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# Maternal Pregnancy Outcomes: The Teratogeniceffects Of In-Utero Exposure To Varied Doses Of Lamotrigine In Albino Rats (Rattus Norvegicus)

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**ABSTRACT:**In-utero exposure toLamotrigine (LMT), asecond-generation anticonvulsant medicine ofphenyltriazine derivative that is widely and increasingly being prescribed as first line medicine by women of childbearing age in management of maternal conditions like partial and generalized epileptic seizures, a neuromodulator in mood disordersamong others, have past controversial literatures concerning its safety profile to the expectant women and the developing fetus. While some studies have considered lamotrigine to be a safer first line generation medicines because of its efficacy, tolerability and minimal teratogenic effects to the developing fetus, others have advocated for further studies since their results are not conclusive on these effects. Data on maternal pregnancy outcomes following administration of varying doses of lamotrigine at different gestation periods is therefore of paramount importance to enhance maximum benefit to the expectant women and minimal effects to the developing fetuses. The broad objective of this study was therefore to evaluate the maternal pregnancy outcomes following in-utero exposure to varied doses of lamotrigine when administered at different gestational periods in albino rats.

**Materials and methods:** This study adopteda post-test only control experimental study design. The animal experimentation and measurement of the maternal pregnancy parameters wascarried out in the animal research facility located in the University of Nairobi, Chiromo campus.

**Sample size determination**: A sample size of 30 albino rat dams (Rattus norvegicus) weighing between 250±30grams were used in the study as determined by use of the resource equation for One Way Analysis of Variance method (ANOVA). The 30 Albino rats were divided into 2 broad groups of 3 control and 27 experimental rats. To evaluate the maternal pregnancy outcomes of lamotrigine on differing doses, the 27 rats in the experimental group were further subdivided into three study groups of 9 rats as follows; (i) Low lamotrigine group (25 mg/kg) (ii) Medium lamotrigine group (235.7 mg/kg) and (iii) High lamotrigine group of (500mg/kg). To further evaluate the comparative effects of lamotrigine on differing gestation periods, the 9 rats in each of the three dose categories were further be sub-divided into three groups of 3 rats according to trimesters as follows; (i) Trimester I-(3rats); (ii) trimester II-(3rats) and (iii) trimester III-(3rats) respectively in each study group

**Data Analysis**-The maternal pregnancy parameters that included mean daily maternal weight gain, mean litter size, mean dead fetuses, mean resorbed glands that formedthe parametric datawas collected using structured checklists then stored and coded in excel spreadsheets windows 10, version 2013. It was then exported for analysis in SPSS for windows version 25 (Chicago Illinois). Statistical analysis was analyzed using one-way analysis of variance (ANOVA),followed by Tukey's post hoc multiple comparison tests.Results were expressed as mean± standard error of the mean(SEM) and all valueswhose $P<0.05$ was considered to be significant.

**Study findings**-Study findings from the current study have shown that lamotrigine has a direct dose effects and inverse gestational effects when exposed in-utero. Higher doses of lamotrigine (HLMTG),

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have been shown to have the highest statistical significance effects to the maternal pregnancy outcomes (P<0.05) when compared with the control as compared to medium and low dosages ((MLMTG and(LLMTG)).Similarly, these effects were high when lamotrigine was administered during the first trimester($TM_1$), followed by second trimester ($TM_2$) and were least when lamotrigine was administered during the third trimester.($TM_3$),

**Conclusion-** High lamotrigine dosages and especially during first trimester should be avoided since they are associated with adverse effects to the maternal pregnancy parameters which reciprocate the effects to the developing fetus. Further studies with higher primates closer to human species as well as clinical trials are therefore recommended to rule out the safety index of lamotrigineduring pregnancy.

**KEYWORDS:**Lamotrigine,Anticonvulsant, Teratogenic

## I. INTRODUCTION

Though lamotrigine is second-generation and a category C anticonvulsants medicine used as first line in management of maternal conditions such as epilepsy, bipolar disorders among others, it is currently faced with a controversy due to its unclear safety index when exposed in-utero,Kutb& Omer, (2019), Elgndy et al., 2019. This is because of the fact that all anticonvulsant medicine once prescribed in women of child-bearing potential with such conditions are known to cause teratogenicity to the developing fetus as they are capable of crossing thematernal placenta barrier due induced fluctuating levels of drug-metabolizing enzymes during pregnancy(Kaplan (2004); Tomson and Battino, 2008; Hill et al., 2010), Prakash et al.,2007

Inconclusive studies have associatedlamotrigine with good efficacy, tolerability and minimal teratogenic effects to the developing fetus while administered in-utero, Veroniki et al., 2017; Bansal et al., 2018; Yasama et al., 2016; French & Gazzola (2011),while others have advocated for further studies since they present varying result of its teratogenicity(Kamali et al., 2020; Marchi et al., 2001).

In this contexttherefore,it is of paramount importance to establish data that is lacking on the maternal pregnancy outcomes, following in-utero exposure to lamotrigine at varying dosages and at different gestation periods to guide the clinicians on its safety profile, its most vulnerable period of in-utero exposure and the most teratogenic dose. Such data will enhance maximum benefits to the mothers and minimal teratogenic effects to the developing foetuses.

