ORIGINAL RESEARCH ARTICLE

The growth and development outcomes of foetuses born of albino rats *(Rattus Norvegicus) prenatally* exposed to varying doses of lamotrigine

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ABSTRACT

The growth and development outcomes of the foetuses born by mothers who prenatally get exposed to lamotrigine (LAMT) have not been well established. Lamotrigine is an anticonvulsant medicine used in the management of acute epileptic seizures, Lennox-Gastaut syndrome, fibromyalgia, schizophrenia, unipolar depression, bipolar I disorder maintenance among others. Though currently lamotrigine is being prescribed as a first line medicine in the management of these maternal conditions, past studies are not conclusive on its teratogenic effects on growth and development of embryos and foetuses upon its in-utero exposure, with some demonstrating no effects, while others recommend further studies. Data on growth and development effects upon administration of lamotrigine at varying dosages at different trimesters will therefore be of help to the expectant mothers who consume lamotrigine, developing embryos and foetuses as well as guide the clinicians on the dosage and when to prescribe lamotrigine. A post-test-only experimental design was adopted using 30 female sexually mature rats of 250 $\pm$ 30grams.These female albino rats were divided into two main groups of 3 rats in the control group and 27 rats in the dosage group. Excel spreadsheets were used to code the data and was analyzed in SPSS. Study findings were expressed as mean $\pm$ standard error of the mean (SEM). Values whose $p<.05$ were reported as being statistically significant different. Study findings depicted a reduction in mean fetal weight (FW), mean crown-rump length (CRL), mean bi-parietal diameter (BD), mean head circumference (HC) as well as mean head length (HL) in a time and dose related manner. More reduction in foetal growth and development parameters were observed in high lamotrigine dosages, especially when administrations were done during the first and the second trimesters. Further studies with animals close to human species are recommended to guide on the safety human therapeutic dosages.

URL: https://ojs.jkuat.ac.ke/index.php/JAGST
ISSN 1561-7645 (online)
doi: 10.4314/jagst.v22i3.10

Keywords: Lamotrigine, Teratogenic, Anticonvulsants, Gestation period.

1.0 Introduction

The safety of embryos and foetuses upon prenatal administration of lamotrigine at different doses and during varied trimesters is not well elucidated (Etemad *et al*., 2012). Though the efficacy and safety of lamotrigine on foetal growth and development have been demonstrated in some past study results, (Besag *et al.,* 2021, Diav-Citrin *et al*., 2017) others have associated its use with adverse teratogenic effects similar to those of older-generation anticonvulsants (Vajda *et al*., 2013, Sabers *et al.,* 2004). Further, some other past results are as well not conclusive, advocating for further studies to be carried out (Tennis *et al.,* 2002, Cunnington *et al.,* 2005). On the other hand, anticonvulsant medicines like lamotrigine cross the maternal placenta barrier due to reduction in maternal serum albumin, leading to higher levels of free drugs as well as bioavailability that results to fetal toxicity (Al-Enazy *et al.,* 2017).Data on the fetal pregnancy outcomes as a result of in-utero administration of varying dosages of lamotrigine during different trimesters is therefore important as it will serve as a guide to the clinicians on its safety profile, the gestation period that is prone to its teratogenicity, and the dose that has effects to the developing foetuses. This will result in overall benefits to the expectant mothers by managing maternal conditions, with minimal teratogenic effects on the developing foetuses.

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

A post-test only experimental design was used in this study

2.3 Acquisition of Albino rats

30 sexually mature female albino dams obtained from the Institute of Primates based in Nairobi County. They weighed between 250+30g.

2.4 Albino rats description

Albino rat species were used because of the following known scientific facts; (i) are resistant to various ailments (ii) are of calm temperament (iii) are easy to handle (iv) have large litter size, (v) require low maintenance cost (vi) not prone to getting congenital defects, (vii), their gestation period is short (viii) their reproductive data is available (Kweri *et al.,* 2023).

2.5 Sample size determination

Sample size was calculated using the resource equation as determined by **(**Charan and Kantharia, 2013) 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. DF ranges between 10and 20. Therefore, K = 10, n = 20/10+1 = 3. (10 groups x 3 rats) = 30 rats. Since a female albino rat has a normal

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ISSN 1561-7645 (online)
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litter size of between 3 and16 foetuses) by use of simple random 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 of 3 rats in the control group and 27 in the dosage group. In order to determine whether the teratogenic effects of lamotrigine and levetiracetam on fetal growth and development were dose-dependent, the dosage category of 27 rats was further sub-divided into three smaller groups of 9 rats of low lamotrigine group, medium lamotrigine group, and high lamotrigine group. Similarly, to determine whether the effects of lamotrigine were time-dependent, the 3 study categories were further subdivided into three subgroups of 3 rats for 1st trimester, 3 rats for 2nd trimester, and 3 rats for 3rd trimester

2.7 Conjugation and validation of pregnancy

The mating process was done by introducing two sexually 15 mature male albino 15 rats overnight and returning them to their cages after 12 hours (Dikshit & Taskar 1959). 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

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

2.9 Acquisition of lamotrigine and determination of lamotrigine dosages

Lamotrigine tablets batch number M2017103 from an Indian company by the name 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 use of a guide as outlined by (Nair and Jacob, 2016).

