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The Maternal Pregnancy Outcomes Following Prenatal Administration of Varied Doses of Carbamazepine inAlbino rats (Rattus *norvegicus*)

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Abstract: *TheIn-utero exposure to carbamazepine has been shown to perturb maternal digestion as well as cell and tissue metabolic processes when used during pregnancy. Literature has shown thatit perturb the endogenous bioelectrical mechanisms and voltage gradients that guides maternal metabolic pathways of cells and tissues. Further, it also disturbs the fetal growth and development as it interferes with fetal patterning programs,cell division, cell positioning, and cell differentiation as it readily crosses the maternal placental barrier. Though, literature has shown an association between carbamazepine use and adverse pregnancy outcomes when applied in utero, the specific adverse effects on pregnancy outcomesincluding; maternal weight trends during the gestational period, the numbers of litter sizes, fetal resorptions, congenital malformation, and morphological features of the placenta are yet to be elucidated. Further, whether or not the observed adverse pregnancy outcomes are dose and time dependent is yet to be determined. This study aimedto establish the adverse maternal pregnancy outcomes following administration of varied doses of cabermazepin at different gestational trimesters.In carrying out the study, a total of 30 nulliparous female Albino rats (Rattusnorvegicus) weighing between 150 - 250g were randomly assigned into four study groups follows; 3 control, and 27 experimental groups of LCG, MCG and HCG each composed of nine rats each, these 9 rats in each of the experimental group were further subdivided into 3 study rats into TM1, TM2, and TM3 with three rats each. Carbamazepine was administered to the treatment groups though the oral route by use of a gavage needle. The control group received food and water ad-libitum/day while the experimental groups received varied doses of cabermazepin as follows 20.7, 72.5, 124g/kg/Bwof carbamazepine/day for Low dose, medium and high doses groups respectively as well as water ad-libitum. Daily maternal trends were taken and recorded. At 20th day of gestation, all animals were euthanized and sacrificed by hysterectomy. Litter size, fetal weight, placenta weight, number of resorbed/devoured endometrial glands, number of fetuses with congenital malformations and dead fetuses were examined and recorded accordingly. Data was then entered into the computer and analyzed using Statistical Package for Social scientists version 24 for windows Chicago Illinois. The liner regression statistics,intra and intergroup comparisons were done using one-way analysis of variances (ANOVA) and P-values of less than 0.05 were taken to be significant. The finding of the study showed that there was statistical significant decrease indaily maternal trends(p=0.0001), Litter size(P=0.003), Fetal weight (0.0001) and placenta weight (p=0.002) when experimental groups were compared with the control.Consequently, there was a significant increase in the number of devoured/resorbed fetuses (p=0.010),number of fetuses with congenital malformations (0.042) and the dead fetuses (0.004) in the treatment groups when they were compared with the control group. It was therefore established that the effects of carbamazepine on maternal pregnancy outcomes were dose and time dependent .The findings of this study sets a basis for further studies with higher primates as well as advocate for clinical trials that would lead in cabermazepin dose rationalization to enhance maximum maternal benefits when used during pregnancy, while on the other hand, enhance safety of the fetuses.*

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I. Introduction

Though some literatures have recommended use of carbamazepine as a relatively safer medicationin management of antiepileptic seizures in pregnant women who requires anticonvulsant therapy for the first time[1], others have associated it with adverseeffectsto the maternal fetal outcomes when used in the treatment of conditions likeepileptic seizures, trigeminal neuralgia, attention-defect hyperactivity disorder, schizophrenia, among others[2,3,4].These maternal adverse effects after ingestion of carbamazepine results in fetal cell and tissue growth disruptions during embryogenesis manifested by both morphological and measurement parameters during the gestation period and at the time of delivery[5,6,7], there is paucity of data on maternal fatal outcomes that would guide in rational use of carbamazepine for the benefit the mother without causing fetal harm. In addition, information whether these effects are dose and time dependant is yet to be established. The present study therefore, aim at evaluating whether effects of carbamazepine on maternal pregnancy outcomes depends on the time of carbamazepine exposure and the dose administered.

II. Material and methods

Study site/area: 30 Female nulliparous Albino rats were used in this study, obtained from the Safari Animal house of JKUAT.All the animals weighed between 150 and 250 grams and were fed on a standard diet obtained from UNGA mealsand water *ad libitum*. They were kept in spacious polycarbonate plastic cages with wire mesh at the top. Acclimatization was allowed for a period of seven days.

