ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Alcohol Affects Pregnancy by Hypothalamic- Pituitary-Gonadal Axis Derangement.

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ABSTRACT

The present study investigated the deleterious effects of alcohol exposure on reproductive hormones during pregnancy. Forty Wistar albino rats (30 female & 10 male) were mated and randomized into 6 groups (n=5) and then administered with 25% alcohol daily through orogastric cannula from gestation day 0 to day 7 (Group 1), day 8 to day 14 (group 2) and day 15 to 21 (group 3). Group 4, 5 and 6 were control for 1, 2 and 3 respectively. At the end of each trimester, five rats were sacrificed from each experimental and corresponding control group and blood samples collected for FSH, LH, oestrogen and progesterone assay. The male rats were used for mating purposes only. One way analysis of Variance was used to compare means, *p*-value < 0.05 was considered significant. The result showed that alcohol decreased the FSH, LH, estrogen and progesterone levels during the course of the pregnancy with significance ($p<0.05$) especially in the third trimester. It was expected that there will be a rise in level of FSH and LH in response to decreasing oestrogen and progesterone level but that was not the case here This study therefore demonstrates that alcohol exposure adversely affects pregnancy through decrease in hormones that help in maintaining pregnancy especially in the third trimester possibly due to a derangement in the Hypothalamic- Pituitary-Gonadal (HPG) axis.

Keywords: Alcohol, Pregnancy, Hypothalamic-Pituitary-Gonadal axis, Female Hormones

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ISSN: 0975-8585

INTRODUCTION

In a pregnant woman, alcohol induced alterations in endocrine activity may affect not only her health but also her ability to maintain a successful pregnancy. Moreover, alcohol consumption during pregnancy can directly affect fetal development because alcohol readily crosses the placenta. Alcohol consumed during pregnancy may alter fetal development indirectly by disrupting the normal hormonal interactions between the mother and the fetus.

Ethanol (EtOH) is considered to be one of most common teratogenic substance, and prenatal alcohol exposure is a leading preventable cause of birth defects, mental retardation and neurodevelopmental disorders [1]. The increase in alcohol consumption during the past decades and, as a consequence, the increase in social problems, morbidity and mortality related to alcohol makes it one of the most important issues in the health policies in most countries [2] . Prenatal alcohol exposure has marked effects on the development of the foetus including the foetal hypothalamic-pituitary gonadal (HPG) axis in the offspring [3]. It has been observed that alcohol consumption during pregnancy leads to Foetal Alcohol Syndrome (FAS) in humans and other species which is characterized by growth deficiency, microcephaly and central nervous system dysfunction [4]. Neonatal alcohol exposure has been shown to cause cerebellar defects [5]. If neonatal alcohol exposure can affect the development of cerebellum, it is likely that other parts of the brain like the hypothalamus can be affected leading to disruption in hypothalamic-pituitary-gonadal (HPG) axis regulation. It is also possible that postnatal alcohol exposure could affect brain development if exposure coincides with the period of maximal vulnerability to environmental insults. This could also lead to marked effects on the development of HPG axis which plays a critical role in the control of reproduction [6]. This effect on HPG disrupts hormone release from pituitary gland and hypothalamus which can cause problems for female reproductive and sexual functions [7].

Several studies in both rats and monkeys have demonstrated alcohol–induced reproductive disruptions similar to those seen in humans. These studies have provided some information on how both acute and chronic alcohol exposure can alter the animals' reproductive systems [8]. Acute alcohol exposure given as a bolus to mimic binge drinking has been reported to disrupt the normal cycle at the time of exposure, with a return to normal by the following cycle [9]. This study therefore aim to assess the different trimester changes induced by alcohol on some female reproductive hormones in pregnant Wistar rats

MATERIALS AND METHODS

Alcohol

Alcohol in form of ethanol (EtOH) was obtained from the Department of Human Anatomy, Delta State University, Abraka. The concentration of ethanol used in this study was 25% at a dose of 0.015ml/g based on a previous study[10].