## II. MATERIALS AND METHODS

**Study Location/ Setting:**All experimental procedures that included breeding, mating, daily weighing, feeding, administration of lamotrigine, humane sacrificing of the rats, measurements and recording of the maternal pregnancyparameters were carried out at the animal facility situated in the University of Nairobi (UON), Chiromo Campus.

**Study Design:**A posttest-only with control experimental study design was adopted where 30 female albino rats were randomly assigned to either control or experimental group.

**Acquisition and description of Albino rats:**Sexually mature female albino dams (6wks)of pure breed ($4^{th}$ series breed) weighing between 250±30g were obtained from the department of biomedical science, Chiromo campus. They were used in the study due to following known scientific facts; (i) Resistant to various ailments (ii)calm temperament (iii) Are easy to handle(i)Large litter size, (ii)low maintenance cost (iii)low incidence of spontaneously occurring congenital defects, (iv)Relatively short gestational span and, (v)considerable amount of the reproductive data on the rat is already available (Bryda, (2013). Bailey et al., 2014; Pritchett & Corning, 2016). Sexually mature male rats of the same family of albino rats were used for mating purposes. Rats were kept in spacious polycarbonate plastic cages as determined by (Kuramoto et al., 2012, Allen et al., 2016).

**Sample Size Determination:** Sample size was determined by use of resource equation for group comparisons using One-Way Analysis of Variance (ANOVA). Based on this approach, the acceptable range of degrees of freedom (DF) for the analysis of variance (ANOVA) is between 10 to 20. The formula is n = DF/k + 1, where DF = total number of subjects, k = number of groups, and n = number of subjects per group. **(**Charan & Kantharia, 2013). **n**=20/10+1 =3.Therefore, number ofdams is **30.** Every adult female rat is assumed to have a minimum average of six (3) fetuses per pregnancy. The expected number of fetuses were determined as follows 3 x 30=90 fetuses. All fetuses were obtained by use of simple convenient sampling method

**Grouping of rats in the study:**After confirmation of pregnancy, the rats were assigned into two broad

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study categories of 3 rats in control group and 27 rats in experimental group. The 27 rats in the experimental group were further divided into three sub-groups of 3 rats each assigned according to the dose administered as low (LLMTG), Medium (MLMTG) and High lamotrigine group (HLMTG). To determine whether the effects of lamotrigine are time dependant, each of the subgroups of the LLMTG, MLMTG and HLMTG were further subdivided into smaller sub-groups according to the time of administration as first ($TM_1$), second ($TM_2$) and third ($TM_3$) trimesters comprising of 3 rats each

**Mating and confirmation of pregnancy:The mating process was done by** Two male sexually mature of albino rat breed were introduced into a standard polycarbonatecage with four female rats overnight, after which males were removed and returned to their separate cages the following morning, Slonaker, (1918), Dikshit & Taskar (1959). Confirmation of pregnancy was done by taking a vaginal swab from the mated rats and smearing it on a slide and observing them under the microscope for presence of spermatozoon and changes in epithelial cells Shedrack et al., 2006). The rats that did not conceive were given more chances with the males for mating again till they conceived.

**Feeding of the albino rats:** All rats were fed on a standard diet as determined by American institute of nutrition (2011) that included rodent pellets from UNGA meals limited (Nairobi), and water adlibitum.Food and water were administered through a mesh in a standard polycarbonate cage (fig 2.1).

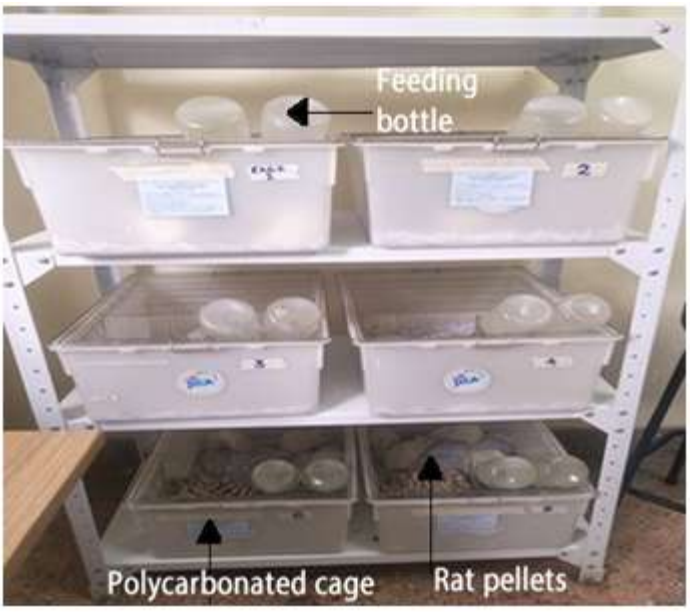


**Fig 2.1: Showing how feeding of the rats was done by use of rodent pellets)from a wire-mesh at the polycarbonate plastic cages) and water ad-libitum (using the plastic bottles).**

