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Evaluation of in-Utero Effects on Fetal Growth and Development Following Prenatal Exposure to Varied Doses of Levetiracetum in Albino Rats (Rattus Norvegicus).

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ABSTRACT: The teratogenic effects of in-utero-exposure to varied doses of levetiracetam, a commonly used second line anticonvulsant medicine on growth and development of the fetuses remains unclear. Past literature has advocated for further studies on levetiracetam concerning its safety profile on growth and development of the fetuses, following prenatal exposure to varied doses of levetiracetam and at differing gestational periods. The broad objective of this study was therefore to evaluate the fetal pregnancy outcomes following in-utero exposure to levetiracetam when administered at different gestational periods and at varied doses in albino rats. A post-test only control experimental study design was adopted in conducting this study. Animal experimentation and measurement of the fetal growth and development parameters was carried out in the animal facility located in the University of Nairobi, Chiromo campus. A sample size of 30 albino rat dams (Rattus norvegicus) weighing between 220+30 grams were used in the study as determined by use of the resource equation for One Way Analysis of Variance method (ANOVA). These rats were divided into 2 broad groups of 3 control and 27 experimental rats. To evaluate the fetal pregnancy outcomes on differing doses of levetiracetam, the 27 rats in the experimental group were further subdivided into three study groups of 9 rats as follows; (i) Low levetiracetam group (1000mg/kg) (ii) Medium levetiracetam group (2000mg/kg) and (iii) High levetiracetam group of (3000mg/kg). To further evaluate the comparative effects of levetiracetam on differing gestation periods, the 9 rats in each of the three dose categories were further 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. Fetal growth and development parameters that included fetal weight (FW), crown rump length CRL), bi-parietal diameter (BD), head length (HL) and head circumference (HC) formed the parametric data. This data was collected using digital Vaniercallipers (sealing product-Japan model 1.13.2017),calibrated ruler and an electronic weighing machine, entered intostructured checklists, thencoded and stored in excel spreadsheets windows 10, version 2013. It was further exported to SPSS programmes windows version 25 for analysis (Chicago Illinois) using one-way analysis of variance (ANOVA) followed by Tukey's post hoc multiple comparison tests for comparison of means. Data was expressed as mean± standard error of the mean (SEM) for all values. All results whose $P<0.05$ were considered to be significant.The study findings showed that the teratogenic effects to the developing fetus were time and dose dependent in that the severestteratogenic effects were observed during the first trimester while the least teratogenic effects were observed during the third trimester. It was further observed that the dose associated with themost teratogenic effects was at 78.64mg(High dose) in the first trimester while the dose associated with the least teratogenic effects was at 25.07mg (Low dose)in trimester 3. The study recommends that further studies be carried on in higher non-human primates to ascertain its teratogenicity in relation to doses.

KEYWORDS: Anticonvulsants, Teratogenic, Levetiracetam.

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I. INTRODUCTION

Though levetiracetam is one of the most prescribed second line anticonvulsant medicine in management of maternal conditions like epileptic seizures, bipolar disorders, depression among others (Bansal et al., 2018, Koubeissi (2013), there is a controversy of its safety on growth and development of the developing fetuses when exposed in-utero (Chaudhry et al., 2014). Due to these effects, clinicians have always had difficulties in prescribing anticonvulsants medicines like levetiracetam to expectant mothers who require anticonvulsant medicine due to their unclear safety index (Yi et al., 2018, French et al., 2001). Though levetiracetam is greatly preferred because of its efficacy, tolerability and minimal teratogenic effects to the developing fetus (Veroniki et al., 2017; Bansal et al., 2018; Prakash et al., 2007; Yasama et al., 2016; French & Gazzola. (2011)), it has however been established that all anticonvulsant medicines are teratogenic to the developing fetuses (Güveli et al., 2017; Tomson & Battino 2012). In this context, there is paucity of data on the effects of levetiracetam on growth and development of the fetuses when administered at varied dosages and during varying gestational periods. Such data would be key in guiding the clinicians in choosing the best dosages and the best gestational period that is less vulnerable to the developing fetuses.

