A COMPARATIVE STUDY OF THE TERATOGENIC EFFECTS OF ANTIEPILEPTIC DRUGS: LAMOTRIGINE AND LEVETIRACETAM ON ADULT ALBINO RATS

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ABSTRACT

Background: Lamotrigine (LTG) and levetiracetam (LEV) are widely and increasingly prescribed second generation antiepileptic drugs for women with epilepsy during childbearing age. However, data pertaining to their congenital malformations are lacking. **Aim:** This study aimed to investigate and compare the teratogenic effects of LTG and LEV on normal adult female albino rats and their fetuses in order to find out the least teratogenic one of them. **Materials and methods:** Ninety-six adult albino rats (64 virgin females and 32 males) of almost the same range of weight and age were used. Pregnant rats were divided into 4 groups. The 1st group (control; received 1 ml of distilled water) and the 2nd group (vehicle; received 1 ml of 2% Arabic gum), while the 3rd (LTG-treated) and 4th (LEV-treated) groups received 50 mg/kg/b.wt. of LTG and 310 mg/kg/b.wt. of LEV, respectively. All substances were administered as single oral dose starting from gestational day (GD) 7 to 15. On GD 20, all dams were weighted then sacrificed and subjected to Cesarean section. The total numbers of ovarian corpora lutea and the status of all implantation sites (the total numbers of resorption sites, live and dead fetuses, and the total implantations) were counted. The gravid uteri were subsequently removed, weighted, and fetuses were delivered. The fetuses' numbers, weights, different body lengths, gross abnormalities, and skeletal malformations were recorded. **Results:** On GD 20, maternal weight gains and gravid uteri weights were statistically significantly lower in both treated groups than control and these differences were more significant in LTG than LEV. The percentages of pre-implantation and post-implantation losses in LTG and LEV exhibited statistically significant increase and non-significant differences compared with control, respectively, and the latter was more pronounced in LTG than LEV. As regard the numbers, weights, crown-rump lengths, biparietal diameters and head lengths of the fetuses, both treated groups showed significant differences in comparison to the control with higher abnormalities in LTG-treated than LEV-treated groups. Fetuses from treated groups revealed various gross abnormalities in the internal organs. Fetuses' skeletons examination revealed bone defects in both treated groups. Skull, vertebrae, and hind limb skeletal malformations were more prevalent in LTG-treated group, while sternum was more affected in LEV-treated group. **Conclusion:** Both antiepileptic drugs were teratogenic in variable degrees; however, LEV appears to be less teratogenic than LTG.

Keywords: Lamotrigine, Levetiracetam, Teratogenicity, Reproductive outcome, Gross and Skeletal abnormalities.

INTRODUCTION

Epilepsy is one of the most prevalent neurological diseases and its spread depends on age, racial, social class, as well as geographic and national boundaries. It affects approximately 50 million people all over the world; 2 millions of them were recorded in the United States (**El-Sayyad et al., 2013**). Patients with epilepsy who become pregnant are at risk of complications, including changes in seizure frequency, maternal morbidity and mortality, and congenital anomalies due to antiepileptic drug exposure (**Borgelt et al., 2016**).

Management of pregnant women with epilepsy is problematic as seizures need to be prevented because they clearly increase the risk of maternal and foetal injury, miscarriage, epilepsy in the offspring, and developmental delay. On the other hand, foetal exposure to antiepileptic drugs is associated with increased risk of congenital malformation, congenital anomalies, intrauterine growth retardation, and neonatal haemorrhage. Physicians mostly encounter the problem of choosing monotheraphy with minimal teratogenic effect, plus adequate seizure control in pregnant woman with epilepsy (**Ozer et al., 2012**).

Reproductive-aged women with epilepsy may present a number of specific issues to be managed in daily clinical practice. The impact of epileptic seizures and antiepileptic therapy on pregnancy outcome and the risk of teratogenicity should be minimized, which require careful attention and cooperation between obstetric gynecologyst and neurologist. There is evidence that certain antiepileptic drugs (AEDs) are teratogenic and are associated with an increased risk of congenital malformation. The majority of women with epilepsy continue taking AEDs throughout pregnancy; therefore it is important that comprehensive information on the potential risks associated with AED treatment is available (**Vanya et al., 2016**).

The first generation antiepileptic drugs like phenytoin, carbamazepine and sodium valproate are widely used but they have increased risk of adverse reactions and drug interactions and require therapeutic monitoring (**Landmark and Patsalos, 2010**). Therefore, the second generation drugs are preferred due to favourable side effect profile and less chance of drug interactions (**Perucca, 2002**).

Lamotrigine (LTG), a second-generation antiepileptic agent of phenyltriazine derivatives, is most widely used for treatment of both partial and generalised seizures. On the other hand, its use in pregnancy is associated with risk of seizure deterioration because its clearance is accelerated in pregnancy. This reveals the need of additional information on the therapeutic window of LTG and its possible toxic effects in pregnancy (**Sathiya et al., 2014**). Although LTG monotherapy during pregnancy is assumed to be relatively safe, its teratogenic effects has been reported previously (**Degirmencioglu et al., 2016**).

Levetiracetam (LEV) is a broad-spectrum AED which is currently licensed in the United States and the United Kingdom and Ireland for use as adjunctive treatment of focal-onset seizures and myoclonic seizures or generalized tonic-clonic seizures, occurring as part of generalized epilepsy syndromes. In the United

Kingdom and Ireland, it is also licensed as monotherapy treatment for focal-onset seizures. Previous small studies have suggested a low risk for major congenital malformations (MCM) with LEV use in pregnancy **(Mawhinney et al., 2013).**

Exposure to LTG and LEV carried the lowest risk of overall malformation; however, data pertaining to specific malformations are lacking. Physicians should discuss both the risks and treatment efficacy with the patient prior to commencing treatment **(Weston et al., 2016).**

The aim of this study was to investigate and compare the teratogenic effects of the second generation antiepileptic drugs LTG and LEV on normal adult pregnant female albino rats and their fetuses, in order to find out the safest and the least teratogenic one of them.

MATERIALS & METHODS

Tested Drugs and Dosage Regimen:

Lamotrigine (LTG), 50-mg tablets, was obtained from Multi-Apex Company; they are white, rounded, and compressed tablets. Levetiracetam (LEV), 500-mg film-coated tablets purchased from Sigma for Pharmaceutical Industries (S.P.I), for Al Andalus Medical Company. The administered doses were 50 mg/kg/b.wt. for LTG and 310 mg/kg/b.wt. for LEV and chosen according to **Sarangi et al. (2016).** All doses were suspended in freshly prepared 2% Arabic gum (acacia gum) to obtain the necessary concentration of each drug in 1 ml. The dosage volumes for animals were calculated according to their daily body weights.

Animals:

Ninety-six adult albino rats were used in this study (64 virgin females and 32 males of almost the same range of weight and age). They were of Sprague Dawley strain, weighing 180-200-gm at the start of the experiment, about 3 months old, and purchased from Helwan farm belonging to the Holding Company for Biological Products and Vaccines, VACSERA, Egypt. After experimental protocol approval, the animals were handled according to the guidelines of the Ethics Committee of Scientific Research, Faculty of Medicine, Banha University, Egypt. They were kept at the animal facility of Benha Faculty of Medicine under standard laboratory conditions of husbandry (12-hr light/dark cycles at 25 ± 2°C room temperature and 50-55% relative humidity) with food and water ad libitum. Each 5 rats were kept in separate cage and all rats were allowed to adapt to the laboratory environment for 1 week before being of the study.

Experimental design and procedures:

Mating procedure. Each two adult virgin females in proestrus were placed overnight with one normal mature male. Successful copulation was established and confirmed by presence of sperms in vaginal smears according to the method of **Matthews and Kenyon (1984).** Females with positive vaginal smears were considered pregnant at zero day of gestation. Each mated female was singly housed in clear polycarbonate cages with stainless steel wire lids and corn cob granules as bedding and was given a blind test letter and number.

All pregnant females were equally divided into four main groups (each

group contained 16 rats). The first group (control) received 1 ml of double distilled water. The second group (vehicle) received 1 ml of 2% Arabic gum. The third group (LTG-treated group) was gavaged with 50 mg/kg/b.wt. Suspension of lamotrigine and the fourth group (LEV-treated group) was gavaged with 310 mg/kg/b.wt. Suspension of levetiracetam. Treatment regimen started between gestational day 7 to 15, the period when major organogenesis takes place, and each fasted dam received its corresponding substance by oral gavage cannula.

Accurate evaluation of the experimental data in this study was conducted according to the scheme originally laid down by **Wilson (1965).** On the 20th day of gestation (one day before the expected date of delivery to prevent the mothers from devouring any damaged offspring), all pregnant rats were sacrificed by cervical decapitation under ether anesthesia then subjected to Cesarean section. All ovaries were examined using a magnifying lens and the total numbers of corpora lutea (appearing large and yellowish tinge in color) were counted. All gravid uteri were carefully inspected and the status of all implantation sites were recorded (i.e. the total numbers of resorption sites, live and dead fetuses, and the total implantations). Resorptions were determined as early (dark brown blood spot with just placental tissue) and late (large blood clot attached to the uterine wall with placental and embryonic tissue). The gravid uteri were harvested after cutting of the mesometrium, mesovarium, and vagina then uterine horns were cut longitudinally very gently with the tip of blunt scissor to deliver fetuses. Each live fetus was washed with normal saline then dried on a bloating paper. The numbers and weights the fetuses (live or dead) were recorded. The fetuses' crown rump length, head length, and biparietal diameter were measured using a calibrated metallic gauge. Additionally, using a magnifying lens each fetus was carefully examined for any apparent external gross abnormality in an ordinary manner from the head to the tail.

After recording all measurements and parameters, fetuses from each group were equally divided into two groups. The first group was fixed in Bouin's solution for efficient decalcification in order to allow easier performance of free hand serial sections in the soft fetal tissues, while the second group was prepared for skeletal examination.