**Acquisition of lamotrigine and Determination of Lamotrigine dosages:** Lamotrigine tablets from Vega Biotec Private Limited (Gujarat India) batch number M2017103 were obtained from a government chemist in Nairobi, Kenya. They were reconstituted using distilled water and administered using an oral gavage needle gauge 16. Dosages were determined by use of a simple guide for conversion of animal dosages from human dosage as determined by (Nair & Jacob, 2016) as follows; The correction factor (Km) is estimated by dividing the average body weight (kg) of species to its body surface area (m2). For example, the average human body weight is 60 kg, and the body surface area is 1.62 m2. Therefore, the Km factor for human is calculated by dividing 60 by 1.62, which is 37. The Km factor values of a rat is used to estimate the HED as: HED mg / kg = Rat dose mg / kg Animal K /Human K Eq. As the Km factor for each species is constant, the Kmratio is used to simplify calculations. Hence, Equation is modified as: 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. Administration of lamotrigine: All rats in trimester one ($TM_1$) group in the Low, Medium

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and High dose categories received lamotrigine from gestation day $GD_1$-$GD_{20}$ while the rats in second trimester ($TM_2$) group in Low, Medium and High ($TM_3$) group in Low, Medium and High dose categories received lamotrigine from gestation day $GD_{14}$-$GD_{20}$

**Humane sacrificing of the pregnant albino rats and harvesting of fetuses:** All rats were humanly dose categories received lamotrigine from gestation day $GD_7$-$GD_{20}$. Rats in third trimester

sacrificed on day 20th just before delivery to avoid devouring any devoured fetus, by use of concentrated carbon dioxide soaked in a cotton wool and put in a bell-jar. (Figure 2.2 and figure 2.3)

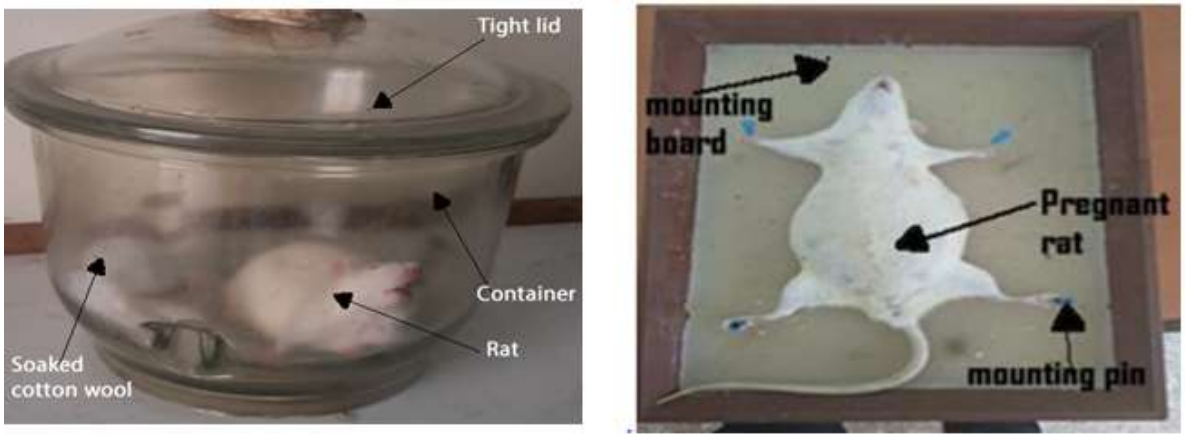


**Figure 2.2: Showing howA; Pregnant rats were euthanized by use of concentrated carbon dioxide put in a bell jar B: How the pregnant rat was mounted on a board using pins for fetal harvesting of fetuses.**

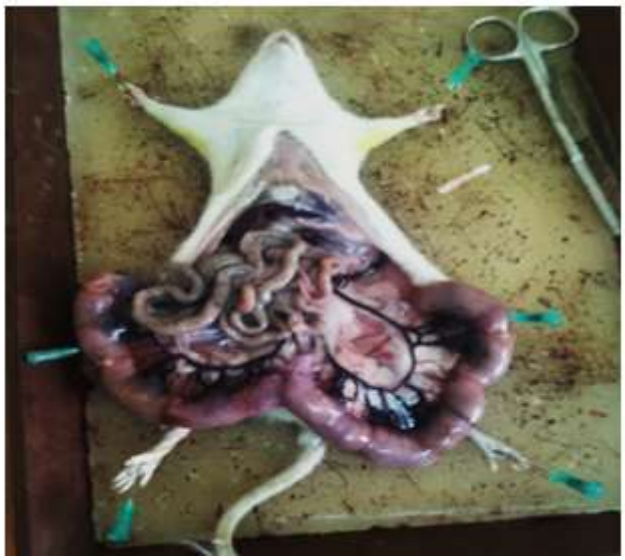

**Figure 2.3: Showing howanterior abdominal wall of the pregnant rat was incised along the linear alba to expose the fetuses.**

**Ethical consideration and clearance**

Animals used in the study and procedures carried out were in accordance with the guidelines of the National Institutes of Health Animal Care and the animal research. Approvals were sought and given by the Animal Care and Use Committee based in the University of Nairobi (UON), Faculty of Veterinary medicine, Department of veterinary Anatomy and Physiology, before initiation of the study. (REF: FVM BAUEC/2021/323)

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**Data collection and statistical analysis**

Data on maternal pregnancy outcomes that includes; daily weight gain, litter size, placenta weight, resorbed endometrial glands/devoured fetuses and dead fetuses forms quantitative parametric data. Itwas collected using structured checklists, stored and coded in excel spreadsheetswindows 10, version 2013. It was then be exported for analysis to SPSS programme for windows version 25 for analysis (Chicago Illinois). Data was analyzed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc multiple comparison tests and was expressed as mean+ standard error of the mean(SEM) for all values. All results whose $P<0.05$ will be considered to be significant considered.