Study Design: Laboratory experimental study

Study Location: All experiments including breeding, handling, weighing carbamazepine administration, sacrificing animals, and measurements of maternal parameters was done at the Safari Animal house in the School of biomedical Sciences of JKUAT

Study Duration: The study was carried out from November 2018 to January 2019

Sample size calculation: The sample size was determined using the resource equation method since the standard deviation from previous studies was not available as well as the effect size[8,9].
Total number of groups=10
Total number of animals=30
E=30-10
Every adult female rat is assumed to have a minimum average of six (6) fetuses per pregnancy.
The expected number of fetuses were determined as follows 6 x 30=**180 fetuses.**
All fetuses were weighted and three fetuses with the median weights per rat were taken for study making a total of 3 x 30= **90 fetuses**

Sample size: 90 fetuses were used in the study.

Grouping of animals; Animals were randomly assigned to either the control or the experimental group (i.e 3 rats as control group and 27 rats as experimental). The 27 rats in the experimental group were further divided into three broad study groups of 3 rats each assigned :- low (LCG), Medium (MCG) and High cabermazepin group (HCG) each of the broad subgroups of the LCG, MCG and HCG were further subdivided into first (TM1), second(TM2) and third(TM3) trimesters comprising of 3 rats each.

Determination of the cabermazepin doses for the experiment; Doses were determined by use of asimple guide for conversion of animal dosages from human dosages[10,11,12,13,14,15]
The Km factor values of various animal species is used to estimate the HED as:

HED mg / kg = Animal dose mg / kg Animal K /Human K Eq.
HED mg / kg = Animal dose mg / kg K ratio Eq.
The Km ratio values are already provided and are obtained by dividing human Km factor by animal Km factor or vice versa.

Calculation and administration of the doses*:* A 200mg carbamazepine tablet obtained from Novartis pharma batch number 891 was used to make the reconstitutions. Carbamazepine tablets were diluted in 5% DMSO

- All trimester ones (TM_1) animals:- (LCG,MCG,HCG) categories received cabermazepin from gestation day GD1-GD20
- All trimester twos (TM_2) animals:- (LCG,MCG,HCG) categories received cabermazepin doses from gestation day GD7-GD20

- All trimester three (TM_3) animals:- (LCG,MCG,HCG) categories received cabermazepin doses from gestation day GD14-GD20
-

Determination of the critical dose of cabermazepin

Animal groupings was done as follows; In each of the groups (LCG, MCG, HCG), the 9 dams were randomly sub divided in three sub-groups the Trimester 1(TM_1) = 3dams, Trimester 2 (TM_2) = 3dams and Trimester 3 TM_3=3 dams.

Determination of maternal outcomes

Maternal daily weightplacenta weight were determined by use of a weighing scale while littersize, , number of resorbed glands, number of congenital abnormalities and number of dead fetuses were counted and recorded

Ethical clearance

The ethical clearance was sought from JKUAT Animal Ethical Committee (AEC) before initiation of the study.

Statistical analysis

Data was analyzed using SPSS version 24.0 (SPSS Inc., Chicago, IL). One-way Analysis of Variance ANOVA followed by Tukey's post hoc multiple comparison tests was done and results were expressed as mean ± standard error of the mean (SEM) for all values. The results were considered to be significant at P<0.05.Pearson correlation coefficient was used to compare between means of different variables.

III. Results

Influence of carbamazepine on maternal weights during the gestation period

Table 1: A mean comparative Inter and intragroup comparison of weight gain, litter size, number of resorbed glands and placenta weight in the control, low, medium and high dosage groups in the first Trimester

PARAMETERS	CONTROL GROUP (CG)	LOW CARBAMAZEPINE GROUP(LCG-20.7g/kg)			MEDIUM CARBAMAZEPINE GROUP(MCG-72.5g/kg)			HIGHCARBAMAZEPINE GROUP(HCG-124g/kg)		
		TM1	TM2	TM3	TM1	TM2	TM3	TM1	TM2	TM3
weight gain(gms)	130.67±5.78 a	105.7±5. 55ab	112.67 ±7.42a	116.7±1 3.860ab	88.3±1 2.1b*	81.00± 3.512b *	83.33±5.84 0bc*	37.7±7.3 c*	60.67± 2.67b*	60.33±5.9 3c*
Fetal weight (gms)	6.73±0.026a *	6.42±0.0 07b*	6.57±0. 011b*	6.66±0.0 168a*	6.31±0. 046 b*	6.42±0. 018c*	6.533±0.00 4b*	5.42±0.0 2 c*	5.92±0. 0035d*	6.21±0.01 0c*
litter size	13.33±0.88a	10.00±1. 15ab	13.33± 0.882a	12±0.57 7a	7±1.53 bc*	11.33± 0.667a b*	11±0.577ab *	5.00±0.0 0c*	7±0.57 7c*	8.67±0.33 3b*
Placenta weight	5.58±0.021a	4.90±0.0 49b	5.30±0. 049b*	5.40±0.0 50a*	4.633± 0.034c *	5.03±0. 034c*	5.133±0.06 12b*	4.23±0.0 18d*	4.64±0. 0200d*	4.96±0.03 0b*
Number of resorbed glands/Devoured fetuses	0.67±0.67a	0.67±0.6 7a	0.33±0. 333a	0.67±0.6 67a	1.33±1. 33a	0.67±0. 667a	0.667±0.33 3a	7±1.53b *	3±0.00 0b	0.700±0.6 506a
Number of congenital malformations	0.33±0.333a	0.33±0.3 33a	0.00±0. 000a	0.00±0.0 0a	0.33±0. 333a	0.33±0. 333a	0.00±0.00a	1±0.58a	0.67±0. 333a	0.333±0.3 33a
Number of dead fetuses	0.33±0.33a	0.33±0.3 33a	0.33±0. 333a	0.33±0.3 33a	0.67±0. 67a	0.33±0. 333a	0.33±0.333 a	1.67±0.8 82a	1.33±0. 667a	1.00±0.57 7a

