33±1.76ab	4.33±0.333b	3.67±1.45b	5.98	0.019*
Fetal Weight	6.27±0.033a	4.18±0.117b	4.07±0.056b	3.63±0.088c	216.23	0.000*
Number of Congenital Malformation	0.00±0.00a	3.00±1.15ab	3.67±0.88ab	4.67±1.20b	4.54	0.039*
Number of resorbed embryo	0.00±0.00a	1.00±0.58ab	3.67±2.03ab	6.67±1.45b	5.45	0.025*
Placenta Weight	0.543±0.023a	0.39±0.015b	0.39±0.007b	0.30±0.00c	4.948	0.000*

*Notes: The means, followed by the same letter in a row are not statistically different at (P<0.05) using one way ANOVA.withTukey test on post-hoc t-tests. * indicates significance (p<0.05).*

The results in table 1 above shows that the litter size in the control group was significantly higher than that in the medium and high dose group when ethanol was administered throughout the gestation, F (3, 8) = 5.98, p = 0.019. However the litter size in low dose was not statistically different from that in the control.

Fetal weight in the control group was significantly higher than that in the low, medium and high dose, F (3, 8) = 216.23, p = < 0.0001. The weight in low dose and the medium dose was not statistically different but was found to be lower in the high dose group.

The number of congenital malformations as well as resorbed embryo were foundto be significantly high in the low, medium and high dose, F (3, 8) = 4.54, P= 0.039, F (3, 8) = 5.45, P=0.025 respectively as compared to the control group.

The Placenta weight for the control group was found to be significantly different from that of the low dose, medium dose and high dose groups, F (3, 8) = 4.948, p=0.000. The placenta weight in the high dose was different from that of the medium and that of the low dose groups which were not significantly different.

Table 2: Shows inter group comparison of different maternalparameters in the control, low, medium and high dosage groups in the second Trimester

Parameter	Control group	Low alcohol group TM2	Medium alcohol group TM2	High alcohol group TM2	F	P-value
Litter Size	10.33±0.882a	7.0±1.73b	5.67±1.202bc	5.00±0.577c	4.1	0.049*
Fetal Weight	6.27±0.033a	5.17±0.067b	4097±0.033b	4.87±0.088c	115.4	0.000*
Congenital Malformation	0.00±0.0a	1.33±0.67ab	2.0±0.58ab	2.33±0.33b	4.792	0.034*
Number of resorbed embryo	0.00±0.00a	1.67±0.33a	2.67±1.20a	3.67±2.03a	1.725	0.239
Placenta Weight	0.54±0.023a	0.48±0.012ab	0.45±0.03b	0.42±0.007b	8.323	0.008*

*Notes: The means, followed by the same letter in a row are not statistically different at (P<0.05) using one way ANOVA.withTukey test on post-hoc t-tests. * indicates significance (p<0.05).*

The results in table 2 above revealed that the litter size in the control group wassignificantly different from that in the low, medium and high dose, F (3, 8) = 4.1, p = 0.049.

Fetal weight in the control group was significantly higher than that in the low, medium and high dose, F (3, 8) = 4.792, p = < 0.0001. The weight in low dose and the medium dose was not statistically different but was found to be lower in the high dose group.

The number of congenital malformations were foundto be significantly high in the high dose, F (3, 8) = 4.54, P= 0.034, as compared to the control however there was no significant difference observed between the low , medium and the high dose group. On the other hand, the number of resorbed embryo were not significantly different between the control and treatment groups.