**The maternal pregnancy outcomes**

Daily maternal weights and placenta weights were obtained by use of a digital weighing scale (figure 2.4), while the number of devoured and resorbed glands, litter size and the number of dead fetuses were also counted and recorded.


**Figure 2.5; Showing how maternal weight was measured**

using scout pro model SPU4001 S/N B519923500 from Uhaus Corp- USA)**digital weighing scale.**

## III. RESULTS

### 3.1 Influence of Lamotrigine on Maternal Weights Trends Throughout the Gestation Period

It can be observed that weight trends during trimester one, trimester two and trimester three ($TM_1$, $TM_2$ and $TM_3$) decreased with increase in dosage in experimental groups as compared with the control group throughout the gestation period ($GD_1$-$GD_{20}$). The first three to four days following lamotrigine administration at trimester one ($TM_1$), was marked with significant decrease in weight which was higher in high dosage groups (HLMTG), Followed by medium dosage group (MLMTG) and lastly in low lamotrigine group (LLMTG). This was followed by a steady increase in weight gain up to the day of sacrificing the rats ($_{GD20}$). This phenomenon that could be attributed to the lamotrigine acclimatization factor (figure 3.1A).

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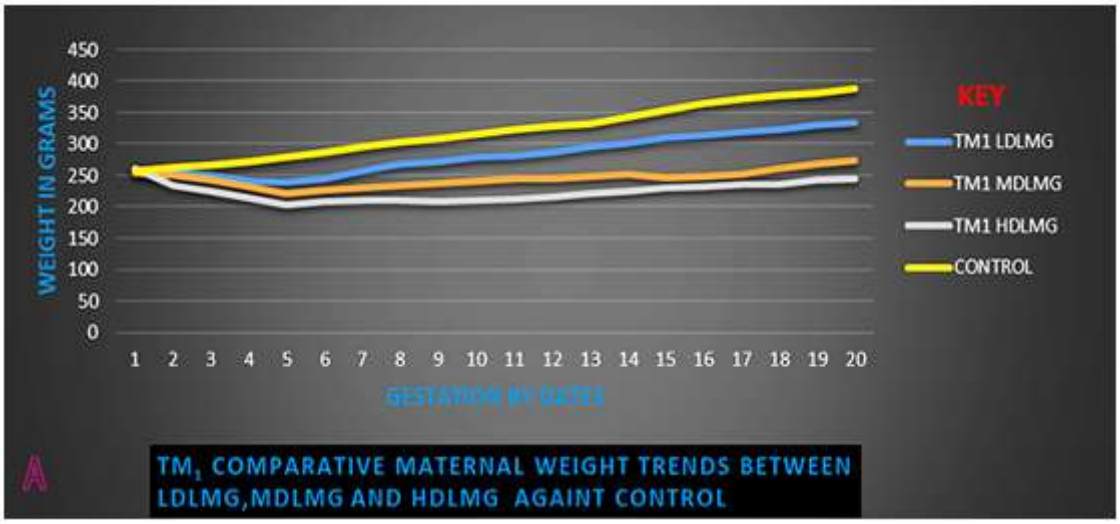


**Fig 3.1A: $TM_1$ Comparative Maternal Weight Trends between Low dose Lamotrigine group (LDLMTG), Low Dose Lamotrigine group (MDLMTG) and High dose Lamotrigine group (HDLMTG) Against Control Group**

Similarly, during the second trimester $TM_2$(from the 8th day), there was markeddecrease in weight for a duration of three days which was higher in high dosage groups (HLMTG), followed by medium dosage group (MLMTG) and lastly in low lamotrigine group (LLMTG). This was similarly followed by a rise in weight gain up to the last day ofgestation ($_{GD20}$), (figure 3.1B).