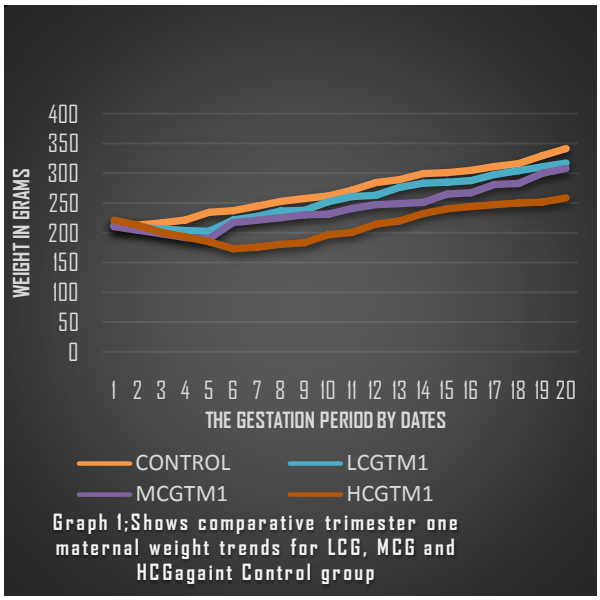
*The means, followed by the same letter in a row and same trimester are not statistically different at (P<0.05) using one way ANOVA with Tukey test on post-hoc t-tests. * indicates significance (p<0.05).*

The results for trimester one in the table 1 above shows that weight trend in the control group (130.67±5.78)was significantly higher than that of the medium and high groups, F(3,8) = 23.5, p=0.0001 in trimester one. However, it was not significantly different in the low dose group as compared with the control group. The Post hoc results went forth to show that the medium dose was again significantly different from the high dose group but not with the low dose group in trimester one. The litter size in the control dose group was significantly different from that in the medium and the high dose groups, F(3, 8) = 11.9, p=0.003. However,

litter size in the control group was not significantly different from that in the low dose group. The number of resorbed glands in the control group was significantly lower than that of the high dose group, F(3,8) = 7.5, p=0.010. However, it was not significantly different for the low dose and the medium dose groups.Placenta weight in the control group was significantly higher than that of the low, Medium and high groups, F(3,8) = 3012.548, p=0.0001. Post hoc tests also revealed that the weight was also significantly different in the low, medium and high dose groups. There was no significant difference in the number of dead fetuses in all the four groups under study, F(3,4)1.103, p = 0.403.

