ORIGINAL RESEARCH ARTICLE

The pregnancy outcomes of female albino rats *(Rattus Norvegicus)* exposed prenatally to varied doses of lamotrigine

***Ann W. Mwangi*[1], *Joseph K. Kweri*[1], *Cyrus K. Kamau*[1], *James M. Kanyoni*[1], *Alex M. Kigundu*[2], *Elijah Mwangi*[3], *Dominic Marera*[4]**

[1]*Department of Human Anatomy, School of Medicine (SOMED), College of Health Sciences (COHES) Jomo Kenyatta University of Agriculture and Technology (JKUAT) Nairobi, Kenya.*
[2]*School of Pharmacy, College of Health Sciences (COHES) Jomo Kenyatta University of Agriculture and Technology (JKUAT) Nairobi, Kenya.*
[3]*School of Nursing, College of Health Sciences (COHES) Jomo Kenyatta University of Agriculture and Technology (JKUAT) Nairobi, Kenya.*
[4]*School of Medicine (SOMED), College of Health Sciences (COHES), Maseno University, Maseno, Kenya.*

Corresponding email: annmwangi155@gmail.com

ABSTRACT

The maternal pregnancy outcomes following the *in-utero* exposure to lamotrigine (LAMT), a second-generation anticonvulsant medicine, have not been well elucidated. Lamotrigine is currently being prescribed widely and increasingly as a first-line medicine in the management of maternal conditions such as partial and generalised epileptic seizures, neuromodulators in mood disorders among others. Previous results have not been conclusive on its safety profile when administered to the expectant women, with some study results reporting that it is safe, and others advocating for more research to be carried out since their results are inconclusive. Data on the effects of prenatal exposure to lamotrigine on maternal pregnancy outcomes following prenatal exposure to varying doses of lamotrigine when administered at different trimesters is therefore of key importance, in order to maximise benefits to expectant women while minimising effects on developing fetuses. A post -test only-control experimental design was adopted using 30 female sexually mature rats weighing 250 $\pm$ 30 grammes. These female albino rats were divided into two main groups: three rats in the control group and 27 rats in the experimental group. Excel spreadsheets were used to code the data, which was then analysed in SPSS. The study's findings were presented as mean + standard error of the mean (SEM). $P<0.05$ values were considered statistically significant. Study findings depicted a reduction in daily maternal weight trends, mean maternal weight gain (WG), mean placenta weight (PW), litter size (LS), total number of resorbed glands (RG), and total number of dead foetuses (DF) in a time- and dose-related manner, with the reduction being more pronounced at medium and high lamotrigine dosages, especially when it was administered during the first and the second trimesters. Further studies with higher primates close to humans and clinical trials are recommended to rule out the safety index of lamotrigine during pregnancy.

Keywords: Lamotrigine, gestation period, anticonvulsants, trimester, teratogenic.

URL: https://ojs.jkuat.ac.ke/index.php/JAGST
ISSN 1561-7645 (online)
doi: 10.4314/jagst.v22i2.3

1.0 Introduction

Though lamotrigine is a second-generation and a category C anticonvulsant medicine used as the first line in the management of maternal conditions such as epilepsy and bipolar disorders among others, it is currently faced with controversy due to its unclear safety index when exposed in utero (Elgndy *et al.,* 2019). This is because all anticonvulsant medicines cause teratogenicity in developing foetuses since they are capable of crossing the maternal placenta barrier. This is induced via a reduction of maternal serum albumin, leading to higher levels of free drugs (Prakash *et al., 2007*).

Previous inconclusive studies have linked lamotrigine to reduced prenatal effects on embryos and fetuses, Bansal *et al.* (2018), while others have called for more research studies due to insufficient sample sizes. In this context, it is therefore important to establish the data that is lacking on the prenatal exposure to differing doses of lamotrigine at different gestation periods. The availability of such data will guide clinicians on its safety profile, its most vulnerable period of in utero exposure, and the most teratogenic dose. As a result, the mothers will receive maximum benefits while the developing foetuses will experience minimal teratogenic effects.

2.0 Methodology

2.1 Site of the study

The experimentation was carried out at the University of Nairobi, Chiromo Campus. Tissue processing was done in the histology laboratory in the Department of Human Anatomy, JKUAT.

2.2 Study design

The study made use of a post-test only-control experimental design.

2.3 Acquisition of albino rats'

30 sexually mature female albino dams weighing between 250 $\pm$ 30g were obtained from the Institute of Primates based in Nairobi County

2.4 Albino rats' description

Albino rat species were chosen because of the following known scientific facts: (a) they are resistant to a variety of ailments; (b) they have a calm temperament; (c) they are easy to handle; (d) they have large litter sizes; (e) they have low maintenance costs; (f) they are not prone to congenital defects; and (g) their reproductive data is available (Ellenbroek & Youn, 2016).