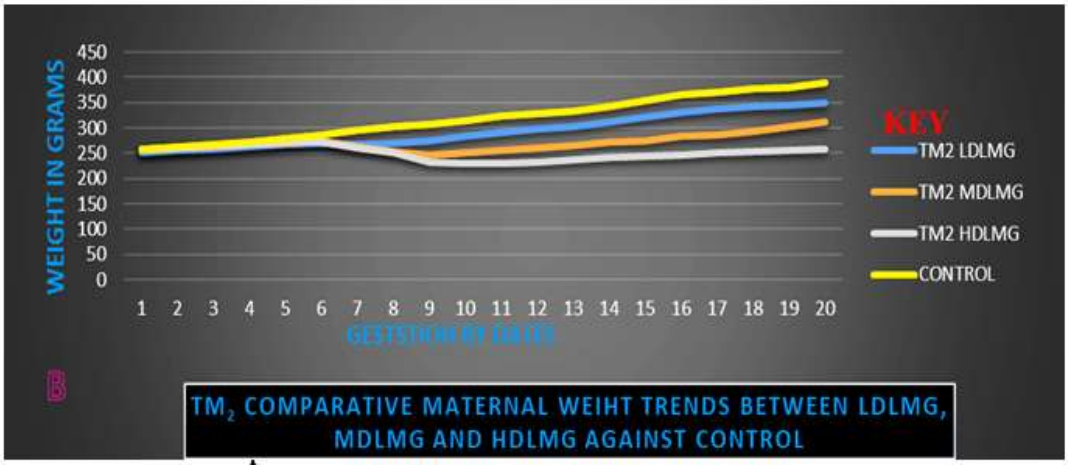


**Fig 2.5B: $TM_2$ Comparative Maternal Weight Trends between Low dose Lamotrigine group (LDLMTG), Low Dose Lamotrigine group (MDLMTG) and High dose Lamotrigine group (HDLMTG) Against Control Group**

When lamotrigine was administered during trimester three($TM_3$), a similar scenario was observed. There was a notable decrease in weight in all treatment groups but more marked in high dosage group (HLMTG), followed by medium dosage group (MLMTG) and lastly in low lamotrigine group (LLMTG), (figure 3.1C).

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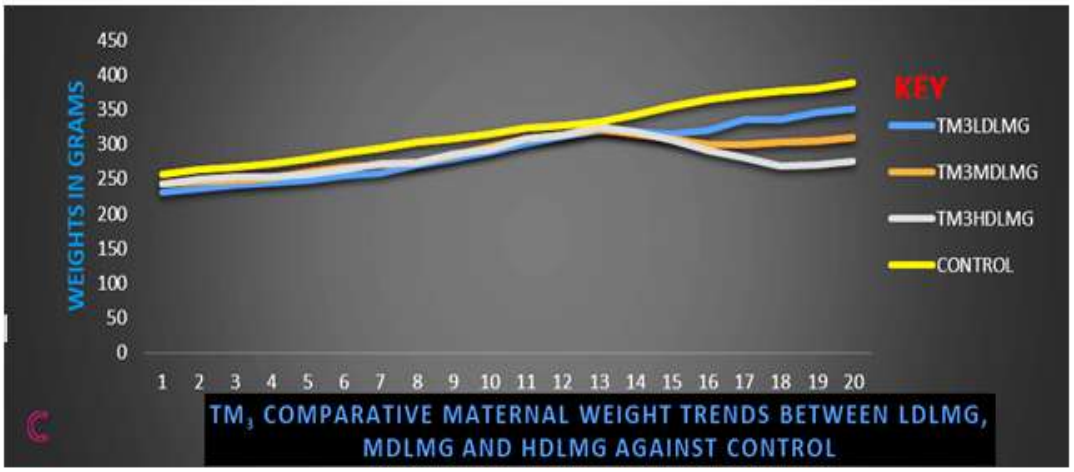


**Fig 3.1C: $TM_3$ Comparative Maternal Weight Trends between Low dose Lamotrigine group (LDLMTG), Low Dose Lamotrigine group (MDLMTG) and High dose Lamotrigine group (HDLMTG) Against Control Group**

### 3.2 Influence of Lamotrigine on Mean Maternal Weight Gain Throughout the Gestation Period

When the statistical analysis was done to depict whether or not the mean maternal weight gain (grams) has a dose and time dependent relationship, it was established that when treatment was instituted during trimester one and two ($TM_1$&$TM_2$), there was significant reduction in maternal weight gain in all the treatment groups (LLMG, MLMG, HLMG) (P=0.002). This is unlike in $TM_3$ where there was no significant difference for the low and medium dose groups compared with the control (P=0.21), apart from the high dose.

The mean placental weight that is usually a key indicator of maternal nutritional exchange with the fetus was also observed to have an inverse dose response relationship with the dose of treatment and the time of exposure. The lowest placental weight recorded was in high lamotrigine treated group at $TM_1$ and was lowest in the low carbamazepine group at $TM_3$ (**table 1**).

**Table 3.1: TheMean Maternal Weight Gain for the Levetiracetam Treatment Groups (LLAMTG, MLAMTG and HLAMTG) with the Time of Exposure ($TM_1$, $TM_2$ and $TM_3$) against the Control Group**

| Parameter | Control (C) | Low Lamotrigine Group (LLMG)(25mg/kg) | | | Medium Lamotrigine Group (MLMG) (327.5mg/kg) | | | High Lamotrigine Group (HLMG) (500mg/kg) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | TM1 | TM 2 | TM3 | TM1 | TM 2 | TM3 | TM1 | TM2 | TM3 |
| **Mean Maternal weight Gain(g) ± SEM** | 130.67±5.78 | 105.7 ±5.55* | 112.67 ±7.42* | 116.7 ±13.860 | 88.3 ±12.1* | 83.33 ±5.840* | 81.00 ±3.512* | 37.7 ±7.3* | 60.33 ±5.93* | 60.6 ±2.67* |

**Key:** All value that bear (*) as a superscript indicates that they depict a statistical significance difference
($p<0.05$) when compared with the control using one way ANOVA with Turkey post-hoc t-tests

### 3.3 Influence of Lamotrigine on litter size

It can be observed from the bar-graph below that in trimester one, trimester two and trimester three ($TM_1$, $TM_2$ and $TM_3$) experimental groups, there was a marked reduction in litter size in a dose dependent manner. Higher doses had the least litter size as compared to medium and low dosages. However, the control group had the highest litter size (figure 3.2).