2.10 Calculation and administration of varying lamotrigen dosages

Humans have an average weight of 60kg

a) Calculation of low lamotrigine dosage

- ✓ low dose of lamotrigine in humans = 25mg

25mg = 60kg

X = 1kg

X = 1x25/60 =0.417mg/kg

AED = HED X Km factor

Therefore, 0.417mg/kg x 6.2 = 3mg/kg bw

b) Calculation of medium lamotrigine dosage

- ✓ Medium dose of lamotrigine in humans = 236mg

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ISSN 1561-7645 (online)
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235.7mg = 60kg X = 1kg
X = 1x235.7/60 = 3.928mg/kg
AED = HED X Km factor
Therefore, 3.928mg/kg x 6.2 = 24mg/kg bw

c) Calculation of high lamotrigine dosage
- ✓ High dose lamotrigine in humans = 500mg

500m = 60kg X=1kg
X=1x500/60 = 20mg/kg
AED = HED X Km factor
Therefore, 8.3mg/kg x 6.2 = 52mg/kg bw

The duration of rats' pregnancy is 21 days and is divided into three trimesters, with each trimester having seven days. Trimester one (TM_1) rat's category received low, medium, and high lamotrigine dosages from the first day of gestation ($GD_{1)}$ to the last gestation date (GD_{20}). Trimester two (TM_2) rat's category received low, medium, and high lamotrigine dosages from the seventh day of gestation ($GD_{7)}$ to the last gestation date (GD_{20}) while trimester three (TM_3) rat category received of low, medium and high lamotrigine dosages from the fourteenth day of gestation ($GD_{14)}$ to the last gestation date (GD_{20}).

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

2.12 Data collection and statistical analysis

Excel spreadsheets were used to code the data and was analyzed in SPSS. Study findings were expressed as mean $\pm$ standard error of the mean (SEM). Values whose $P < .05$ were reported as being statistically significantly different

2.13 Fetal growth and development parameters

All foetuses were weighed immediately after their resection from uterine horns. Head measurements and crown-rump length were taken using calibrated vernier calipers, a piece of thread and a calibrated ruler.

3.0 Results

3.1 Effects of lamotrigine on mean weight of the foetuses (FW) and mean fetal length (CRL).

Upon analysis of mean fetal weight as well as mean crown-rump length using One Way ANOVA, the highest means were observed in the control group (7.750 ± .026(g), 7.945 ± .026(mm)) respectively as compared with the treatment groups. Further, when Turkey's post hoc results on the mean foetal body weight in both intergroup and intragroup was analyzed, the dosage

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ISSN 1561-7645 (online)
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groups showed that fetal body weight was dependent on the dose administered. Low treatment group (LLAMTG) was associated with a statistically significantly higher mean FW, followed by medium dosage group (MLAMTG) while high dosage group (HLAMTG) had the lowest mean fetal weight when comparison was done with the control group (P = 0.001). Further, mean FW was dependent with the time of exposure in that it was highest upon administration of lamotrigine during the third trimester (TM_3), followed by trimester two (TM_2) and lastly, the FW were the lowest when treatments were instituted during the first trimester (TM_1). It was noted however that low and medium dosages during the third trimester (TM_3) had no significant difference when comparison was done with the control group (p = .073, P = .054) respectively.

The mean crown-rump length (CRL) was observed to decrease as the lamotrigine dosage increased in that, the low dosage group (LLAMTG) had the highest means, followed by medium dosage groups (MLAMTG), and finally were lowest in high dosage groups (HLAMTG). All these measurements were observed to have a statistical significance difference with the control group (p =.001) using Turkey's Post hock multiple comparison test except for low dose trimester three that were not statistically different with the control group (p = .081). Further, the mean CRL was higher during the third trimester (TM_3), then lower during the second trimester (TM_2). When lamotrigine was instituted in trimester one (TM_1), it was associated with the lowest mean CRL (Table 1).