The Placenta weight for the control group was found to be significantly different from that of the medium dose and high dose groups, F (3, 8) = 8.323, p=0.008. The placenta weight in the all treatment groups as well as low and control group were not different from each other

Table 3: intergroup comparison of different maternal parameters in the control, low, medium and high dosage groups in the third Trimester

Parameter	**Control** group	**Low** alcohol group TM3	**Medium** alcohol group TM3	**High** alcohol group TM3	**F**	**P-value**
Litter Size	10.33±0.882a	8.33±0.882ab	7.33±0.333bc	6.33±0.882c	4.773	0.034*
Fetal Weight	6.27±0.033a	6.10±0.058a	6.13±0.03ab	5.8±0.12c	8.22	0.008*
Congenital Malformation	0.00±0.0a	1.0±0.58a	2.0±1.0a	2.33±0.88a	2.11	0.178
Number of resorbed embryo	0.00±0.0a	0.33±0.33a	0.33±0.33a	0.33±0.33a	1.267	0.349
Placenta Weight	0.54±0.02a	0.58±0.01ab	0.52±0.01ab	0.50±0.003b	6.14	0.018*

*Notes: The means, followed by the same letter in a row are not statistically different at (P<0.05) using one way ANOVA.withTukey test on post-hoc t-tests. * indicates significance (p<0.05).*

The results in table 3 above shows that the litter size in the control group was significantly higher than that in the medium and high dose, $F(3, 8) = 4.773$, $p = 0.034$. However the litter size in low dose was not statistically different from that in the control.

Fetal weight in the control group was significantly higher than that in the high dose, $F(3, 8) = 8.22$, $p = 0.008$. The weight in low dose and the medium dose was not statistically different but was found to be lower in the control group.

The number of congenital malformations as well as resorbed embryo in low, medium and the high dose group were not significantly different , $F(3, 8) = 2.11$and 1.267 , $P= 0.178$, 0.349 respectivelywhen compared to the control group.

The Placenta weight for the control group was found to be significantly different from that of the high dose groups, $F(3, 8) = 6.14$, $p=0.018$. However the placenta weight in the low and medium alcohol group were not significantly different when compared with control group. The low, medium and high ethanol groups were not significantly different from each other.

IV. Discussion

Ethanol is a human teratogen (15,16).In addition, ethanol is a low molecular substance and is therefore quite capable of crossing the placental barrier and entering the fetus, causing the level of alcohol in the fetus to be approximate to that of the mother(5)The range of effect in individuals exposed to ethanol prenatally is broad and referred to as fetal alcohol spectrum disorder(FASD) that includes variety of structural and behavioral deficits(17). Among the developmental defects that ethanol has been implicated in are limb defects, vertebral defects and craniofacial defects among others(5). Ethanol causes the teratogenic effects through several mechanisms. Among this, some requires its oxidative metabolism that leads to production of a variant of oxidant species, producing an overall condition of oxidative stress(15,18). On the other hand, ethanol itself has solvent properties and can perturb biological membranes among other mechanisms therefore causing different developmental defects(19,20).In the current study, alcohol administration at high, medium and low dose was shown to cause injurious effects on the mother and the developing fetal organs. This effects were manifested by reduced fetal weight, reduced litter size, developmental defects and resorbed glands among others.

Fetal weight

In the current study, the fetal weight was significantly high in the control group as compared to ethanol treatment groups $p=0.0001$ which was less than 0.05 significance level as shown in table 1, 2 and 3. This concurs with a study which was done by **Michele Ramsay**,**(2010)** who correlated fetal alcohol spectrum disorder with level and nature of alcohol exposure where he observed that clinical severity upon in-utero ethanol exposure were time and dose dependent(12). Similar effects were also described by **Anulika*et al*(2018)**who associated teratogenic effects of alcohol on litter size and fetal weight(21). On the other hand, it has been demonstrated that newborns who are born to alcoholic mothers have weight deficits for a given gestational age(22).Ethanol has been shown cause fetal weight deficit by interfering with nutritional supply to the fetus via fetal-placental unit as well as through disruption of iron absorption, transport and storage by the developing fetus (1,10,13).Another study which was done by**Ertem *et al*,(2006)** contradicts the current study where no significant difference in fetal birth weight was observed upon prenatal maternal exposure to ethanol and this may have been due to the methodology used(23).