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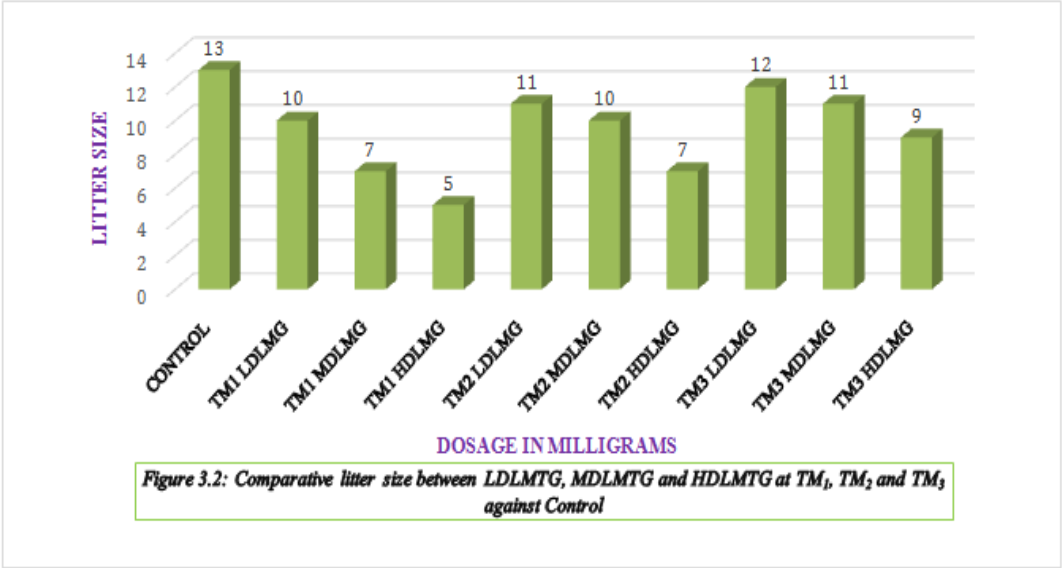


*Figure 3.2: Comparative litter size between LDLMTG, MDLMTG and HDLMTG at $TM_1$, $TM_2$ and $TM_3$ against Control*

### 3.4 Influence of Lamotrigine on mean litter size

**Table 3.2: The Mean Litter Size for the Lamotrigine Treatment Groups (LLAMTG, MLAMTG and HLAMTG) with the Time of Exposure ($TM_1$, $TM_2$ and $TM_3$) against the Control Group**

| Parameter | Control (C) | Low Lamotrigine Group (LLMG)(25mg/kg) | | | Medium Lamotrigine Group (MLMG) (327.5mg/kg) | | | High Lamotrigine Group (HLMG) (500mg/kg) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | TM1 | TM2 | TM3 | TM1 | TM2 | TM 3 | TM1 | TM2 | TM 3 |
| **Mean Litter Size± SEM** | 130.67±5.78 | 105.7 ±5.55* | 112.67 ±7.42* | 116.7 ±13.860 | 88.33 ±12.1* | 83.33 ±5.840* | 81.00 ±3.512* | 37.7 ±7.3* | 60.33 ±5.93* | 60.6 ±2.67* |

**Key:** All value that bear (*) as a superscript indicates that they depict a statistical significance difference ($p<0.05$) when compared with the control using one way ANOVA with Turkey post-hoc t-tests

### 3.5 Influence of lamotrigine on the number of dead fetuses

From the bar-graph below, it can be observed that the number of dead fetuses increased with increase in dosages in that the number was highest in high dosage group (HLMTG), followed by medium dosage group (MLMTG) and lastly in low lamotrigine group (LLMTG). When lamotrigine was administered during different gestation periods, the number of dead fetuses was higher when it was administered during trimester one ($TM_1$), followed by trimester two ($TM_2$), and finally at trimester three ($TM_3$). However, the number of dead fetuses was low in control group (figure 3.3)