The percentage of pre-implantation loss was calculated as: [(total number of corpora lutea – total number of implantation sites) / total number of corpora lutea] x 100. The percentage of post-implantation loss was calculated as: [(total number of implantation sites – total number of live embryos) / total number of implantation sites] x 100.

Razor sections preparation

According to **Kotb (1973)**, serial sections of 1mm thickness were performed at different landmarks and levels along the fetuses' bodies that were examined under the magnification of the binocular dissecting microscope for the presence of any gross abnormalities in the internal organs.

Skeletal preparations of fetuses

For the skeletal studies, staining was performed with alizarin red stain according to the method described by **Dawson (1926)**. Briefly, fetuses were

skinned, fixed, and dehydrated in 95% ethyl alcohol for seven days then placed for 1-2 days in 1% KOH solution, thoroughly washed with tap water before placing it in reagent solution (a mixture of 150 ml glycerin, 800 ml distilled water, and 10 grams solid KOH to which a few drops of 1% alizarin red solution added). The bony parts of the skeleton were stained with a deep red violet colour. Then the fetuses transferred to fresh reagent solution for 7-14 days to remove staining of soft tissues. After staining, the fetuses were dehydrated by passing them slowly through mixtures of alcohol, glycerin and water in different percentages, after which, they were preserved in 100% glycerin with addition of 2 drops of formalin to prevent putrefaction. The stained preparations were carefully examined under the dissecting binocular microscope to study the various parts of the axial and appendicular skeleton for any skeletal abnormalities.

Statistical Methods:

The collected data were tabulated and analyzed using SPSS version 16 software (SPSS Inc, Chicago, IL Company). Categorical data were presented as number and percentages while quantitative data were expressed as mean and standard deviation. The one-way analysis of variance (ANOVA) and Z-test were used as test of significance. Significant ANOVA was followed by post hoc multiple comparisons using Bonferroni to detect significant pairs. The accepted level of significance was stated at 0.05 (P <0.05 was considered significant).

RESULTS

Table (1) shows the reproductive outcome of control, vehicle, LTG, and LEV treated groups. Each of control, vehicle, and LEV treated group included 16 pregnant rats, while LTG-treated group included 14 dams (2 dams died between gestational day 13 and 15).

The results of reproductive outcome revealed non-significant changes in all analyzed parameters when vehicle treated group was compared with control group. In addition, the results of comparison between vehicle group with both LTG and LEV groups were statistically identical to those data of control group when compared with treated groups indicating that Arabic gum has no teratogenic properties.

At the end of the 2nd week of gestation and on 20th day of gestational, the mean values of maternal weight gain of LTG group (24.75 ± 4.34 and 50.23 ± 4.15, respectively) were statistically significantly lower ($p<0.05$) than the corresponding values of both LEV (30.81 ± 4.62 and 69.17 ± 4.26, respectively) and control (33.82 ± 5.23 and 73.67 ± 3.1, respectively) groups. While, on gestational day 20, the mean value of maternal weight gain of LEV-treated group showed statistically significant decrease as compared with control group ($p<0.05$).

The mean weight values of gravid uteri of LTG (30.23 ± 5.75) and LEV (41.55 ± 6.94) groups showed statistically significant reduction ($p<0.05$) in comparison with control group (50.35 ± 8.45) and this difference was statistically significantly lower ($p<0.05$) in LTG group than LEV group.

The present results showed non-significant differences (p>0.05) in the mean values of corpora lutea and implantation sites after treatment of the dams with LTG (10.14±2.34 and 8.5±3.5, respectively) and LEV (10.1±2.15 and 8.75±3.4, respectively) as compared to the corresponding values in the control group (9.88±1.72 and 9.63±2.8, respectively) as well as each other.

The mean value of pre-implantation loss of LTG group (1.64±1.984) exhibited statistically significant increase (p<0.05) and non-significant difference (p>0.05) as compared with control (0.25±0.683) and LEV (1.31±1.537) parallel values, whereas that of post-implantation loss and resorption (4±3.162) displayed statistically significant rise (p<0.05) as compared with both control (0.0±0.0) and LEV (1.06±2.294) parallel values. There were non-significant differences (p>0.05) between LEV and control groups regarding the pre-implantation loss and post-implantation loss and resorption.

Table (2): illustrates live fetuses growth characteristics among control, vehicle, LTG, and LEV treated groups. No fetal deaths recorded among all tested groups. The highest mean values as regards offspring/dam, body weight, crown rump length (CRL), biparietal diameter (BPD), and head length (HL) of live fetuses were noticed among control group (9.37±1.63, 4.48±0.15, 4.13±0.26, 9.046±0.311, and 1.618±0.077, respectively), followed in frequency by LEV-treated group (6.37±3.4, 2.69±0.81, 3.29±0.21, 8.403±0.328, and 1.347±0.072, respectively) then LTG-treated group (2.85±4.15, 2.63±0.64, 2.76±0.17, 7.622±0.647, and 1.224±0.161,

respectively). These differences were statistically significantly reduced (p<0.05) in both LTG and LEV groups in relation to control group.

In addition, the statistical differences of the mean values regarding offspring/dam, CRL, BPD, and HL variables were significantly lower in LTG group (p<0.05) than LEV group with the exception of body weight, which showed non-significant differences (p>0.05) between both groups.

Table (3) shows the incidence of external and internal gross morphological abnormalities in fetuses from dams administrated LTG and LEV. The proportions of hematomas (55.56% vs 0.00%) as well as brain (44.44% vs 7.69%), heart (38.89% vs 0.00%), and lung (27.78% vs 0.00%) abnormalities were higher in fetuses of LTG-treated group than LEV-treated group, while liver (53.85% vs 11.11%) and stomach (46.15% vs 11.11%) abnormalities were higher in fetuses of LEV-treated group than LTG-treated group. There were statistically significant differences (p<0.05) between both groups regarding the aforementioned variables.

Table (4) summarizes the incidence of skeletal malformations in fetuses from dams administrated LTG and LEV. The proportions of skull (100% vs 47.6%), vertebra (100% vs 38%), and hindlimb (87.5% vs 38%) malformations were higher in fetuses of LTG-treated group than LEV-treated group, whereas sternal defect (47.6% vs 12.5%) was higher in fetuses of LEV-treated group than LTG-treated group. There were statistically significant differences (p<0.05) between both groups regarding the aforementioned variables.

Although the proportion of forelimb defect (25% vs 14.3%) was higher in LTG-treated than LEV-treated dams and the proportions of ribs (23.8% vs 18.75%) and metacarpal and metatarsal (28.6% vs 18.75%) defects were higher in LEV-treated than LTG-treated dams, however, the statistical comparison between both groups regarding these parameters showed non-significant differences (p>0.05).

External gross morphological examination (Fig. 1 to 9)

Normal corpus lutea of pregnancy appears yellowish tinge in color and normal pregnant uterus with live fetuses and without resorption sites among control group (Fig.1 and 2).

Pregnant rats treated with LTG exhibited empty uterine horns with dark brown spots (indicating early post-implantation loss) and large blood clots (indicating sites of late post-implantation resorption) (Fig. 3 and 4).

With respect to the external features of the fetuses obtained from control, LTG, and LEV treated mothers, no severe morphological alterations were observed. However, fetal growth retardation was the main change observed and the shortest fetal CRL was noticed in the LTG-treated dams, followed by LEV-treated dams in comparison with the control fetus (Fig. 5). Also, a fetal back hematoma was recorded secondary to administration of LTG to dams (Fig. 6).

Razor sections at different levels revealed gross abnormalities in the internal organs in different groups. At the level of the largest transverse diameter of the head (Fig. 7 and 8), fetal bilaterally dilated lateral ventricles, cardiac defects, and malformed lungs were observed in LTG-treated group. While at the level

of the abdominal region just above the umbilicus, the fetus from LEV-treated group showed hemorrhagic liver spots and shrunken stomach (Fig.9).

Skeletal examination (Fig. 10 to 19)

Alizarin red stain was used to detect skeletal deformities of the fetuses. The completely ossified bones take the stain completely and appear red in colour, incompletely ossified bones partially take the stain and appear lightly stained. However, non-ossified bones don't take the stain completely.

The skeletal system of the rat consists of two main groups; the axial skeleton and appendicular skeleton. The axial skeleton comprises bones of the skull, vertebral column, ribs and sternum, while the appendicular skeleton consists of bones of pectoral girdle and fore limbs, pelvic girdle and hind limbs. In the fetuses of control group most of the bones were normally ossified (Fig. 10).

The Skull (Fig. 11-13):

The skull elements of the control fetuses are in a good ossified condition. The vault (nasal, frontal, parietal, interparietal, and supraoccipital) (Fig. 11A), the basal skull (premaxilla, maxilla, palatine, zygomatic, presphenoid, basisphenoid, squamosal, tympanic bulla, basioccipital, exooccipital, supraoccipital) (Fig. 12A), and the mandibular bones (Fig. 13A) appeared well ossified.

In LTG-treated group, the degree of ossifications of the fetuses' skull bones was moderately to severely affected as compared to the control fetuses. Fetuses of LTG-treated mothers showed partial or delayed ossification of frontal, parietal (Fig. 11B), zygomatic, palatine, presphenoid, basisphenoid, basioccipital, exooccipital (Fig. 12B),

and mandibular (Fig. 13B) bones as well as absent ossification of nasal, interparietal, supraoccipital (Fig. 11B), premaxilla, maxilla, tympanic bulla, and squamosal bones (Fig. 12B).

In LEV-treated group (Fig. 11C, 12C, and 13C), the degree of ossifications of the fetuses' skull bones were mildly to moderately affected as compared to the control fetuses. The most obvious findings were delayed ossification of almost skull bones (Fig. 11C) with complete absence of ossification of interparietal (Fig. 11C) and exooccipital (Fig. 12C) bones.

