

Teratogenic effect of Carbamazepine use during pregnancy in the mice

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Abstract: Carbamazepine use is the first choice of antiepileptic drugs among epileptic pregnant females. There are many inconclusive studies regard the safety of carbamazepine use during pregnancy. This study aims to investigate the morphological and histopathological teratogenic effects of carbamazepine use during pregnancy. The healthy pregnant females mice divided into equal five groups (each n=20). The first (control) group received distilled water/day. Second, third, fourth and fifth group received 8.75, 22.75, 52.5, 65 mg of carbamazepine/day respectively. Carbamazepine and water were given by gastric gavage throughout gestational period. Fetuses were delivered on the 18th day of gestation by hysterectomy. Fetal measurements and appearance were assessed with investigation the histopathological changes of brain and spinal cord. There was a significant decrease of weight, different organs weight, length, upper and lower limb length of mice in the first day of delivery in fifth group. There was a significant increase of weight, different organs weight, length, upper and lower limb length in the third group. Many congenital anomalies such as spina bifida, meromelia, microphthalmia, oligodactyly, anencephaly, neurodegeneration of brain and spinal cord were noticed in fifth group. Teratogenic effect of carbamazepine represented as growth retardation and neurodevelopmental toxicity depending on its overdose degree.

Keywords: Carbamazepine, pregnancy, teratogenic.

INTRODUCTION

Teratology is a congenital malformations induced by environmental factors. Some drugs act on the fetus as teratogens causing preventable congenital anomalies (Ornoy, 2006). There is a relationship between dose of teratogen, its effect and time of administration during pregnancy period. The effect of teratogen ranges from no effect to malformations or intrauterine fetal death depending on the dose (Harden *et al.*, 2009).

There are many human developmental phases such as embryonic phase. It ranges from 18 to 60 days after the conception and sensitive to any teratogenicity because it is a stage of basic organogenesis. The effect of teratogen depends on time of fetal developmental stage exposure (Tomson, 2004). Systems differentiations at the time of exposure determine patterns of congenital anomalies (Perucca, 2005). We can predict the mechanism of teratogenicity and human teratogenesis from animal researches and similar congenital malformations in different animal species (Vajda *et al.*, 2007).

Some drugs are safe during pregnancy while others may have side effects on the fetus. There are five FDA (United States Food and Drug Administration) pregnancy categories for the most drugs to determine the possible risk. The FDA has designed five categories reported about the fetal dangerous drug according to the risk to benefit

ratio (TSPAC, 1994) (Friedman and Polifka, 2000). Carbamazepine is one of the most commonly used antiepileptic drugs in the world among pregnant. It is used to treat epilepsy, trigeminal neuralgia, bipolar disorder and diabetic neuropathy (Morrow *et al.*, 2006). There are many inconclusive studies about safety of carbamazepine use during pregnancy. Some epidemiological human studies reported that teratogenic effect of carbamazepine use during pregnancy due to its high level of developmental toxicity. The incidence of congenital anomalies is three times in babies of mothers who use carbamazepine during pregnancy than those in general population (Briggs *et al.*, 2008). On the contrary, other studies confirmed that carbamazepine has not any adverse effects on the central nervous system development of infants exposed to carbamazepine during intrauterine life (Meador *et al.*, 2006). There is a feature relationship between carbamazepine use during pregnancy, developmental defects and fetal carbamazepine syndrome according to clinical and epidemiological studies (Adams *et al.*, 2006). The aim of this study is assessment of histological and morphological teratogenic effects of carbamazepine use during pregnancy.

MATERIALS AND METHODS

Hundred virgin female albino mice, 6-8 weeks of age, weighing (25-35g) were subjected for the study. They bought from animal house of King Abdel Aziz University and maintained for 4-5 days on a standard laboratory chow and tap water in room temperature at 22°C and on

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12hr light/day in the animal house of College of Medicine, Taif University. After one week, the animals mated (1 male: 3 female). Success of mating process was confirmed by vaginal smear on the next morning. Presence of spermatozoa means successful mating (the first day of pregnancy). Appearance of vaginal plug was considered a day zero of pregnancy. The healthy pregnant females were caged separately and allocated into equal five groups (each=20). First group: was the control group; each pregnant mouse received 1ml of distilled water/day orally throughout their gestational period. Second group: received 8.75 mg/day of carbamazepine dissolved in distilled water orally. Third group: received 22.75 mg/day of carbamazepine dissolved in distilled water orally. Fourth group: received 52.5mg/day of carbamazepine dissolved in distilled water orally. Fifth group: received 65 mg/day of carbamazepine dissolved in distilled water orally. Oral administration of carbamazepine was achieved by gastric gavage from the first day until the 18th day of gestation (Bauer *et al.*, 2002; Williams *et al.*, 2001). Carbamazepine drug was in the tablet form and obtained from Novartis Parma S.P.A., Torre Annunziata, Italy for Novartis Pharma AG Basle, Switzerland. One tablet contains 400mg of active ingredient was grinded, dispersed and dissolved in 10ml distilled water at room temperature until complete dissolving to obtain a solution (freshly prepared).

On the 18th day of gestation, all animals were killed by cervical dislocation and fetuses delivered by hysterectomy. Weight, length and limb length of each fetus recorded. Fetal morphological changes inspected by a light microscope and then every fetus euthanized by decapitation. Mid line incision was performed exposing head, neck, chest and abdominal viscera of each fetus. Brain, spinal cord, heart, kidney, lung and liver were removed and weighed. Fixation of fetal tissues was done

in 10% formalin, embedded in paraffin and cut into 5µm sections. Subsequently, the sections were stained with Haematoxylin and eosin (H & E) and examined under light microscope to evaluate the histopathological changes according to (Bancroft and Gamble, 2002).

STATISTICAL ANALYSIS

Statistical analysis was achieved by SPSS version 16. Variability of results was expressed as mean ±SD. The significance of differences between mean values was determined using one way analysis of variance (ANOVA) test and followed by post hoc (L.S.D) test. P <0.05 represents level of significance.

Ethical considerations

The most appropriate animal species was chosen for this research. Promotion of a high standard care and animal well-being at all times was done. Appropriate sample size was calculated by using the fewest number of animals to obtain statistically valid results. Painful procedures were performed with ether inhalation to avoid distress and pain. Our standards of animal care and administration met those required by applicable international laws and regulations. It was approved by the Institutional Animal Ethics Committee.

