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Embryo Toxicity of Antidepressant Drug (Trazodone HCl) on Albino Rat Fetuses.

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ABSTRACT

Trazodone is an antidepressant drug of the serotonin antagonist and reuptake inhibitor. Antidepressant drugs have been widely used during pregnancy. However, most studies reported several birth defects that result from using these drugs, there is not enough information about the risk or safety of trazodone using in pregnancy.Therefore, this work was initiated to study the effect of prenatal exposure of trazodone HCL on fetuses of albino rats.The study was conducted on pregnant rats to observe the safety profile oftrazodone in comparison to control. Pregnant albino rats (*Rattusnorvegicus*) were administrated during organogenesis period with therapeutic dose. Fetuses were removed from the uterus and evaluated for mortality rate, growth parameters, morphological and skeletal malformation as well as histological study of liver, kidney and brain.Our results showed fetal growth retardation during gestational period. Hematomas and deformation of limbs were noticed in the fetuses of treated groups. Fetal skeletal abnormalities were also observed mainly in the portion of ribs included defective ossification, costal separation and wavy ribs. Histopathological studies of fetuses during gestational period revealed degeneration of hepatocytes, vacuolization and necrotic areas within the cytoplasm. Swelling of glomeruli and degeneration of cells lining renal tubules were observed in the kidney of fetuses of treated groups. Also degenerative changes were observed in the brain following trazodone administration. Our findings suggest the need for great caution to handle trazodone especially during pregnancy.

Keywords: Depression- Antidepressants-TrazodoneHcl- Embryotoxicity- Albino rat- Fetus.

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INTRODUCTION

In general teratogenicity refers to the occurrence of biologically adverse effects on the pregnancy outcomes that may result from chemical exposure to several environmental agents. The exposure of teratogenic chemical prior to conception, during prenatal or postnatal development leads to manifestations of developmental toxicity including the death of the developing organism, structural abnormality, altered growth, and functional deficiency [1,2].

Teratogenic agent is a chemical, infectious agent, physical condition, or deficiency that, on fetal exposure, can affect fetal morphology or subsequent function. Teratogenicity relies on number of factors like, permeability of the placenta, susceptibility of the embryo to the teratogenic agent and the stage of development. Amid the most basic time frame in the fetus advancement, organogenesis, if the developing life is subjected to teratogens, major morphological changes will happen in light of the fact that this is the phase of most fast cell division and differentiation [3,4].

Reproductive and developmental toxicity studies in rats and rabbits are vital for safety assessment of pharmaceutical medications, pesticides and nourishment added substances. The placenta is one of the essential organs for the assessment of dangers for dams and developing embryo/fetuses in these toxicity studies. The placenta develops quickly, and displays stamped changes in morphological structure as indicated by fetal development. Despite the fact that the placenta is a brief organ, it is the interface between the dam and creating developing embryo/fetuses, and a multifaceted organ that plays out various imperative capacities all through gestation. These capacities incorporate tying down the creating baby to the uterine divider, mediating maternal immune tolerance, O2/CO2 exchange, giving supplements to the fetuse and expelling waste items amid embryonic development [5].

Depression is a typical psychiatric issue during the gestational period, influencing up to 14% of pregnant ladies [6-8]. Depression is a condition of low disposition that can influence a person's contemplations, conduct, emotions, and feeling of prosperity. Woman with a discouraged state of mind can feel dismal, on edge, miserable, vulnerable, crabby, irate, and embarrassed. They may lose enthusiasm for exercises, encounter loss of craving or indulging, have issues thinking, endeavor or submit suicide. A sleeping disorder, over the top dozing, weariness, hurts, torments, stomach related issues, or lessened vitality may likewise be available [9].

Various psychiatric disorders highlight discouraged state of mind as a principle side effect. The mood disorders are a gathering of scatters thought to be essential unsettling influences of temperament. These incorporate major depressive disorder (MDD; commonly called major depression or clinical depression) where a man has no less than two weeks of discouraged mind-set or lost intrigue or joy in about all exercises; and dysthymia, a condition of unending discouraged disposition, the manifestations of which don't meet the seriousness of a noteworthy depressive scene [9].

Major depressive disorder (MDD) and lifted depressive manifestations are basic in pregnancy and both have been connected to pregnancy and birth entanglement [10].

The reason for significant depressive issue is obscure. The bio-psychosocial demonstrate suggests that biological, psychological, and variables all assume a part in creating depression.

The gestational period is a physiologic marvel. It is portrayed by a many changes as, physical, hormonal, psychic and social changes that can specifically impact a ladies' mental health. The rise of pregnancy hormones level, estrogen and progesterone, can bring about mental issue, which can be less or more viable relying upon the affectability of every lady.