The Vertebral Column (Fig. 10C and 14):

The vertebral column of control fetuses consists of well ossified vertebrae which are represented by 7 cervical, 12 thoracic, 7 lumber, 4 sacral and at least 10 caudal vertebrae with clearly ossified body and arches (Fig. 10C).

In LTG-treated group, fetal vertebral column showed vertebral dislocation (due to absence and delayed ossification of thoracic and lumbar vertebrae centers), caudal regression (due to delayed centra and absent ossification of upper sacral arches and centra) (Fig. 14A), and vertebral scoliosis (Fig. 14B).

On the other hand, mild effects on fetal vertebral bodies with partial ossification of lumbar and sacral bones were noticed in LEV-treated group (Fig. 14C).

Ribs (Fig. 15):

The control fetuses possess 13 pairs of ribs with well ossified vertebral portions and the sternal portions of ribs appear cartilaginous in nature (Fig. 15A).

The ribs of fetuses obtained from mothers treated with LTG and LEV showed no variations in number and in the ossified condition compared to the control. However, fusion of two or more fetal ribs in LTG-treated group (Fig. 15B) and missed fetal ribs in LEV-treated group (Fig. 15C) were observed.

Sternebrae (Fig. 16):

Most of the control fetuses possess 6 parts of well ossified sternebrae and the last one of them is the xiphisternum (Fig. 16A). The sternebrae obtained from fetuses of LTG-treated and LEV-treated dams were, respectively, slightly (Fig. 16B) and severely (shorter than normal control with only 3 or 4 sternebrae) (Fig. 16C) affected.

The pectoral girdle and forelimb (Fig. 17):

The pectoral girdle of the control fetuses comprised a well ossified scapula and clavicle. The forelimb components were the ossified scapula, humerus, radius, ulna, metacarpal bones and phalanges (Fig. 17A). In LTG-treated mothers, the degree of ossification of the fetal scapula, humerus, radius and ulna were slightly affected with absent ossification of metacarpal bones (Fig. 17B). In LEV-treated dams, the fetus showed nearly complete ossification of all forelimb bones, except for delayed development of metacarpal bones (Fig. 17C).

The pelvic girdle and hind limb (Fig. 18 and 19):

The pelvic girdle of the control fetus consists of three well ossified bones; ilium, ischium and pubis and the hind limb consists of well ossified femur, tibia, fibula bones, series of phalanges in the four digits, and cartilaginous tarsals and metatarsals (Fig.18A).

The fetal pelvic girdle obtained from LTG-treated mothers showed

incomplete ossification of ilium, ischium, femur, tibia, and fibula and absent ossification of metatarsal bones as well as mild to moderate caudal dysgenesis (manifested by shortage in length of the components of the pelvic girdle with absence of caudal vertebrae) (Fig.18B and 19A).

While fetal pelvic girdle of LEV-treated mothers showed nearly complete ossification of all pelvic girdle and hindlimb bones as well as partial ossification of lacrimal, frontal, maxilla, mandibular, metacarpal, and metatarsal bones (Fig.18C and 19B).

Table (1): Reproductive outcome of control, vehicle, LTG, and LEV treated groups.

Parameters	Groups				
	Control	Vehicle	LTG	LEV	LTG vs LEV
Number of live dams	16	16	14	16	
Number of dead dams	0	0	2	0	
Maternal weight gain					
End of 2nd week (gm)					
Mean ± SD	33.82±5.23	32.46±4.85^{NS}	24.75±4.34$^{*\&\$}$	30.81±4.62$^{NS@}$	
P-value		0.8523^{NS}	0.0000*; 0.0003$^{\&}$	0.2937^{NS}; 0.7640$^{@}$	0.0055$^{\$}$
At the 20th day (gm)					
Mean ± SD	73.67±3.1	75.64±3.17^{NS}	50.23±4.15$^{*\&\$}$	69.17±4.26$^{*\&}$	
P-value		0.4389^{NS}	0.0000*; 0.0000$^{\&}$	0.0057*; 0.0000$^{\&}$	0.0000$^{\$}$
Gravid uteri weights (gm)					
Mean ± SD	50.35±8.45	48.59±7.83^{NS}	30.23±5.75$^{*\&\$}$	41.55±6.94$^{*\&}$	
P-value		0.9057^{NS}	0.0000*; 0.0000$^{\&}$	0.0069*; 0.0432$^{\&}$	0.0005$^{\$}$
Corpora lutea					
Mean ± SD	9.88±1.72	9.56±1.94^{NS}	10.14±2.34$^{NS@\#}$	10.1±2.15$^{NS@}$	
P-value		0.9706^{NS}	0.9853^{NS}; 0.8646$^{@}$	0.9900^{NS}; 0.8768$^{@}$	1.0006$^{\#}$
Implantation sites					
Mean ± SD	9.63±2.8	9.31±3.1^{NS}	8.5±3.5$^{NS@\#}$	8.75±3.4$^{NS@}$	
P-value		0.9920^{NS}	0.7700^{NS}; 0.9000$^{@}$	0.8643^{NS}; 0.9599$^{@}$	0.9965$^{\#}$

	Control	Vehicle	LTG	LEV	LTG vs LEV
Pre-implantation loss (%)					
Mean ± SD	0.25±0.683	0.26±0.738^{NS}	1.64±1.984$^{*\&\#}$	1.31±1.537$^{NS@}$	
P-value		1.1031^{NS}	0.0286*; 0.0301$^{\&}$	0.1185^{NS}; 0.1239$^{@}$	0.9039$^{\#}$
Post-implantation loss (%)					
Mean ± SD	0.0±0.0	0.0±0.0^{NaN}	4±3.162$^{*\&\$}$	1.06±2.294$^{NS@}$	
P-value		NaN^{NS}	0.0000*; 0.0000$^{\&}$	0.3971^{NS}; 0.3971$^{@}$	0.0005$^{\$}$

LTG=Lamotrigine; LEV=Levetiracetam; 2nd =Second; gm=Gram; NS=Non-significant difference compared to control group; @=Non-significant difference compared to vehicle group; #=Non-significant difference between LTG and LEV treated groups; NaN=Not a number (0.0); *=Significant difference compared to control group; &=Significant difference compared to vehicle group; \$=Significant difference between LTG and LEV treated groups. Data shown as mean ± standard deviation; P-value of >0.05 is considered non-significant; P-value of <0.05 is considered significant.

Table (2): Live fetuses growth characteristics among control, vehicle, LTG, and LEV treated groups.

Parameters	Groups				
	Control	**Vehicle**	**LTG**	**LEV**	**LTG vs LEV**
Number/dams Ψ	150/16	145/16	40/14	102/16	
Offspring/dam					
Mean ± SD	9.37±1.63	9.22±1.6	2.85±4.15	6.37±3.4	
P-value		0.9988^{NS}	0.0000*; 0.0000$^{\&}$	0.0223*; 0.0327$^{\&}$	0.0074$^{\$}$
Body weight (gm)					
Mean ± SD	4.48±0.15	4.37±0.14^{NS}	2.63±0.64$^{*\&\#}$	2.69±0.81$^{*\&}$	
P-value		0.9328^{NS}	0.0000*; 0.0000$^{\&}$	0.0000*; 0.0000$^{\&}$	0.9892$^{\#}$
CRL (cm)					
Mean ± SD	4.13±0.26	3.98±0.25^{NS}	2.76±0.17$^{*\&\$}$	3.29±0.21$^{*\&}$	
P-value		0.2526^{NS}	0.0000*; 0.0000$^{\&}$	0.0000*; 0.0000$^{\&}$	0.0000$^{\$}$
BPD (cm)					
Mean ± SD	9.046±0.311	8.952±0.307^{NS}	7.622±0.647$^{*\&\$}$	8.403±0.328$^{*\&}$	

P-value		0.9040[NS]	0.0000[*]; 0.0000[&]	0.0002[*]; 0.0023[&]	0.0000[$]
HL (cm)					
Mean ± SD	1.618±0.077	1.595±0.075[NS]	1.224±0.161[*][&][$]	1.347±0.072[*][&]	
P-value		0.9165	0.0000[*]; 0.0000[&]	0.0000[*]; 0.0000[&]	0.0078[$]

LTG=Lamotrigine; LEV=Levetiracetam; Ψ=No fetal deaths recorded, cm=Centimeter; CRL=Crown rump length; BPD=Biparietal diameter; HL=Head length; NS=Non-significant difference compared to control group; @=Non-significant difference compared to vehicle group; #=Non-significant difference between LTG and LEV treated groups; NaN=Not a number (0.0); *=Significant difference compared to control group; &=Significant difference compared to vehicle group; $=Significant difference between LTG and LEV treated groups. Data shown as mean ± standard deviation; P-value of >0.05 is considered non-significant; P-value of <0.05 is considered significant.

Table (3): Incidence of external and internal gross morphological abnormalities in fetuses from dams administrated LTG and LEV.