Litter sizeand embryonic resorption

Small litter size observed in the ethanol treatment groups as compared to the control group suggested the detrimental effects of ethanol on fetuses, indicating that ethanol can play an important role on embryo lethality as shown in table 1, 2 and 3. **Bosco*et al (*2012)**, reported that chronic ethanol use caused fetal resorption in the early stages of intrauterine development through placental oxidative stress that consequently interfered with placental villi formation leading to embryo death andresorption by maternal immune system(24,25). This concurs withanother study which was done by**Musumeci*et al*(2015),**and found that prenatalunder nutritiondue to ethanol reduced litter size by increasing embryo resorption and uterine embryo death(26).

On the other hand, embryonic resorption which is prenatal death followed by subsequent degeneration of the conceptus(27) was found to be statistically significant in the high ethanol group $p= 0.025$ when compared to the control group, however it was not found to be statistically significant in the second and third trimester as seen in table 1. The increased frequency of desorption in the first trimester indicates the adverse effects of in-utero ethanol exposure on fetal viability.This may have been due to the fact that ethanol interfered with placental villus formation as well as placental function therefore intrauterine embryo death which subsequently is recognized as foreign by maternal immune system hence resorption(6).This concurs with a study which was

done by**Mishra*et al* (2015),** who also found time and dose dependent embryo resorption upon ethanol administration to mouse(28)

Gross developmental defects

The present study has demonstrated that chronic ethanol consumption is teratogenic. Congenital defects observed in the present study were limb defects, vertebral defects and craniofacial defects among others. They were found to be significantly high $p<0.05$ in the high and medium ethanol groups when compared to the control group probably due to the prolonged exposure and dose of the ethanol as presented in table 1-3. This results agrees with other studieswhen alcohol was administered before and during pregnancy(6,24,29). Ethanol causes this defects through several mechanisms;including interference with growth factors, apoptosis of fetal cells, alteration of glucose transport and uptake by the cells as well as alteration of homeobox genes among others(30,31).

Placental weights

Low placental weight was recorded in the ethanol treatment groups $p= 0.0001$ which was less than 0.05 significance level (table 1-3) as compared to the control group when ethanol was administered in different trimesters revealing the effects of ethanol on the placenta. This study was with agreement with one conducted by **Lui*et al*(2014)** who indicated that ethanol causes oxidative stress that interferes with placental villi formation and placental blood flow through vasoconstriction consequently leading to local placental ischemia, infarction and reduced fetal growth(24). Similar effects were also observed by **Bosco*et al*(2012),** who stated that intra uterine ethanol exposure reduced placental glucose utilization, caused vascular abnormalities and reduced trophoblastic proliferation therefore this was associated with placental weight deficits(6).**Burd*et al*(2014)**, also found that ethanol induces dose dependent vasoconstriction which affects both placental and fetal weights(7)

V. Conclusion

It can be concluded that ethanol is teratogenic. It interferes with the placental functions and results in resorption of embryo. The dose effect relationship and time effect relationship was established conveying that the amount of alcohol ingested, the length of period in alcohol consumption and the developmental stage of the fetus at exposure mediate the effects of ethanol intake on the developing fetus. However public health messages about abstaining from alcohol when expectant and planning to conceive need to be promoted.

Acknowledgements

Author is grateful to Dr. Kweri J. Kariuki, The Chairman of Department in Human Anatomy, Jomo Kenyatta University of Agriculture & Technology for his unrelenting support and inspiration at each stage of this study.

Ethical Approval

Author hereby affirms that the experimental protocol was approved by the Jomo Kenyatta University of Agriculture and Technology Animal ethical Committee (JKUAT AEC). The animals were only used once. They were all sacrificed using humane end points at the end of the study. The protocol followed to the letter the Guidelines for Care and Use of Laboratory Animals in Biomedical Research.

CONFLICT OF INTEREST: None

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IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS) is UGC approved Journal with Sl. No. 5012, Journal no. 49063.

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