EFFECTS OF PREGNANCY AND PROGESTERONE ON THE CONSUMPTION OF ETHANOL BY THE HIGH ETHANOL PREFERING (HEP) RAT

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Abstract — A significant fraction of women continue to drink heavily during pregnancy, which is associated with the fetal alcohol syndrome, alcohol-related birth defects, alcohol-related neurodevelopmental disorder, and spontaneous abortion. The objective of this study was to determine whether the selectively bred genetic drinking Myers High Ethanol Preferring (HEP) rat would continue to drink through pregnancy. Rats from the F7 generation were screened by a 10-day 3–30% (v/v) ethanol concentration ‘step up’ procedure in order to determine the concentration which resulted in maximal drinking with an ethanol solution to total fluid ratio closest to 0.5. After baseline drinking of the preferred concentrations was established, female HEP rats were randomly selected for mating and their ethanol bottles were removed. Upon finding a ‘sperm plug’, male rats were removed and the ethanol was returned. A second group received injections of progesterone in sesame oil beginning with a 1.0 mg/kg/day dose which was increased to 3.0 mg/kg/day on gravid days (GD) 5–20. Vaginal smears confirmed that progesterone rendered the rats anoestrous. Neither pregnancy nor progesterone changed either the amount or proportion of ethanol consumed compared to the baseline period. The rats drank an average of 8.4 g/kg daily throughout pregnancy. A sharp drop in food intake was noted the day after mating. Beginning on GD 13, it was observed that pregnant rats showed a marked increase in the variance for proportion of ethanol consumed and body weight. Subsequently, only one of the eight impregnated rats successfully delivered a litter. The ethanol solution was removed and these rats mated again: seven of the eight rats delivered litters. These two findings suggest that the pregnant females must have begun to lose their litters on or after GD 13. Further, pregnancy does not affect the consumption of ethanol in the HEP rat. In addition, due to the fact that drinking by HEP rats during pregnancy leads to such a high rate of resorption of the fetus, this hybrid strain may also constitute a useful model for the study of alcohol-induced spontaneous abortion.

INTRODUCTION

The primary objective of this research was to investigate the effects of pregnancy or progesterone on the consumption of ethanol by the Myers High Ethanol Preferring (HEP) rat in order to find a valid model for the severe female alcoholic. It has been clear for many years that genetics plays a role in human alcoholism (Cloninger et al., 1981; Cloninger, 1987; McGue et al., 1992). The HEP rat meets the two criteria needed in order for an animal to be considered a valid genetic model of the human alcoholic (Lankford et al., 1991; McMillen, 1997). First, it imbibes high concentrations and copious amounts of ethanol in water for a pharmacological effect, which is indicated by high blood-ethanol levels (Myers et al., 1998; West et al., 1999). Second, it continues to do this when a nutritional, highly palatable alternative, such as a chocolate solution, is offered in addition to an ethanol solution and water (Myers et al., 1998). The sixth generation of female HEP rats consumed more ethanol (a mean of 10.3 g/kg at a mean concentration of 15.7%) than any other rat previously selectively bred to drink alcohol, including the HEP males. Another noteworthy characteristic is that ethanol consumption does not vary during the oestrus cycle (Myers et al., 1998), which has been apparent in outbred strains of rats (Forger and Morin, 1982). In addition, the HEP rat drinks ethanol immediately at first exposure, even at 30 days of age (Myers et al., 1998).

Data collected on humans suggest that most non-alcoholic women decrease their alcohol consumption during the first trimester of pregnancy, citing a distaste for alcohol as the reason for the reduction (Little et al., 1976). Another study conducted on 530 pregnant women, 90% of whom drank before and during their pregnancies, demonstrated that the proportion of drinking women decreased with advancing gestational age. Fifty per cent of the women retrospectively reported drinking after 32 weeks and only 20% reported drinking during the last week of gestation (Halmesmaki et al., 1987). These percentages indicate that a significant number of women continue to drink during pregnancy.

The trend of decreasing alcohol consumption during pregnancy occurs in other animals that drink alcohol, including mice (Emerson et al., 1952), rats (Means and Goy, 1982; Sandberg et al., 1982), hamsters (Carver et al., 1953; Morin and Forger, 1982), and monkeys (Elton and Wilson, 1977). The fact that this occurs in a number of different species in conjunction with the observation that a substantial amount of women acquire a taste aversion for alcohol during pregnancy (Little et al., 1976) suggests that there is a protective mechanism for the fetus, mediated by reproductive hormones, that has evolved to cause the gravid female to reject potentially toxic substances.