Morphological abnormalities	LTG group (N=18 fetuses)		LEV group (N=13 fetuses)		Z	P
	Defects	%	Defects	%		
Hematomas	10	55.56	0	0.00	3.3	0.0011[*]
Brain	8	44.44	1	7.69	2.2	0.0261[*]
Heart	7	38.89	0	0.00	2.6	0.0106[*]
Lungs	5	27.78	0	0.00	2.1	0.038[*]
Liver	2	11.11	7	53.85	2.6	0.0097[*]
Stomach	2	11.11	6	46.15	2.2	0.0278[*]

LTG=Lamotrigine; LEV=Levetiracetam; N=Number of fetuses with external and internal gross morphological abnormalities; %=Percentage; *=Significant difference (P-value of <0.05)

**Table (4):** Incidence of skeletal malformations in fetuses from dams administrated LTG and LEV.

Skeletal Malformations	LTG group (N=16 fetuses)		LEV group (N=21 fetuses)		Z	P
	Defects	%	Defects	%		
Skull	16	100	10	47.6	3.5	0.0006[*]
Vertebral	16	100	8	38	3.9	0.0001[*]
Ribs defects	3	18.75	5	23.8	0.37	0.71[NS]
Sternal	2	12.5	10	47.6	2.3	0.0238[*]
Forelimb	4	25	3	14.3	0.82	0.4[NS]
Hindlimb	14	87.5	8	38	3	0.0024[*]
Metacarpal & metatarsal	3	18.75	6	28.6	0.69	0.49[NS]

LTG=Lamotrigine; LEV=Levetiracetam; N=Number of fetuses with skeletal malformations; %=Percentage; *=Significant difference (P-value of <0.05); NS=Non-significant difference (P-value of >0.05).
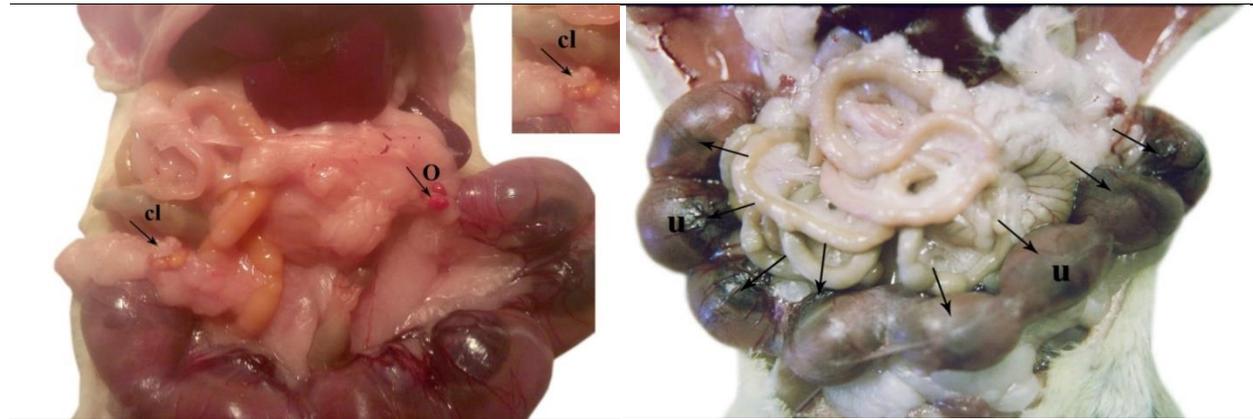
Fig. (1): A photograph of the control pregnant rat showing the ovary (o) containing corpus lutea (cl) of pregnancy (arrow) which appears large, with yellowish tinge color.


Fig. (2): A photograph of the control pregnant rat showing four fetuses (arrows) in one uterine horn (u) and four fetuses (arrows) in the other horn.
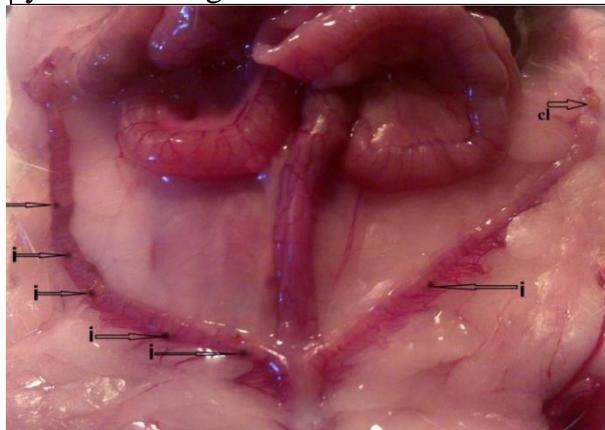

Fig. (3): A photograph of LTG-treated dam showing the uterine horns with dark brown spots (arrows) indicating early resorption sites (i). Also, corpus lutea (cl) of pregnancy (arrow) can be noticed in the ovary.
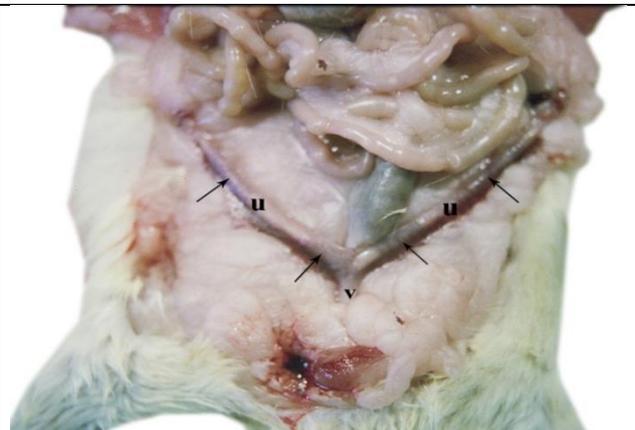
Fig. (4): A photograph of LTG-treated dam showing vagina (v) and large blood clots (arrows) in both uterine horns (u) indicating late resorption sites.
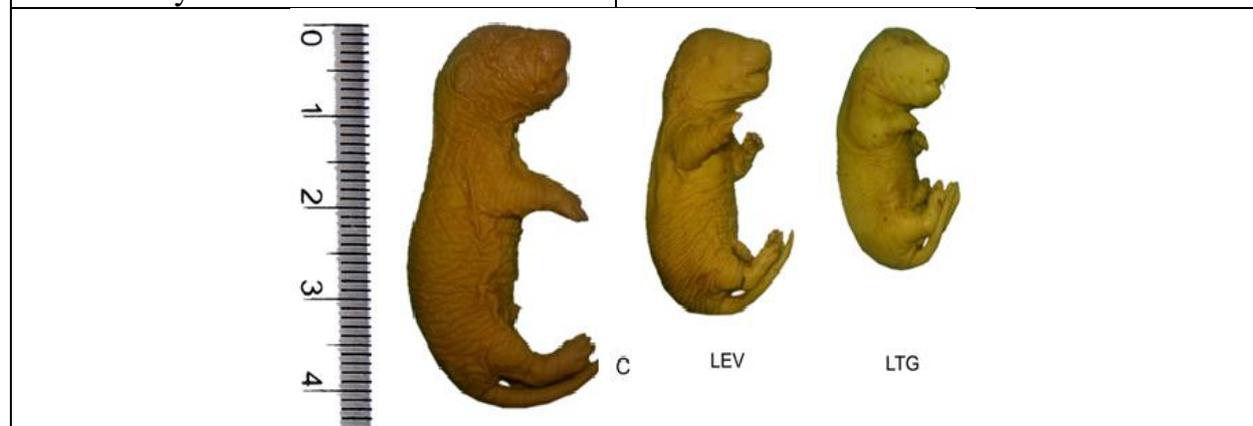