II. MATERIALS AND METHODS

Study Location/ Setting: All experimental procedures that included breeding, mating, daily weighing, administration of levetiracetam, general observations of the rats, humane sacrificing of the rats and measurements of the maternal and fetal parameters were carried out at the animal facility situated in the University of Nairobi (UON), Chiromo Campus. Processing for light microscopy and stereology was carried out in the department of Human Anatomy based in Jomo Kenyatta University of Agriculture and Technology (JKUAT) Juja main campus.

Study Design: A post-test only control experimental study design was adopted where 30 female albino rats were randomly assigned to either control or experimental group. After being sacrificed, fetuses were obtained and various parameters measured and recorded.

Acquisition and description of Albino rats: Female albino dams of pure breed weighing between 250±30g were obtained from the department of biomedical science based in the University of Nairobi (UON)Chiromo campus. They were used in the study due to following known scientific facts; (a)low incidence of spontaneously occurring congenital defects, (b)Large litter size, (d)low cost of maintaining the animals (d)relatively short gestational span and, (v)considerable amount of the reproductive data on the rat is already available (Bailey et al., 2014; Pritchett & Corning, 2016). Pure breed male rats of the same albino rat's family were used for mating purposes. Rats were kept in spacious polycarbonate plastic cages as determined by (Allen et al., 2016).

Sample Size Determination: Sample size for the number of rats to use for the study was determined by use of resource equation for group comparisons of One-Way Analysis of Variance (ANOVA). Based on this approach, the acceptable range of degrees of freedom (DF) for the error term in analysis of variance (ANOVA) is between10 to 20. The formula is **n = DF/k+ 1,** where DF = error of degree of freedom, k = number of groups and n = number of subjects per group. **(**Charan & Kantharia, 2013).Therefore, **n=20/10+1 =3.** Therefore, number ofdams was **30.** Sample size for the number of fetuses to use for the study was determined as follows, fromevery adult pregnant female rat, three fetuses were picked from its total litter size by use of simple convenient random sampling method.The expected number of fetuses for analysis was determined as follows 3 x 30=90 fetuses.

Mating and confirmation of pregnancy: Two male albino rats from 3rd series breed of a pure colony and sexually mature were introduced into a standard cage with four female rats overnight (2400hrs) and males removed and returned to their separate cages the following morning. 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

Grouping of rats: After confirmation of pregnancy, the rats were randomly assigned into two broad study groups 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 levetiracetam

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exposed group (LLEG), Medium levetiracetam exposed group (MLEG) and High levetiracetam exposed group (HLEG). Each of the subgroups of the LLEG, MLEG and HLEG 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**.**

Feeding of the 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.

Acquisition of Levetiracetam and Determination of dosages: Levetiracetam tablets from Glaxo Smith Kline British Multinational Pharmaceutical Company Limited (England-London), batch number CHEMBL741, 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 (m^2). For example, the average human body weight is 60 kg, and the body surface area is 1.62 m^2. Therefore, the Km factor for human is calculated by dividing 60 by 1.62 m^2, 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 Km ratio 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 levetiracetam: All rats in trimester one (TM_1) group in the Low, Medium and High dose categories received levetiracetam from gestation day GD_1-GD_{20} while the rats in second trimester (TM_2) group in Low, Medium and High dose categories received levetiracetam from gestation day GD_7-GD_{20}. Rats in third trimester (TM_3) group in Low, Medium and High dose categories received levetiracetam from gestation day GD_{14}-GD_{20}

Humane sacrificing of the pregnant albino rats: All rats were humanely sacrificed on day 20th just before delivery by use of concentrated carbon dioxide soaked in a cotton wool and put in a bell-jar.

Ethical considerations and clearance: Ethical considerations and clearance was sought and approved 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)

Statistical analysis: Data on fetal pregnancy outcomes that includes fetal weight (FW), crown rump length CRL), bi-parietal diameter (BD), head length (HL) and head circumference (HC) that formed the parametric data (inferential data) was collected using structured checklists, stored and coded in excel spreadsheets windows 10, version 2013. It was then be exported to 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. It was analyzed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc multiple comparison tests. All results whose $P<0.05$ was considered to be significant considered.