RESULTS

Measurements parameters

Table (1) shows significant increase of weight in the third group and significant decrease of weight of fifth group when compared with the control group. It shows also significant increase of length in the third group and significant decrease of length of fifth group when compared with the control group. There was a significant increase of liver and kidney weight in the third group and

Table 1: Mean ± SD of weight and length values of mice in the first day of delivery in different groups

Group \ Parameter	Control	Second	Third	Fourth	Fifth
Weight	1.2550±.039	1.1250±.029	1.4970±.055	1.3250±.029	.9450 ±.029
Length	4.3380±.292	4.1850±.210	4.6210±.289	4.5130±.045	3.2200±.204

Table 2: Comparison between Mean ± SD of different organs weight of mice in the first day of delivery in different groups

Group \ Organ	Control	Second	Third	Fourth	Fifth
Liver	.0450±.005	.0420±.007	.0660±.014	.0340±.005	.0330±.004
Kidney	.0290±.008	.0290±.008	.0350±.008	.0200±.001	.0120±.004
Heart	.0260±.006	.0260±.006	.0340±.006	.0540±.010	.0120±.004
Brain	.2270±.006	.1930±.013	.1700±.017	.1680±.007	.1330±.016
Lungs	.0390±.007	.0340±.005	.0540±.008	.0420±.004	.0100±.001

Number per group = 20, SD = standard deviation, p<0.05

First group received 1ml of distilled water/day. Second group received 8.75 mg/day of carbamazepine. Third group received 22.75 mg/day of carbamazepine. Fourth group received 52.5 mg/day of carbamazepine. Fifth group received 65 mg/day of carbamazepine.

significant decrease of liver weight of fourth & fifth groups when compared with the control group. There was a significance increase of heart weight in third and fourth groups and significance decrease of heart weight of fifth group when compared with the control group. Weight of lungs was increased significantly in third group and decreased significantly in fifth group when compared with the control group. On the other hand, Weight of brain was decreased significantly in all groups when compared with the control group table 2.

Fig. 1 represents a significant increase in the length of upper limb of mice in the first day of delivery in second and third group when compared with the control group. Also, there is a significant increase in the length of upper limb of mice in the first day delivery in fourth group when compared with the control group while there is a significant decrease when compared with the third group. Furthermore, there is a significant decrease in the length of upper limb of mice in the first day of delivery in fifth group when compared with the control group. Fig. 2 shows a significant increase in the length of lower limb of mice in the first day of delivery in second and third groups when compared with the control group. But, there is a significant decrease of limb length of mice in the first day of delivery in fourth and fifth groups when compared with second and third groups while there is a significant increase when compared with the control group.

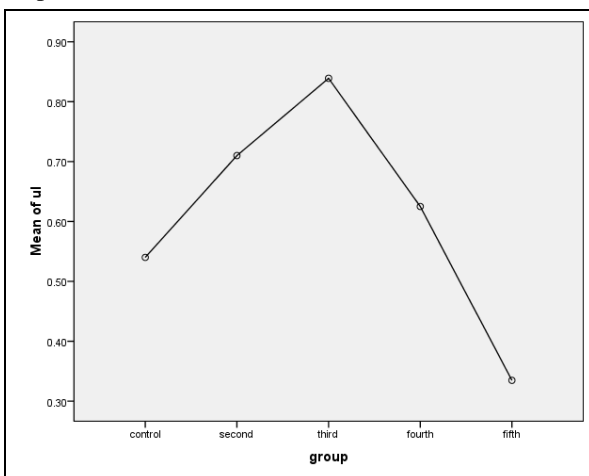


Fig.1: Mean + SD values of upper limb length of mice in the first day of delivery in different groups.

Fig.3 shows comparison between means of all different parameters among study groups. It shows that all parameters (weight and length of newborn, upper limb and lower limb length, weight of liver, kidney, heart and lung), have a significant increase in the third group while there is a significant decrease of weight and length of mice in the fifth group where F values are 596.8 and 121.5 respectively. Upper and lower limb length of fifth group has a significant decrease where F values are 29.2 and 4.5 respectively. Weight of liver and kidney are

significant decreased in fourth and fifth groups where F values are 51.09 and 35.3 respectively. Weight of brain is decreased in all groups (F=139.6). Weight of lung and heart are significant decreased in fifth group where F values are 162.8 and 89.2 respectively. Level of significance is determined as $P < 0.05$. There is also 95% confidence interval for the mean of all parameters (weight and length of newborn, upper limb and lower limb length, weight of liver, kidney, heart and lung) between control and other groups (second, third, fourth and fifth groups).

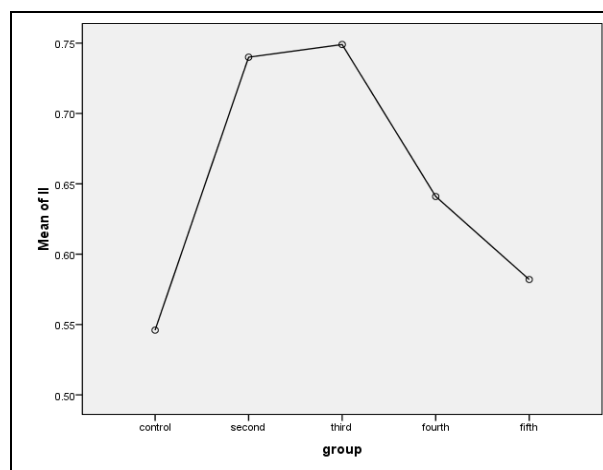


Fig. 2: Mean + SD values of lower limb length of mice in the first day of delivery in different groups.

External features

Upper limb findings

Hand of mice in the first day of delivery in the first group (control) shows normal bones of carpal, metacarpal and phalanges (fig. 4). But the hand of mice in the first day of delivery in the fourth group shows small size of carpal, metacarpal bones and phalanges with absence of the first finger (oligodactyly) (fig. 5) where mean \pm SD of bone length is $.5400 \pm .23$ and $.6250 \pm .06$ respectively and significantly correlated at $P < 0.05$.

Lower limb findings

Foot of mice in the first day of delivery in the first group (control) shows normal bones of tarsal, metatarsal and phalanges (fig. 6). But foot of mice in the first day of delivery in the fourth group shows size reduction of tarsal, metatarsal and phalanges with absence of the first toe and fifth toes (oligodactyly) (fig. 7) where mean \pm SD of bone length is $.5460 \pm .103$ and $.6410 \pm 0.67$ respectively. The mice in the first day of delivery in the first group (control) shows normal upper and lower limb, and tail (fig. 8) where mean \pm SD of upper limb length is $.7100 \pm .05$ and mean \pm SD of lower limb length is $.7400 \pm .09$. In contrast, in the fifth group, left lower limb of mice in the first day of delivery is well developed while the right lower limb is undevelopment (meromelia) with its tail (fig. 9), where mean \pm SD of bone length is $.5820 \pm .39$ with statistical significance level at $P < 0.05$.

Head findings

Head of mice of the first day of delivery in the first group (control), second and third groups is normal (fig. 8). On the other hand, head of mice of the first day of delivery in the fourth and fifth groups, shows anencephaly with undevelopment of skull bones (fig. 10) associated with undevelopment of eye (microphthalmia) and upper limb (meromelia) (fig. 11).