Fig. (5): A photograph of control rat fetus (C), fetus from LTG-treated group, and fetus from LEV-treated group. The smallest size is noticed in the fetus of LTG-treated group, followed by LEV-treated group as compared to the control.
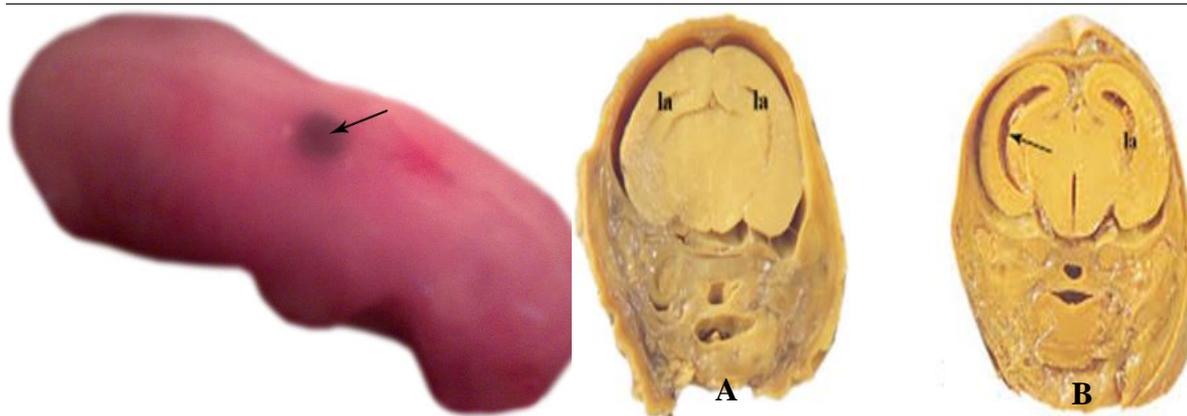
|	
Fig. (6): A photograph of fetus from LTG-treated group showing back hematoma (arrow).	**Fig. (7):** A photograph of a coronal **Razor Section** at the greatest transverse diameter of the fetal head. **(A)** Control fetus showing normal lateral ventricle (la). **(B)** Fetus from LTG-treated group showing moderate dilatation of the lateral ventricles (arrow).
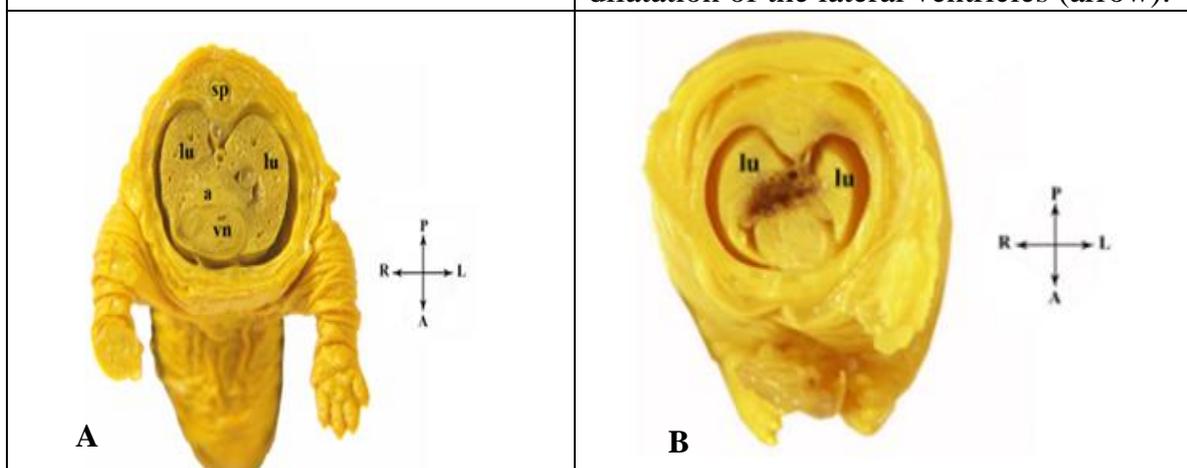
Fig. (8): Photographs of coronal **Razor Sections** at the level of the thoracic region just below the axilla. **(A)** Control fetus showing normal spinal cord (sp), lungs (lu), and normal heart with two ventricles (vn) and atria (a). **(B)** Fetus from LTG-treated group showing malformed heart with large hematoma and small malformed lungs (lu).
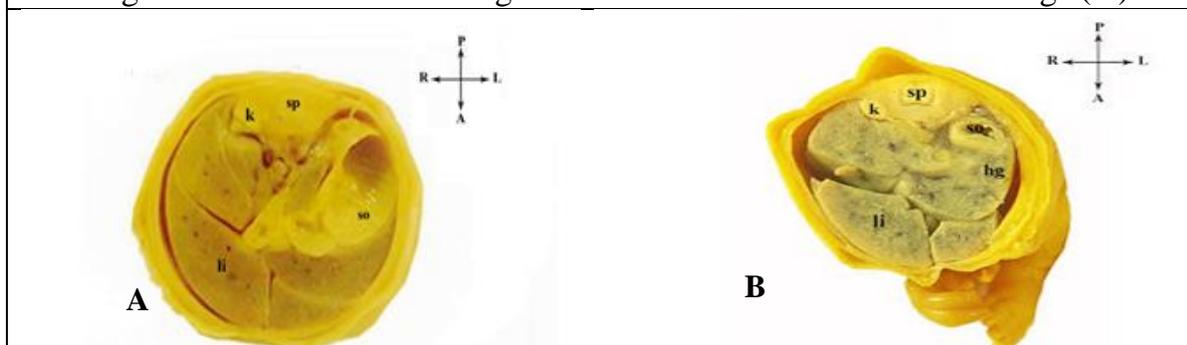
Fig. (9): Photographs of coronal **Razor Sections** at the level of the abdominal region just above the umbilicus. **(A)** Control fetus showing normal spinal cord (sp), kidney (k), stomach (so) and liver (li). **(B)** Fetus from LEV-treated group showing hemorrhagic liver spots (hg) and shrunken stomach (so).
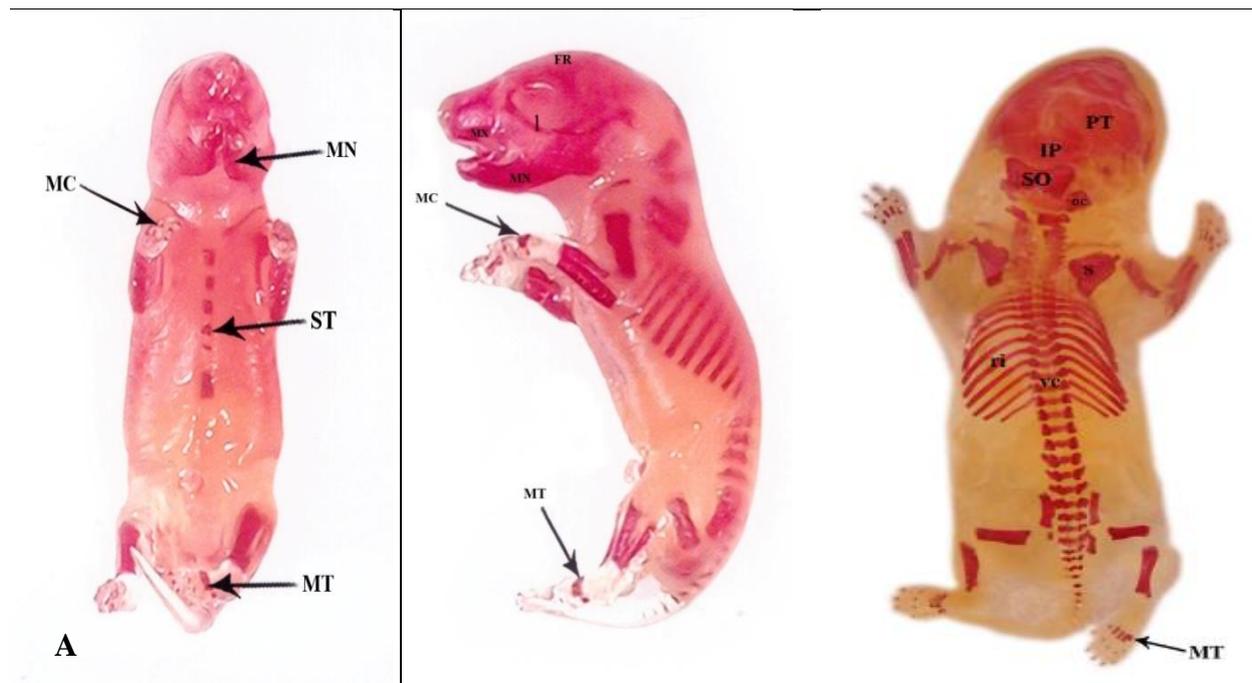
Fig. (10): Photographs of the control fetus stained with **Alizarin Red**. **(A) Anterior view:** showing completely ossified mandible (MN), sternum (ST), metacarpal (MC) and metatarsal (MT) bones. **(B) Lateral view:** showing completely ossified frontal (FR), lacrimal (l), maxilla (MX), MN, MC, and MT bones. **(C) Posterior view:** showing completely ossified parietal (PT), Interparietal (IP), supraoccipital (SO), and occipital (OC) skull bones as well as scapula (S), ribs (ri), vertebrae (ve), and MT bones.
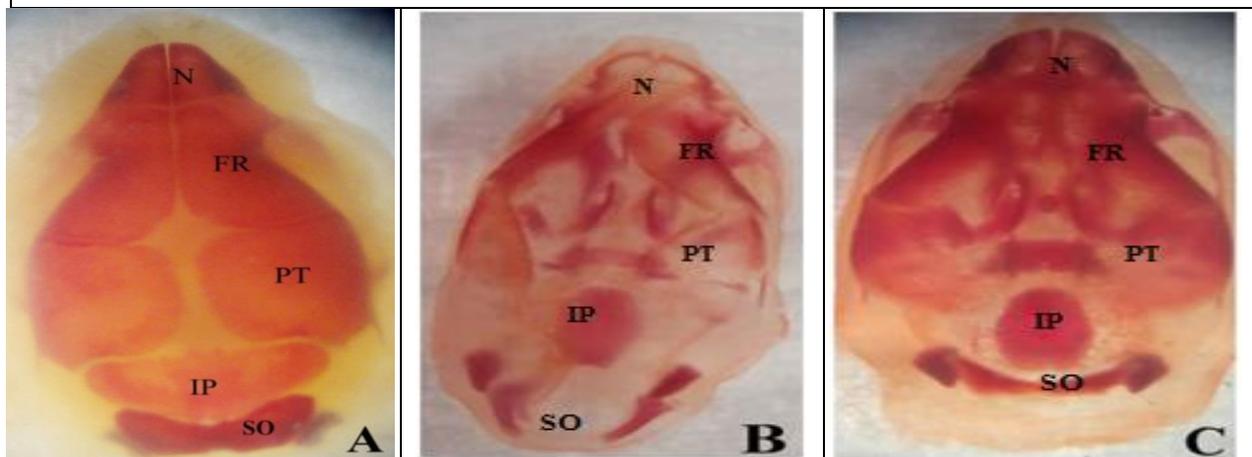
Fig. (11): Photographs showing dorsal view of fetuses' skulls stained with **Alizarin Red**. **(A)** Control fetus showing complete ossification of nasal (N), frontal (FR), parietal (PT), interparietal (IP), supraoccipital (SO) bones. **(B)** LTG-treated group showing partial ossification of FR and PT as well as absent ossification of N, IP, and SO bones. **(C)** LEV-treated group showing partial ossification of N, FR, PT, and SO as well as absent ossification of IP bones.
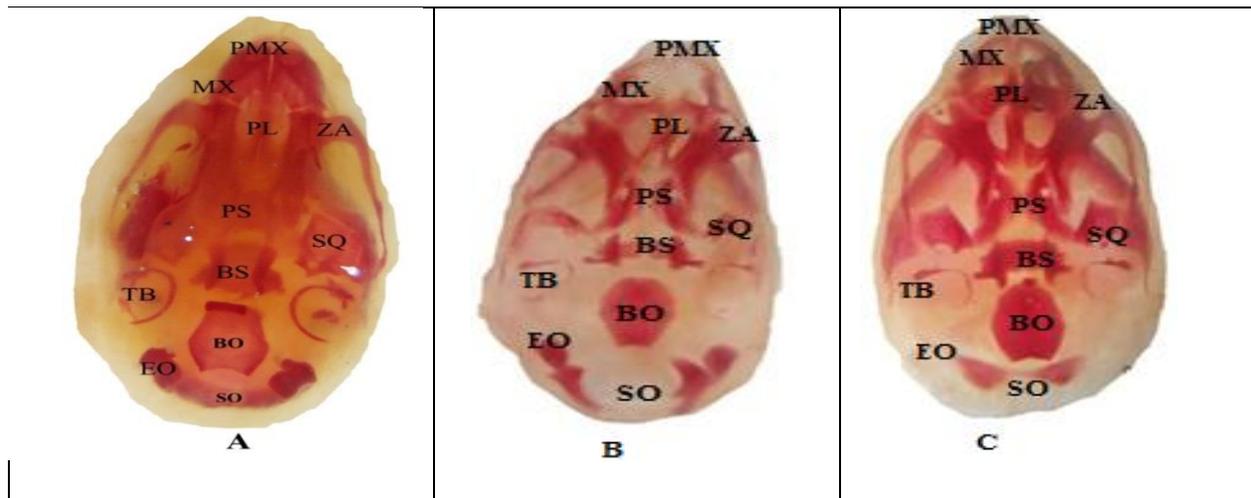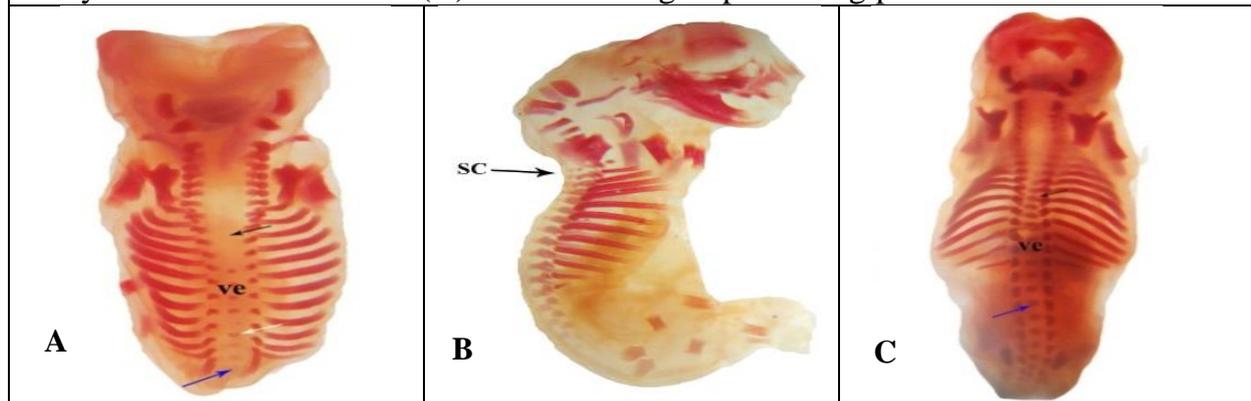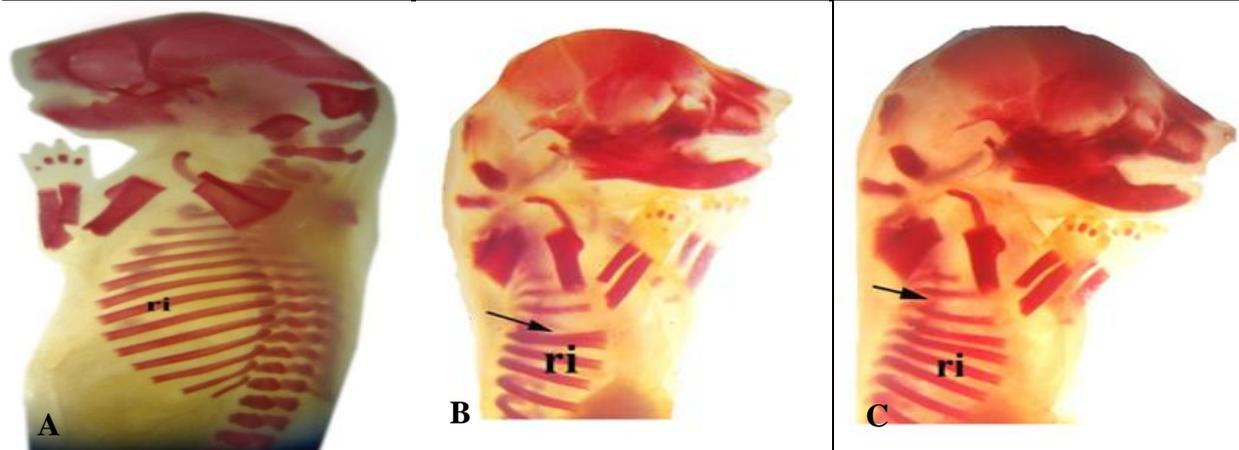
Fig. (12): Photographs showing ventral view of fetuses' skulls stained with **Alizarin Red**. **(A)** Control fetus showing complete ossification of premaxilla (PMX), maxilla (MX), zygomatic (ZA), palatine (PL), presphenoid (PS), basisphenoid (BS), tympanic bulla (TB), squamosal (SQ), basioccipital (BO), exoccipital (EO) and supraoccipital (SO) bones. **(B)** LTG-treated group showing severe delayed in ossification of ZA, PL, PS, BS, BO, and EO as well as absent ossification of PMX, MX, TB, SQ, and SO bones. **(C)** LEV-treated group showing partial ossification of PMX, MX, ZA, PL, PS, BS, TB, SQ, BO and SO as well as absent ossification of EO bones.
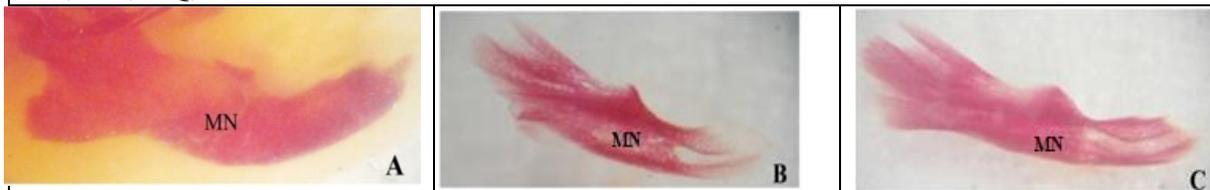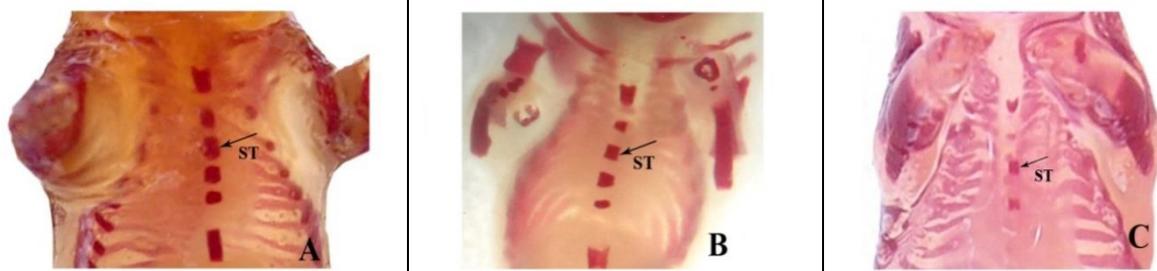

