

Effect of Buspirone on the Histological and Immunohistochemical Alterations on Pancreas of Fetuses in Pregnant Rats

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ABSTRACT

Aim of the work: Buspar drug (buspirone) is an anti-anxiety agent for the treatment of anxiety, and there are no adequate studies of Buspar in pregnant women which made this issue an exciting research area; so that our aim was to study the effects of buspirone on the structure of pancreatic tissue of the maternally treated rat fetuses.

Material and methods: Buspirone hydrochloride tablets were obtained from Beecham, Haram, Giza, Egypt. Animals were divided into three groups (Ten pregnant rats in each group). Group I: (The control group) pregnant rats administered orally distilled water only; Group II: pregnant rats were given oral dosages of buspirone hydrochloride at a dose level of 0.27 mg/100g b.w./day, daily for 15 days from the 6th day to the 20th day of gestation; Group III: pregnant rats were treated with the same manner with buspirone hydrochloride at a dose level of 0.41 mg/100g b.w./day for 15 days from the 6th to the 20th day of gestation. Samples were taken from pregnant rats of all groups which sacrificed at 20th day of gestation and fetuses were picked out for histological, histochemical and immunohistochemical studies for pancreatic anti-insulin and caspase-3 monoclonal antibody markers.

Results: Treatment of pregnant rats with buspirone showed histopathological alterations in the pancreas of their fetuses; these alterations were well marked in the high dose maternally treated fetuses, and resulted in deformity in the pancreatic tissues. **Conclusion:** The present study showed that administration of buspirone may result in several histological and immunohistochemical deformity in the fetal pancreatic tissues.

Keywords: Buspar drug, Caspase-3, Histopathology, Immunohistochemical and fetal pancreas.

INTRODUCTION

Anxiety is mainly characterized by an unpleasant state of internal sensation accompanied with many neurological behaviors⁽¹⁾. These disorders which associated with anxiety are mostly increased in women during pregnancy due to changes in the levels of progesterone and estrogen in the blood levels. These changes can exacerbate these emotional difficulties⁽²⁾. Generalized anxiety disorder (GAD) shows a high prevalence through the general population⁽³⁾; epidemiologically its prevalence ranging from 1.8% to 6.9% among adults⁽⁴⁾ and from 0.3% to 5.8% among youth⁽⁵⁾.

The main criteria of GAD are excessive anxiety and chronic worry that is difficult to control and frequently occurs concomitantly with other disorder symptoms (restlessness, irritability, difficulty concentrating, muscle tension, sleep disturbances, and being easily fatigued) and its duration last for 6 months⁽⁶⁾.

These disorders also include Oxidative Stress (OS), which occurs due to increasing the levels of reactive oxygen species (ROS)⁽⁷⁾. The most harmful effect of ROS (lipid peroxidation) leads to the breakdown of lipids and the formation of a variety of products such as malondialdehyde (MDA)⁽⁸⁾.

Many psychoactive agents are currently possible for the treatment of anxiety; benzodiazepines are useful first-line agents for most of the anxiety disorders in the world⁽⁹⁾. Hydroxy tryptamine 1A (5-HT_{1A}) receptors are considered the most important targets for the treatment of mood disorders⁽¹⁰⁾. Animal models are

useful in giving insight into the etiology, neurobiology and the therapy of human anxiety disorders⁽¹¹⁾.

Buspirone hydrochloride molecular formula is C₂₁H₃₁N₅O₂·HCl, and its molecular weight is 421.96⁽¹²⁾. Its 5-HT_{1A} receptor partial agonist is mainly approved to be useful in generalized anxiety disorders⁽¹³⁾. It is effective in the treatment of depression because of its molecular properties⁽¹⁴⁾ and it takes from one to three weeks to become clinically effective⁽¹⁵⁾.

As anxiolytics, buspirone have an effect on glycemic control in diabetics⁽¹²⁾, and it was thought to be responsible for hyperglycemia in rats⁽¹⁶⁾, and it was found to produce a significant alteration in blood glucose level in healthy humans⁽¹⁷⁾.

To date, there is no reviews has been performed to evaluate the available effect of such a drug despite its different effects in acute and chronic use. Thus in this study we aim to evaluate the histological and immunohistochemical effect of administration of buspirone and the possible alterations in the pancreatic tissue of fetuses of pregnant rats.

MATERIALS AND METHODS

1- Drug:

Buspirone hydrochloride, Buspare was obtained as tablets from Beecham, Haram, Giza, Egypt. It was dissolved in distilled water and administered orally by a gastric tube. Daily single oral doses (0.27 mg and 0.41 mg /100g body weight/day) represented the low and high therapeutic doses in humans were calculated for rats according to **Paget and Barnes**⁽¹⁸⁾.

2- Animals and treatments:

Adult male and female Sprague Dawley rats weighing between 150-200g were obtained from the animal house of the National Organization for Drug Control and Research, Egypt. They were mated in the proportion of two females for one male overnight. Each morning a vaginal smear was taken to check the presence of sperms or plug in the vagina. Zero day of pregnancy was considered the day on which the sperms were found in the vagina. They were maintained on a standard rodent diet composed of 20% casein, 15% corn oil, 55% corn starch, 5 % salt mixture and 5% vitamin and starch. A total number of thirty adult pregnant rats were used in the present investigation. Maintenance of animals and experimental procedures were approved by the animal ethical ZU-IACUC committee with approval number (ZU-IACUC/1/F/74/2019) in accordance with the guide for care and use of laboratory animals. **The study was approved by the Ethics Board of Al-Azhar University.**

The following treatment protocol was used for this experiment:

Table 1. Grouping and treatment of experimental animals

Groups	Treatments
I- Control group (n=10)	Pregnant rats of this group served as a control group and were administrated distilled water only.
II-Low therapeutic dose treated group (n=10)	Pregnant animals of this group were orally administrated buspirone hydrochloride, daily at a dose level of 0.27 mg/ 100gb.w./ day for 15 days from the 6 th day to the 20 th day of gestation.
III-High therapeutic dose treated group (n=10)	Pregnant animals of this group were orally administrated buspirone hydrochloride, daily at a dose level of 0.41 mg/ 100g b.w./day for 15 days from the 6 th day to the 20 th day of gestation.