2.5 Sample size determination

The sample size was calculated by using the resource equation for One Way Analysis of Variance (ANOVA) as follows: n = DF/k + 1, where DF is the total number of subjects, k is the number of groups, and n is the number of subjects per group. The acceptable range of degrees of freedom (DF) for the error term in the analysis of variance (ANOVA) was taken to be between

URL: https://ojs.jkuat.ac.ke/index.php/JAGST
ISSN 1561-7645 (online)
doi: 10.4314/jagst.v22i2.3

10 and 20. Therefore, K = 10, n = 20/10 + 1 = 3. (10 groups x 3 rats) = 30 rats. Since a female albino rat has a normal litter size of between 3 and 16 foetuses (Charan & Kantharia, 2013)., by use of simple convenient sampling method, 3 foetuses were chosen from each of the 30 rats to make a total sample size of 90 fetuses

2.6 Grouping of rats'

Female albino rats were divided into two main groups: 3 rats in the control group and 27 in the experimental group. The experimental group was further divided into three dosage groups of (low, medium and high) with 9 rats each and further into 3 trimesters (TM_1, TM_2 and TM_3) of 3 rats each

2.7 Conjugation and validation of pregnancy

The mating process was done by introducing two sexually mature albino male rats overnight and returning them to their cages after 1200hours (Marcondes *et al.,* 2002). For pregnancy confirmation, a swab was taken from the vagina, smeared on a glass slide and observed using a light microscope. The presence of spermatozoa and increased epithelial cells denoted pregnancy (Shedrack *et al.,* 2006).

2.8 Feeding process

Rodent pellets and water *adlibitum* were used to feed the rats in the polycarbonate plastic cages fitted with a wire mesh (Kanyoni *et al.,* 2023; Frohlich, 2020; Waita *et al.,* 2015).

2.9 Acquisition of lamotrigine and determination of dosages

Tablets of lamotrigine, batch number M2017103, from an Indian company by the name of Vega Biotec Private Limited (BPL) were obtained from a government pharmacy in Nairobi, Kenya. They were reconstituted using distilled water and administered using an oral gavage needle, gauge 16. Dosages for the rats were calculated by using a human to animal conversion guide (Nair & Jacob, 2016).

2.10 Fetal pregnancy outcomes

All foetuses were measured immediately after their resection from the uterine horns by use of digital electronic weighing scale, while their head measurements and crown-rump lengths were taken using calibrated scientific tools.

2.11 Sacrificing of rats

The 30 pregnant albino rats were sacrificed humanely on day 20 of gestation period, using concentrated carbon dioxide that was soaked in a cotton wool, and put in a tight-fitting lid bell jar. The rats were mounted on a dissection board with the dorsal side facing the board using mounting pins and an incision was made along the linear alba from the xiphisternal joint to the symphysis pubis to expose fetuses, and fetuses were resected from the uterine horns.

URL: https://ojs.jkuat.ac.ke/index.php/JAGST
ISSN 1561-7645 (online)
doi: 10.4314/jagst.v22i2.3

2.12 Fetal brains harvesting

The foetal brains were harvested as follows: (a) Each foetus was mounted on the dissection board; (b) the lower margins of the skull cap were removed using a pair of forceps and scissors; (c) the foetal brains were identified by the use of a magnifying glass; (d) the brain coverings were opened longitudinally along the midline; (e) at the level of the largest foramen at the base of the skull, the brains were scooped out; (f) the feotal brains were examined; (g) brain measurements were taken; (f) the brains were dipped in the formaldehyde for tissue processing 12 hours later.

2.13 Light microscopic procedure.

(a) Fixation of brains for 24 hours in formaldehyde solution (b) Water was removed using concentrations of alcohol in ascending grades (50%, 60%, 70%, 80%, 90%, 95%, and 100% for one hour in each solution, (c) clearing was done for 12 hours by immersing the tissues in an oil (cedar wood); (d) a paraplast was used for 12 hours to infiltrate the tissues with wax. (e) Brain tissues were oriented longitudinally from the frontal to the occipital lobes, (f) paraffin wax was used to embed the tissues on the wooden blocks(g) trimming off the excess wax was done to expose the brain. (h) using a Leitz sledge rotary microtome, longitudinal sections of 5µm thickness were cut; (i) the brain tissues were spread at 37^0 F in water; (j) using egg albumin, the sections were stuck onto glass slides; (k) for 24 hours, the brain tissues were dried at 37 degrees, (l) the research assistant blinded the researcher by coding all the slides in her absence (m) staining was done by use of hematoxylin and eosin (H&E), and observed under the light microscope.

2.14 Data collection and statistical analysis

Parametric data on pregnancy outcomes collected using structured checklists, stored and coded in excel spreadsheets windows 10, version 2019, then was exported for analysis into SPSS programme for windows version 25 for analysis (Chicago Illinois). Data was expressed as mean$\pm$ standard error of the mean (SEM) for all values. Analysis was done by one-way analysis of variance (ANOVA) followed by Tukey's post hoc multiple comparison tests. All results whose $P<0.05$ were considered significant. Data was presented in form of tables and graphs.