Fig. (13): Photographs of fetuses' mandibles (MN) stained with **Alizarin red. (A)** Control group showing complete ossification. **(B)** LTG-treated group showing severe delayed in MN ossification. **(C)** LEV-treated group showing partial MN ossification.

Fig. (14): Photographs showing posterior view of fetuses' skeletons stained with **Alizarin red. (A)** LTG- treated group showing vertebral dislocation (dark arrow), delayed centra and dumbel shaped (white arrow), and absent ossification of upper sacral arches and centra (caudal regression) "blue arrow". **(B)** LTG-treated group showing lateral view of fetus with vertebral scoliosis (SC). **(C)** LEV-treated group showing normal ossification of the fetal thoracic vertebral centers (dark arrow) and partial ossification of lumbar and sacral vertebrae (blue arrow).

Fig. (15): Photographs showing lateral view of fetuses' ribs stained with **Alizarin red.** **(A)** Control fetus showing 13 pairs of ribs (ri) with well ossified vertebral portions. **(B)** LTG-treated group showing fusion of two fetal ribs (arrow). **(C)** LEV-treated group showing missed fetal rib (arrow).
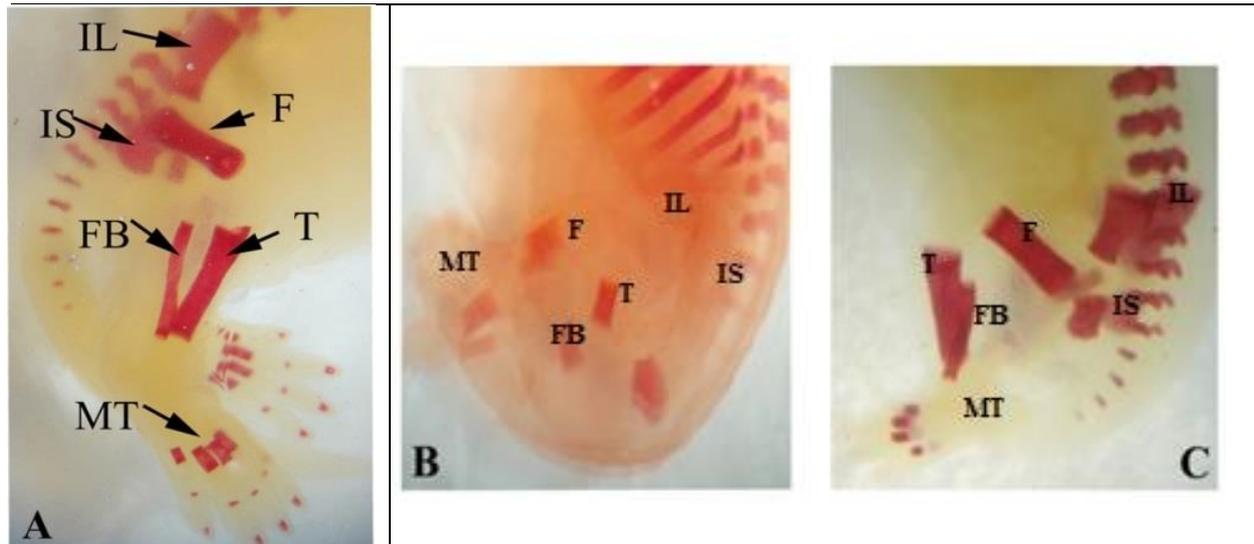