3- Histological Study:

Immediately on the 20th day of gestation after 4 hours from the last dose administration, the fetuses were picked up and fixed in 10 % neutral buffered formalin for 24 hours, dehydrated via gradual alcohols series, cleared in xylene and embedded in paraffin wax. Paraffin sections were mounted for routine histology study and stained by hematoxylin and eosin (H&E)

staining method⁽¹⁹⁾. The severity of cells was calculated using a grading scale of 0 to 4 , as follows: 0 = indistinguishable from controls , 1 = minimal, $\leq 25\%$ of cells affected , 2 = mild, $25\% \geq 50\%$ of cells affected, 3 = moderate, $50\% \geq 75\%$ of cells affected , 4 = marked, 75% of cells affected. This grading scale is according to National Toxicology Program⁽²⁰⁾.

4- Histochemical Study:

Special stains were applied for localization of carbohydrate, total protein, amyloid protein and collagen fibers in pancreatic tissue. Paraffin sections were treated with Periodic acid Schiff's (PAS) reaction⁽²¹⁾ for demonstration of polysaccharides, as well as, mercuric bromophenol blue⁽²²⁾ for total protein. Congo red technique⁽²³⁾, for amyloid- β protein and Mallory's trichrome stain⁽²⁴⁾ method for demonstration of collagen fibers. The optical density of PAS and mercuric bromophenol blue stained sections of pancreatic tissue of the control and treated groups were recorded using software image analysis image J. The mean optical density (OMD) was used to compare the PAS positive materials and total protein content in the different groups. Then the percentage of change was established for comparison between the treated and the control groups.

5. Immunohistochemical Study

In brief, formalin-fixed, paraffin-embedded fetal tissues were deparaffinized and then treated with 0.2% hydrogen peroxide in PBS to block endogenous peroxidase for 30min. The sections were then incubated overnight in a humid chamber with the primary anti-rat antibody against cysteine-aspartic proteases (caspase-3) (diluted 1:100) and for insulin (diluted 1:200) at 4°C (New Markers, Lab Vision, Fremont California, USA). The sections were then rinsed three times in PBS and incubated with goat anti-rat peroxidase-conjugated secondary antibody (peroxidase-labeled streptavidin) for 1h at room temperature and rinsed again three times in PBS. The immunoreactivity was visualized using 3,3'-diaminobenzidine hydrogen peroxide as a chromogen and the whole procedure was finished after the sections were counterstained with hematoxylin⁽²⁵⁾.

RESULTS

Histopathological observations:

1-Group I (Control group):

Examination of serial sections from pancreas of control rat fetuses at the 20th day of gestation revealed the presence of primitively developed pancreas surrounded by primitive gut and liver tissues. The histological observations denoted the presence of partially developed pancreatic acini and duct system .The cells of each pancreatic acinus have a triangular shape, abundant cytoplasm containing faint eosinophilic granules. The islets were distributed in the pancreatic

tissue; they were irregular in shape, containing variable number of ill-distinct round cells with large or medium size nuclei and their cytoplasm contain faint eosinophilic or basophilic granular secretory granules. An ill –distinct capsule and myxomatous fibrous stroma are the supporting structures of the pancreas. (Figs 1, A, B, C&D; Table1).

2- Group II (Low therapeutic dose treated group) : Examination of serial sections from pancreas of maternally treated rat fetuses at the 20th day of gestation revealed the presence of less developed pancreas. Some acini showed partial failure of the development, homogenous deep eosinophilic cytoplasmic materials beside degenerative and necrotic changes in some cells. Some of the interstitial blood vessels were mildly congested. Some acini revealed disorganized developmental changes with irregularly formed acini. The islets cells were disorganized with dispersed cells and focally degenerated and necrotizing cells. (Fig.2& Table1).

3-Group III (High therapeutic dose treated group): Examination of serial sections from pancreas of rat fetuses maternally treated with the high therapeutic dose at the 20th day of gestation revealed presence of primitively and less developed pancreas as compared with control or second group specimens (maternally treated with the low therapeutic dose). Nearly all the above mentioned changes in the pancreas of fetuses maternally treated with the low therapeutic dose involving the acinar and islets structures were also observed. However the degrees of developmental, degenerative, and necrotic changes were more pronounced. Few number of cells showed apoptotic changes(Fig.3&Table1).

Histochemical observations

Reaction with PAS showed polysaccharides in fetal pancreas with normal magenta-coloured particles aggregated together in cytoplasm of pancreatic cells of control group. On the other hand, examination of pancreatic sections of fetuses maternally treated with the low and high therapeutic doses indicated a slight decrease in the carbohydrate material as compared to the control ones (Figs 4, A,B&C). The MOD values reached 206.26 ± 1.98 and 196.57 ± 1.97 in the low and high therapeutic doses treated groups , respectively as compared to the control group (228.38 ± 0.40) (Table 2).

Mercury bromophenol blue stain showed total proteins appeared in the form of bluish granules of various sizes distributed randomly in a weakly to moderately stained cytoplasm in control group , which became mild in fetuses maternally treated with the low therapeutic dose and showed a marked reduction in those maternally treated with the high therapeutic dose. The proteinic remnants were obviously less reactive

with bromophenol blue compared with other groups (Figs 4, D,E&F).The MOD values reached 115.41 ± 4.52 and 79.65 ± 9.22 in specimens treated with the low and the high therapeutic doses, respectively as compared to the control group (132.32 ± 2.86) as shown in Table 3.