URL: https://ojs.jkuat.ac.ke/index.php/JAGST
ISSN 1561-7645 (online)
doi: 10.4314/jagst.v22i2.3

3. 0 Results

3.1 The means of initial maternal weights, terminal weights and weight gain between the low, medium and high doses of lamotrigine at TM_1, TM_2 and TM_3

From Table 1 below, it can be seen that all the rats in the study had initial weights which were not statistically different from each other ($P > 0.05$). This clearly indicates that there was no biasness as regarding the weight of the rats at the beginning of the study. The terminal weights however, were all statistically different in both lamotrigine treated groups and the control group ($P < 0.05$). This was due to the effects of lamotrigine on mean terminal weights at varying dosages and across the various gestation periods (table 1). For instance, high lamotrigine dosages (HLAMTG) were associated with the lowest mean maternal weight gain, followed by the medium dosage group (MLAMTG), and finally the low dosage group (LLAMTG) had higher mean maternal weight gain in comparison with the control group (CG). When mean maternal weight gain was analyzed across different trimesters, it was evident that rats that received lamotrigine during the first trimester (TM_1) had the lowest maternal weight gain, followed by TM_2 rats. Trimester 3 (TM_3) rats however, had the highest weight gain, which was closer to those of the control group (CG).

Table 1: The means of initial maternal weight (IW), terminal weight (TW) and weight gain (WG) following administration of low, medium and high lamotrigine doses at (TM_1, TM_2 and TM_3) as compared with the control group (CG).

Time of exposure to lamotrigine	Study groups	Mean initial weight (LAMTG) (g) ± SEM)	Mean terminal weight (LAMTG) (g) ± SEM)	Mean Weight gain (LAMTG) (g) ± SEM)
None	Control group (C)	257.3±4.1	388.3±1.2^{a}	131.0±0.0^{a}
Trimester one	LLAMTG (3mg/kg bw)	260.3±2.6	295.3±0.7*^{b}	36.0±2.7*^{b}
	MLAMTG (24mg/kg bw)	255.3±1.2	233.3±1.2*^{c}	-21.7±2.4*^{c}
	HLAMTG (52mg/kg bw)	250.7±0.3	195.7±0.9*^{d}	-55.0±1.0*^{d}
Trimester two	LLAMTG (3mg/kg bw)	258.3±0.9	333.3±6.1*^{e}	75.0±6.4*^{b}
	MLAMTG (24mg/kg bw)	255.7±2.4	311.7±1.8*^{e}	56.0±2.0*^{b}
	HLAMTG (52mg/kg bw)	259.3±1.5	233.7±0.7*^{f}	-25.0±1.7*^{c}
Trimester three	LLAMTG (3mg/kg bw)	251.7±0.6	325.3±0.9*^{b}	73.0±0.9*^{b}
	MLAMTG (24mg/kg bw)	252.3±2.1	266.7±1.5*^{c}	14.0±0.7*^{b}
	HLAMTG (52mg/kg bw)	259.7±0.3	235.7±10.3*^{d}	24.0±10.6*^{c}

Key: Values with (*) means that they are statistical significantly different with the control group ($P<0.05$), while those with similar letters in a column are not statistically different at ($P>0.05$) using One Way ANOVA with Tukey post hoc multiple comparison t-test.

.

URL: https://ojs.jkuat.ac.ke/index.php/JAGST
ISSN 1561-7645 (online)
doi: 10.4314/jagst.v22i2.3

3.2 The means of daily maternal weight trends between the low, medium and high doses of lamotrigine at TM_1, TM_2 and TM_3