A few ladies of childbearing age experience the ill effects of sadness and presented to antidepressants right on time in pregnancy [11]. There are a few sorts of antidepressant medications, their instrument of activity generally includes expanding cerebrum convergence of the biogenic amine/catecholamine neurotransmitters. For instance monoamine oxidase inhibitors (MAOI), tricyclic antidepressants (TCA) and serotonin reuptake inhibitors (SSRI). SSRI antidepressants have turned out to be more particular in hindering the serotonin reuptake and not norepinephrin. Doctors feel good recommending specific serotonin reuptake

inhibitor (SSRI) antidepressants in light of the fact that these medications have been accessible for a long time and an extensive group of proof records their wellbeing amid pregnancy [12-15].

Trazodone hydrochloride

It is an antidepressant of the serotonin antagonist reuptake inhibitor (SARI) class. It is a phenylpipirazine compound. Trazodone also has anti-anxiety and sleep-inducing effects [16].

Trazodone hydrochloride is an antidepressant chemically unrelated to tricyclic, tetracyclic, or other known antidepressant agents. Trazodone hydrochloride is a triazolopyridine derivative designated as 2-[3-[4-(3-chlorophenyl)-1-piperazinyl] propyl]-1,2,4- triazolo [4,3-a] pyridin-3(2H)-one hydrochloride. It is a white, odorless, crystalline powder which is freely soluble in water. Its molecular weight is 408.3.

Trazodone is an oral antidepressant drug that influences the synthetic errand people (neurotransmitters) inside the cerebrum that nerves use to speak with (empower) each other. The significant neurotransmitters are acetylcholine, norepinephrine, dopamine and serotonin. Trazodone was endorsed by the FDA in 1982 [17].

At present no adequate data is available illustrates the safety use of trazodone HCL on the pregnant female and their embryos if given orally during pregnancy. So, in the present study we examined the embryo toxic effects of Trazodone HCL on embryos if given orally at a recommended dose for 14 consecutive days during pregnancy.

MATERIALS AND METHODS

All the experimental protocols and procedures used in this study were approved by the Cairo University, Faculty of Science Institutional Animal Care and Use Committee (IACUC) (Egypt), (CUFS/Comp&Emb/24/15).

Sound grown-up female and male rats with a normal time of around 2 to 2.5 months and weighing 170-180 grams were arbitrarily chosen. They were housed at a temperature of 22◦C and humidity of 70% and presented to 12 hours programmed light dull cycle with *ad libitum* access to food and water [18].

Female rats were mated with sexually developed male in the proportion of two females to one male for each cage. The next day, vaginal spread examination was performed in female rats. A little measure of saline was flushed into the vagina gap of rats utilizing a pipette tip. Maybe a couple drops of the subsequent vaginal liquid contained cell suspension then dribbled into a slide. When the smears were dried out, they were recolored with 0.1% methylene blue then analyzed under a magnifying instrument utilizing amplification of 400x. Gestational day 0 was dictated by the nearness of vaginal attachments or sperm in vaginal smears [19].

Antidepressant drug Trittico (TrazodoneHcl) Tablets produced by EIPICO, Egyptian international pharmaceutical industries company. Each tablet contains 100 mg of TrazodoneHcl. The tablets were soluble in water.

In the present investigation, the recommended maximum dose for human is 300 mg/daily. The dose was modified to suit the weight of rats according to [20].

The tablets were dissolved in distilled water and administrated orally. Organogenesis phase was the most critical period during gestation. Female rats were administrated orally (by gavage) once daily in the morning from 5 day to 19 day of gestation. Group A served as control group was received dist. water from 5 day to 19 day of gestation. Group B (treated group) was received 30.8mg/ Kg day of TrazodoneHcl from 5 day to 19 day of gestation.

All females were sacrificed by decapitation on the 20 day of gestation and their uteri were exposed by lower midline abdominal incision. The uteri horns were dissected in order to examine the position and number of viable, resorbed, or dead fetuses. The fetuses and placentas were separated and the placentas were examined carefully and their weights were recorded. The surviving fetuses were weighed and the length from

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crown to rump was measured and examined for any external gross malformations (exencephaly, cleft palate, abdominal hernia, polydactyl, open eyelid, etc.) was performed under a dissecting microscope. Positional anomalies, limb abnormalities, and structural defects were considered as abnormal fetuses [21]. The others fetuses were stained by alizarin red for skeletal examination [22]. Cross-sections through the placenta, brain, liver and kidney of fetuses at 20 day of gestation were done and stained with haematoxylin and eosin for histopathological examinations [23,24]. Statistical analysis was performed using the Analysis Of Variance (ANOVA) and Duncan's multiple Range Test to determine differences between treatments, means at significance level of 0.05. Standard errors of treatment means were also estimated. All statistics were carried out using Statistical Analysis Systems (SAS) program.