To date, a limited number of studies have utilized genetic female drinking rats, and no research has been done on these animals during pregnancy. Two independent studies have shown that outbred strains of rats decreased their proportion and consumption of ethanol during pregnancy (Means and Goy, 1982; Sandberg et al., 1982), but the ethanol solution contained saccharin and these rats were probably drinking for either caloric value or taste (Reid, 1996). The HEP rat, on the other hand, consumes ethanol for a pharmacological effect,
and will develop significant blood-alcohol concentrations (Myers et al., 1998). The female HEP rat therefore may provide a model for the testing of behavioural and drug interventions on drinking, as has been attempted in the present study.

MATERIALS AND METHODS

Twenty-five female rats from the F7 generation of the HEP colony started at East Carolina University were divided into three groups and maintained in a temperature- and humidity-controlled room with a light cycle of 14 h on : 10 h off. The P1 generation for these rats consisted of three male alcohol-prefering P rats obtained through T-K. Li at the Indiana University Alcohol Research Center, USA and three female Sprague-Dawley rats purchased from Harlan Sprague-Dawley. Each new generation was bred by selecting high drinking male and female rats from different litters for mating. The rats were allowed free access to food and water. Beginning at 40 days of age and again at 80 days of age, each rat was individually housed in a stainless-steel suspended cage and presented with three drinking bottles; one containing water, one empty, and one containing 3% (v/v) ethanol. The concentration of ethanol was increased daily to: 5, 7, 9, 11, 13, 15, 20, 25, and 30%. Food, fluids, and body weight were measured daily and the position of the bottles rotated in a semi-random sequence in order to prevent development of a side preference. During the interval between these two screens and afterwards, each rat was housed individually in standard plastic cages with corncob bedding. After the second step-up procedure, the concentration of ethanol which produced the maximum amount of ethanol consumed with a proportion of ethanol to total fluids closest to 0.5 was chosen as the preferred concentration for each rat for the remainder of the study. The proportion of 0.5 was chosen to allow for any large increases or decreases in proportion throughout the test period.

The rats were placed into three conditions: either impregnated by F7 male HEP rats: given injections of progesterone to mimic pregnancy; or served as controls while their drinking was monitored. The 25 rats were divided into two groups: a group of 11 and a group of 14. The difference between the two groups was the environment in which they were tested. The first group of 11 rats were housed on the stainless-steel battery. Due to the fact that three of four presumed pregnant rats in this group failed to deliver pups, it was thought that the stainless-steel cages may have been a factor in the pregnancy failures. Therefore, the second group of 14 were housed in standard plastic cages with corncob bedding which is the environment normally used by the Department of Comparative Medicine for breeding. This change necessitated two separate protocols: one for the first group of 11 rats and another for the second group of 14 rats.

Protocol 1

After a 10-day stabilization period of drinking ethanol at each rat’s preferred concentration, the 11 rats were divided into three groups (pregnant, progesterone injection, or control). This division was based on each rat’s daily g/kg consumption of ethanol, so that each of the three groups had approximately the same level of intake. This division resulted in four rats that were impregnated, three rats that received progesterone injections, and a group of four controls.

To impregnate the females, the alcohol tube was removed each night and a high alcohol-consuming male HEP rat was placed in the cage for co-habitation. The male rat was removed in the morning and the alcohol bottle returned. This was repeated until a sperm plug was found in the litter tray under each cage of the four rats. The day the sperm plug was observed was designated day 1 of pregnancy or gravid day 1 (GD1). The rats were then, once again, allowed 24-h access to the alcohol solution. Each day, the volume of fluids, body weight, and amount of food (Pro Lab Chow) consumed were recorded. At GD17, a paper towel was placed in each of the cages on the battery that contained a pregnant female, so that she could begin nest-building activities. In addition, a piece of screen was placed on the floor of each cage so that the newborn pups would not fall through the grid floor. Three of the females in this group did not give birth and were later reimpregnated in the absence of alcohol and kept in standard cages with corncob bedding to show that they were capable of delivering a litter.