Table 1: The means of fetal weight and crown-rump length following administration of low, medium and high lamotrigine doses at (TM1, TM2and TM3) as compared with the control group (CG)

The time of exposure to LAMT treatment	The Study groups	Mean Fetal Weight (LAMTG) (g) ± SE)	Mean CRL (LAMTG) (g) ± SE)
None	**Control group (C)**	7.750±0.026[a]	7.945±0.026[a]
Trimester One	**LLAMG (3mg/kg)**	6.444±0.006*[b]	4.132±0.009*[b]
	MLAMG (24mg/kg)	6.343±0.048*[c]	3.879±0.039*[b]
	HLAMG (52mg/kg)	5.443±0.022*[c]	3.376±0.023*[c]
Trimester Two	**LLAMG (3mg/kg)**	6.590±0.007*[d]	4.450±0.008*[d]
	MLAMG (24mg/kg)	6.439±0.015*[e]	4.155±0.000*[e]
	HLAMG (52mg/kg)	5.949±0.007*[f]	4.054±0.002*[f]
Trimester Three	**LLAMG (3mg/kg)**	6.683±0.014[a]	4.545±0.027[a]
	MLAMG (24mg/kg)	6.558±0.010[a]	4.437±0.028*[g]
	HLAMG (52mg/kg)	6.237±0.010*[g]	4.400±0.011*[h]

Key: Values with (*) means that they are statistical significantly different with the control group(P <.05), while those with similar letters in a column are not statistically different at (P > .05) using One Way ANOVA with Tukey post hoc multiple comparison t-test.

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ISSN 1561-7645 (online)
doi: 10.4314/jagst.v22i3.10

3.2 Effects of lamotrigine on mean head mesuremets (mean fetal head circumference (HC) mean fetal bi-parietal diameter (BPD), and mean fetal head length (HL).

Results of analysis of mean head measurements (HC, BPD, and HL) using One Way ANOVA depicted that the highest means were observed in the control group 4.200 ± 0.027, 3.297 ± 0.027, 1.541 ± 0.000(mm) respectively. In the treatment groups, Turkey's post hoc results in both intergroup and intragroup groups showed that fetal head circumference were dependent of the dose administered in that the low treatment groups (LLAMTG) were associated with a statistically significantly higher mean HC, followed by medium dosage group (MLAMTG) while high dosage group (HLAMTG) had the lowest mean HC as comparisons were done with the control group (p = .001). Low dose trimester three had no significance difference (p = .093) when comparison was done with the control group. Further, HC was dependent on the time of exposure in that it was higher when treatments were administered during the third trimester (TM_3), followed by trimester two (TM_2) and lastly, they were lowest when treatments were instituted during the first trimester (TM_1) (Table 2).

Upon comparison of mean BPD in the groups that received lamotrigine with the control group, it was observed that there was a decrease in mean BPD with the increase in dosages in that, the low dosage group (LLAMTG) had the highest means, followed by medium dosage groups (MLAMTG), and finally were lowest in high lamotrigine dosage group (HLAMTG). All measurements of BPD were observed to have a lower statistical difference (p=.001), when comparison was done with that of the control group. This was in exception of low and medium third trimester group (TM_3), treatment groups (LLAMTG, MLAMTG) (p = .243, p = 1.002) respectively. Further, these measurements were observed to be higher when treatments were instituted during the third trimester (TM_3), then by second trimester (TM_2). When lamotrigine was instituted during the first trimester of gestation period (TM_1), the mean BPD was lowest (Table 2).

The mean HL was observed to decrease with an increase in dosage in that, the low dosage group had the highest means, followed by medium dosage groups, and finally were lowest in high dosage groups. All these measurements were observed to have a statistical significance difference when it was compared with the control group (p = .001). On further analysis of HL measurement during different gestation periods, were observed to be higher when treatments were instituted during the third trimester (TM_3), then by second trimester (TM_2). When lamotrigine was instituted in the first trimester (TM_1) the mean HL was lowest (Table 2).

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ISSN 1561-7645 (online)
doi: 10.4314/jagst.v22i3.10

Table 2: The means of fetal head circumference, bi-parietal diameter and head length following administration of low, medium and high lamotrigine doses at (TM1, TM2and TM3) as compared with the control group (CG)

The time of exposure to LEV/LAMT treatment	The Study groups	Mean (LEVG/LAMT) Head Circumference (HC) (mm) ± SE)	Mean (LEVG/LAMTG) Bi-parietal Diameter (BD) (mm) ± SE)	Mean (LEVG/LAMTG) Head Length (HL) (mm) ± SE)
None	**Control group (C)**	4.200±0.027[a]	3.297±0.027[a]	1.541±0.000[a]
Trimester One	**LLAMG (52mg/kg)**	3.263±0.029*[b]	2.516±0.097*[b]	1.273±0.002*[b]
	MLAMG (24mg/kg)	3.035 ±0.032*[b]	2.461±0.639*[b]	1.243±0.002*[c]
	HLAMG (3mg/kg)	2.397±0.012*[c]	2.201±0.036*[c]	1.184±0.003*[d]
Trimester Two		3.497±0.029*[b]	2.758±0.036*[b]	1.305±0.001*[b]
	LLAMG (52mg/kg)	3.288±0.018*[b]	2.406±0.041*[b]	1.278±0.001*[c]
	MLAMG (24mg/kg)	3.074±0.022*[c]	2.266±0.031*[b]	1.252±0.001*[d]
	HLAMG (3mg/kg)			
Trimester Three	**LLAMG (52mg/kg)**	3.609±0.038[a]	2.902±0.006[a]	1.315±0.001*[b]
	MLAMG (24mg/kg)	3.548±0.015*[b]	2.572±0.017	1.306±0 000*[b]
	HLAMG (3mg/kg)	3.450±0.089*[c]	2.356±0.030*[c]	1.292±0.001*[C]