The Fetal Pregnancy Outcomes Parameters: Fetal weight (FW), Crown Rump Length (CRL), Head circumference (HC), Bi-parietal diameter (BD) and Head Length (HL) were obtained (figure 2.1, 2.2 and 2.3)

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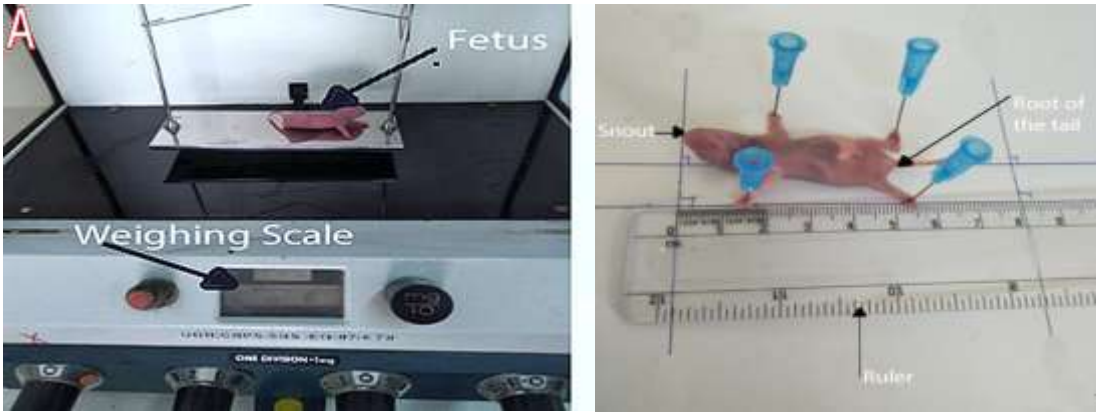

Figure 2.1 A: How fetal weights were taken using an electronic weighing machine. B: how the CRL measurements were taken using a calibrated ruler beginning from the tip of the nose (snout) to the root of tail with the rats lying supine against lines drawn at right angles).

Figure 2.2 A: Showing how the head length measurements were taken; from the back of the skull from superior nuchal line of occipital bone to the extremity of the nose B:How the bi-parietal diameter measurements taken from the junction of the posterior third of the superior temporal line on both side (using a digital Vernier caliper from Hercules sealing products Japan model 1.13.2017)

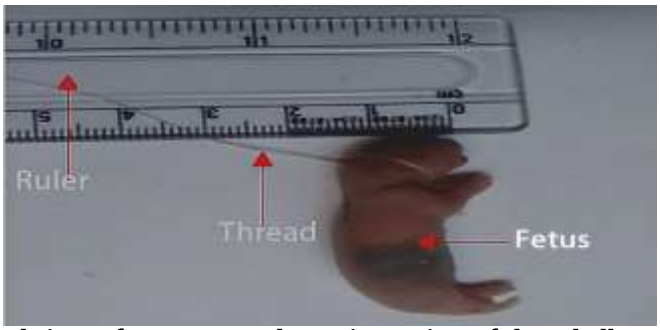

Figure 2.3: How fetal head circumference was taken using a piece of thread all-round the head, (passing below the chin on the right, moving up anterior to the right ear, passing over the vertex and moving down anterior to the left ear and down to the left chin)then the string measured straight against a calibrated ruler.

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III. RESULTS

3.1 Influence of Levetiracetam on Fetal Body Weights, Crown -rump Length and Head Circumference

The study found that the mean fetal weights, crown rump lengths and mean fetal head circumference depicted an inverse dose response relationship and at the same time depicted a direct response relationship with the time of exposure. Across all trimester groups, there was a statistically significant difference (P=0.001) in different trimesters with the highest fetal body weights, crown rump length and head circumference being observed in trimester three (TM_3), followed by trimester two (TM_2) and lastly by trimester one (TM_1). When dose comparisons were done, it was observed that low dosages group (LLEVG) were being associated with high fetal body weights, crown rump length and head circumference, followed by medium dosage group (MLEVG) and lastly by high dosage group (HLEVG), (**table 3.1)**