Feulgen reaction revealed the DNA - containing (chromatin) particles in the form of abundant, densely stained red purple-colored particles in the nucleoplasm, either distributed equally in the nucleoplasm or restricted to the peripheral rim of the nuclei of pancreatic cells of control group. In fetuses maternally treated with the low therapeutic dose the nuclei appeared markedly torn and shrunk , while in those maternally treated with the high dose, the nuclei became swollen and their DNA-containing bodies appeared as reddish violet stained granular elements (Figs 5, A,B&C). The MOD values reached 176.73 ± 3.82 and 175.61 ± 3 in specimens treated with the low and the high therapeutic doses, respectively as compared to the control group (184.55 ± 1.17) as shown in Table 4.

Examination of **Mallory's trichome stain** sections showed collagen fibers in control group in thin distinct amount which increased in the cytoplasm of fetal pancreatic cells in specimens treated with the low therapeutic dose and became markedly increased in those treated with the high therapeutic dose (Figs 5, D,E&F)..

Congo red stain showed amyloid- β protein with a slight deposition in the fetal pancreatic cells in control group and with a marked increase in low therapeutic dose treated-group, and became more pronounced in specimens treated with the low therapeutic dose (Figs 6, A,B&C).

Immunohistochemical observations

A-Caspase 3:

Examination of serial sections from pancreas of control rat fetuses at the 20th day of gestation treated with anticaspase 3 monoclonal antibodies revealed the following:

Control group : Almost all the pancreatic structures including the primitive acini and the islets cells were negatively stained for the apoptotic marker caspase 3 (Fig.5).

Low and high therapeutic dose treated groups: Nearly all the pancreatic structures including the primitive acini and the islets cells were negatively stained for the apoptotic marker caspase 3 (Figs 6, D,E&F).

B-Insulin marker :

Examination of serial sections from pancreas of control rat fetuses treated with anti-insulin monoclonal antibodies revealed the following :

Control group : All examined sections revealed primitive pancreatic acini and islets of Langerhans. The latter appeared randomly distributed among pancreatic

tissue with a variable number of cell populations. Most of the islets cells are large, round and contained positively stained secretory granules for the insulin marker (85-90%) (Figs 7, A&B).

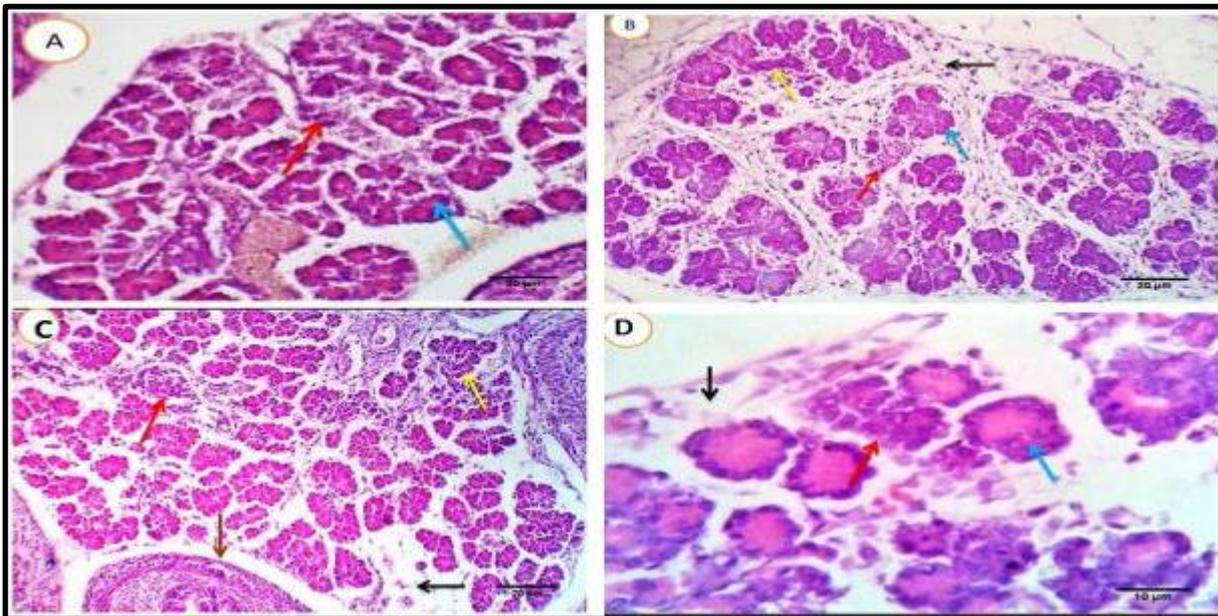
In **Group II** (maternally treated with the low therapeutic dose), all sections revealed primitive pancreatic acini and islets of Langerhans. The islets cells are few in number , small in size and contained very few number of Beta and alpha cells . Most of the beta cells were positively stained for the insulin marker (75-85%) (Figs7, C&D).

In **Group III**(maternally treated with the low therapeutic dose), examined serial sections showed primitive pancreatic acini and islets of Langerhans. The latter appeared randomly distributed among pancreatic tissue but they were comparatively larger in size and showed a cellular population compared to that of the control ; although the insulin positive cells were fewer and seen in about 50-60% of cells. (Figs 7, E&F) .