Fig. (16): Photographs showing anterior view of fetuses' sternebrae stained with **Alizarin red.** **(A)** Control group showing complete ossification of fetal sternum (ST) and all 6 sternebrae take the red color. **(B)** LTG-treated group showing slight partial ossification of fetal ST, decrease the thickness of 2-5-6 sternebrae. **(C)** LEV-treated group showing incomplete ossification of fetal ST and only 3 sternebrae were ossified and partially stained.
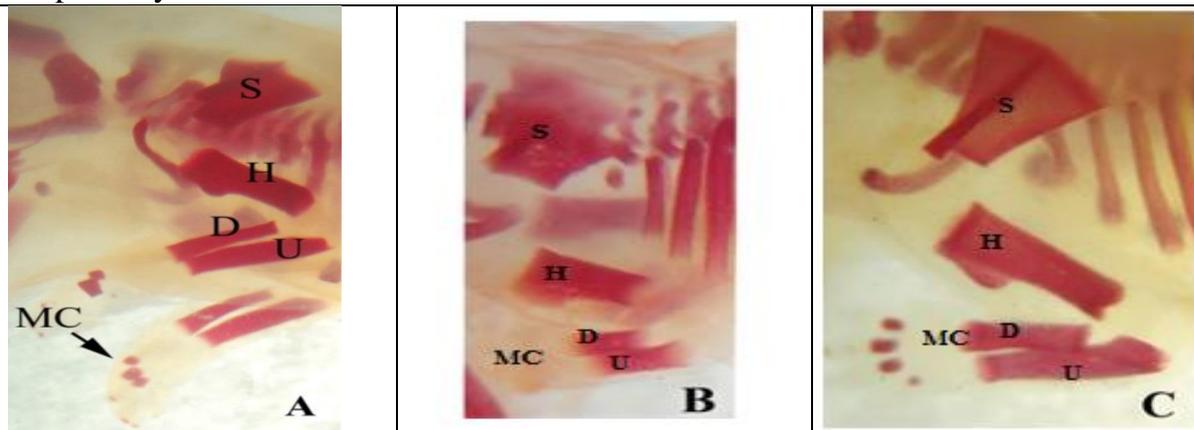
Fig. (17): Photographs showing lateral view of pectoral girdle and forelimb of fetuses' skeletons stained with **Alizarin Red**. **(A)** Control group showing complete ossification of scapula (S), humerus (H), radius (D), ulna (U), metacarpal (MC) bones. **(B)** LTG-treated group showing partial ossification of S, H, D, and U and absent ossification of MC bones. **(C)** LEV-treated group showing nearly complete ossification of all bones of forelimb, except delayed development of MC bones.

Fig. (18): Photographs showing lateral view of pelvic girdles and hindlimbs of fetuses' skeletons stained with **Alizarin Red. (A)** Control group showing complete ossification of ilium (IL), ischium (IS), femur (F), Tibia (T), fibula (FB) and metatarsal (MT) bones. **(B)** LTG-treated group showing incomplete ossification of fetal IL, IS, F, T, and FB as well as absent ossification of MT bones. **(C)** LEV-treated group showing nearly complete ossification of all bones of the pelvic girdle and hindlimb, except partial ossification of MT bones.
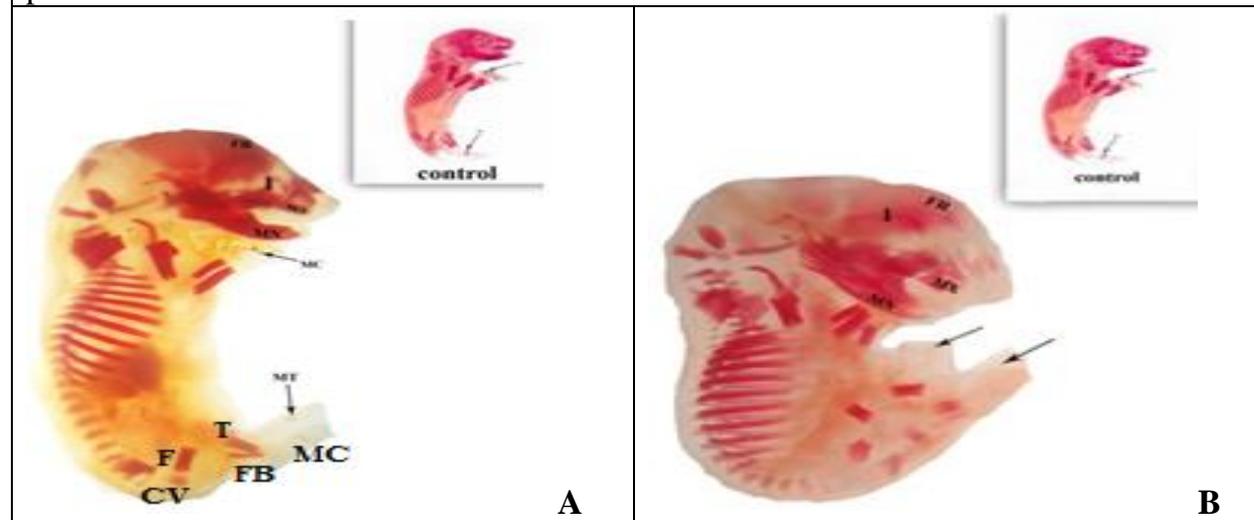
Fig. (19): Photographs showing lateral view of fetuses' skeletons stained with **Alizarin Red**. **(A)** LTG-treated group showing incomplete ossification of fetal lacrimal (l), frontal (FR), maxilla (MX), and mandibular (MN) skull bones as well as absence of caudal vertebrae (CV), incomplete ossification of femur (F), tibia (T), and fibula (FB) and absent ossification of metacarpal (MC) and metatarsal (MT) bones. **(B)** LEV-treated group showing partial ossification of l, FR, MX, and MN skull bones as well as partial ossification of MC and metatarsal (arrows) bones.

DISCUSSION

The use of antiepileptic drugs (AEDs) in pregnancy always presents challenges to doctors and their patients as they may have deleterious effects on the developing embryo (**Prakash et al., 2007**). None of them are considered to be safe and are categorized by Food and Drug Administration as class C or D drugs (**Bruno and Harden, 2002**). The use of lamotrigine (LTG) and levetiracetam (LEV) are substantially increasing in women with epilepsy of reproductive age, probably owing to their good efficacy coupled with a high level of tolerability, and the general belief that these drugs may be safer than the older AEDs. However, the teratogenic effects of LEV are virtually unknown (**Hunt et al., 2009; Meador et al., 2009**).

In the current study, Arabic gum had negative effects on fetuses' development and no teratogenic responses were seen. Similarly, numerous other studies that were conducted in experimental animals did not reveal any teratogenic potential of Arabic gum (**Collins et al., 1987; Phillips et al., 2008**).

The results of the present study demonstrated that LTG-induced severe maternal toxicity in the form of death of two dams and a significant decrease in maternal weight gain throughout the study, while LEV-treated groups showed minimal maternal toxicity manifested by a significant decrease in maternal weight gain at the 20th day of gestation. These results are in line with many other authors who stated that administration of LTG produced severe signs of toxicity, including death of the some dams (**Sathiya et al., 2014**). In addition, administration of different doses of LTG to pregnant rats (**El-Sayyad et al., 2013; Sathiya et al., 2014**) and mice (**Padmanabhan et al., 2003**) induced a significant decrease in their body weight gain throughout gestational period. Also, reduction in maternal weight gain was associated with LEV administration to pregnant rats (**Isoherranen et al., 2003**). On the contrary, **Manent et al. (2008)** found that pregnant rats treated with LTG (at lower doses than this study) and LEV had no effect on maternal weight gain. This decrease in maternal body weight gain may be attributed to decrease in food and water intake (**Sathiya et al., 2014**) and/or intrauterine growth retardation (**Padmanabhan et al., 2003**).

In this study, the weight of gravid uteri of LTG and LEV groups were statistically lower than the control group and this difference was statistically significantly lower in LTG group than LEV group. Also, pre-implantation loss and post-implantation loss and resorption in LTG-treated dams and those in LEV-treated dams were significantly high and insignificantly different, respectively, as compared with control and post-implantation loss and resorption was statistically higher in LTG group than LEV group. Analogously, administration of multiple doses of LTG to pregnant mice resulted in increased incidence of embryonic resorption (**Padmanabhan et al., 2003**), additionally, rabbits (**Genton and Van Vleymen, 2000**) and mice (**Isoherranen et al., 2003**) treated with LEV during organogenesis had increased rates of resorptions.

Reduction in gravid uterine weights may be attributed to intrauterine fetal growth retardation (**Rahmani et al., 2006; Manent et al., 2008**). Also,

Sidhu et al. (2006) showed that LTG administration increased the follicle stimulating hormone and luteinizing hormone which in turn stimulated estrogen secretion. Increased estrogen secretion results in maturation of graaffian follicle followed by ovulation which leads to embryo detachment. This may be the possible reason for the observed resorbed fetuses.

As regard the weight, crown-rump length, biparietal diameter, and head length of the fetuses, this study revealed that both treated groups have significant decreases in comparison to the control, with more reduction in the mean values of LTG than LEV-treated groups. These findings are in agreement with the results of several authors who reported significant reductions in body weight and dimensions in fetuses from dams exposed to LTG (**Padmanabhan et al., 2003; Rahmani et al., 2006; Mohanty et al., 2011**) and LEV (**Genton and Van Vleymen, 2000; Berg et al., 2005**). On the contrary, administration of LTG (**Sathiya et al., 2014**) and LEV (**Long, 2003; Mawhinney et al., 2013**) during pregnancy did not influence the mean birth weight or mean gestational age of the offsprings.