Table 3.1: The Intra and Inter group Means of the Fetal Body weight, Crown-rump length and Head Circumference for Levetiracetam Treatment Groups (LDLEVG, MDLEVand HDLEVG) with the Time of Exposure (TM_1, TM_2 and TM_3) against the Control Group

Study groups	Time of Exposure to Levetiracetam Treatment	Mean Fetal Body Weight (mg) ± SEM	Mean Fetal CRL (cm) ± SEM	Mean Head Circumference (cm) ± SEM
Control group	----------	7.7500±0.0235	7.9785±0.0121	4.2003±0.0273
Low dose group (1000mg/kg)	(TM1) (TM2) (TM3)	6.444±0.0059* 6.5897±0.0075* 6.6834±0.0139*	7.3169±0.1733* 7.4540±0.0102* 7.7498±0.0403*	3.6862±0.0534* 3.8340±0.0052* 4.0403±0.0040*
Medium dose group (2000mg/kg)	(TM1) (TM2) (TM3)	6.3432±0.0477* 6.4389±0.0147* 6.5573±0.0096*	6.8777±0.0383* 7.1311±0.0034* 7.5043±0.0453*	3.466±0.0267* 3.7104±0.0207* 3.8440±0.0148*
High dose group (3000mg/kg).	(TM1) (TM2) (TM3)	5.4434±0.02193* 5.9490±0.0065* 6.2368±0.0098*	5.4453±0.0471* 6.0646±0.0059* 6.4368±0.2972*	3.0029±0.0430* 3.6035±0.0409* 3.5397±0.0115*

Key: All value that bear (*) as a superscript indicates that they depict a statistical significance difference ($p<0.05$) when compared with the control.

3.2 Pearson Correlation Co-efficient (rho p) on Mean Foetal Weight, Mean Crown-rump length and Mean Head circumference in Levetiracetam Treated Groups.

When Pearson correlational statistic was done, it depicted a strong positive linear relationship (0.718-0.997) and a statistical significance difference (P=0.001) between mean Crown-rump length, mean Head circumference and mean Foetal weight when treatments were administered during the first trimester (TM_1), second trimester TM_2) and third trimester (TM_3**). (Table 3.2)**.

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Table 3.2: Intra and inter-group Pearson correlational comparisons of Mean Foetal Weight, Mean CRL, and Mean Head Circumference for the LDLEVG, MDLEVG and HDLEVG at TM_1, TM_2 and TM_3 against the control group

		T1 FOETAL WT	T2 FOETAL WT	T3 FOETAL WT	T1 CRL	T2 CRL	T3 CRL	T1 HC	T2 HC	T3 HC
T1 FETAL WT	r	1	.990**	.976**	.928**	.924**	.842**	.975**	.960**	.929**
	p		0.000	0.000	0.000	0.000	0.001	0.000	0.000	0.000
T2 FETAL WT	r	.990**	1	.997**	.881**	.874**	.770**	.961**	.980**	.895**
	p	0.000		0.000	0.000	0.000	0.003	0.000	0.000	0.000
T3 FETAL WT	r	.976**	.997**	1	.844**	.834**	.718**	.939**	.979**	.863**
	p	0.000	0.000		0.001	0.001	0.009	0.000	0.000	0.000
T1 CRL	r	.928**	.881**	.844**	1	.985**	.963**	.945**	.858**	.976**
	p	0.000	0.000	0.001		0.000	0.000	0.000	0.000	0.000
T2 CRL	r	.924**	.874**	.834**	.985**	1	.979**	.954**	.846**	.982**
	p	0.000	0.000	0.001	0.000		0.000	0.000	0.001	0.000
T3 CRL	r	.842**	.770**	.718**	.963**	.979**	1	.884**	.734**	.946**
	p	0.001	0.003	0.009	0.000	0.000		0.000	0.007	0.000
T1 HC	r	.975**	.961**	.939**	.945**	.954**	.884**	1	.947**	.970**
	p	0.000	0.000	0.000	0.000	0.000	0.000		0.000	0.000
T2 HC	r	.960**	.980**	.979**	.858**	.846**	.734**	.947**	1	.885**
	p	0.000	0.000	0.000	0.000	0.001	0.007	0.000		0.000
T3 HC	r	.929**	.895**	.863**	.976**	.982**	.946**	.970**	.885**	1
	p	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	