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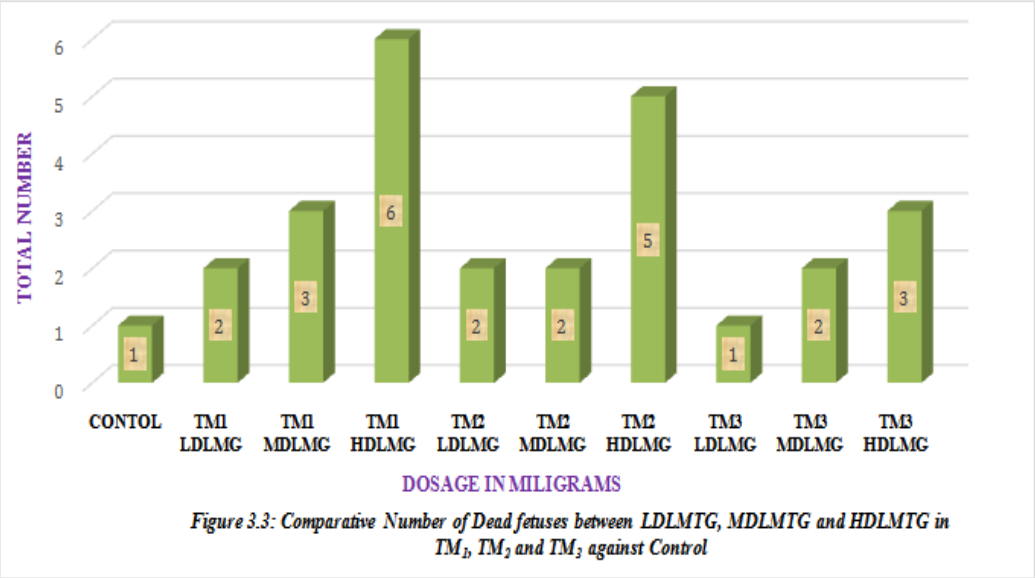


*Figure 3.3: Comparative Number of Dead fetuses between LDLMTG, MDLMTG and HDLMTG in $TM_1$, $TM_2$ and $TM_3$ against Control*

### 3.6 Influence of lamotrigine on mean dead fetuses

**Table 3.3: The Mean Dead Fetuses for the Lamotrigine Treatment Groups (LLAMTG, MLAMTG and HLAMTG) with the Time of Exposure ($TM_1$, $TM_2$ and $TM_3$) against the Control Group**

| Parameter | Control (C) | Low Lamotrigine Group (LLMG)(25mg/kg) | | | Medium Lamotrigine Group (MLMG) (327.5mg/kg) | | | High Lamotrigine Group (HLMG) (500mg/kg) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | TM1 | TM2 | TM3 | TM1 | TM2 | TM3 | TM 1 | TM 2 | TM3 |
| Mean Dead Fetuses± SEM | 130.67±5.78 | 105.7 ±5.55* | 112.67 ±7.42* | 116.7 ±13.860 | 88.3 ±12.1* | 83.33 ±5.840* | 81.00 ±3.512* | 37.7 ±7.3* | 60.33 ±5.93* | 60.6 ±2.67* |

**Key:** All value that bear (*) as a superscript indicates that they depict a statistical significance difference ($p<0.05$) when compared with the control using one way ANOVA with Turkey post-hoc t-tests

### 3.7 Influence of Lamotrigine on the number of Devoured and Resorbed fetuses

The number of devoured fetuses and resorbed glands was observed to increase in a dose related manner. the number was highest in high dosage group (HLMTG), followed by medium dosage group (MLMTG) and lastly in low lamotrigine group (LLMTG). When lamotrigine was administered during different gestation periods, the number of dead fetuses was higher when it was administered during trimester one ($TM_1$), followed by trimester two ($TM_2$), and finally at trimester three ($TM_3$). However, the number of dead fetuses was low in control group (figure 3.4A-3.4B)

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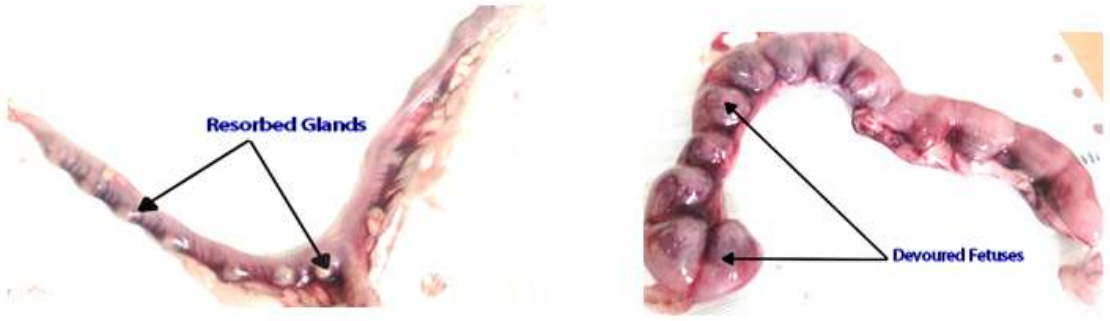