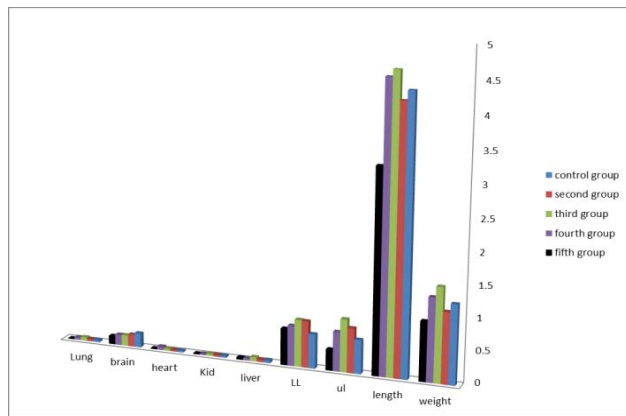


Fig. 3: Distribution of means for different parameters among study groups.

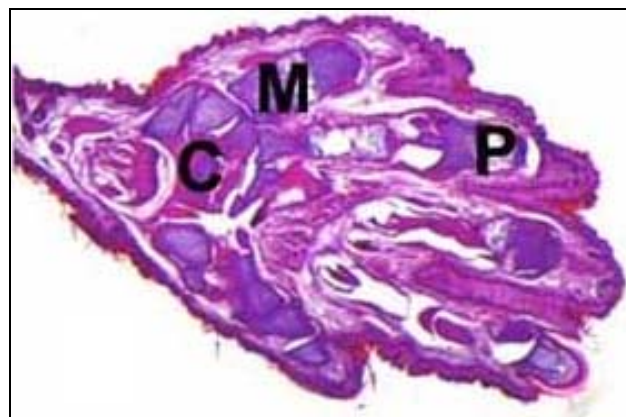


Fig.4: A photomicrograph of hand of mice in the first day of delivery of the control group shows normal carpal bones(C), metacarpal bones (M) and normal phalanges (P).

Spinal cord findings

Back of mice in the first day of delivery of the first group (control) is normal (figs. 8, 13). But in fourth and fifth groups, back of mice in the first day of delivery shows spina bifida (fig. 12).

Histopathological findings

Central nervous system

Spinal cord

Examination of spinal cord of mice in the first day of delivery of the first group (control group), shows normal structure of white matter and gray matter (fig. 13). But the spinal cord section of mice in the first day of delivery of the second group shows degeneration of white and grey

matter with degenerated nuclei of some cells, pycknotic nuclei of others and scattered vacuoles in white and grey matter (fig. 14). Moreover, Spinal cord section of third group mice shows a moderate degeneration of the outer white matter and inner gray matter with scattered large vacuoles and degenerated ependymal cells of the central canal (fig. 15). In the same way, spinal cord section of the fourth group shows severe degeneration of white matter and gray matter with marked degenerated nuclei of some cells, pycknotic nuclei and scattered vacuoles in white and grey matter compared with third group (fig. 16). The observed changes of spinal cord section of mice in the fifth group are more than changes of spinal cord section of mice in the fourth group (fig. 17).



Fig. 5: A photomicrograph of hand of mice in the first day of delivery in the fourth group. It shows small size of carpal bones (C), metacarpal bones (M) and phalanges (P) with absence of the first finger (oligodactyly).

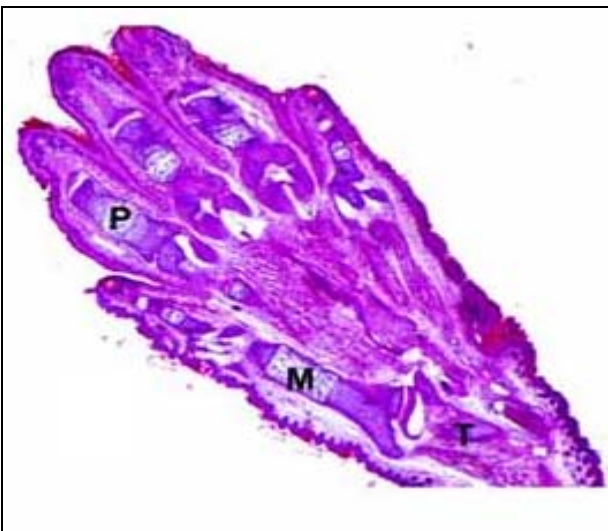


Fig.6: A photomicrograph of foot of mice in the first day of delivery of the first group shows normal tarsal bones (T), metatarsal bones (M) and normal phalanges (P).

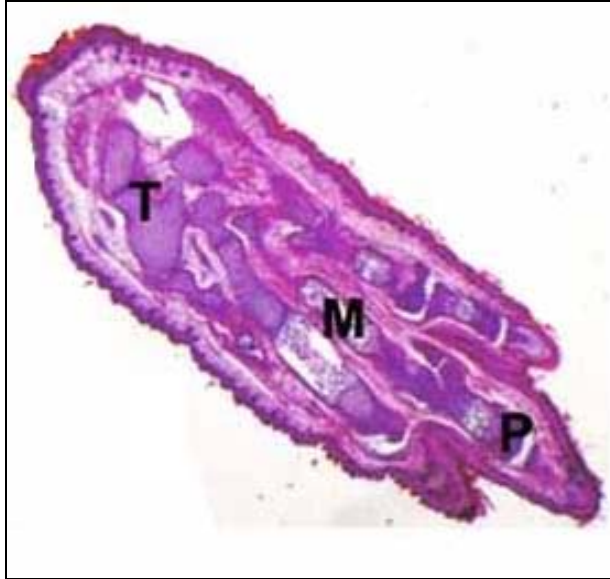


Fig.7: A photomicrograph of foot of mice in the first day of delivery in the fourth group. It shows small size of tarsal bones (T), metatarsal bones (M) and phalanges (P) with absence of metatarsal and phalanges of the 1st and 5th toes (oligodactyly).

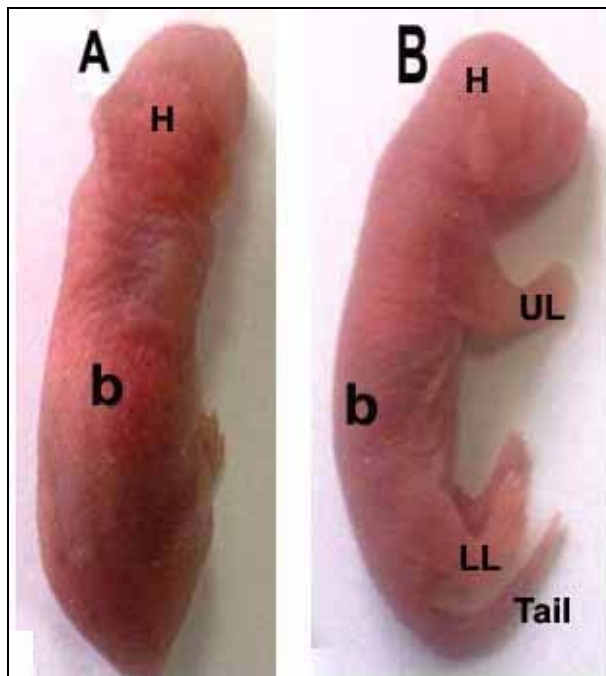


Fig. 8: A photograph of mice in the first day of delivery in the first group (control), second and third groups shows normal upper limb (UL), lower limb (LL), tail, normal head (H) and normal back (b) in posterior-anterior view (A) and lateral view (B).