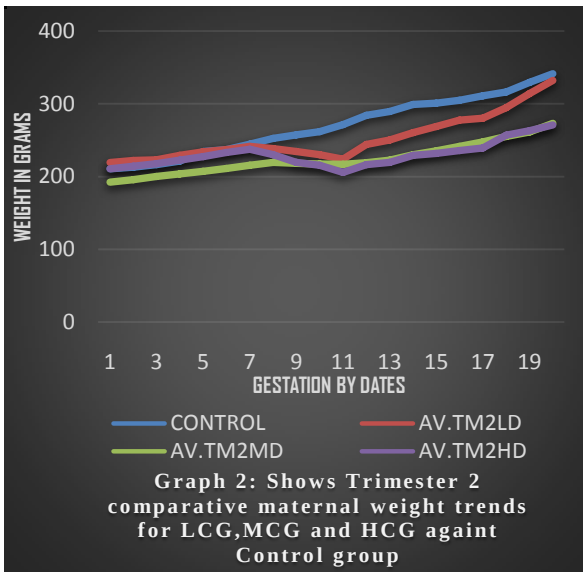
The results of second trimester indicates that the weight gain in the control group was significantly higher than that of the Medium and high groups, F(3,8) = 36.5, p=0.0001. However, it was not significantly different for the low dose group. The Post hoc results went forth to show that the medium was not significantly different from the high dose group.The litter size in the control dose group was significantly different from that in the medium and the high dose groups, F(3, 8) = 14.96, p=0.001. However, litter size in the control group was not significantly different from that in the low dose group.The number of resorbed glands in the control group was significantly different from that of the high dose group, F(3,8) = 4.10, p=0.048. However, it was not significantly different for the low dose and the medium dose groups.Placenta weight in the control group was significantly higher than that of the low, Medium and high groups, F(3,8) = 146.8, p=0.000. Post hoc tests also revealed that the weight was also significantly different in the low, medium and high dose groups. There was no significant difference in the number of dead fetuses in all the four groups under study, F(3,4)=1.29, p = 0.34.
During the third trimester, weight gain in the control group was significantly higher than that of the Medium and high groups, F(3,8) = 13.80, p=0.002. However, it was not significantly different for the low dose group. The medium and the high groups were not significantly different.The litter size in the control dose group was significantly different from that in the high dose group, F(3, 8) = 9.98, p=0.004. However, litter size in the control group was not significantly different from that in the low and medium dose groups.Placenta weight in the control group was significantly higher than that of the Medium and high groups, F (3, 8) = 40.1, p=0.0001. Post hoc tests also revealed that the weight was not significantly different in the medium and high dose groups. There was no significant difference in the number of Number of resorbed glands in all the four groups under study, F (3, 8) = 0.67, p = 0.60. There was also no significant difference in the number of dead fetuses in all the four groups under study, F (3, 8) = 0.110, p = 0.95.

A

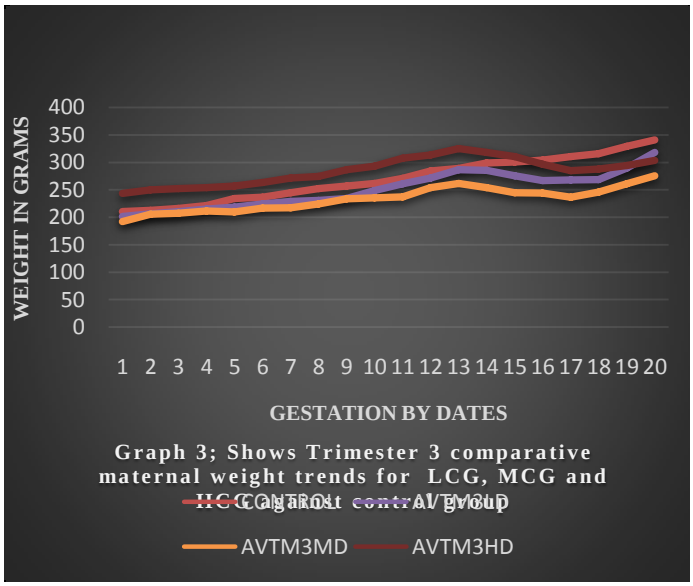


Graph 1;Shows comparative trimester one maternal weight trends for LCG, MCG and HCGagaint Control group

B



Graph 2: Shows Trimester 2 comparative maternal weight trends for LCG,MCG and HCG againt Control group



Line graph 1: Line graphs showing trimester 1(TM1), trimester 2(TM2), andtrimester 3(TM3)comparative maternal weight trends for LCG, MCG,HCG against the control.

It can be observed from line graph 1 above (A, B and C**)**, there was a notable decrease in maternal weight trend in trimester one, trimester two and trimester three(TM1, TM2 and TM3) experimental groups as compared against the control group throughout the gestation period (GD1-20). The first three to four days following carbamazepine administration in all the treatment groups were marked with significant decrease in weight,and then a steady increase in weight gain up to GD20. This phenomenon that could be attributed to the carbamazepine acclimatization factor. These maternal weight rends were found to be statistically significant when compared with the control (p=0.0001) which is less than 0.05 significant level.