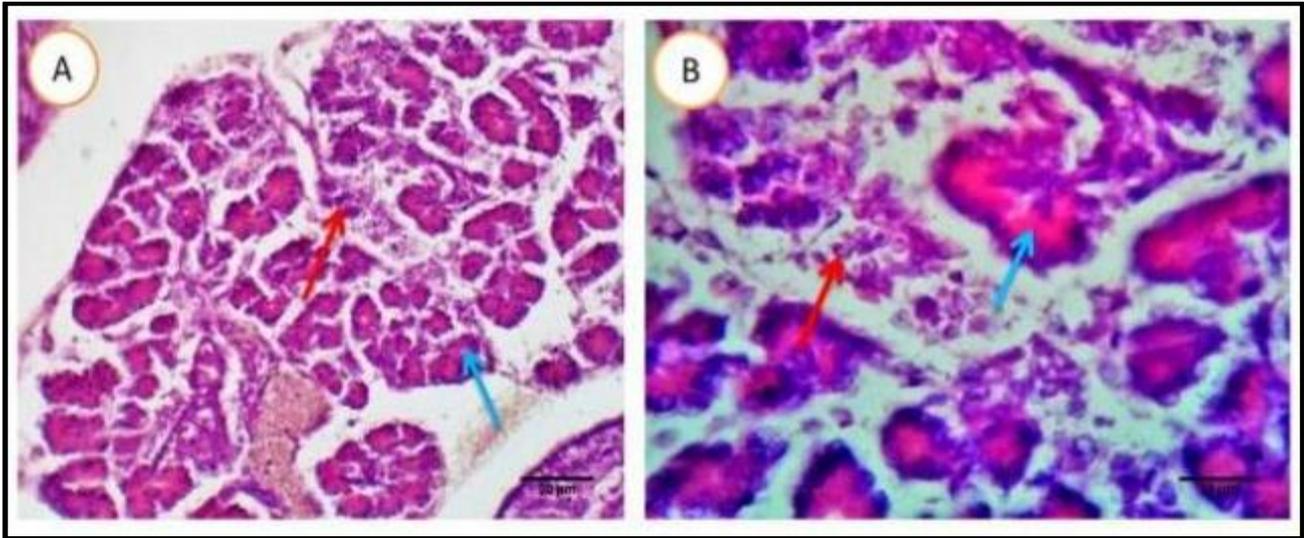
TABLE(1)

Histopathological scoring obtained from light microscopic analysis of pancreatic tissue sections of all treated groups :

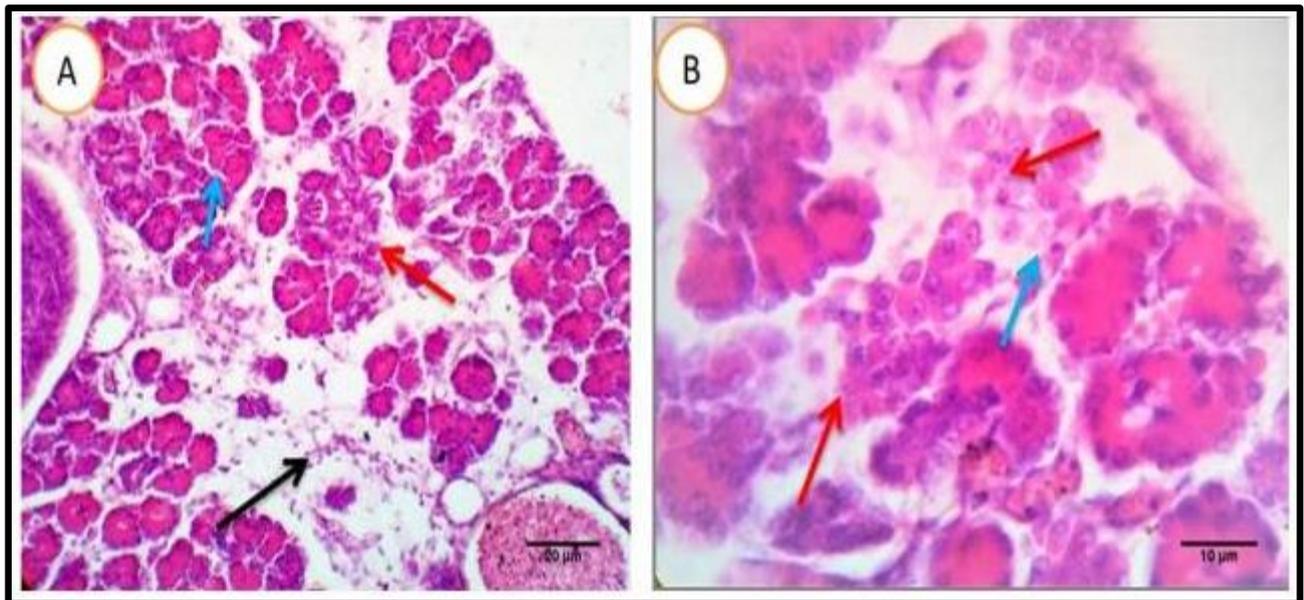
Group Grade	0	1	2	3	4
Group I (Control) n=10	8	2	0	0	0
Group II (Low therapeutic dose treated group (n=10)	0	3	4	2	1
Group III (High therapeutic dose treated group (n=10)	0	1	2	4	3