**. Correlation r is significant at the 0.01 level (2-tailed).
P value ≤0.05 is significant

3.3 Influence of Levetiracetam on Fetal Bi-parietal diameter and Head Length

The mean bi-parietal diameter and head length in levetiracetam treatment groupsdepicted an inverse dose and a direct time response relationship when compared with the control group. Both the mean bi-parietal diameters and head lengths were statistically higher when treatments were instituted at trimester three (TM_3), followed by trimester two (TM_2) and finally by trimester one (TM_1) (P=0.001). Higher dosages (HDLEVG) were associated with low bi-parietal diameter and head length, followed by medium dosages (MDLEVG) and lastly at low dosages (LDLEVG) (P=0.001).**(table 3.3)**

Table 3.3: The Intra and Inter group Means of the Fetal Bi-parietal Diameter and head length for Levetiracetam Treatment Groups (LDLEVG, MDLEVG and HDLEVG) with the Time of Exposure (TM_1, TM_2 and TM_3) against the Control Group

Study groups	The time of exposure to Levetiracetam treatment	Mean bi-parietal diameter (cm) ± SEM	Mean Head Length (cm) ± SEM
Control group	----------	4.2003±0.0273	1.5406±0.0001

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Low dose group (1000mg/kg)	(TM1) (TM2) (TM3)	3.6862±0.0534* 3.8340±0.0052* 4.0403±0.0040*	1.2725±0.0018** 1.3045±0.0007** 1.3152±0.0008*
Medium dose group (2000mg/kg)	(TM1) (TM2) (TM3)	3.466±0.0267* 3.7104±0.0207* 3.8440±0.0148*	1.2434±0.0017** 1.2784±0.0009** 1.3062±0 0004**
High dose group (3000mg/kg)	(TM1) (TM2) (TM3)	3.0029±0.0430* 3.5035±0.0409* 3.5397±0.0115*	1.1837±0.0026** 1.2524±0.0004** 1.2923±0.0010**

Key: All value that bear (*) as a superscript indicates that they depict a statistical significance difference ($p<0.05$) when compared with the control.

3.4 Pearson Correlation Co-efficient (rho p) on Mean Bi-parietal diameter and Mean Head Length in Levetiracetam Treated Groups

The study found that a strong positive linear relationship between mean Bi-parietal Diameter and Mean Head Length was depicted by use of Pearson linear correlational statistics (0.879-0.996), when treatments were administered during the first trimester (TM_1), second trimester TM_2) and third trimester (TM_3) respectively. There was also a statistical significance difference (P=0.001) between mean Bi-parietal Diameter and Mean Head Length across all the trimesters (**table 3.4)**.

Table 3.4: Intra and inter-group Pearson Correlational Comparisons of Mean Bi-Parietal Diameter and Mean Head Length for the LLEVG, MLEVG and HLEVTG at TM_1, TM_2 and TM_3 against the control group

		T1 BD	T2 BD	T3 BD	T1 HL	T2 HL	T3 HL
T1 BD	r	1	0.965	0.941	0.953	0.912	0.879
	p		0.000	0.000	0.000	0.000	0.000
T2 BD	r	0.965	1	0.976	0.988	0.962	0.943
	p	0.000		0.000	0.000	0.000	0.000
T3 BD	r	0.941	0.976	1	0.991	0.986	0.975
	p	0.000	0.000		0.000	0.000	0.000
T1 HL	r	0.953	0.988	0.991	1	0.989	0.977
	p	0.000	0.000	0.000		0.000	0.000
T2 HL	r	0.912	0.962	0.986	0.989	1	0.996
	p	0.000	0.000	0.000	0.000		0.000

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T3 HL	r	0.879	0.943	0.975	0.977	0.996	1
	p	0.000	0.000	0.000	0.000	0.000	