Brain

Examination of brain section of mice in the first day of delivery of the first group (control group), shows normal structure of white matter, gray matter, pyramidal, glial cells, and hippocampus fig (18, 23). But brain of mice in the first day of delivery of second group shows congested

pyramidal cells, glial cells and areas of vacuoles. Hippocampus has lessened in size of molecular layer, granular layer cells and hilus with hydropic degeneration of granular layer cells fig (19, 24). The brain of mice in the third group shows degenerated pyramidal cells and glial cells with areas of vacuoles. Hippocampus has a reduction in size of granular layer, molecular layer and hilus cells fig (20, 25). Furthermore, in the fourth group, the brain shows a loss of normal architecture, widespread of degenerated areas, degeneration of pyramidal and glial cells with increased areas of vacuoles. Hippocampus has diminished in size of granular layer, molecular layer and hilus cells compared with the third group. Also, a huge number of fragmented nuclei and vacuoles in granular layer cells are noticed fig (21, 26). Moreover, brain of mice of fifth group shows widespread of degenerated areas, shrinkage and degeneration of pyramidal and glial cells, pycknotic nuclei with increased size of vacuoles. Hippocampus shows atrophy of granular layer, decrease in size of molecular layer cells and hilus, huge number of vacuoles and fragmented nuclei of granular layer cells fig (22, 27)

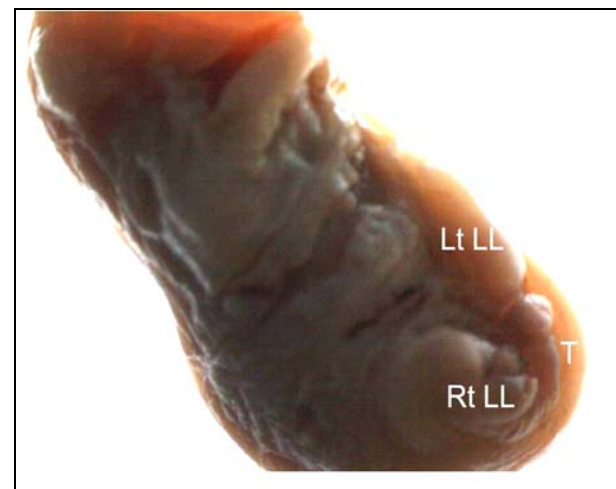


Fig.9: A photograph of mice in the first day of delivery in the fifth group. It shows development of left lower limb (Lt. LL), undevelopment of right lower limb (Rt. LL) (meromelia) and its tail (T).

DISCUSSION

Carbamazepine is used as a monotherapy anticonvulsant agent for treating epilepsy. It is associated with better seizure control and seizure rating score. It is considered as mood stabilizer also. The dosage of carbamazepine for adult ranged from 600–1600 mg/day. The starting dose is 200 mg twice /day and increased by 200 mg/day every 3 to 5 days. Samren *et al.* (2003), Briggs *et al.* (2008) recommended that carbamazepine is the drug of choice in pregnant woman who requires anticonvulsant therapy for the first time. It may cause harm to the fetus because it crosses the placenta and then there is a high risk for use of carbamazepine during pregnancy. The present study

assesses teratogenic effects of carbamazepine by simulation the human therapeutic regimen and overdoses.

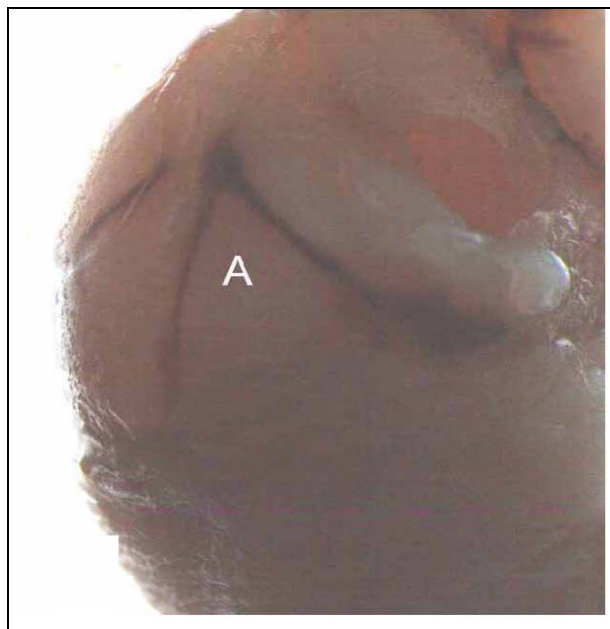


Fig. 10: A photograph of skull of mice in the first day of delivery in the fourth and fifth groups. It shows anencephaly with undevelopment of bones of skull, A (brain).

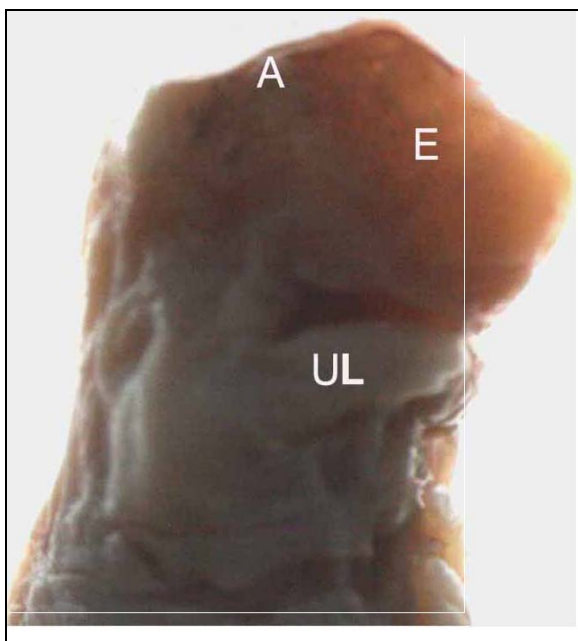


Fig. 11: A photograph of skull and upper half of mice in the first day of delivery in the fourth and fifth groups. It shows anencephaly with undevelopment of eye and upper limb. A (skull), E (undevelopment of eye) and UL (undevelopment of upper limb)

Regarding the results of the present study, weight and length of mice in the first day of delivery in the fifth group was significant decrease and this consistent with

Sucheston *et al.* (1986), who showed that high dose toxic effects of carbamazepine leads to intrauterine growth retardation which is manifested by low body weight and length reduction. The previous study confirmed that decrease of mice length due to retarded ossification of the long bones and there is a relationship between decrease of long bone ossification centers and fetal weight reduction.