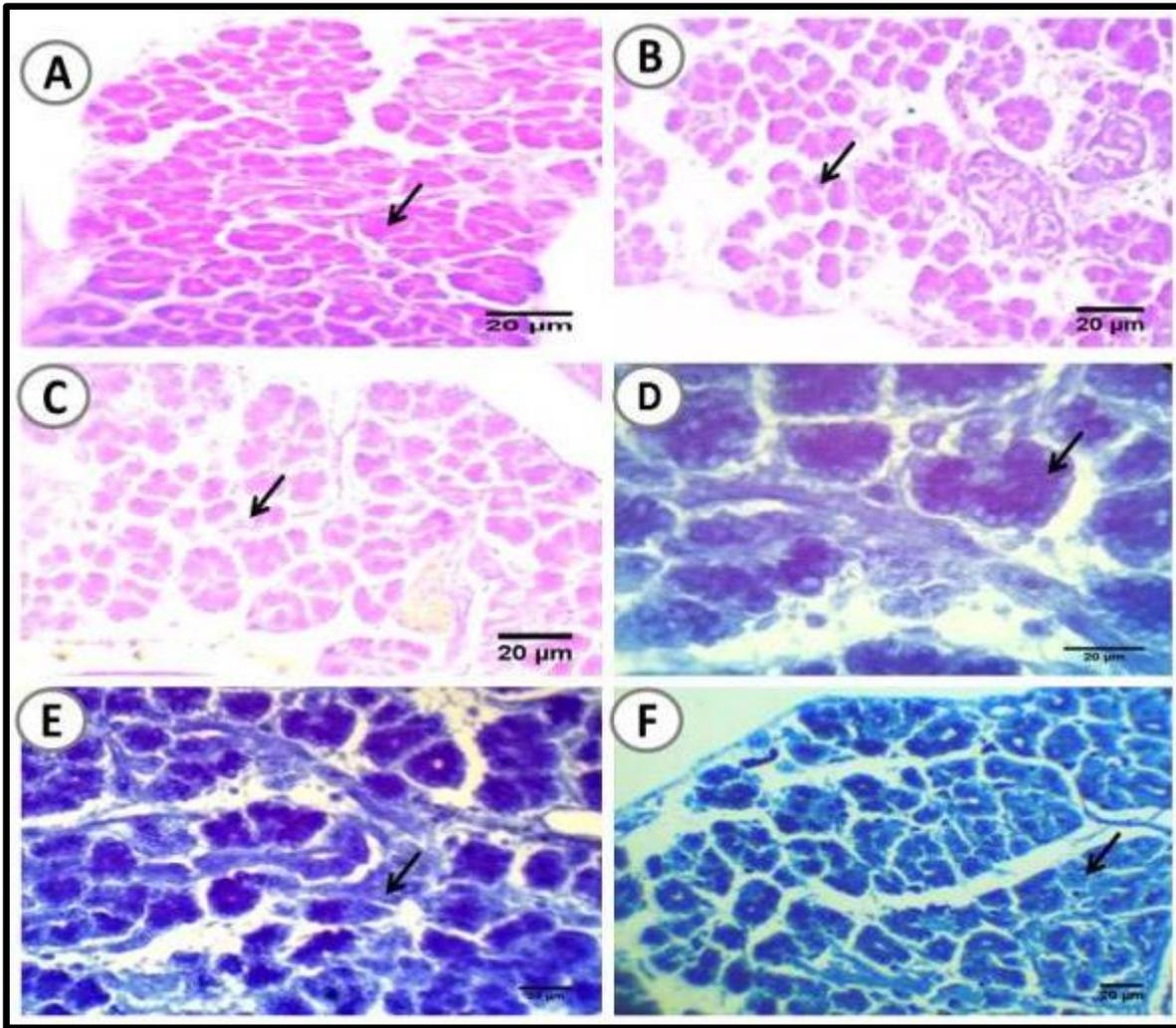
Figs.1(A, B, C&D) Photomicrographs of sections of the pancreas of 20-days old control rat fetus showing partially developed pancreatic acini (blue arrows) and duct system (yellow arrows). The acini were lined by cuboidal epithelium with centrally located nuclei and abundant cytoplasm containing faint eosinophilic granules. The islets are irregular in shape (red arrows), containing variable number of ill-distinct round cells with large or medium size nuclei and their cytoplasm contains faint eosinophilic or basophilic granular secretory granules. Myxomatous fibrous stroma is also seen (black arrows). In **C**, pancreas surrounded by a primitive gut (brown arrows) H&E. Scale bars correspond A, B& C =20 μ m and D =10 μ m.



Figs.2: Photomicrographs of sections of the pancreas of 20-days old maternally treated rat fetuses (low therapeutic dose group) illustrating in **A** and **B** some acini show partial failure of the development, homogenous deep eosinophilic cytoplasmic materials beside degenerative and necrotic changes in some cells (blue arrows). Some acini revealed disorganized developmental changes with irregularly formed acini. The islets cells appear disorganized with dispersed cells and focally degenerated and necrotizing cells. Some of the interstitial blood vessels are mildly congested. The islet cells are disorganized with dispersed cells and focally degenerated and necrotizing cells (red arrows). H&E X 1000, 400 .Scale bars correspond A, =20 μm and B =10 μm.



Figs..3. Photomicrographs of sections of the pancreas of maternally treated rat fetuses (high therapeutic dose group) at the 20thday of gestation showing in **A** and **B** primitive pancreas. Nearly all the changes involving the acinar and islets structures in the previous figure are also seen, however the degrees of developmental, degenerative, and necrotic changes are more pronounced. A very few number of cells show apoptotic changes (red ,blue and black arrows). H&E X 100, 400.



Figs..4 Photomicrographs of sections of the pancreas of fetus of rat at the 20th day of gestation stained with PAS showing a normal purple color granules in control group of different sizes aggregated in the form of dense patches (black arrow ↑) (A). Section of the pancreas of rat fetus maternally treated with the low dose showed little amounts of PAS - positive materials (black arrow ↑) (B). Section of the pancreas of fetus maternally treated with the high dose showed a prominent reduction in the PAS reactivity (black arrow ↑) (C). And with mercury bromophenol blue in (D,E,F) showing D in control group with a marked positive reaction in Purkinje cell in the form of small bluish granular particles (black arrow ↑), E in low therapeutic dose treated group showing a marked depletion of the protein content in pancreatic cells (black arrow ↑), F in high therapeutic dose treated group showing an obvious increase in protein content in the nuclear membranes and the chromatin bodies (black and yellow arrow ↑), Scale bars correspond A,B,C,D,E,F =20 μm.