The progesterone group of three rats received injections of progesterone in sesame oil in order to mimic the pregnant state. The sesame oil was used as a depot to slow and prolong progesterone absorption. On gravid days (GD) 1 and 2, the rats received a 1.0 mg/kg dose of progesterone in sesame oil. On GD 3 and 4, the rats received a 2.0 mg/kg dose of progesterone in sesame oil. And on GD 5 to 20, the rats received a 3.0 mg/kg dose of progesterone in sesame oil. The 3.0 mg/kg dose of progesterone is reported to inhibit cycling by females and mimic the pregnant state and this sequence mimics the rise in progesterone after impregnation (Zarrow et al., 1964). As with the impregnated dams, body weight, food intake, and fluid consumption were recorded. Vaginal smears were also performed on this group in order to confirm that progesterone inhibited cycling (Weill, 1996).

The control group of four rats received no treatment. After data were collected on the control group, they were impregnated to show that they were capable of reproduction. Therefore, any differences in consumption between the controls and the experimental groups could not be attributed to differences in reproductive potential (Means and Goy, 1982).

Protocol 2

A second group of HEP female rats went through the standard 10-day stabilization period on the battery. It was at this point that the decision was made to alter the living environment to increase the likelihood of the females giving birth. The entire group of 14 female rats was taken off the battery and placed in individual plastic cages adapted to hold three drinking bottles on one end. Therefore, the stabilization period was repeated with the rats in their new environments. After this second 10-day stabilization period was repeated, the 14 rats were divided into three groups (pregnant, progesterone injection, or injection control) as before. This division was based on each rat’s g/kg ethanol consumption during the stabilization period, so that each group had approximately the same level of ethanol consumption. The division resulted in a group of four impregnated dams, five rats that received injections of progesterone, and a group of five controls which
received injections of sesame oil. Combined with the rats from protocol 1, this resulted in a total of eight pregnant females, eight females which received injections of progesterone, and nine controls, for the entire experiment.

Impregnation of the four females was accomplished by taking them out of their standard plastic cages each night and placing them in individual cages on the stainless-steel battery with two water bottles and a high ethanol-consuming male HEP rat. The female was placed back in her standard cage with alcohol each morning and back on the battery at night. The day a sperm plug was found was designated GD1 and the placing them in individual cages on the stainless-steel battery.

Each day, the volume of fluids, body weight and amount of food consumed were recorded. At GD17, bedding materials were placed in each of the four cages, so that the pregnant mothers could begin nest-building activities. None of the four females delivered, so they were re-impregnated in the absence of alcohol to show that they were capable of delivering a litter.

The injection group of five rats was administered by s.c. injections of progesterone in sesame oil to mimic the pregnant state in the same manner as in protocol 1. The only difference was that these females were in standard cages, as opposed to the cages on the battery.

The control group received injections of sesame oil only, to test for the possibility that the injections themselves or the vehicle had an effect on ethanol consumption. After data were collected for this group of controls, each of the five females was impregnated for the same reason stated in protocol 1.

STATISTICAL METHODS

Intra-group g/kg consumption, proportion of ethanol to total fluid consumed, changes in body weight, and food consumed were analysed for significance by repeated measures one-way analysis of variance (ANOVA) utilizing GB-STAT 5.4 (Dynamic Microsystems Inc., Silver Spring, MD, USA). Individual time points were compared to baseline, an average of the 4 days prior to GD 1, using Dunnett’s (treatments vs control) test. Inter-group comparisons of the same dependent variables were also analysed for significance by ANOVA. Data are expressed as means ± SEM with significance (P < 0.05) displayed with a symbol (either an asterisk, a plus sign, or a letter) on the figures. Some values present the standard error of the mean (SEM) in order to illustrate changes in variance.

RESULTS

Pregnancy outcomes

In the first group of 11 females, one of four pregnant females successfully delivered. The one HEP rat which did deliver did so rather unexpectedly, 3 to 4 days later than normal. After no pups could be palpated in the rat’s abdomen on GD 23, it was taken off the battery and put in a standard cage with just a water bottle. On GD 25, it gave birth to a small litter of eight pups (six viable, two dead), with the six weighing a total of 36 g. It was this unexpected result that led to the change in environment in which the second group of 14 rats was housed. This was done in an effort to determine if the environment offered by the small stainless-steel cages of the battery contributed to the high rate of fetus resorption. Although the high rate of resorption could have been due to the fact that the pregnant mothers were imbibing copious amounts of ethanol, it is possible that the confined environment in which they lived contributed to the resorptions. None of the females in the second group of 14 delivered. All of the females that failed to deliver (seven of eight in the pregnant group) apparently resorbed their fetuses, because there was no evidence of parturition in any of the cages.