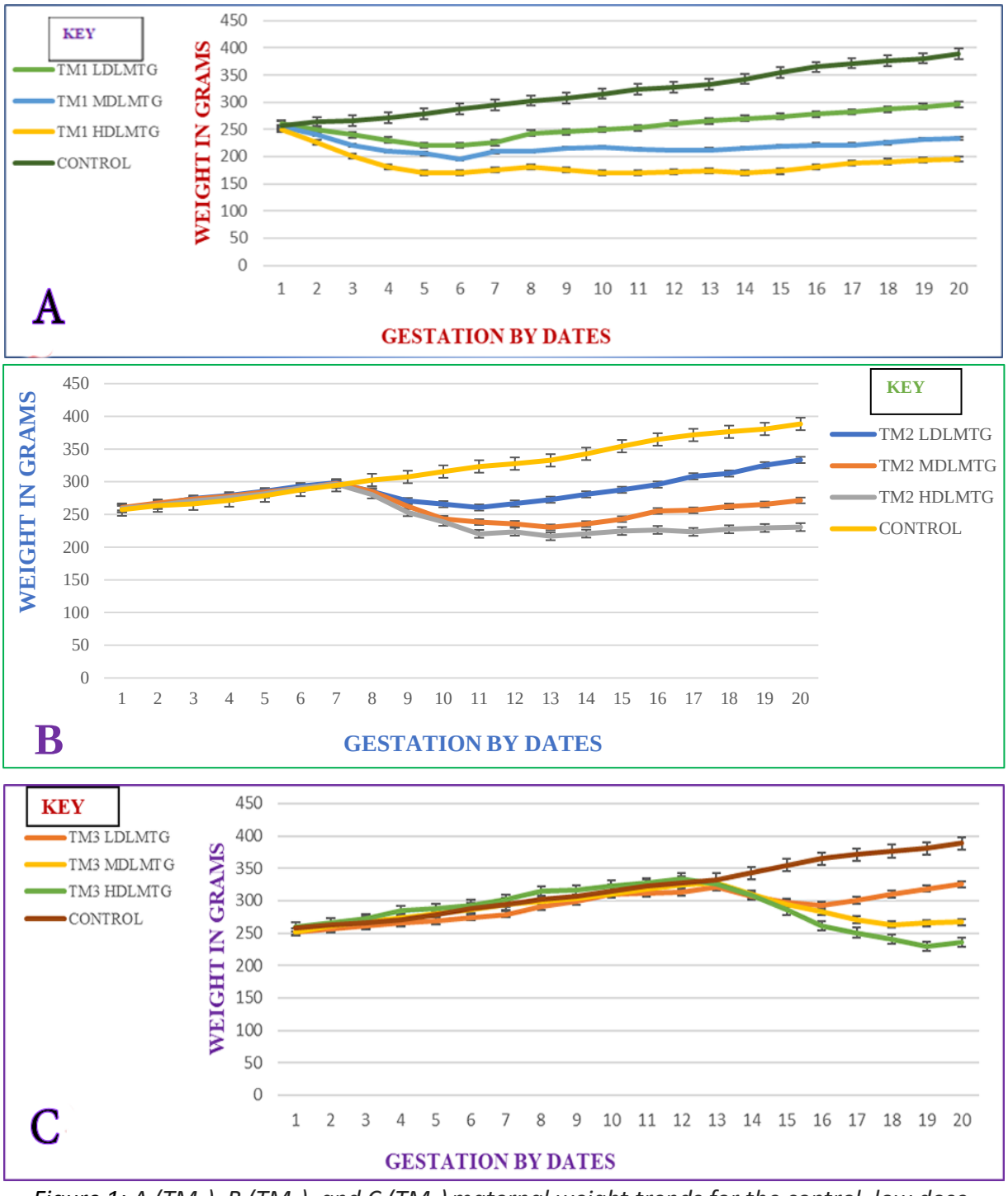

Figure 1: A (TM_1), B (TM_2), and C (TM_3) maternal weight trends for the control, low dose, medium dose, and high dose in the lamotrigine treatment group (LAMTG).

URL: https://ojs.jkuat.ac.ke/index.php/JAGST
ISSN 1561-7645 (online)
doi: 10.4314/jagst.v22i2.3

It can be observed from figure 1 above that upon prenatal exposure of expectant albino rats to varied lamotrigine dosages (LLAMTG, MLAMTG, and HLAMTG), there were accompanying effects on daily mean maternal weights in that there was a notable decrease in mean maternal weights when comparison was made with the mean weight of the control group. The highest mean daily weights were recorded in the control group, followed by the low lamotrigine group (LLAMTG), then the medium dose lamotrigine group (MLAMTG), and the lowest mean daily weights were associated with high dose lamotrigine group (HLAMTG). On the other hand, when mean daily weights were observed at varying gestation periods, it was evident that rats that received lamotrigine during the first trimester (TM_1) had the lowest mean daily weight, followed by TM_2 rats. Trimester 3 (TM_3) rats had the highest mean daily weights, which were closer to those of the control group (CG). It was further noted that for a period of approximately three days after initiating lamotrigine medicine, the rats lost weight, after which it began to increase again due to acclimatization factor (figure 1).

3.3 The means of placenta weights between the low, medium and high doses of lamotrigine at TM_1, TM_2 and TM_3

The mean weights of the placenta were highest in the control group (CG) (5.613± 0.020) when compared to the groups that received lamotrigine (LDLAMTG, MDLAMTG, and HDLAMTG) (table 2 below). Further use of the post hoc multiple comparison test revealed that a statistically significant difference existed when comparison was done with the rats that did not receive lamotrigine (CG) ($P < 0.05$). PW varied according to dose, with the high-dose group (HLAMTG) having the lowest PW, followed by the medium-dose group (MLAMTG), and finally the low-dose group (LLAMTG) having a higher PW. When mean PW was analysed in different trimesters, it was evident that rats that received lamotrigine during the first trimester (TM_1) had the lowest PW, followed by trimester two (TM_2) rats. Trimester 3 (TM_3) rats had the highest PW, which was not statistically different in the medium and low dosage groups, as comparisons were done with the control group (CG) ($P = 0.981$, $P = 0.431$) (table 2).