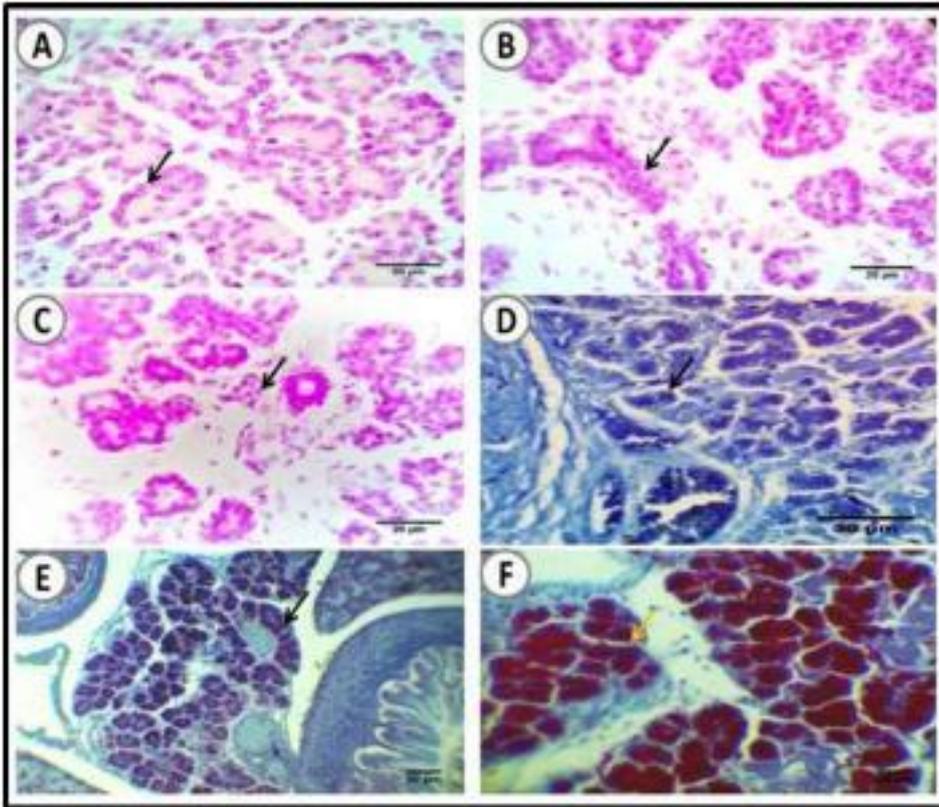


Figure 5:A photomicrograph of a section of rat's embryo at the 20thday of gestation stained with Fulgen reaction (A,B,C) showing in , **A** control group DNA -containing (chromatin) particles in the form of abundant, densely stained red puple-coloured particles located in the nucleoplasm (black arrow ↑), in **B** (low therapeutic dose) treated group showing a few swollen nuclei appeared packed with intensely stained DNA-containing particles (black arrow ↑) , in **C** (high therapeutic dose) treated group showing a swollen nuclei appeared packed with intensely stained DNA-containing particles (black arrow ↑) . In (D,E,F) sections stained with Mallory's trichome stain showing in , **D** control group a distinct amount of collagen fibers in pancreatic acini (black arrow ↑) , **E** in (therapeutic dose) deposition increase especially in pancreatic cells (black arrow ↑), in **F** (Toxic dose) group a marked increase of collagen fibers (black arrow ↑) , Scale bars correspond A,B,C,D,E.F =20 μm.