Vaginal smears

Vaginal smears confirmed that the 3.0 mg/kg daily dosage of progesterone made the rats anoestrous. Anoestrous is the non-receptive period of the oestrous cycle, and is characterized by small, round, immature epithelial cells with large nuclei. A smeared slide typically has a few cells: two to five per low power field. Confirmation of cycling by the control rats which were re-mated and subsequently failed to deliver, and the one rat from the pregnant group which also failed to deliver after being taken off the alcohol, was also provided by vaginal smears. After removal of ethanol, oestrous in these rats was demonstrated by the large numbers of angular, anuclear, cornified epithelial cells found in clumps on smeared slides (Weil, 1996).

Consumption of ethanol

Consumption of ethanol for each of the three groups of HEP rats (pregnant, progesterone, and control) primarily ranged from 6 to 10 g/kg per day. Overall, daily consumption during the baseline period averaged 7.10 ± 0.65 g/kg for the controls, 7.69 ± 0.94 g/kg for the pregnant rats, and 7.02 ± 1.21 g/kg for the progesterone treated rats (Fig. 1). The average preferred concentration of ethanol for each group was 14.4, 17.9, and 16.0%, respectively. There was no effect of housing condition, stainless-steel vs standard plastic cages, on the amount of ethanol consumed. Drinking was remarkably steady over the 25-day testing period, with two exceptions, but ANOVA revealed differences from baseline during the experiment: for the combined control animals, \( F(8,24) = 2.046, P < 0.01 \); for the pregnant group, \( F(7,27) = 1.714, P < 0.05 \); and for the progesterone group, \( F(7,25) = 0.933 \), n.s. On GD 16, the control group’s consumption (9.71 ± 1.42 g/kg) varied from baseline (\( P < 0.01 \)), and on GD 17 the pregnant group’s consumption (12.17 ± 3.4 g/kg) varied from their baseline (\( P < 0.05 \)). The pregnant group exhibited a decrease in drinking following cohabitation on GD 1, and an increase on GD 3, neither of which was statistically significant (Fig. 1A).

Proportion

No significant differences were noted for any of the three groups with regard to the proportion of ethanol to the total volume of fluids consumed. Average proportion was approximately 0.5, with a range of 0.4–0.6 (Fig. 1B). Recall that the concentration of alcohol was selected for each rat to be near a proportion of 0.5.

An increase in variance was demonstrated by the pregnant group, which began on GD 14 and continued until GD 19. The increase in variance was not due to a consistent change in one or two females, but rather all of the females exhibited an increased variance. By comparing the range of values for
proportion for each rat on GD 8–13, the 5 days prior to the increase in variance, to the range of values on GD 14–20, it was discovered that every rat had at least 1 day with a lower value for proportion, and five of the eight had at least 1 day higher. For example, one rat had values for proportion that ranged from 0.50 to 0.625 during GD 8–13. This same rat had values for proportion that ranged from 0.327 to 0.785 during GD 14–20. These highs and lows occurred on different days for different rats. No significant increases in variance of proportion were noted in the control or progesterone-treated groups (Fig. 3A).

Food consumption

No significant increases in food consumption were found; however, significant decreases were noted for all three groups: over time, ANOVA revealed for the control group $F(8,25) = 5.353$, $P < 0.001$; for the pregnant group $F(7,27) = 3.415$, $P < 0.001$; and for the progesterone group $F(7,27) = 6.534$, $P < 0.0001$ (Fig. 2A). Of the three, the pregnant group exhibited the greatest decrease in food consumption, which occurred on GD 1, with a mean consumption of $7.73 \pm 1.26$ g ($P < 0.01$). Significant decreases were noted on GD 7, 15, and 17 for the progesterone group with means for consumption of $10.83 \pm 1.68$, 11.95 $\pm 0.75$, and $11.83 \pm 1.26$ g respectively. The control group consumed significantly less food on GD 1, with a mean consumption of $11.06 \pm 2.62$ g (Fig. 2A). Two of the animals in this group did not eat on that day. The pregnant group did not show the same consistent change in variance as it did on other measures later in the study period.
Changes in body weight