Table 2: The means of placenta weight (PWT) following administration of low, medium and high lamotrigine doses at (TM_1, TM_2 and TM_3) as compared with the control group (CG).

The time of exposure to lamotrigine	The Study groups	Mean Placenta Weight (LAMTG) (g) ± SEM)
None	Control group (C)	5.613±0.020[a]
Trimester one (TM_1)	LLAMTG (3mg/kg bw)	3.539±0.020*[b]
	MLAMTG (24mg/kg bw)	3.480±0.032*[b]
	HLAMTG (52mg/kg bw)	3.233±0.011*[c]
Trimester two (TM_2)	LLAMTG (3mg/kg bw)	4.117±0.007*[d]
	MLAMTG (24mg/kg bw)	4.030±0.003*[d]
	HLAMTG (52mg/kg bw)	3.648±0.003*[e]
Trimester three (TM_3)	LLAMTG (3mg/kg bw)	4.449±0.003[a]
	MLAMTG (24mg/kg bw)	4.227±0.093[a]
	HLAMTG (52mg/kg bw)	3.931±0.193*[f]

Key: Values with (*) means that they are statistical significantly different with the control group ($P<0.05$), while those with similar letters in a column are not statistically different at ($P>0.05$) using One Way ANOVA with Tukey post hoc multiple comparison t-test.

URL: https://ojs.jkuat.ac.ke/index.php/JAGST
ISSN 1561-7645 (online)
doi: 10.4314/jagst.v22i2.3

3.4 The total number of resorbed endometrial glands/ devoured fetuses between the low, medium and high doses of lamotrigine at TM1, TM2 and TM3

The bar graph below shows that litter size was highest in the control group (13) as compared to the lamotrigine treated groups. Further, in the treatment groups, litter size differed depending on the doses exposed to the rats in that, the high dose group (HLAMTG) had the lowest litter size, followed by the medium dosage group (MLAMTG), and finally the low dose group (LLAMTG). In addition, litter size was highest in the rats that received lamotrigine during the first trimester (TM_1) followed by those that received lamotrigine during the second trimester (TM_2) and was highest in the rats that received lamotrigine doses during the third trimester (TM_3) (Figure 2).

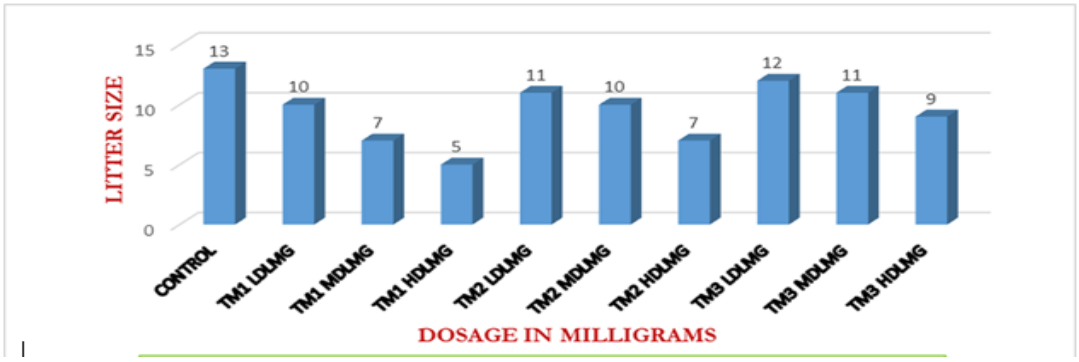

Figure 2: Comparative litter size in low, medium and high lamotrigine groups administered during TM_1, TM_2, and TM_3 against the control group

3.5 The total number of Intra-uterine death (embryolrthality) between the low, medium and high doses of lamotrigine at TM_1, TM_2 and TM_3

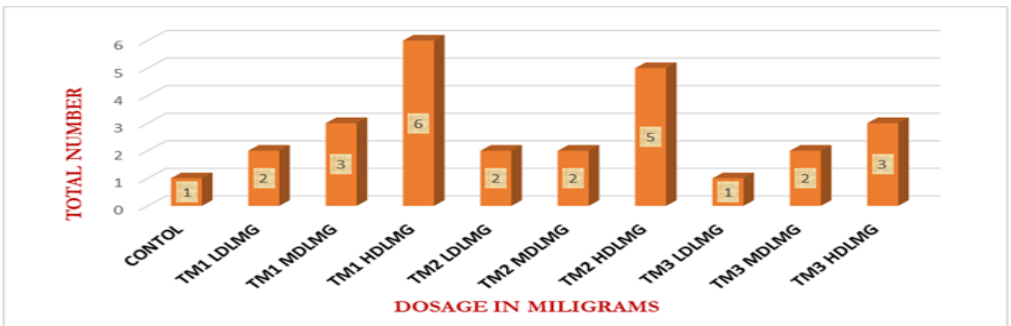

Figure 3: Comparative number of dead fetuses (embryolethality) in low, medium and high lamotrigine groups administered during TM_1, TM_2, and TM_3 against the control group