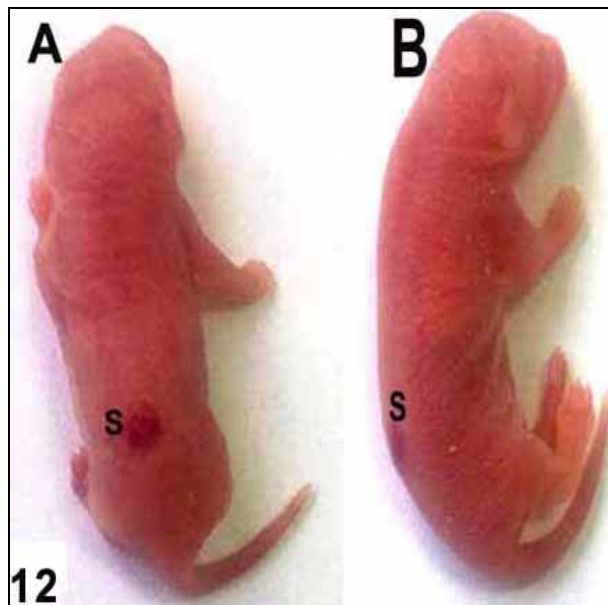


Fig. 12: A photograph of back mice in the first day of delivery in fourth and fifth groups. It shows spina bifida (Posterior-anterior view "A" and lateral view "B").

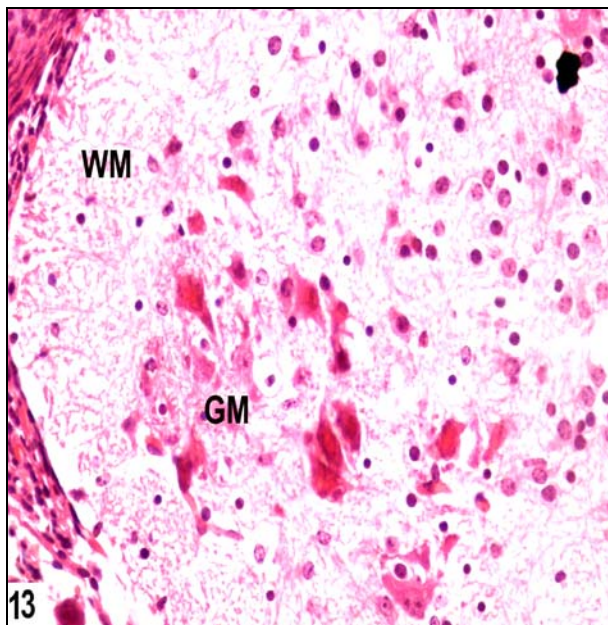


Fig. 13: A photomicrograph of spinal cord tissue of mice in the first day of delivery in the control group. It shows an outer white matter (WM), which consists of many myelinated nerve fibers. The inner gray shows many neurons present in both the dorsal and ventral horns (GM).

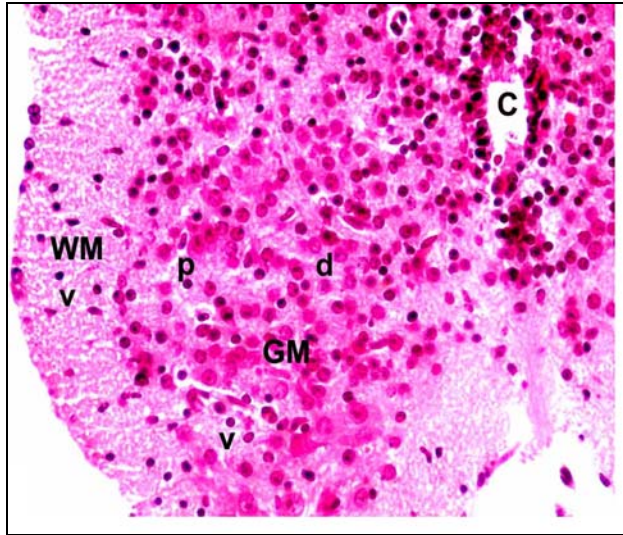


Fig. 14: A photomicrograph of spinal cord tissue of mice of the first day of delivery in the second group. It shows a mild degeneration of the outer white matter (WM) and inner gray matter (GM). Some cells shows degenerated nuclei (d) and other shows pyknotic nuclei (p) with scattered vacuoles in the white and grey matter. There are degenerated ependymal cells of the central canal (C).

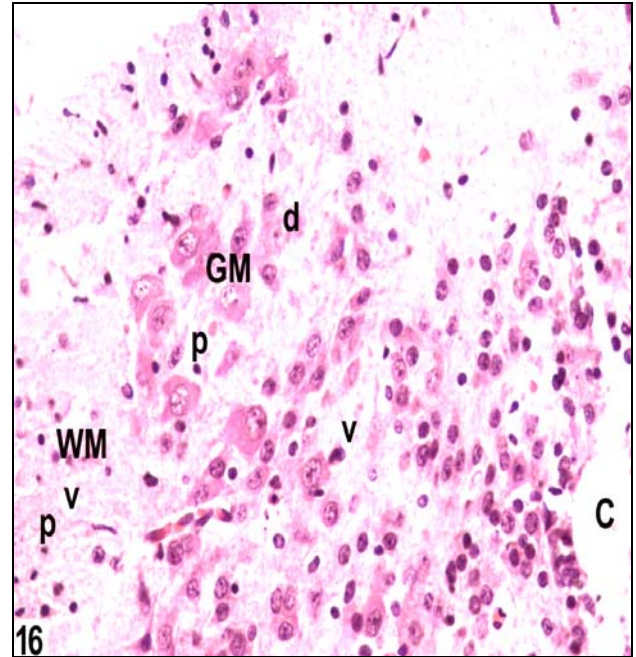


Fig.16: A photomicrograph of spinal cord tissue of mice of the first day of delivery in the fourth group. It shows a more degeneration of the outer white matter (WM) and inner gray matter (GM). Some cells have degenerated nuclei (d) and other has a pyknotic nuclei (p) with scattered vacuoles in white and grey matter. There is an increase of size and number of vacuoles in white and grey matter with degenerated ependymal cells of the central canal (C).

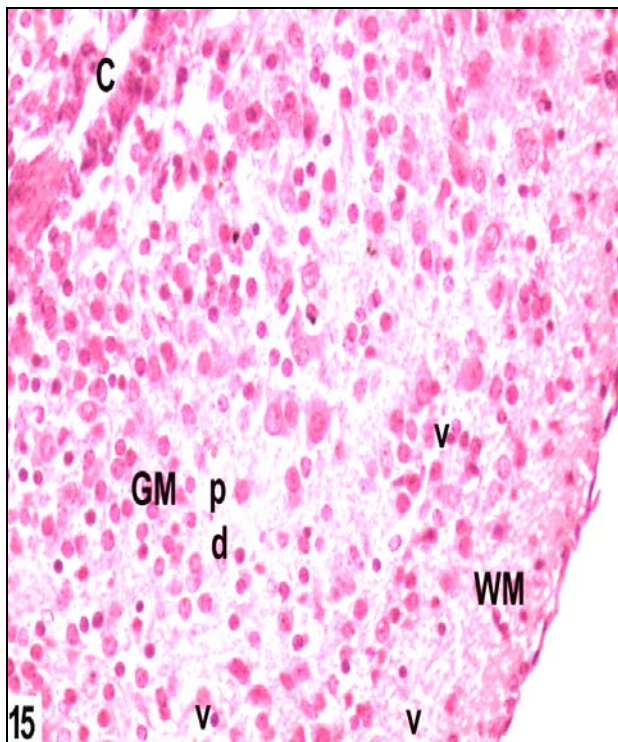


Fig. 15: A photomicrograph of spinal cord tissue of mice of the first day of delivery in the third group. It shows a moderate degeneration of the outer white matter (WM) and inner gray matter (GM). Some cells have degenerated nuclei (d) and other has a pyknotic nuclei (P) with scattered vacuoles (V) in white and grey matter. There is an increase of size and number of vacuoles in white and grey matter with degenerated ependymal cells of the central canal (C).