Animals

Thirty (30) adult female albino Wistar rats weighing between 170 to 190 g and ten (10) adult male rats weighing between 200 to 220 g were obtained from the animal house of the Faculty of Basic Medical Science, Delta State University, Abraka, Nigeria. The animals were housed five per cage, male separated from female and with a 12 h light/dark cycle. They were fed with standard laboratory chow and tap water *ad libitum*. The experimental procedures were approved by the Research and Ethics Committee, Faculty of Basic Medical Science, Delta State University, Abraka

Experimental design

Animals were divided into six (6) different groups (Group 1-6) and allowed to mate freely. Group 1-3 were experimental groups representing first, second and third trimester of pregnancy respectively while group 4-6 were controls for the experimental groups respectively. Mating was confirmed through vaginal smear examination by the presence of vaginal copulation plug. The pregnant rats were randomized into six (6) experimental groups of five (5) rats each. Group 1 was given 0.015ml/g of 25% alcohol intraperitoneally daily from day 0 to day 7, group 2 from day 8 to day 14 and group 3 from day 15 to day 21 of pregnancy. The control groups (4-6) were pregnant rats with no alcohol given but were also separated into the three trimesters.

ISSN: 0975-8585

Sample collection and hormonal assay

Light ether anaethesia was used to put the animals to sleep. The animals were sacrificed and blood samples collected into plain bottles. The sera were collected and stored at 10ºC and later assayed for follicle stimulating hormone, luteinizing hormone, estrogen and progesterone.

Statistical analysis

Statistical analyses of data were performed using SPSS 20 software. Data were expressed as means ± standard deviation. Statistical differences between the groups were evaluated by one way analysis of variance (ANOVA). Differences yielding p-values < 0.05 were considered statistically significant.

RESULTS

Fig 1 showed that alcohol decreased the mean progesterone level with each successive trimester. There was significant ($p<0.05$) decrease when the progesterone of rats treated with 25% alcohol in the 1st and 2nd trimester were compared with the progesterone of 3rd trimester rats treated with 25% alcohol. There was also significant ($p<0.05$) decrease in mean progesterone when the control rats were compared with the 25% alcohol treated rats in the 2nd trimester and 3rd trimester.

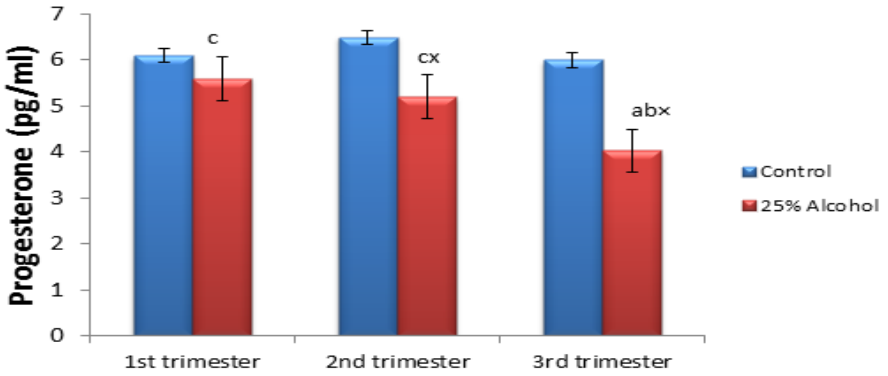

Fig 1 Effect of Alcohol on Progesterone level *(n=6);*

[a]p < 0.05 compared with 25% alcohol 1st trimester group; [b]p < 0.05 compared with 25% alcohol 2nd trimester group' [c]p < 0.05 compared with 25% alcohol 3rd trimester group [x]p < 0.05 compared with control group;

Fig 2 showed that estrogen increased throughout the duration of pregnancy in the control rats while it decreased in the rats treated with 25% alcohol. There was significant ($p<0.05$) decrease in the estrogen level in the rats treated with alcohol when compared with estrogen level in the control rats in the 3rd trimester.