Reduced maternal food and water intake might had some influence on the fetal outcome but data on maternal food restriction or short episodes of starvation during gestation in rats and rabbits indicate that this may be the case as regards to increased resorption or growth retardation but not fetal malformations (**Petrere et al., 1993; Padmanabhan et al., 2003**).

Regarding external examination in the present work, hematomas were detected in LTG-treated group, while not observed in LEV-treated group.

These results go in hand with **Mohanty et al. (2011)**, who demonstrated that the offsprings of LTG-treated rat had hemorrhages over the body in some of these fetuses. Also, in a mouse model of teratogenicity, no gross external malformations were observed in offspring prenatally exposed to LEV (**Isoherranen et al., 2003**). On the other hand, **El-Ghareeb et al. (2015)** found that LEV caused gross subcutaneous hematoma in albino rat fetuses during pregnancy.

The literatures concerning the teratogenic effects of LTG and LEV in humans are controversial. In various epidemiological studies, the rate of major congenital malformations (MCM) regarding LTG monotherapy during pregnancy ranged between 1.4%- 5.2% (**Morrow et al., 2006; Cunnington et al., 2007; Vajda et al., 2007 and 2012**), however, the prevalence of MCM with LEV appears to be low (ranged between 0.7%- 2.0%) (**Vajda et al., 2010; Mawhinney et al., 2013**). On the other side, the fetal malformation rates for LTG and LEV in pregnant women were not statistically significantly different (**Koubeissi et al., 2008; Vajda et al., 2014**). Also, **Vajda et al. (2012) and Morrow et al. (2006)** found no evidence of fetal malformation in association with LEV monotherapy or polytherapy.

In the present study, gross anomalies were present in both treated groups. The anomalies found in LTG-treated groups were dilatation of lateral ventricles, cardiac defects, and malformed lungs, while the abnormalities in LEV-treated group were hemorrhagic liver spots and shrunken stomach. Correspondingly, in other experimental researches neuronal

alterations like ventricle dilatation, enhancement of subcortical density, increase in cerebral volume and diameter were associated with administration of LTG to pregnant animals during the organogenesis period **(de Marchi et al., 2001; Mohanty et al., 2011).** In addition, different types of MCM including neural and cardiac defects were detected in offspring of women exposed to LTG during pregnancy **(Meador et al, 2006; Morrow et al., 2006; Cunnington et al., 2007; Tomson et al., 2011).** Moreover, **El-Ghareeb et al. (2015)** reported mild degenerative changes in the fetuses' livers following LEV administration to pregnant rats. On the contrary, preclinical experimental studies in mice, rats and rabbits did not reveal any evidence of LTG-induced teratogenicity at doses ranging from 3-10 times the maximal recommended human dose **(Tennis and Eldridge, 2002).** Additionally, it was reported that LEV neither caused neural tube defects in chick embryos **(Guvenc et al., 2013)** nor induced MCM in mice embryos (**Isoherranen et al., 2003**).

In the present study, staining the skeletons of the rat fetuses by alizarin red stain revealed that both treated groups have teratogenic effects on the fetal bones. These effects were more extensive in LTG-treated group especially on skull, vertebrae and hind limb, while sternum was more affected in LEV group. These results are in agreement with **Rahmani et al. (2006)** who found that LTG increased malformations of vertebral columns and limbs in mouse fetus in a dose dependent fashion. Also, skeletal malformations and developmental delay of the skeleton were observed both in single and multiple doses of LTG

administered by intraperitoneal injection to mice **(Padmanabhan et al., 2003).** Also, two cases of skeletal malformations secodnary to fetal exposure to LTG during pregnancy were reported by **Morrow et al. (2006).**

Rat and rabbit data on fetal exposure to LEV demonstrated increased risks of skeletal abnormalities; these abnormalities were observed at doses 12 times the maximum recommended dose in humans **(Hunt et al., 2006).** Also, intraperitoneal daily injection of 1200 mg/kg/day LEV during the period of organogenesis to pregnant mice increased the overall frequency of fetal skeletal abnormalities **(Isoherranen et al., 2003).** Similarly, fetal skeletal abnormalities were increased in rats and rabbits treated with LEV throughout gestation and/or during organogenesis **Wlodarczyk et al., 2012).** Also, in humans, many cases of skeletal abnormalities related to fetal exposure to LEV in the first trimester were reported by **Montouris et al. (2010) and French (2001).**

On the contrary, according to **Guvenc et al. (2013**) study, developmental anomalies were not seen at low doses of LEV in an early chick embryo model, and this finding may indicate that there were no developmental anomalies during pregnancy.

The exact mechanism by which the AEDs mediate abnormalities in the fetus is uncertain. However, there are several hypotheses to explain them. LTG induces the secretion of parathyroid hormone (PTH) thereby modulating calcium homeostasis leading to osteoporosis **(Valsamis et al., 2006).** Increased serum calcium levels by PTH reduce the fetal

osteogenesis during embryonic development in LTG administered rats (**Sathiya et al., 2014**). Other important mechanisms include folate-related actions, ischemia, reactive intermediates (e.g., free radicals), and genetic susceptibility. Thus, understanding the mechanisms of AED-related abnormalities is of vital importance for the care of epileptic women and their offspring (**Etemad et al., 2012**).

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دراسة مقارنة لآثار التشوهات الخلقية للأدوية المضادة للصرع: لاموترجين وليفيتيراسيتام على الفئران البيضاء البالغة

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الملخص العربى

نبذة مختصرة: لاموترجين وليفيتيراسيتام من الجيل الثاني للأدوية المضادة للصرع توصف على نطاق واسع وعلى نحو متزايد للنساء المريضة بالصرع في سن الإنجاب. ومع ذلك، فإن المعلومات المتعلقة بتشوهاتها الخلقية قليلة. **الهدف:** هدفت هذه الدراسة إلى بحث و مقارنة آثار التشوهات الخلقية لكل مـن دواء لاموترجين وليفيتيراسيتام على إناث الفئران البيضاء البالغة الطبيعية وأجنتهم من أجل معرفة أى من الدوائين ينجم عنه تأثيرات ماسخة أقل. **المواد والطرق:** تم استخدام 96 فأراً من الفئران البيضاء البالغة (64 من الإناث البكر و 32 من الذكور) من نفس الوزن والسن تقريبا. تم تقسيم الفئران الحامل إلى 4 مجموعات، المجموعة الأولى (الضابطة، تم اعطائهم 1 ملى من الماء المقطر) والمجموعة الثانية (المذيب، تم اعطائهم 1 ملى من الصمغ العربي بتركيز 2٪) ، في حين تم اعطاء المجموعات الثالثة (لاموترجين) والرابعة (ليفيتيراسيتام) 50 ملغم/ كغم/ وزن الجسم من لاموترجين و310 ملغم/ كغم/ وزن الجسم من ليفيتيراسيتام، على التوالي. تم إعطاء جميع المواد بجرعة واحدة عن طريق الفم بدءا من اليوم السابع إلى اليوم الخامس عشر من فترة الحمل. فى يوم الحمل العشرين، تم وزن جميع الأمهات ثم ذبحها واجراء عملية قيصرية. تم حساب العدد الكلي للأجسـام الصـفراء بالمبايض وحالة جميع أماكن انغراس البويضات الملقحة (إجمـالي عدد كل من أماكن الإرتشـاف، والأجنة الحيـة والميتة، والانغراس الكلي). وبعد ذلك تم تشريح الأرحام الحامل واستخراجها، ووزنها، واستخراج الأجنة منها. ثم تسجيل عدد الأجنة، وأوزانها، وأطوال أجسامها المختلفة، والتشوهات الظاهرية للأجنة، والتشوهات الهيكلية العظمية. **النتائج:** فى اليوم العشرين من الحمل، أظهرت الزيادة فى أوزان الأمهات وأوزان الأرحام الحامل انخفاض ذو دلالة إحصائية في كلًا من المجموعتين المعالجتين عن المجموعة الضابطة وكانت هذه الاختلافات ذات دلالة كبيرة في مجموعة اللاموترجين عن مجموعة الليفيتيراسيتام. أظهرت النسب المئوية فى الفقدان السابق للانغراس والتالي للانغراس لمجموعتى لاموترجين وليفيتيراسيتام زيادة ذو دلالة إحصائية واختلافات ليست ذو دلالة إحصائية مقارنة بالمجموعة الضابطة، على التوالي، وكان حدوث الفقدان التالي للانغراس أكثر وضوحا في لاموترجين عن ليفيتيراسيتام. أما فيما يتعلق بأعداد وأوزان والأطوال التاجية الردفية والأقطار بين الجدارين وأطول الرأس للأجنة، فقد أظهرت كلًا من المجموعتين المعالجتين فروقا معنوية ذات دلالة إحصائية بالمقارنة مع المجموعة الضابطة مع وجود تشوهات أكثر فى المجموعة المعالجة بـاللاموترجين عن المجموعة المعالجة بالليفيتيراسيتام. كما أظهرت الأجنة من المجموعات المعالجة تشوهات ظاهرية مختلفة في أعضاء الجسم الداخلية. كذلك أظهر فحص الهياكل العظمية وجود تشوهات بالعظام في كل من المجموعتين المعالجتين. وكانت التشوهات الهيكلية فى عظام الجمجمة والفقرات والأطراف الخلفية أكثر شيوعاً في مجموعة اللاموترجين، في حين أظهرت عظام القص أكثر تأثرًا في بالنسبة لمجموعة اليفيتيراسيتام. **الاستنتاج:** أحدث كلًا من الدوائين المضادين للصرع تشوهات بالأجنة بدرجات متفاوتة، وكان ليفيتيراسيتام أقل تأثيراً من لاموترجين.