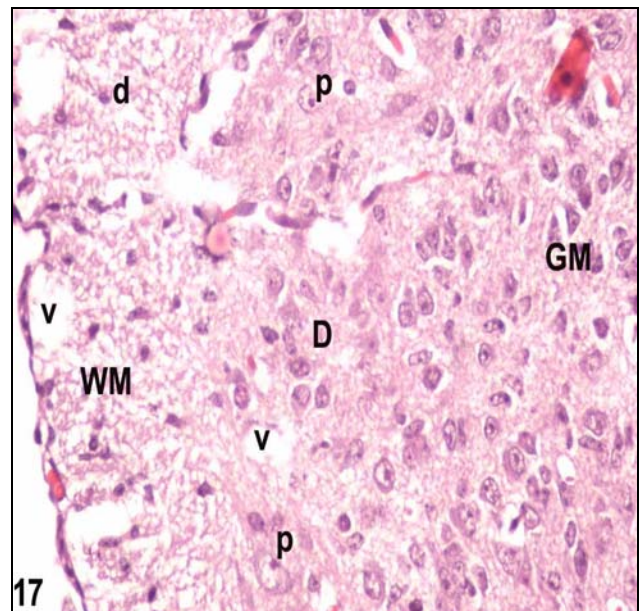


Fig. 17: A photomicrograph of spinal cord tissue of mice of the first day of delivery in the fifth group. It shows more degenerated areas (D) with huge size and number of vacuoles (v) in the outer white matter (WM) and inner gray matter (GM). There are a huge number of cells with degenerated nuclei (d) and other with pyknotic nuclei (p).

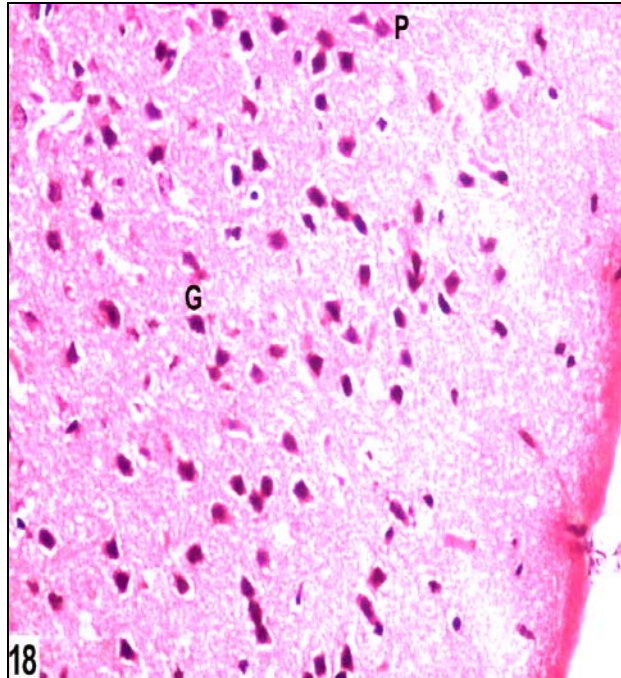


Fig.18: A photomicrograph of brain tissue of mice in the first day of delivery in the control group shows normal pyramidal cells (P) and glial cells (G).

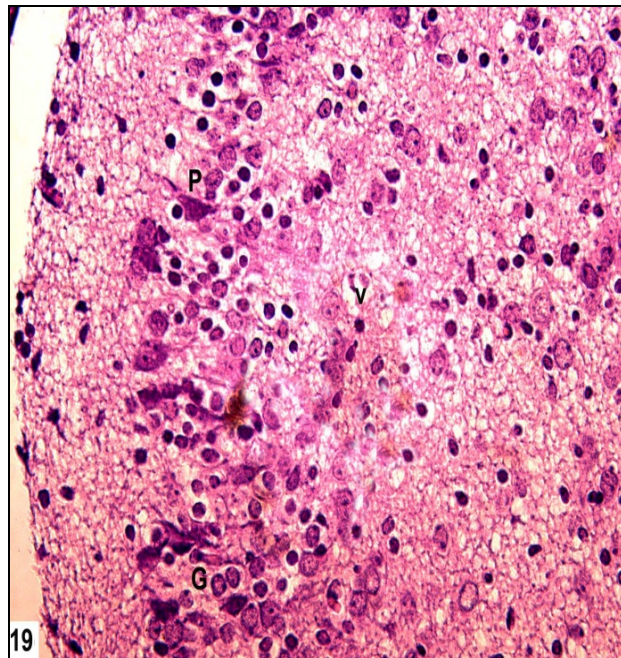


Fig. 19: A photomicrograph of brain tissue of mice in the first day of delivery in the second group. It shows congested pyramidal cells (P) and glial cells (G) with areas of vacuoles (v).

Pérez *et al.* (2008) explained that growth retardation of mice in the first day of delivery depends on anti-proliferative effects of carbamazepine and showed that these effects due to an increase in mitotic index and persistent block at the boundary of metaphase and anaphase associated with cell proliferation inhibition.

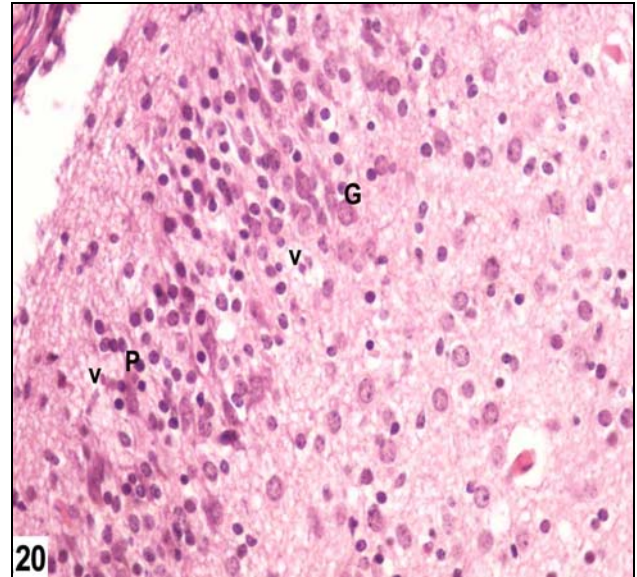


Fig.20: A photomicrograph of brain tissue of mice in the first day of delivery in the third group. It shows degenerated pyramidal cells (P) and glial cells (G) with areas of vacuoles (v).