Some photographs of the measured maternal outcome parameters

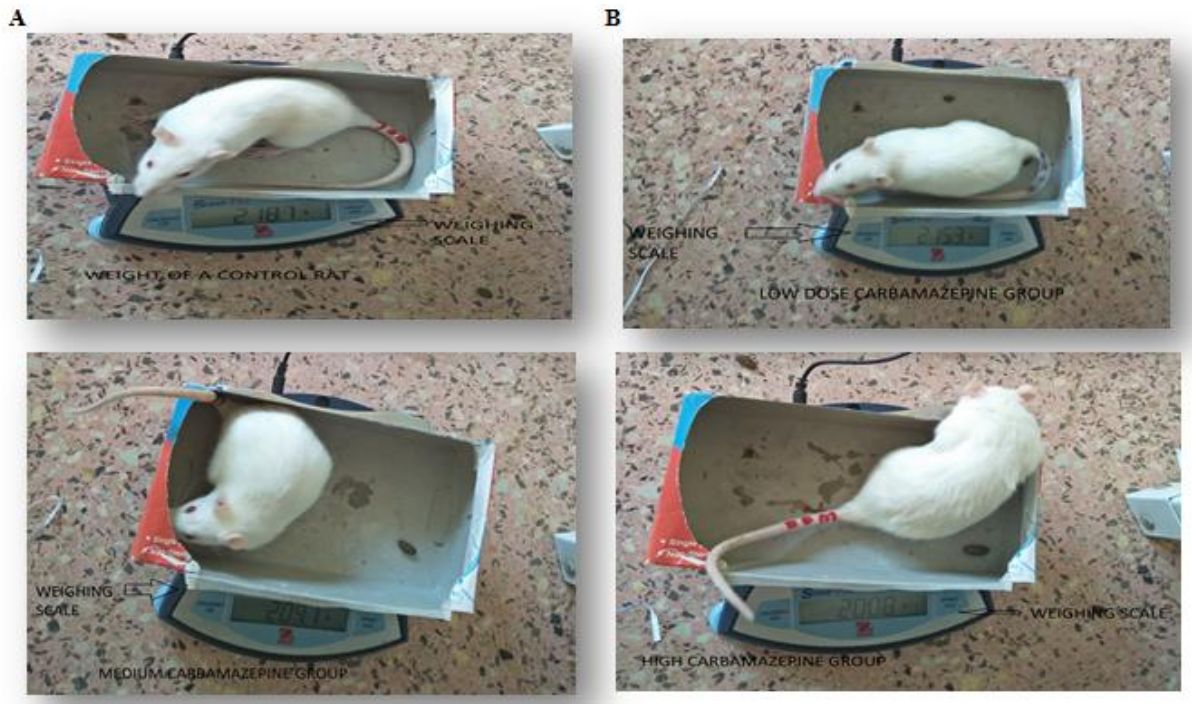


Fig 1; PhotographsA, B, C and D showing daily measurements of maternal weight in the low carbamazepine group(LCG), Medium carbamazepine group(MCG) and high carbamazepine group (HCG) against the Control group (CG).

NB/The measurements were taken using (Scout pro model SPU4001 S/N B519923500 from Uhaus Corporation, USA)

From the Photographs above, it can be observed that both control and carbamazepine treatment groups recorded different daily body weight measurements which were taken between 8.00am-9,00am.Daily weight trends recorded were observed to be dose and time dependent