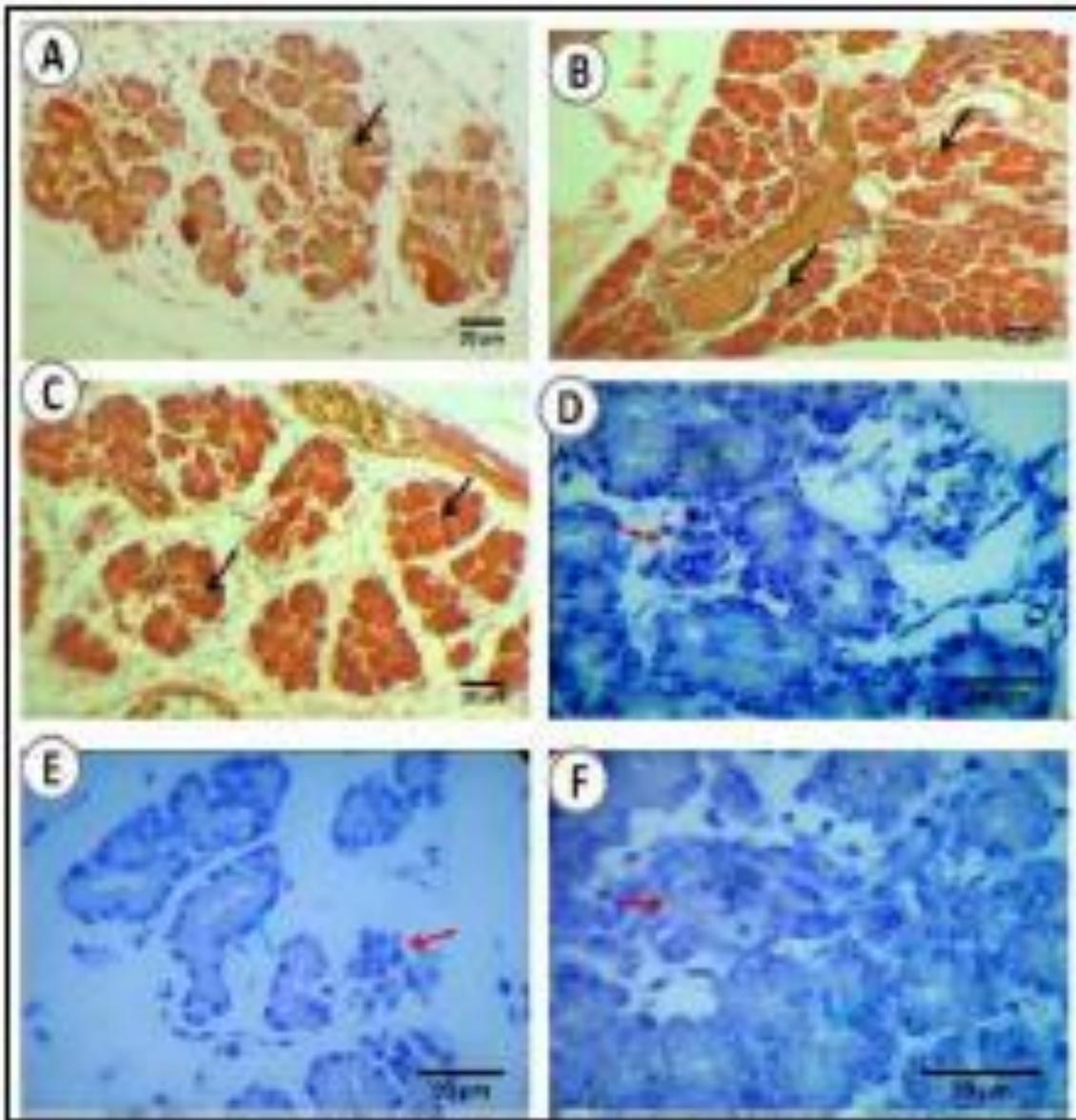


Figure 6: A photomicrograph of a section of rat's embryo at the 20th day of gestation stained with Congo red stain in (A, B, C) showing in **A** control group a slight amount of amyloids inside nuclei of pancreatic acini (black arrow ↑), in **B** (low therapeutic dose) treated group showing a relatively increase in intensity of amyloids (black arrow ↑), in **C** (high therapeutic dose) treated group showing a marked increase in deposition of amyloids (black arrow ↑). In (D, E, F) sections stained immunohistochemistry with the apoptotic marker caspase 3 showing: **D** control group pancreatic structures including the primitive acini and the islets cells negatively stained for the apoptotic marker caspase 3 (black arrow ↑); **E** (low therapeutic dose) and **F** (high therapeutic dose) nearly all the pancreatic structures including the primitive acini and the islets cells were negatively stained for the apoptotic marker caspase 3 (black arrow ↑). Scale bars correspond A, B, C, D, E, F = 20 μm.

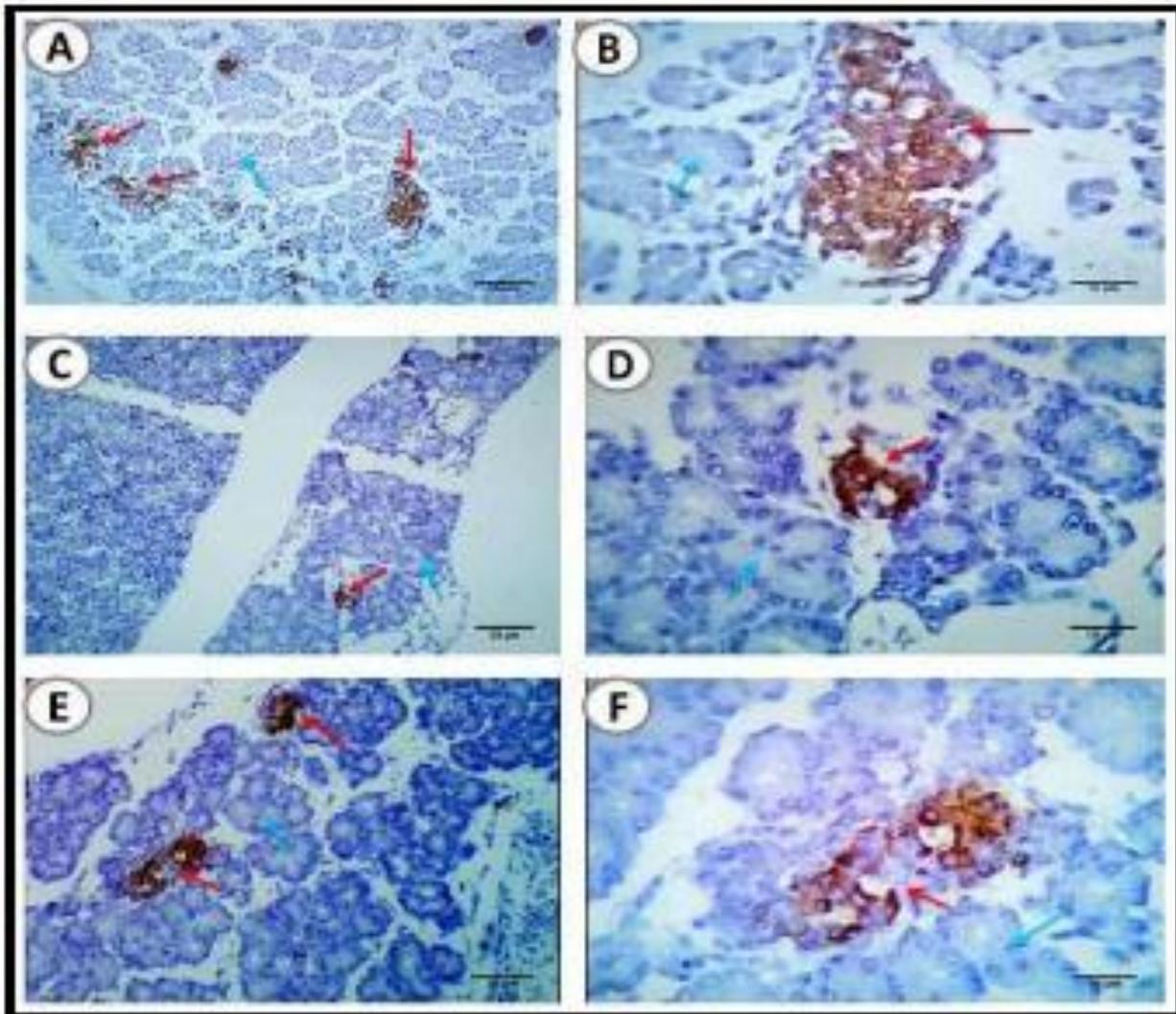


Figure 7: A photomicrograph of a section of rat’s embryo at the 20thday of gestation stained with insulin marker showing in , **A&B** control group the pancreatic acini and islets of Langerhans. The latter appears randomly distributed among pancreatic tissue with a variable number of cell populations. Most of the islets cells are large, round and contained insulin marker positively stained secretory granules in about 85-90% of cells (red arrow ↑), also in **C&D** (low therapeutic dose) group the pancreatic acini and islets of Langerhans. The latter appears few in number, small in size and contained very few number of Beta and alpha cells . Most of the beta cells appears positively stained for the insulin marker (red arrow ↑), and in **E& F** (high therapeutic dose) the pancreatic acini and islets of Langerhans. The latter appears randomly distributed among pancreatic tissue , shows cellular population comparative to that of the control rat’s fetus pancreas, although the insulin positive cells are fewer and seen in about 50-60% of cells (black arrow ↑). Scale bars correspond A,B,C,D,E,F =20 μm.