Overall, the weights of each group increased during the 25-day test period (Fig. 2B). over time, ANOVA revealed for the control group $F(8,25) = 4.937, P < 0.0001$; for the pregnant group $F(7.27) = 16.616, P < 0.0001$; and for the progesterone group $F(7.25) = 11.586, P < 0.0001$. The pregnant group exhibited the most weight gain by far, 0.028 kg, which was an expected result. Weight gain for this group reached a significant level on GD 5, with a mean weight of $0.281 \pm 0.007$ kg ($P < 0.01$), and remained significant for the remainder of the experiment. The control group and the progesterone-treated group also showed significant, but smaller gains in weight. For the control group, weight gain reached a significant level on GD 10, with an average weight of $0.277 \pm 0.007$ kg ($P < 0.01$). Total weight gain for this group over the test period was 0.011 kg. Weight gain reached a significant level at GD 12 for the progesterone group, with a mean weight of $0.283 \pm 0.007$ kg ($P < 0.01$). The composite weight gain for this group was 0.015 kg (Fig. 2B). Beginning at GD 13, the SEM for the body weight of the pregnant group markedly increased, reaching a peak of 0.011 kg on GD 20. Variance for the other two groups remained fairly constant at lower levels (Fig. 3B).

DISCUSSION

Neither pregnancy nor injections of progesterone given to the HEP female rats modified their consumption of ethanol. It should be pointed out that seven of eight of the impregnated rats had lost their pregnancies either before or during the last week of gestation and that the consumption of alcohol solutions during this period of time was not by pregnant animals. The proportion of ethanol to total fluid consumed also was unaffected. Both of these findings conflict with findings from other studies conducted on outbred strains of rats. Outbred strains of rats, Wistar and Long-Evans hooded rats, reduced their intake and proportion of ethanol to total fluid during pregnancy (Means and Goy, 1982; Sandberg et al., 1982). The HEP rats continued to consume copious quantities of ethanol at a proportion near 0.5. Thus, inbred genetic drinkers did not follow the pattern of outbred strains.

Weight gain by the pregnant group was considerably less than that which is normally expected by pregnant rats. The weight gain exhibited by both the control and the progesterone groups was considered normal for a 20-day time period. Pregnant Sprague–Dawley rats housed under the same conditions in the same vivarium without alcohol exhibited a 60% increase in body weight (an approximate gain of 0.15 kg) during pregnancy and had an average litter size of 14 pups (Henderson, 1990). This difference may be due largely to the presumed resorption of the foetuses prior to the final week of gestation when weight gain is greatest. Despite only having eight pups, the one pregnant female that did deliver still managed to gain slightly over 0.1 kg. Most of this weight gain (0.7 kg) came during the final week of pregnancy, which coincides precisely with the time that the other seven pregnant females began losing their pregnancies. Small litter size and delayed delivery are just two of many deleterious effects caused by alcohol on pregnant rats and their offspring (Abel et al., 1979; Sanchis et al., 1986; Streissguth, 1997).

A general trend of increased food consumption was exhibited by the pregnant group. Although this increased consumption was not significant on any given day, it was expected, due to the fact that the demand for nutrients and calories increases during pregnancy. It is unknown why the pregnant animals significantly decreased their consumption of food immediately following cohabitation at day 1. Perhaps, the stress of mating mediated the reduction.

A marked increase in the variance for proportion, but not amount, of ethanol consumed, was shown by the pregnant group beginning at GD 14. Drinking during the last week of pregnancy greatly fluctuated. Perhaps this was mediated by the females apparently undergoing resorption. Due to the fact that the amount of ethanol consumed did not change, with the exception of GD 17 when an increase was noted, the HEP rats must have been drinking more or less water during that time period (depending on the day in question). In fact, each rat had an increased range of values for proportion during the last week of the experiment.

A very similar increase in the variance for body weight was also observed in the pregnant animals beginning on GD 13.
This finding, in conjunction with the increase in variance for proportion, which both began around the same time, led to the conclusion that the pregnant females must have begun to lose their litters at various times thereafter. If the weight for the one dam which maintained its pregnancy is dropped from the data matrix, there is still a 50% increase in the standard deviation during GD 16–21, compared to GD 7–12. Five of the seven remaining rats exhibited an unexpected weight loss, one as much as 0.014 kg from peak weight, during this last week of gestation.

The copious quantities of ethanol that the pregnant females imbibed led to an apparent high rate of foetus resorptions. Seven of the eight females in the pregnant group apparently had resorbed their foetuses. But, when these seven were removed from the ethanol and mated again, six successfully delivered litters. Clearly, ethanol was adversely affecting pregnancy outcomes. Padmanabhan and Hameed (1988) demonstrated that administration of an acute dose of ethanol (0.03 ml/g body weight of 25% v/v absolute ethanol, or approx. 6 g of ethanol/kg) on GD 1–6 markedly increased prenatal mortality (resorptions) in mice. This also suggests that ethanol is lethal to the developing embryo. Administration of ethanol solutions by gavage to pregnant mice from different strains demonstrated that there are also strain-specific sensivities to the teratogenic effects of ethanol (Gilliam and Kitch, 1990; Boehm et al., 1997).