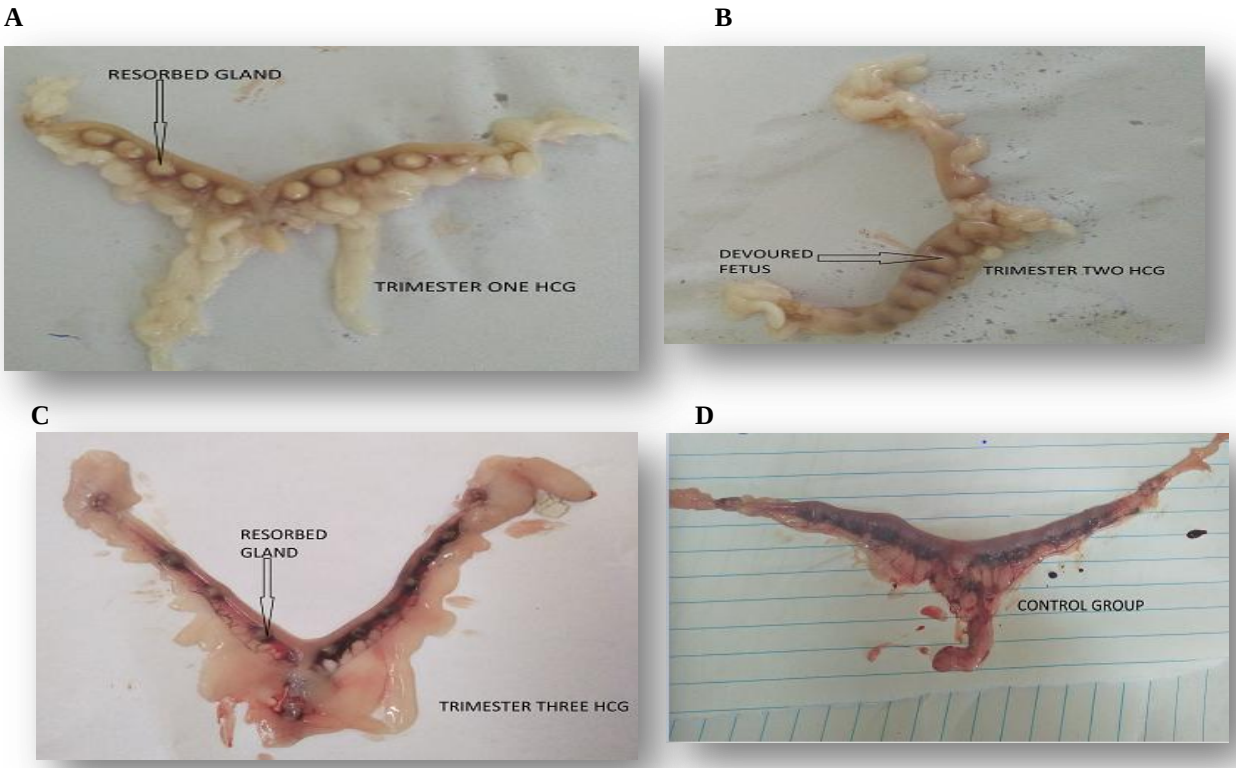


Fig 2; A photograph showing examples of resorbed endometrial glands/Devoured fetuses in Low carbamazepine group (LCG), Medium carbamazepine group (MCG) and high carbamazepine group (HCG) against the Control group (CG) at the 20th day of gestation (GD20)

From the fig 2 above, it can be observed that the number of resorbed/ devoured endometrial glands recorded were more in high dose carbamazepine groups as compared with the control group. They were also observed to be time dependent

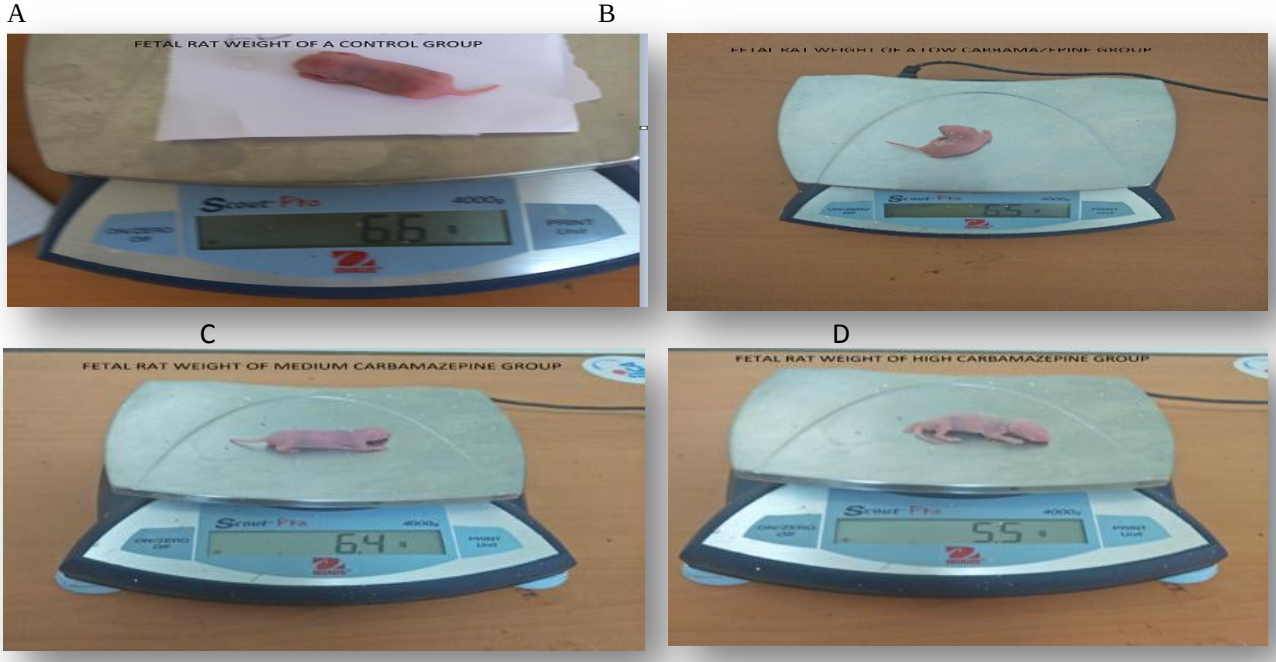


Fig 3: A photograph showing measurements of fetal weights in HCG, MCG and LCG against the control(C) at the 20th day of gestation (GD_{20})

NB/The measurements taken using (Scout pro model SPU4001 S/N B519923500 from Uhaus Corporation, USA)

From the photograph 3 above**:** Carbamazepine treated groups (LCG, MCG, and HCG) have reduced body weight as compared with the control. Intrauterine fetal exposure to Carbamazepine lead to reduction in fetal body weights that is observed to decrease as the dose of carbamazepine increases.