Table 2 : showing the MOD values of PAS +ve in the fetal pancreatic tissue of the control and treated groups

Parameter / Group	Group I (Control)	Group II (Low therapeutic dose)	Group II (High therapeutic dose)
mean ± SD	228.38±0.40	206.26±1.98**	196.57±1.97**
% of change	-	-9.68	-13.9

The values are considered significant at *P ≤ 0.05 and highly significant at **P ≤ 0.01. compared with the control group

Table 2: showing MOD values of total protein content in the fetal pancreatic tissue of the control and treated groups

Parameter / Group	Group I (Control)	Group II (Low therapeutic dose)	Group II (High therapeutic dose)
mean ± SD	132.32±2.86	115.41±4.52*	79.65±9.22**
% of change	-	-12.7	-39.8

The values are considered significant at *P ≤ 0.05 and highly significant at **P ≤ 0.01. compared with the control group

Table 3: showing MOD values of DNA particles in the fetal pancreatic tissue of the control and treated groups

Parameter Group	Group I (Control)	Group II (low therapeutic dose)	Group II (High therapeutic dose)
mean \pm SD	184.55 \pm 1.17	176.73 \pm 3.82**	175.61 \pm 3.07*
% of change	-	-22.6	-4.84

The values are considered significant at * $P \leq 0.05$ and highly significant at ** $P \leq 0.01$. compared with the control group.

DISCUSSION

Buspirone is an anxiolytic drug prescribed highly for anxiety disorder⁽²⁶⁾, with high affinity for the 5-HT_{1A} subtype of serotonin receptors, and thus acts as a partial agonist⁽²⁷⁾. It also has a high affinity for dopamine receptors and has been shown to act as an antagonist at dopamine auto receptors, resulting in an increase in brain dopamine turn over⁽²⁸⁾.

Actually, many previous studies reported in its pathological examinations a distention of the stomach in dead rats treated with BH (Buspirone hydrochloride) orally, and hyper secretion of gastric juice and alterations (edema, necrosis and petechia) on the superficial mucous membrane in the gastro pyloric region in dead dogs treated with BH orally⁽²⁹⁾.

Our study aimed to assess the Histological and immunohistochemical changes of buspirone drug in rat fetuses on the 20th day of gestation, and since there is a lack of detailed clinical literature on the direct anxiogenic effects associated with acute buspirone treatment. Several reports show that patients treated with buspirone initially experience akathisia which characterized by motor restlessness, feeling of muscular quivering and inability to sit still⁽³⁰⁾, thus Our results may be a guide for more studies.

In addition, Buspirone, is a potent anxiolytic compound in animal models, it displays reversibility of synaptic activation of pyramidal cells in the hippocampus⁽³¹⁾. Moreover, other studies found that they were administered oral doses of Buspirone equivalent to 0.27 mg/100g. for 15 days during gestation resulted in some sorts of neurotoxic structural changes in the cerebellum of fetuses of pregnant rats and deformity in the cerebellar layers and degeneration of Purkinje cells⁽³²⁾.

These results were confirmed by our study in which the administration of buspirone hydrochloride (BH) at a dose level of 0.27 mg/ 100g b.w./ day (low therapeutic dose), showed a partial failure of the development of some acini, beside degenerative and necrotic changes in some cells. The islets cells were disorganized with dispersed cells and focally degenerated and necrotizing cells, and a dose level of 0.41 mg/100g b. w./day (high therapeutic dose) showed more pronounced degenerative and necrotic changes. A very few number of cells showed apoptotic changes in fetal pancreatic tissue.

Moreover, glycophagy is a glycogen degradation in both mouse and human β -cells, as substantial numbers of glycogen particles which can be found within autophagosomes and lysosomes⁽³³⁾. The

Histochemical observations showed a mild decrease in the PAS +ve materials in the low and high dose treated groups, such decrease could be attributed to glucose uptake⁽³⁴⁾. These result were supported by our study which indicated a slight decrease in the carbohydrate material as compared to the control ones.

Besides, **Khana and his group**⁽³⁴⁾ found that collagenolytic enzymes synthesis by the impaired cells may be contributed to the accumulation of collagen fibres, and thus the disturbed histochemical pattern of polysaccharides. In addition total proteins and amyloid β -protein reflected the hazardous effects of buspirone in the biochemical and histochemical aspects which revealed the pathological signs⁽³⁵⁾. A detectable decrease in total protein was also noticed⁽³⁵⁾ and such a histopathological changes found in the different areas of brain which may be due to neurotoxic effect of buspirone.

So that, our results supporting such previous studies and showed that collagen fibers and amyloid- β increased in the cytoplasm of fetal pancreatic cell and became markedly increase in toxic dose specially in cytoplasm of pancreatic cells.

Buspirone-induced hyperglycemia and hyperglucagonemia which mediated by adrenaline release from the adrenal gland⁽³⁴⁾, according to this fact our results showed that most of the beta cells were positively stained for the insulin marker (75-85%) and insulin positive cells became more fewer and seen in about 50-60% of cell at toxic dose administrated group. However, no studies discussed the toxic effect of Buspirone on fetal rats from histological and histochemical point of view which make these outcomes have important helpful implications in Buspirone administration.

CONCLUSION

Administration of buspirone hydrochloride (Buspar) for long duration resulted in structural and histochemical changes as evident by deformity of the fetal pancreatic tissues of rat, and increase in amyloid protein.

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