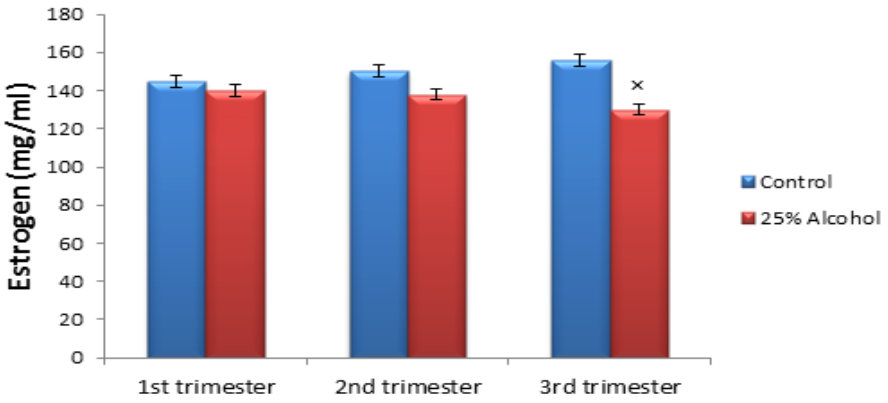

Fig 2 Effect of Alcohol on Estrogen level *(n=6);*

[x]p < 0.05 compared with control group.

ISSN: 0975-8585

Figures 3 and 4 showed that 25% alcohol decreased the follicle stimulating hormone and Luteinizing hormone during the course of pregnancy with significance ($p<0.05$) observed in the third trimester when compared to the first and second trimester FSH. In contrast, the FSH & LH of control animals recorded continuous but non-significant increase with each trimester. Comparing the control and the experimental rats FSH & LH, alcohol decreased the mean values of the hormones with significance ($p<0.05$) in the second and third trimester.

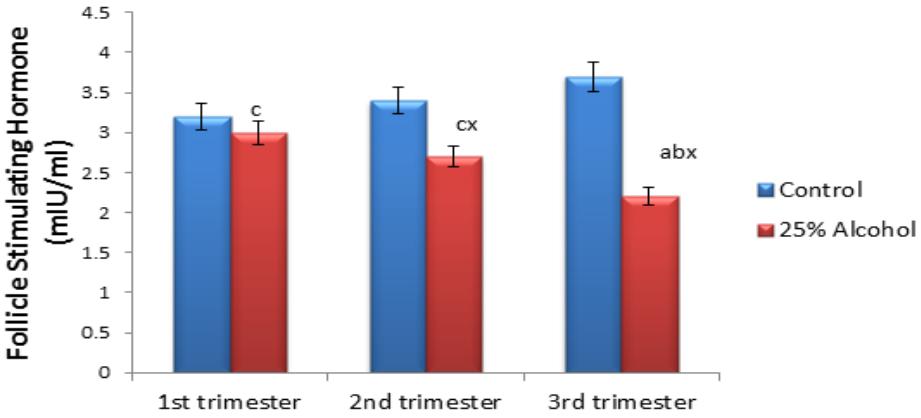

Fig 3 Effect of Alcohol on Follicle Stimulating Hormone level *(n=5);*

[a]p < 0.05 compared with 25% alcohol 1st trimester group; [b]p< 0.05 compared with 25% alcohol 2nd trimester group' [c]p < 0.05 compared with 25% alcohol 3rd trimester group [x]p < 0.05 compared with control group