Table 2: Shows the types of congenital anomalies observed and their distribution across the study groups. (I.e. control, LCG, MCG & HCG) at the 20th day of gestation (GD20)

Type of congenital abnormality observed	Number of fetuses	Control	Low carbamazepine group(20.7g/kg)	Medium carbamazepine group(72.5g/kg)	High carbamazepine group(124g/kg)	Percentage out of the number of fetuses
Spina bifida	10	1	1	2	6	3.497%
Hypospadias	4	0	0	1	3	1.398%
Cleft lip	4	0	1	1	2	1.398%
Anencephaly	8	1	1	2	4	2.797%
Microcephaly	6	0	1	2	3	2.098%
Meromelia	2	0	0	1	1	0.699%
Sadactyly	2	1	0	0	1	0.699%
Oligodactyly **Microphalmia** **Aphalagia**	4 2 2	1 0	0 0	1 1 1	2 1 1	1.398% 0.699% 0.699%
Total	44	4	4	12	24	

From the table 4 above, it can be observed that neural tube defects (spina bifida) carries the highest percentage of congenital malformations recorded(3.497%), with 6 out of the 10 cases having occurred in high carbamazepine doses. The other congenital abnormalities were spread across the study groups, were observed to be time dependent and significantly increased in number as the dosage of carbamazepine increased.

Table 3: Shows the percentage congenital abnormalities and embryo-lethality recorded in control against the LCG, MCGand the HCG.

STUDY GROUPS	PERIOD OF CARBAMAZEPINE ADMINISTRATION	NUMBER AND PERCENTAGE OF CONGENITAL MALFORMATIONS	NUMBER AND PERCENTAGE OF EMBRYLETHALITY
Control (C)	---------- --	(2)0.699%	(1)0.35%
Low dose carbamazepine group (LCG-20.7g/kg)	Trimester 1 (TM1) Trimester 2 (TM2) Trimester 3 (TM3)	(4)1.399% (3)1.0490% (1)0.349%	(2)1.70% (1)0.35% (1)0.35%
Medium dose carbamazepine group (MCG-72.5g/kg)	Trimester 1 (TM1) Trimester 2 (TM2) Trimester 3 (TM3)	(7)2.448% (4)1.399% (1)0.349%	(4)1.40% (1)0.35% (1)0.35%
High dose carbamazepine group (HCG-124g/kg)	Trimester 1 (TM1) Trimester 2 (TM2) Trimester 3 (TM3)	(10)3.497% (7)2.448% (4)1.339%	(7)2.45% (4)1.40% (2)1.70%

From the table above, a total of 44 fetuses were found to have congenital abnormalities, while 24dead fetuses were recorded. The highest rate of congenital abnormalities and dead fetuses was observed in the high dose carbamazepine group (HCG) treated at trimester TM_1**{**(10(3.497%); 7(2.45%)**}** respectively, followed by the medium carbamazepine group administered at trimester oneTM_1 [7(2.448%); 4(1.40%)] and lowest in the trimester three low carbamazepine groups as well as the control [1(0.349%); 1(0.35%)]**.**

IV. Discussion

In the present study, there was alteration of different maternal outcome parameters like daily maternal weight trends, itter size, fetal weight, placenta weight among others, (table1)with similar adverse effects having been reported in the in past studies[2,4]. Carbamazepine was observed to cause decrease in daily maternal weight trends, litter size, placenta weight and fetal weight as well as increase in the number of endometrial resorbed glands/ devoured fetuses, number of congenital malformations and number of dead fetuses. These effects were observed to be time and dose dependent.