**Figure 3.5A: Showing samples of resorbed glands and devoured fetuses**

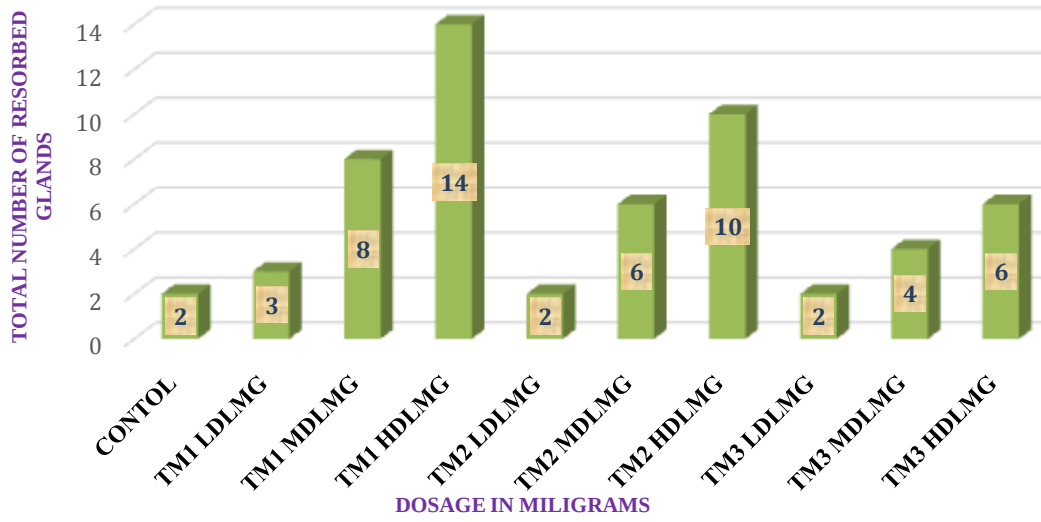


***Figure 7: Comparative Number of Resorbed Glands and Devoured Fetuses in LDLMG, MDLMG and HDLMG in $TM_1$, $TM_2$ and $TM_3$ against Control***

### 3.8 Influence of Lamotrigine on Mean Devoured and Resorbed fetuses

**Table 3.1: The Comparative Mean Litter Size for the Lamotrigine Treatment Groups (LLAMTG, MLAMTG and HLAMTG) with the Time of Exposure ($TM_1$, $TM_2$ and $TM_3$) against the Control Group**

| Parameter | Control (C) | Low Lamotrigine Group (LLMG)(25mg/kg) | | | Medium Lamotrigine Group (MLMG) (327.5mg/kg) | | | High Lamotrigine Group (HLMG) (500mg/kg) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | TM1 | TM2 | TM3 | TM1 | TM2 | TM3 | TM1 | TM 2 | TM3 |
| Mean Devoured Fetuses± SEM | 130.67±5.78 | 105.7 ±5.55* | 112.67 ±7.42* | 116.7 ±13.860 | 88.3 ±12.1* | 83.33 ±5.840* | 81.00 ±3.512* | 37.7 ±7.3* | 60.33 ±5.93* | 60.6 ±2.67* |

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**Key:** All value that bear (*) as a superscript indicates that they depict a statistical significance difference
($p<0.05$) when compared with the control using one way ANOVA with Turkey post-hoc t-tests

## IV. DISCUSSION

In the current study, lamotrigine was observed to have effects on daily maternal weight trends, litter size, placenta weight, number of resorbed endometrial glands/ devoured fetus as well as the number of dead fetuses in a time and dose dependent manner. This is despite the fact that past literature has associated it with high level of tolerability coupled with good efficacy, and have a general belief that it is safer than the older, frontline AEDs (Hill et al., 2010).

Daily maternal weight trends were observed to increase steadily in control group as opposed to the experimental groups (line graphs A, B and C). These trends were observed to be dose dependent in that in high lamotrigine dosages, daily weight was observed to have a minimal increase, followed by medium dosages and finally the low dosage groups as compared to the control. Results of (Punnell, 2008) advised on further studies, since the results available on lamotrigine were not conclusive.

The mean maternal weight gain was statistically reduced ($P<0.05$) in treatment groups as compared with the control (table 1). These results were intendem with those reported by Elshama et al (2015) indicating that high dosages of carbamazepine, an anticonvulsant affects corpus luteum in the pregnant mothers' which secrets progesterone and 20-hydroxy progesterone, that maintains in-utero fetal growth and development. Sucheston et al., (1986) and Marli Gerenutti et al., (2008) also reported that high dose carbamazepine dose exposure during pregnancy leads to delay in growth and development of various fetal organs during embryogenesis leading to low maternal weight gain.

In the current study, the mean placenta weight demonstrated a time and dose relationship in that it was high in low dosages during the third trimester and low in high dosages during trimester one as compared with the control (Table 1) $P<0.05$. These findings were in agreement with those of Christensen et al. (2004) who similarly indicated that low carbamazepine dosages have no effects on weight of the placenta as well as fetus's offspring vitality. Similar effects were also recorded by Marli Gerenutti et al (2008), who stated that high doses of carbamazepine cause 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.

In the current study, litter size was low in lamotrigine treatment groups as compared with the control group (figure 5) in time and dose dependent. Results of Baeward et al., (2005) are in agreement with the current results that 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. 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.

The number of resorbed endometrial glands/devoured fetuses and dead fetuses were observed to be higher in lamotrigine treatment groups when it was administered in the first trimester at high dosages and lowest in control group (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. He further observed presence of a number of external congenital malformations. 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.

## V. CONCLUSION AND RECOMMENDATIONS

The study has established that use of lamotriginehas effects on maternal pregnancy outcomes when administered in utero that are time and dose dependent. Since lamotrigine continues to be prescribed widely by clinicians as the safest and first line anticonvulsant medicine in management of maternal conditions.Further studies in higher primates closer to human species as well as clinical trials should be carried out to rule out safety of lamotrigine during pregnancy.

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