RESULTS

Maternal Effects

There was no maternal death in the treatment group during the experiment. Also there was a significant ($P \leq 0.05$) reduction in the placenta weight compared with the control (Fig. 1). The uterus of control pregnant rats on day 20 of gestation showed normal distribution of the implanted fetuses between the two horns (Fig. 2). The uterus of pregnant rats treated with 30.8 mg/Kg showed normal shape and sometimes with asymmetrical distribution of fetuses in the two uteri, completely resorbed uterus also revealed (Fig. 2).

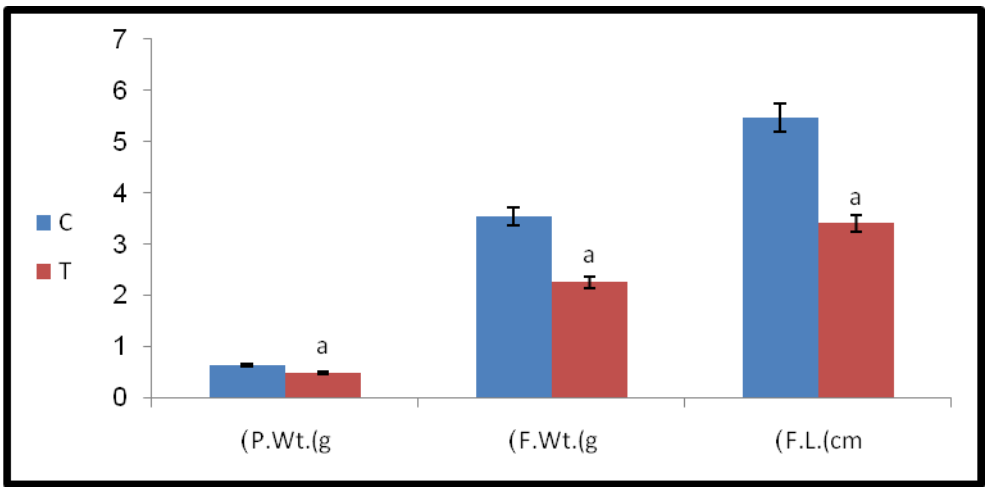

Fig 1: Showing effect of Trazodone on fetus weight, fetus length, placenta weight and mother weight gain at 20th day of gestation.Values are expressed as Mean ± SEM. The statistical differences were analyzed by independent samples T test. a= P ≤ 0.05 compared with control.

Embryonic Effects

The morphological examination of the fetuses showed that the Trazadone caused growth retardation represented by a decrease in fetal body weight and body length (Fig. 1). There was a significant ($P \leq 0.05$) reduction in fetus weight and fetus length in treated group when compared with the control group (A).

The fetus from control animals appeared with normal shape, correct weight and length (Fig. 3), also appeared straight dorsally. Treated group showed several fetuses malformation which manifested in subcutaneous hematoma in many regions as limb, face and phalanges, deformed limbs and club foot (Fig. 3).

At the 20th day of gestation, the cleared cartilage and bone preparations of control rat fetuses have designated that in all parts of the axial skeleton skull, vertebrae and ribs as well as appendicular skeleton comprising the fore and hind limbs, pectoral and pelvic girdles, both chondrification and ossification processes have been obviously completed. The cartilaginous parts of the skull included the nasal region (Fig. 4). On the other hand, fetuses maternally treated with 30.8 mg/Kg of TrazodoneHcl showed lack of ossification of the skull roof (frontal and parietal) and ribs abnormalities, which included wavy shape ribs, curved ribs, incomplete ossification and presence of costal separation (wide angle between ribs) (Fig. 4).