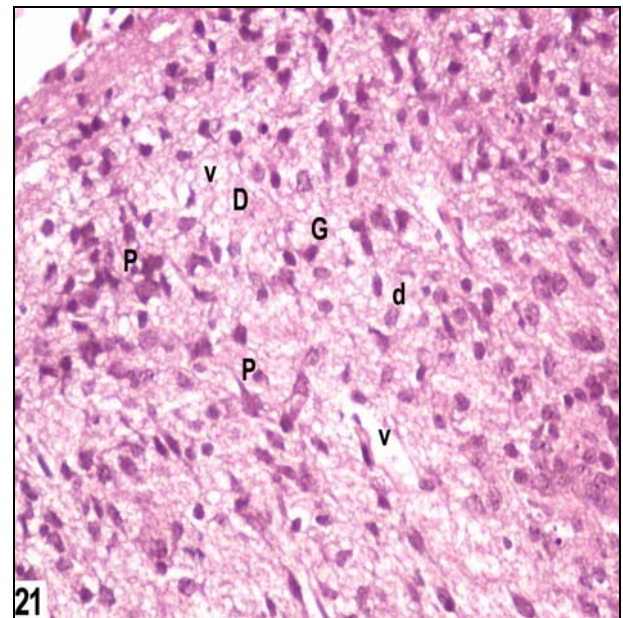


Fig. 21: A photomicrograph of brain tissue of mice in the first day of delivery in the fourth group. It shows loss of normal architecture, widespread of degenerated areas (D), degenerated pyramidal cells (P) and glial cells (G), increased areas of vacuoles (v) and degenerated nuclei (d).

According to Gerenutti *et al.* (2006), perinatal toxicity of any drug depends on reproductive performance of mother and drug dose. Corpus luteum plays an important role for reproductive performance by secretion of progesterone and 20-hydroxy progesterone, which maintains fetal growth. High dose of carbamazepine usually affects corpus luteum and then reproductive performance leading to growth retardation. Afshar *et al.* (2010) referred to

weight reduction of mice in the first day of delivery apart from the dose of carbamazepine and these results are contrasted with our results which indicated that weight reduction may depends on high toxic doses only which approved in comparison between control group and high dose groups using ANOVA test. There's also 95% confidence interval for weight parameter between control and study groups. They detected also various malformations such as underdevelopment of eye and tail and this is in agreement with results of the present study.

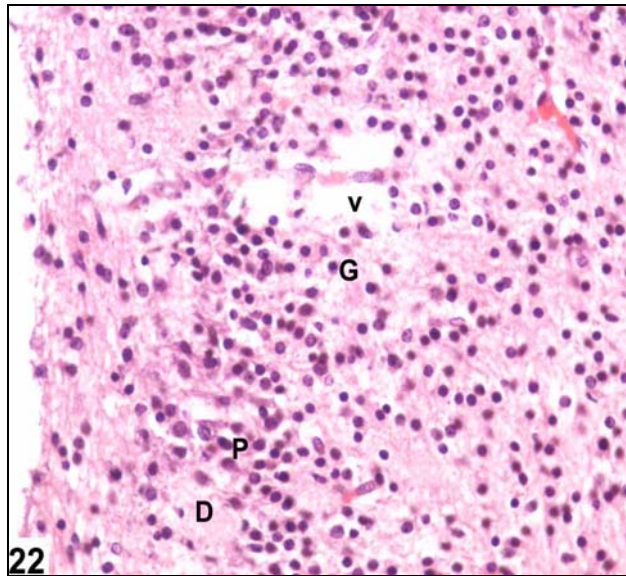


Fig. 22: A photomicrograph of brain of mice of the first day of delivery in the fifth group. It shows loss of normal architecture, widespread of degenerated areas (D), degenerated pyramidal cells (P) and glial cells (G), pyknotic nuclei with increased size of vacuoles (v).

Christensen *et al.*, (2004) indicated that prolonged prenatal exposure of subtoxic therapeutic dose of carbamazepine does not affect on the development of mice. This is consistent with our results, which confirmed that growth and development of mice in the second group were not affected.

Moreover, Artama *et al.* (2005) reported that prenatal exposure to carbamazepine may induce postnatal onset of severe growth retardation, suggesting disturbance of growth hormone-insulin like growth factor-I axis and this is consistent with our results for intrauterine and natal growth retardation in carbamazepine high doses groups. Elphick *et al.* (1990) suggested that Carbamazepine produces an increase in the growth hormone because it may alter brain serotonin and dopamine functions in therapeutic and mild overdoses groups. This may be explanation for the increase of measurements parameters (length, weight, upper and lower limb length) in these groups in the current study.

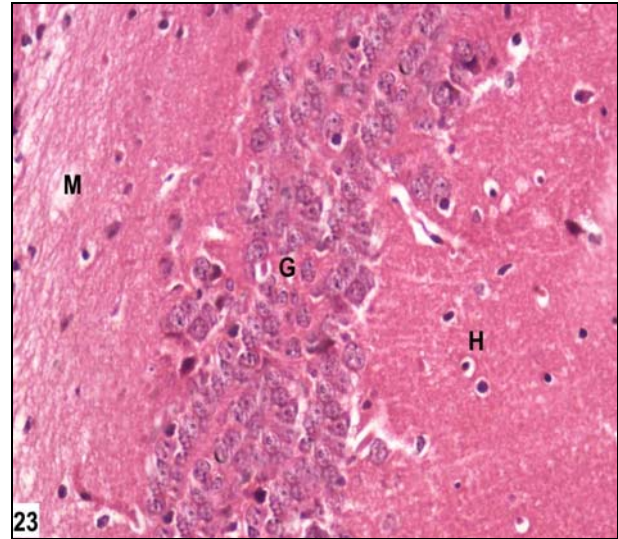


Fig. 23: A photomicrograph of hippocampus of mice in the first day of delivery in the control group. It shows a normal size of molecular layer (M), granular layer cells (G) and hilus (H).

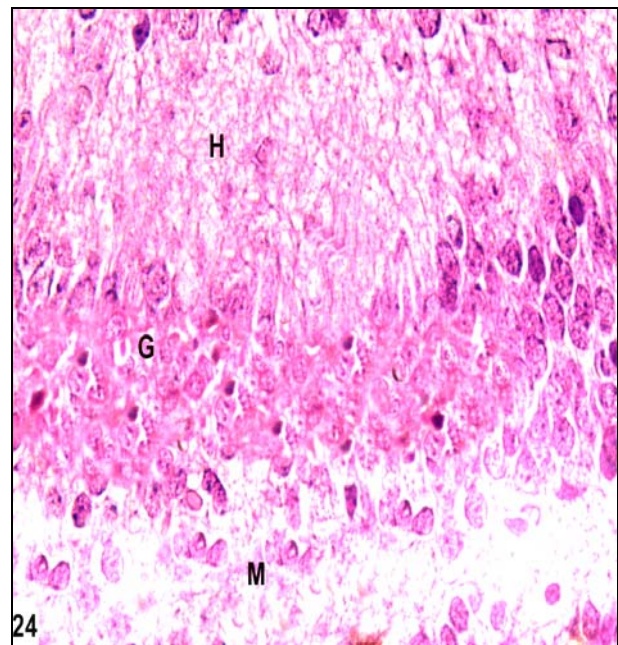


Fig. 24: A photomicrograph of hippocampus of mice in the first day of delivery in the second group. It shows decrease in size of molecular layer (M), granular layer cells (G) and hilus (H) with hydropic degeneration of cells of granular layer.