In the same manner that fecundity decreases with age, drinking during early development has also been shown to decrease fecundity. In fact, the HEP rats were drinking large quantities of ethanol as early as 40 days of age during the first screen. Cebal et al. (1997) observed significantly decreased in vitro fertilization rates when oocytes from prepubertal and pubertal ethanol-treated female mice were inseminated with spermatozoa from adult control males. The aim of that particular study was to investigate the effects of low chronic alcohol intake on fertility. Ethanol in tap water at a concentration of 5% (a low dose) was administered to hybrid F1 mice (C57/B1 X DBA) for 4 weeks. Low chronic ingestion of ethanol sufficiently reduced the percentage of activated oocytes, and increased the number of fragmented oocytes taken from immature females, such that in vitro fertilization rates were decreased. Others have also reported that daily oral administration of ethanol solutions decreased fecundity and increased gestation time in rats (Abel et al., 1979; Sanchis et al., 1986). Other deleterious effects of ethanol on immature female rats include: delayed vaginal opening, decreased uterine and ovarian weights, and depressed ovarian function (Gavalter et al., 1980; Bo et al., 1982). In addition, ovarian failure has been found to occur in rats that are fed high doses of ethanol (Van Thiel et al., 1978). Ethanol is undoubtedly a reproductive toxin as well as a teratogen.

Contemporary studies have shown a correlation between alcohol consumption and an increased risk of spontaneous abortion in women. In the USA, women who had been clinically diagnosed as alcohol abusers were twice as likely as controls to have suffered three or more spontaneous abortions (Sokol et al., 1980). A survey of clinical literature regarding fetal alcohol syndrome (FAS) found that out of 90 women who had given birth to children with FAS, 52% had had at least one spontaneous abortion, and the average rate of spontaneous abortion per mother was 2.2 (Abel, 1990). In spite of the plethora of studies which have been conducted on the matter of spontaneous abortion, no threshold level or critical time period of consumption leading to the occurrence of spontaneous abortion has been established. In a retrospective study, Wilsnack et al. (1984) estimated the threshold for spontaneous abortion at six or more drinks/day consumed at least three times/week. This high level of consumption would be typical of an alcoholic. Lower thresholds have been proposed, which suggest alcohol may harm the fetus not only when alcohol is abused, but also when taken in moderation. In a study of second trimester losses, which in the rat is equivalent to GD 14–20 (the time period in which the females presumably lost their litters), one or two drinks daily doubled the risk of spontaneous abortion, and more than three drinks daily more than tripled the risk (Harlap and Shiono, 1980). Windham et al. (1997) found a twofold increase in the risk of spontaneous abortion with an average consumption of seven or more drinks/week during the first trimester. A doubled risk was also found by Kline et al. (1980) for a weekly consumption of two to six drinks. In addition, risk increased an average of 25% for each additional ounce of alcohol consumed by pregnant women in a study performed by Russell and Skinner (1988).

Some 6–20% of women have been reported to drink heavily during pregnancy (Halmesmaki et al., 1987). Reductions in alcohol consumption in human females tend to be inversely proportional to prior consumption. Therefore, women who drink heavily prior to pregnancy (alcoholics) are most often those who continue to drink heavily throughout their pregnancies (Little et al., 1976). Like these women, female HEP rats do not curtail their drinking during pregnancy, and could therefore be considered valid models of the severe type 2 female alcoholic. The HEP rat’s high level of alcohol consumption during pregnancy led to an apparent high rate of fetal resorptions. Due to this, the HEP rat could also potentially offer a second model for alcohol research — a model of alcohol-induced spontaneous abortion. More research on the effects of ethanol on fecundity and the nature of pregnancy loss will be necessary to better define this animal as a model.

Such models could make additional research possible which in turn could substantially contribute to our understanding of the relationship of dosage, developmental timing, gender differences, genetic susceptibility, and differences in tolerance elicited by hormonal changes during pregnancy. These rats could also be used for testing drug and behavioural treatments. Such research could point towards additional therapeutic approaches that could be used on women who abuse alcohol during their pregnancies. New treatments could significantly improve the quality of life of females afflicted with alcoholism. This in turn would help decrease the prevalence of completely preventable disabilities such as FAS, alcohol-related birth defects, and alcohol-related neurological defects, as well as decrease the incidence of alcohol-induced spontaneous abortions.

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