IV. DISCUSSION

The results of the current study have shown that levetiracetam, a currently used second line anticonvulsant medicine in management of maternal conditions have effects on fetal growth parameters including fetal weight, crown rump length, head circumference, bi-parietal diameter and head length, 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, first line AEDs (Hill et al., 2010). Upon comparison of mean fetal weight, mean crown-rump length and mean head circumference, it was observed that there was a dose dependent decrease in weight in levetiracetam treatment groups as compared with the control. High dose group (HDLEVG) was associated with the lowest mean fetal weight, followed by the medium levetiracetam group (MDLEVG) and lastly by low levetiracetam group(LDLEVG) (table 3.1). When levetiracetam was administered at different gestation periods, the reduction in fetal weight, crown rump length, head circumference were more pronounced when levetiracetam was administered during trimester one TM_1), followed by trimester two (TM_2) and lastly when the medicine was administered during the third trimester (TM_3**).**

The results of the current study concur with those of a previous study by Hamdi et al., (2017) whereby oxycarbazepine, still a newer anticonvulsant medicine currently in use, was associated with a reduction in the fetal weight and length, delayed, weak and incomplete ossification, wavy ribs among others. However, the current study results contradict with a study carried out by Etmand et al. (2012) on new AEDs including lamotrigine, gabapentin, oxycarbazine, topiramate, pregabalin among others in the same class with levetiracetam, whose study results showed that these medicines are better tolerated and preferred because they have a good safety and pharmacokinetic profile that makes then have fewer negative effects on fetal growth and development parameters.

No signi汀cant changes were noticed in fetal growth parameters between Topiramate groups. A positive correlation was found between FW and UCL, PW, CRL, HL and BPD in all examined g Fetal mean bi-parietal and head lengths in this study were also observed to have a direct dose response relationship and inverse time dependent relationship (table 3.3). High dosage was associated with reduction in mean bi-parietal diameter and head lengths, medium dosages had bigger mean diameters and finally biggest mean diameters were observed in low dosages. The results of the current study were similar to those of a previous comparative study between lamotrigine and phenobarbitone (a first and a second-generation anticonvulsant medicine respectively). The results depicted a reduction in fetal body parameters including crown -rump length, body length, bi-parietal diameters among others that were pronounce more in phenobarbitone treatment group as compared to the lamotrigine group (Farghaly et al., 2017).

A Pearson correlational statistic depicted a strong positive linear relationship and a statistical significance difference ($P<0.05$) among the mean fetal weight, mean crown-rump length, mean head circumference, mean bi-parietal diameter and mean head length when treatments were administered during the first trimester (TM_1), second trimester TM_2) and third trimester (TM_3**),** (table 3.2). In another previous study, the results were similar to those of the current study in that significant changes were noticed in growth parameters between Topiramate treatment groups, a 2nd generation anticonvulsant like levetiracetam as compared with the control group. A positive correlation was found between FW and, HL and BPD in all examined groups (Green et al., 2012).

V. CONCLUSION AND RECOMMENDATIONS

The study reveals that Topiramate, at doses equivalent to the human therapeutic doses, induces symmetrical intrauterine growth restriction and a remarkable increase in the rate of resorption and few gross abnormalities in rat fetuses and placentae. The effects of these therapeutic doses are not dose related and Topiramate shouldbe taken with caution during pregnancy as the drug is frequently used by women in childbearing perio

The study has revealed and concluded that levetiracetam at doses equivalent to the human therapeutic doses, leads to remarkable decrease in

fetal parameters for growth and development when exposed in-utero. These effects have been observed to be time and dose dependent with the most critical dose being the high dose and the most critical period being the first trimester.

The study reveals that Topiramate, at doses equivalent to the human therapeutic doses, induces symmetrical intrauterine growth restriction and a remarkable increase in the rate of resorption and few gross abnormalities in rat fetuses and placentae. The effects of these therapeutic doses are not dose related and Topiramate should be taken with caution during pregnancy as the drug is frequently used by women in childbearing perio

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Since levetiracetam continues to be prescribed widely by clinicians as the safest and second line anticonvulsant medicine, further studies in higher primates closer to human species as well as clinical trials are recommended to rule out its safety during pregnancy.

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