In figure 3 above, the bar graph shows that the total number of dead foetuses was lowest in the control group (1) when compared with those in the rats that received lamotrigine treatment. Upon comparison of the total number of dead foetuses in the lamotrigine treated groups, they differed depending on the doses exposed to the rats in that high doses (HLAMTG) had the highest number of dead foetuses, followed by the medium dosage group (MLAMTG),

URL: https://ojs.jkuat.ac.ke/index.php/JAGST
ISSN 1561-7645 (online)
doi: 10.4314/jagst.v22i2.3

and finally they were observed to be low in the low dosage group (LLAMTG). Further, the total number of dead foetuses was highest in the rats that received lamotrigine doses during the first trimester (TM_1) followed by those that received lamotrigine during the second trimester (TM_2), and was lowest in the rats that received lamotrigine doses during the third trimester (TM_3).

3.6 The total number of devoured fetuses and resorbed endometrial glands between the low, medium and high doses of lamotrigine at TM_1, TM_2 and TM_3

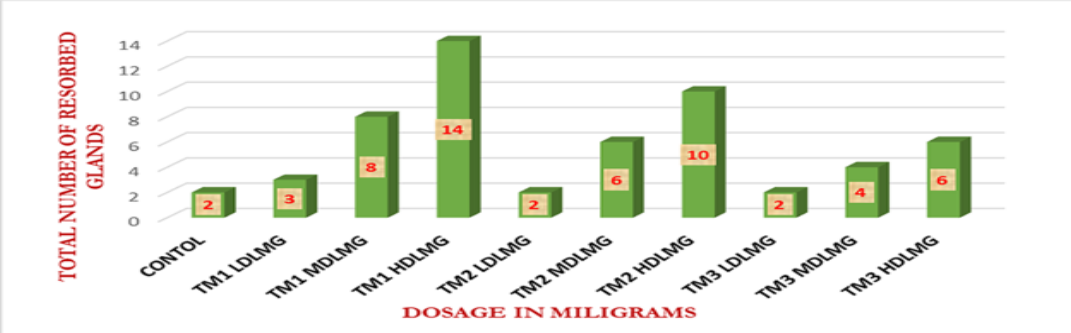

Figure 4: Comparative number of resorbed endometrial glands/devoured foetuses in LDLAMTG, MDLMTG, and HDLAMTG at TM_1, TM_2, and TM_3 against the control group (CG)

Figure 4 above shows that the total number of devoured foetuses and resorbed endometrial glands was lowest in the control group (2) as compared with those in the rats that received lamotrigine treatment. When the total devoured foetuses and resorbed glands in the treatment groups were compared, they differed depending on the doses of lamotrigine given to the rats. High lamotrigine dosage group (HLAMTG) had the highest number of resorbed glands/devoured fetuses, followed by medium lamotrigine dosage group (MLAMTG), and finally were low in low lamotrigine dosage group (LLAMTG).Further, the total number of devoured fetuses and resorbed endometrial glands was highest in the rats that received lamotrigine doses during the first trimester (TM1), followed by those that received lamotrigine during the second trimester (TM_2), and was lowest in the rats that received lamotrigine doses during the third trimester (TM_3).

4.0 Discussion

The current study results shows that lamotrigine has effects on mean daily maternal weights and mean maternal weight gains that is dependent on the amount of lamotrigine administered and the gestation period that lamotrigine is exposed (figure 1). The daily mean weight trends and resultant mean maternal weight gain were highest in the group that never received any treatment, (the control group), followed by the dose group that received low lamotrigine treatment (LLAMTG), then the medium dosage group (MLAMTG), and lastly, the high dosage group (HLAMTG) had the lowest mean daily weight trends and mean maternal weight gains (figure 1A, B, and C/table 1). The analysis done at differing gestation periods depicted that the rats that received lamotrigine during the first trimester (TM_1) had the lowest daily weight,

URL: https://ojs.jkuat.ac.ke/index.php/JAGST
ISSN 1561-7645 (online)
doi: 10.4314/jagst.v22i2.3

followed by TM_2 rats. Trimester 3 (TM_3) rats had the highest weights, which were closer to those of the control group (CG) (figure 1; table 1).