Daily maternal weight gain

Maternal mean weight trends taken on daily bases and recorded were observed to be highest in control group and to decrease as the experimental groups as the dose of carbamazepine increased (Table 1,fig 1)p=0.0001 which was less than 0.05 significance level. Similar effects of adverse effects of high carbamazepine dosages were described by**Said Elshama *et al* (2015)** who reported that high dosagesof carbamazepineaffects corpus luteum in the pregnant mothers which secrets progesterone and 20-hydroxy progesterone, that maintains in-utero fetal growth and development[4]. Similarly, this information was supported by**Numa f *et al*(1983)** and **Al-asmakh*et al* (2007)** who reported that corpus luteum plays an important role in reproduction[16,17]. The above reports are supported by the current study,since the daily maternal weight gain recorded was statistically reduced in treatment groups as compared with the control group with carbamazepine having been administered during the first trimester and at high dosages (1 above P=0.0001 which was less than 0.05 significance level). **Suchestone*t al.* (1986** and **Marli Gerenutti *et al*(2008) also** reported that high dose carbamazepine dose exposure during pregnancyleads to delay in growth and development of various fetal organs during embryogenesis. Fetal limbs measurements in high carbamazepine dosages were observed to reduce, attributed by reduction in length and width of ossified regions of humerus and femur[4,18].This could be attributed by the mode of action of carbamazepine once ingested by the mother during pregnancy, since according to**Kaushik G*et al*(2016)[19]** carbamazepine crosses the maternal placenta barrier leading to adverse effects to the fetuses. This information is as well in agreement with the current study since fetuses born of mothers in the treatment group on high carbamazepine dosages had stunted growth and reduced birthweight (table 1, fig 2).**Gaafarawi *et al*(2015)** in his study reported that anti-proliferative effects of high carbamazepine dosages increases the mitotic index and causes persistent block of the boundary between metaphase and anaphase stages of cells that leads in growth retardation manifested by reduction in weight and length of the fetus[2]. His study was as well supported by the current study since similar results were recorded.

Litter size

In the current study, itter size was significantly high in control group as compared with the carbamazepine treatment groups, P=0.003 which was less than 0.05 significance level. This effectwas observed to be time and dose dependent.**A.R Baeward *et al*(2005)**reported that there is an existence of a correlation between the number of corpus luteum and the number of ovulations as well as the number of embryo implantations since in each ovulation, an oocyte that can be fecundated is released and turns into a pre-embryo[5]. High carbamazepine interferes with these correlationsas it has a negative effect on the corpus luteum. **Christensen et *al.* (2004)**on the other hand has assured that the administration of carbamazepine in the low dosages has no effects on the rate of pre-implantation losses hence no negative effects on the reproductive performance of a female[7]**.** The results of the current data supports the two reports above as litter size in the control group and low carbamazepine dosages were high and noted toreduce as the dose of carbamazepine increased (table 1 above).

Placenta weight

The placenta weight was recorded highest in the control group as compared to the experimental groups, with the lowest weight recorded in high carbamazepine group when carbamazepine was administered in the first trimester P=0.002 which was less than 0.05 significance level (table 1).These results were in agreement with the ones of **Christensen et *al.* (2004)** who similarly indicated thatlow carbamazepine dosages has no effects on weight of the placenta as well as fetuses offspring vitality[5]. Similar effects were also recorded by **Marli Gerenutti *et al* (2008),** who stated that high doses of carbamazepine causes alterations initiated by a simple pharmacologic mechanism: blockage of ion channels in the heart of the growing embryo, that leads to bradycardia hemodynamic alterations, hypoxia and deoxygenation negative effects to fetal organs as well as the placenta[7].The two reports are in agreement with the results of the current study.

Resorbed endometrial glands/Devoured fetuses, congenital malformations and dead fetuses

The number of resorbed endometrial glands/devoured fetuses, congenital malformations and dead fetuses were observed to be lowest in control group and highest in carbamazepine treatment groups when carbamazepine was administered in the first trimester at high dosages (table1). This study concurred with the one conducted **Mohammad Afshar *et al* (2015)** who reported a statistically significant increase in resorptions in treatment groups compared with the control groups as analyzed in the compared litters. He further observed presence of a number of external congenital malformations considered related to CBZ administration[1].**Marli Gerenutti*et al*(2008)**also reported that carbamazepine administration in low dosage of during rats pregnancy period, has not occasioned significant alteration in the external measures of the morphological parameters of the fetuses, congenital malformation implantation sites[7].This information concurs with the current study since the effects were observed in high carbamazepine groups

V. Conclusion and recommendations

It has been observed that the use of CBZ during gestational period have maternal effects on pregnancy outcomes. These effects includes; daily weight gain, litter size, and placenta weight which were significantly reduced in high carbamazepine dosages when administered during the first trimester, as well as increase in the number of resorbed endometrial glands. Since carbamazepine continues to be prescribed in management of various maternal conditions andis readily available even as an over the counter and off-label medicine,further studies in higher primates closer to human species as well as clinical trials should be carried out to rule out its safety during pregnancy.

Acknowledgements

Author is grateful to Dr. Kweri J. Kariuki, The Chairman of Department in Human Anatomy,Jomo Kenyatta University of Agriculture & Technology for his 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[20].The protocol followed to the letter the Guidelines for Care and Use of Laboratory Animals in Biomedical Research[21]

Conflict of interest: None

Refference

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