Key: Values with (*) means that they are statistical significantly different with the control Group (P<.05), while those with similar letters in a column are not statistically different at (P > .05) using One Way ANOVA with Tukey post hoc multiple comparison t-test

4.0 Discussion

The effects of lamotrigine on foetal growth and development in the current study were demonstrated by measurements of the mean fetal weight, mean crown-rump length and mean head measurements. The mean fetal weight was observed to decrease as the dose of lamotrigine increased in that low dosage groups had the highest mean fetal weights, followed by the medium dose groups, and lastly, the lowest treatment groups when comparison was done with the control group. Decrease in mean weight of the foetuses recorded higher when treatments were instituted in the first trimester (TM_1), followed by second trimester (TM_2) and finally in the third gestation period (TM_3). Low and medium dosages during the third trimester (TM_3) however were not statistically difference when comparison was done with the control group (P= .073, P = .054) respectively (Table 1).

The current study results are intendem with results of a previous study by (Hamdi *et al.,* 2017) that showed that oxcarbazepine (OXC), a new anticonvulsant medicine like lamotrigine that is recently being prescribed widely as first line adjunct medicine as well as monotherapy, has a potential risk of causing a reduction in fetal weight. Another previous study results by Harden (2014) reported that upon administration of topiramate and zonisamide, second-generation anticonvulsant medicines in the same category as lamotrigine, there was associated fetal weight loss. This fetal weight loss was sociated with the effects of topiramate and zonisamide effects on the hypothalamic centers concerned with fetal gastric motility and hunger recognition.

URL: https://ojs.jkuat.ac.ke/index.php/JAGST
ISSN 1561-7645 (online)
doi: 10.4314/jagst.v22i3.10

In the current study, the crown-rump length (CRL) was observed to similarly decrease with the increase in lamotrigine dosage as compared with the control group. Upon comparison of its effects at different gestation periods, the first trimester had the lowest means, followed by the second trimester, and was highest when lamotrigine was administered during the third trimester. The low dosage group had no statistical significance difference from the control group (Table 1). The current study results concur with those of a previous study by Abdulrazzaq *et al.,* 1997 which demonstrated that prenatal use of Vigabatrin resulted in growth retardation. However, previous study results by (Fujii *et al*., 2013) on the effects of gabapentin, still a first-line anticonvulsant medicine just like lamotrigine were not conclusive on its effects on mean fetal length and hence the researcher advocated for further studies on the same medicine using a larger sample size to obtain conclusive results.

The prenatal use of lamotrigine as per the current study have shown that the mean head measurements (HC, BPD and HL) were observed to similarly decrease with the increase in lamotrigine dosages. Upon comparison of the effects of lamotrigine when administration was done during different gestation periods, the first trimester had the lowest means, followed by the second trimester, while the effects were highest when lamotrigine was administered during the third trimester. The low dosage groups had no statistical significance difference when comparison was done with the control group (Table 2). The current study results concide with those of (Wairimu *et al*., 2019, Margulis *et al.,* 2017) on effects of anticonvulsant medicines upon prenatal exposure. They observed that upon administration of carbamazepine and valproic acid respectively, there was associated reduction in head measurements.

5.0 Conclusion / Recommendations

The study concludes that effects of lamotrigine on fetal growth and development when exposed prenatally is dependent on the dose and time of exposure. Further studies on animal species close to humans as well as clinical trials are recommended.

6.0 Acknowledgement

6.1 Funding

Self-funded

6.2 Ethical consideration and clearance

The study sought approvals from a committee based at the University of Nairobi (UON), faculty of veterinary medicine, department of veterinary Anatomy and Physiology, before initiation of the study (approval letter; REF: FVM BAUEC/2021/323).

6.3 Conflict of interest

The authors declare no conflict of interest.

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doi: 10.4314/jagst.v22i3.10

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URL: https://ojs.jkuat.ac.ke/index.php/JAGST
ISSN 1561-7645 (online)
doi: 10.4314/jagst.v22i3.10