The current study showed significant decrease of upper and lower limb length of mice in the first day of delivery in fourth and fifth groups. Sucheston *et al.* (1986) argue that the decrease of the length due to reduction of length and width of ossified regions of humerus and femur. Marli *et al.* (2008) referred that low doses of carbamazepine leads to increase of cartilage in the ends of long bones and this is consistent with the results of the present study which showed a significant increase of upper and lower limb length of mice in second and third groups. Eluma *et*

al. (1984), who indicated that the teratogenic and embryotoxic of carbamazepine are associated with different doses. Decrease of fetal organs weight depends on dose and time of carbamazepine administration. This is consistent with our results, which referred to decrease of organs weight of mice with high dose in the fourth and fifth groups. But, it is contrasted with our results for decrease of brain weight in all groups apart from dose of carbamazepine.

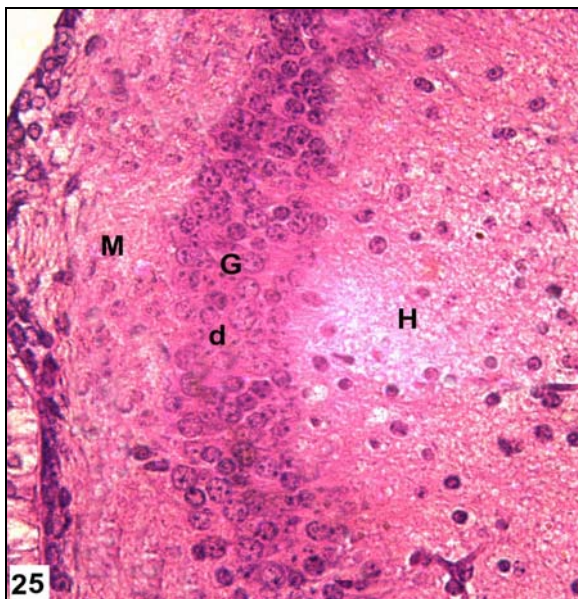


Fig. 25: A photomicrograph of hippocampus of mice in the first day of delivery in the third group. It shows more decrease in size of granular layer cells (G) which have fragmented nuclei (d), molecular layer (M) and hilus (H).

By study external morphological features of mice in the first day of delivery in the current study, we found that most congenital anomalies of carbamazepine in fourth and fifth group which received high toxic doses of the drug. It represents as small size of carpal, metacarpal bones and phalanges, small size of tarsal, metatarsal and phalanges, oligodactyly of hand and foot, meromelia, anencephaly and microphthalmia. Azarbayjani and Danielsson (1998) explained that mechanism of congenital malformations of carbamazepine toxic effects due to block of ion channels in the heart of growing embryo, which results in bradycardia, hemodynamic alterations, hypoxia and reoxygenation. And then, hypoxia can potentially affect the development of more than one organ in the body.

Jinsook *et al.* (2007) suggested that carbamazepine does not increase neurodegeneration when it is given in low doses but it induces a significant cell death at high doses and this is consistent with results of the current study which referred that degree of spinal cord degeneration in different groups depends on dose of carbamazepine. Manent *et al.* (2007), agree with our results for brain weight reduction and their explanation is consistent with

histopathological results of the current study. Neurodevelopmental toxicity represents in our study as neural tubal defect such as spina bifida and anencephaly with undevelopment of skull bones. Bittigau *et al.* (2002) explained that aggravation of folic acid deficiency is caused by high doses of carbamazepine leading to the increase of birth defects incidence.

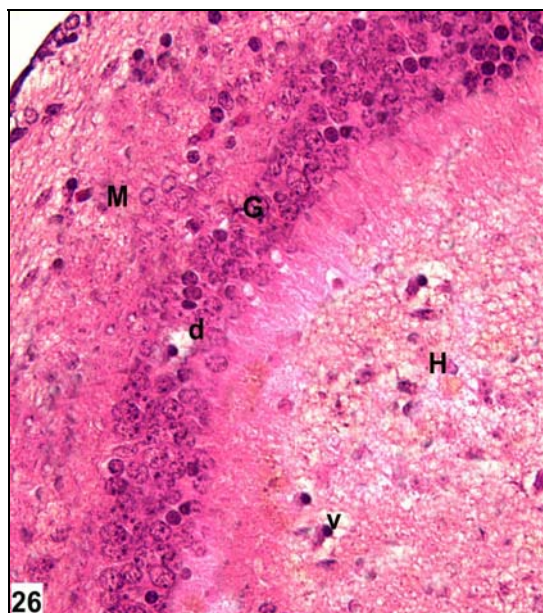


Fig. 26: A photomicrograph of Hippocampus of mice in the first day of delivery in the fourth group. It shows more decrease in size of granular layer cells (G) which have a huge number of fragmented nuclei (d) and vacuoles (v), decrease in size of molecular layer (M) and hilus (H).

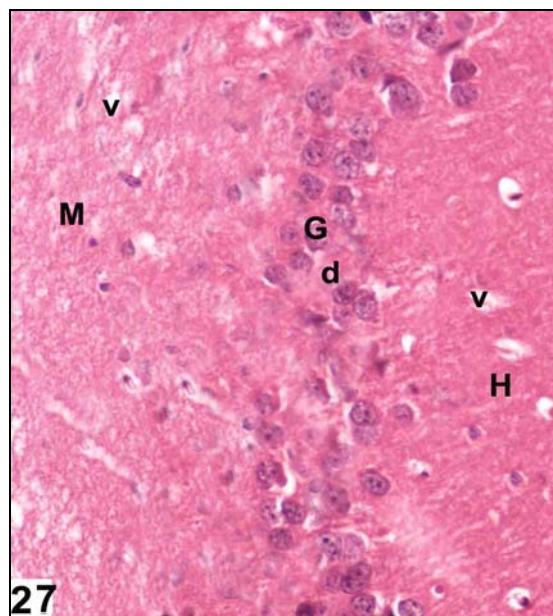


Fig. 27: A photomicrograph of hippocampus of mice in the first day of delivery in the fifth group. It shows atrophy of granular layer (G) which have fragmented nuclei (d), decrease in size of molecular layer cells (M) and hilus (H) with huge number of vacuoles (v).

CONCLUSION

Teratogenic effects of carbamazepine are growth retardation, meromelia, oligodactyly, microphthalmia and neurodevelopmental toxicity. Neurodegeneration, spina bifida and anencephaly are main features of neurodevelopment toxicity. Furthermore, embryo toxicity of Carbamazepine depends on its overdose degree

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