The current study results concur with those of a past study by Wlodarczyk *et al.,* (2012) that showed that exposure to all anticonvulsant medicines results in adverse effects for expectant mothers that includes reduced daily weights that differs with each individual medicine. Most of these medicines were observed to affect centres in the brain concerned with foetal gastric motility and hunger recognition with resultant reduction in mean maternal weights. Other past study results by Khouri (2005) reported that upon administration of topiramate (Topamax), a second-generation anticonvulsant medicine in the same category as lamotrigine, there were associated effects on maternal reproductive fertility and loss of viable foetuses with a resultant reduced maternal daily weight gain.

The mean weights of the placenta (PW) were observed to similarly decrease with the increase in lamotrigine dosage groups as compared with the control group. Upon comparison of its effects when different dosages of lamotrigine were administered, low lamotrigine dosage group (LLAMTG) had the highest means of placenta weight, followed by medium lamotrigine dosage group (MLAMTG), and finally were low in the high lamotrigine dosage group (HLLAMTG). On further analysis of PW measurements during different gestation periods, the mean placenta weight was observed to be highest when treatments were instituted during the third trimester (TM_3), followed by the second trimester (TM_2). When lamotrigine was instituted in the first trimester (TM_1), the mean PW was observed to be the lowest.

The current study results concur with those of a previous study on the effects of valproic acid on placenta weight by (Semczuk-Sikora & Semczuk, 2004). According to the results, valproic acid exposure causes mesenchymal cell degeneration and placental syncytiotrophoblast wasting. Koubeissi *et al*. (2013) had differing results on the effects of levetiracetam, still a first-line anticonvulsant medicine on various maternal and foetal pregnancy parameters, including placenta weight. The study was not conclusive due to the small sample size, and hence, the authors advocated for further studies on the same with a larger sample size.

The number of live foetuses born by the rats (litter size) in the experiment was observed to be highest in the group that did not receive any medication (control group). However, it was lower in groups that received lamotrigine treatment, depending on the dose given and the gestation period of exposure (see Figure 2 above). These current study results on litter size are similar to those of Vinten *et al.* (2005) that demonstrated interference of anticonvulsants on sites of implantation and the resultant reduction of litter size. However, a study by Christensen *et al.* (2004) contradicted the results of the current study in that the results showed that after administration of carbamazepine, especially the lower dosages, implantation sites were not affected.

The prenatal use of lamotrigine in the current study has shown that the number of resorbed endometrial glands and devoured fetuses, as well as dead fetuses, was low in the group that did not receive any medication, the control group (CG). However, in the lamotrigine treated

URL: https://ojs.jkuat.ac.ke/index.php/JAGST
ISSN 1561-7645 (online)
doi: 10.4314/jagst.v22i2.3

groups, an increase in the number of devoured fetuses, resorbed endometrial glands and embryolethality was observed to increase with increase in lamotrigine dosages. Upon comparison of lamotrigine effects at different gestation periods, the first trimester (TM_1) had the highest number of devoured fetuses, resorbed endometrial glands and embryolethality, followed by the second trimester (TM_2), and was lowest when lamotrigine was administered during the third trimester (TM_3) (figures 3 and 4). The results of this study are in accordance with those of Hill *et al.* (2010), whose results showed that upon administration of anticonvulsants, they were associated with resorptions. Another study by de Oliva & Miraglia (2009) showed that low doses of carbamazepine are not associated with interference with the implantation sites.

5.0 Conclusion and recommendations

The effects on the rats of exposure to lamotrigine prenatally are dependent on the dose and timing of exposure. Further studies on animal species close to humans are recommended.

6.0 Acknowledgment

6.1 Funding

Self-funded

6.2 Conflict of interest

None.

6.3 Ethical consideration and clearance

The study sought approval from a committee based at the University of Nairobi (UON), faculty of veterinary medicine, department of veterinary anatomy and physiology, before its initiation, (through approval; ref: FVM BAUEC/2021/323).

7.0 Reference

Bansal, R., Suri, V., Chopra, S., Aggarwal, N., Sikka, P., Saha, S. C., ... & Kumar, P. (2018). Levetiracetam use during pregnancy in women with epilepsy: Preliminary observations from a tertiary care center in Northern India. *Indian Journal of Pharmacology*, *50*(1), 39. http://dx.doi.org/10.4103/ijp.IJP_692_17

Charan, J., & Kantharia, N. D. (2013). How to calculate sample size in animal studies? *Journal of pharmacology & pharmacotherapeutics*, *4*(4), 303– 306. http://dx.doi.org/10.4103/0976-500X.119726

Christensen. H.D., Rayburn, W.F., Parker, K.M., Gonzalez, C.L., Gold, K.P. 2004. Chronic prenatal exposure to carbamazepine and perinatal outcomes of C3H/He mice. *Am J Obstet Gynecol* 190:259-263. https://doi.org/10.1016/s0002-9378(03)00899-8

de Oliva, S. U., & Miraglia, S. M. (2009). Carbamazepine damage to rat spermatogenesis in different sexual developmental phases. *International journal of andrology*, *32*(5), 563–574. https://doi.org/10.1111/j.1365-2605.2008.00898.x