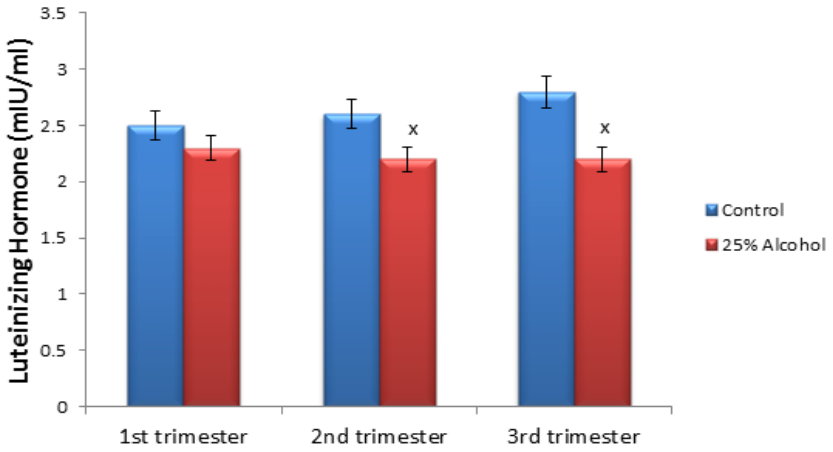

Fig 4 Effect of Alcohol on Luteinizing Hormone level *(n=5);*
[x]p < 0.05 compared with control group

DISCUSSION

The Hypothalamic-Pituitary–Gonadal (HPG) axis is the hormonal control system of reproduction where the hypothalamus secretes releasing hormones, which are transported via the blood to the pituitary gland. There, the releasing hormones induce the production and secretion of gonadotropins (i.e., LH and FSH), which in turn are transported by the blood to the gonads (i.e., the ovaries and testes).

The hormones of the Hypothalamic-Pituitary–Gonadal (HPG) axis, control reproductive functions and behavior. The HHG axis is activated by the secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus. GnRH, in turn, stimulates the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the pituitary. Both LH and FSH regulate the development, growth, maturation, and

reproductive functions of the gonads and stimulate the production of sex hormones, including estrogens and Progesterone.

Generally speaking, in females, LH and FSH stimulate the ovarian follicle that contains the maturing egg to produce estradiol. After ovulation has occurred, LH also promotes production of progesterone and E2 by the corpus luteum. Both hormones participate in a negative feedback mechanism through most of the menstrual cycle, suppressing GnRH release from the hypothalamus and LH release from the pituitary [11,12].

Result from this study showed deleterious effect of alcohol on the follicle stimulating hormone, luteinizing hormone and progesterone and estrogen level of pregnant albino Wistar rats. There was a decrease in the FSH, LH estrogen and progesterone level of pregnant rats treated with 25% alcohol in each trimester, with significance occurring mostly in the third trimester. This could suggest that the most severe hormonal effect of alcohol appears at the final stage of pregnancy. The decrease in these hormones would be attributed to ethanol inhibition of LH-stimulated secretion of estradiol and progesterone in human granulosa cells [13] possibly mediated by a decrease in LH-receptors [14]. Low levels of LH and FSH in spite of low estrogen levels, but a normal response to LHRH, are found among female alcohol abusers with alcoholic liver disease indicating a disturbance at the hypothalamic level of the hypothalamic-pituitary- gonadal –axis[15,16].

Teoh et al., [17] reported that alcohol suppression of progesterone could be as a result of breakdown of alcohol which is accompanied by the conversion of NAD+ to NADH. This in turn would affect adversely the rate of conversion of pregnenolone to progesterone which requires NAD+. Ahluwalia et al.,[18] while carrying out an in vitro study using human placental cells exposed to alcohol concentrations, reported that alcohol caused a significant decrease in progesterone synthesis.

In the present study, it seemed that the feedback mechanism control of decreased level of oestrogen and Progesterone by LH and FSH is lost, may be due to a derangement in the HPG axix control mechanism.

Several contrasting reports on alcohol effect on estrogen as observed in this study has been recorded. Wimalasena et al.,[14] showed that ethanol increase estradiol secretion during non-stimulated conditions in granulosa cells. Reports from Ylikorkala et al., [19] explains the possible reason for these changes observed in this study, with decreased Sex Hormone- Binding-globulin (SHBG)-levels been reported among pregnant women giving birth to infants with fetal alcohol syndrome.

CONCLUSION

The results demonstrated that maternal alcohol exposure adversely affects the pregnancy course, through its decrease in follicle stimulating hormone, luteinizing hormone, progesterone and estrogen level with more critical effect in the third trimester pregnancy. It is therefore recommended that further research be carried out on the structural malformation and changes due to alcohol intake in the different trimesters of pregnancy.

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