Elgndy, I., Hagag, O., EL Khoi, S., Sarg, N., Faragg, A.92019). A Comparative Study of the Teratogenic Effects of Antiepileptic Drugs; LMT and LLEV On Adult Albino Rats. *The Egyptian Journal of Forensic Science and Applied Technology, 16*, 87-111

Ellenbroek, B., & Youn, J. (2016). Rodent models in neuroscience research: is it a rat

URL: https://ojs.jkuat.ac.ke/index.php/JAGST
ISSN 1561-7645 (online)
doi: 10.4314/jagst.v22i2.3

race?. *Disease models & mechanisms*, *9*(10), 1079–1087. http://dx.doi.org/10.1242/dmm.026120

Frohlich J. (2020). Rats and Mice. *Ferrets, Rabbits, and Rodents*, 345–367. https://doi.org/10.1016/B978-0-323-48435-0.00025-3

Hill, D. S., Wlodarczyk, B. J., Palacios, A. M., & Finnell, R. H. (2010). Teratogenic effects of antiepileptic drugs. *Expert review of neurotherapeutics*, *10*(6), 943–959. https://doi.org/10.1586/ern.10.57

KANYONI, J., Kweri,J., Elijah,M., Dominic,M., Mwangi,W., & Walter, R. (2023). The Ameliorative Effects of Graded Intensities of Exercise Training on Anthropometrical Parameters on High Fat Diet and Sucrose-induced Obesity in Wistar Rats: Effects of Exercise on Anthropometrics Parameters. JOURNAL OF AGRICULTURE, SCIENCE AND TECHNOLOGY, 22(1), 26–36. https://doi.org/10.4314/jagst.v22i1.4

Khouri N. A. (2005). Reproductive toxic effects of Topamax ingestion in female Sprague-Dawley rats. *Neuro endocrinology letters*, *26*(6), 843–847.

Koubeissi M. (2013). Levetiracetam: More evidence of safety in pregnancy. *Epilepsy currents*, *13*(6), 279–281. https://doi.org/10.5698%2F1535-7597-13.6.279

Marcondes, F. K., Bianchi, F. J., & Tanno, A. P. (2002). Determination of the estrous cycle phases of rats: some helpful considerations. *Brazilian journal of biology = Revista brasleira de biologia*, *62*(4A), 609–614. https://doi.org/10.1590/s1519-69842002000400008

Nair, A. B. & Jacob, S. (2016). A simple practice guide for dose conversion between animals and Human *Journal of basic and clinical pharmacy*, *7*(2), 27–31. http://dx.doi.org/10.4103/0976-0105.177703

Prakash, Prabhu L. V, Nasar M. A, Rai R., Madhyastha S., G. (2007). Lamotrigine in pregnancy: safety profile and the risk of malformations. *Singapore Med J 48* (10): 882

Semczuk-Sikora, A., & Semczuk, M. (2004). Wpływ leków przeciwpadaczkowych na łozysko i płód [Effect of anti-epileptic drugs on human placenta and the fetus]. *Ginekologia polska*, *75*(2), 166–169

Shedrack, I., Nwocha, C., & Ikechukwu, J. (2006). A New and Simple Method of Confirmatory Detection of Mating in Albino Rats (Rattus norvegicus). https://doi.org/10.4314/ari.v3i3.40784

Slonaker, J. R. (1918). The Care and Breeding of Albino Rats. Science, 47(1224), 594–596. http://www.jstor.org/stable/1643495

Vinten, J., Adab, N., Kini, U., Gorry, J., Gregg, J., Baker, G. A., & Liverpool and Manchester Neurodevelopment Study Group (2005). Neuropsychological effects of exposure to anticonvulsant medication in utero. *Neurology*, *64*(6), 949–954. https://doi.org/10.1212/01.WNL.0000154514.82948.69

Waita, I. M., Karanja, S. M., Kiarie, A. G., & Mania, N. W. (2015). Changes in some Urine Parameters in Vervet Monkey Model of Trypanosomiasis: Towards Non-Invasive Diagnosis of Sleeping Sickness. JOURNAL OF AGRICULTURE, SCIENCE AND TECHNOLOGY, 16(3), 36–45. Retrieved from https://ojs.jkuat.ac.ke/index.php/JAGST/article/view/46

Wlodarczyk, B. J., Palacios, A. M., George, T. M., & Finnell, R. H. (2012). Antiepileptic drugs and pregnancy outcomes. *American journal of medical genetics. Part A*, *158A*(8), 2071–2090. https://doi.org/10.1002/ajmg.a.35438

URL: https://ojs.jkuat.ac.ke/index.php/JAGST
ISSN 1561-7645 (online)
doi: 10.4314/jagst.v22i2.3