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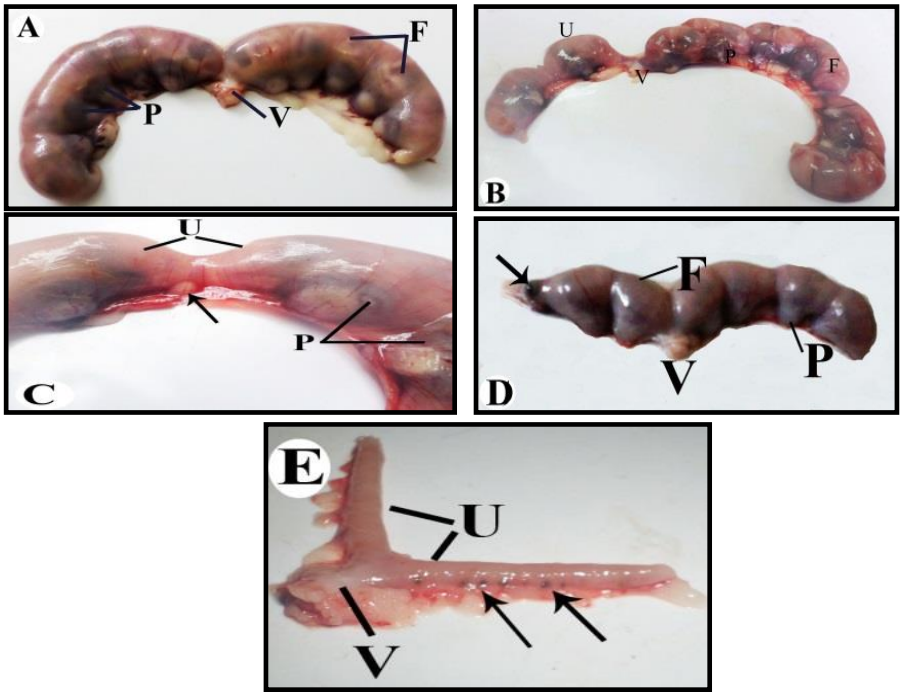

Fig 2: Photographs of uterus of pregnant rat at the 20th day of gestation.
From control group Show A) Normal symmetrical distribution of fetuses in the two uteri horns. From treated group show B) Asymmetrical distribution of fetuses in the two uteri horns. (C&D) Uterine horns showing clearly visible embryonic resorption sites (arrows). (E) Uterine horns showing pinpoint hemorrhagic implantation sites (arrows). U=Uterus, V=Vagina, P=Placenta, F=Fetus.

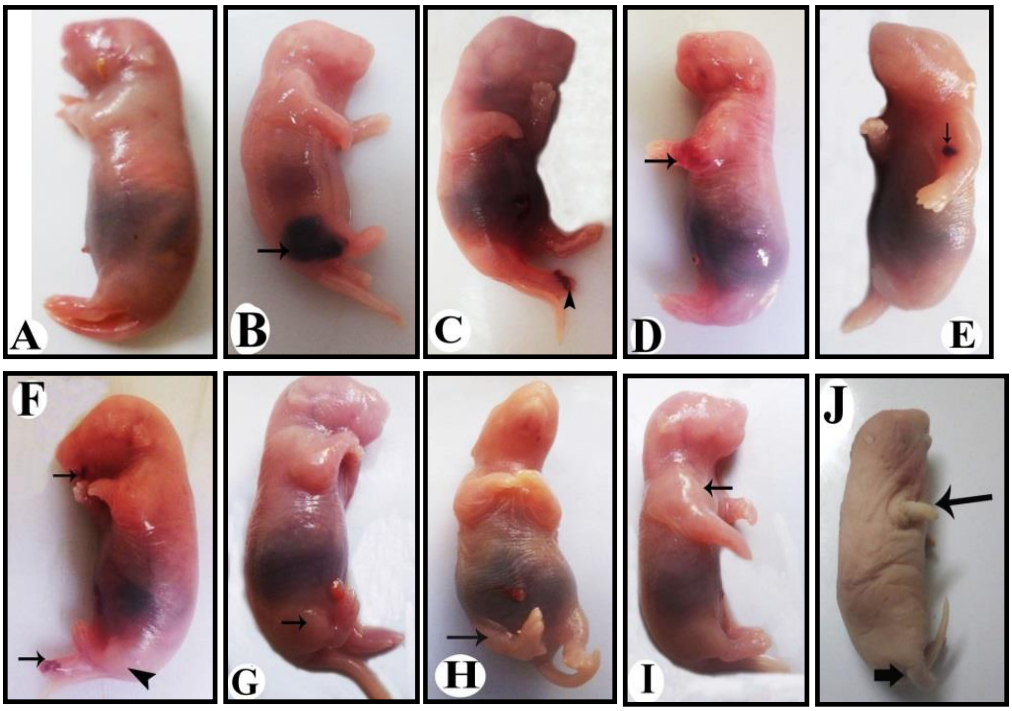

Fig 3: Photographs of fetus at 20th day of gestation.
Fetus of control mother show A) Normal morphology and normal length.
Fetuses of treated group Show(B) Hematoma at the hind limb (arrow).(C) Hematoma at the hind limb (head arrow).(D,E) Hematoma at the fore limb (arrow).(F) Fetus with club foot (head arrow), hematoma at the lower jaw (upper arrow) and hematoma at the hind limb (lower arrow).(G) Fetus with club foot (arrow).(H) Fetus with deformed hind limb (arrow).(I) Fetus with deformed fore limb (arrow).

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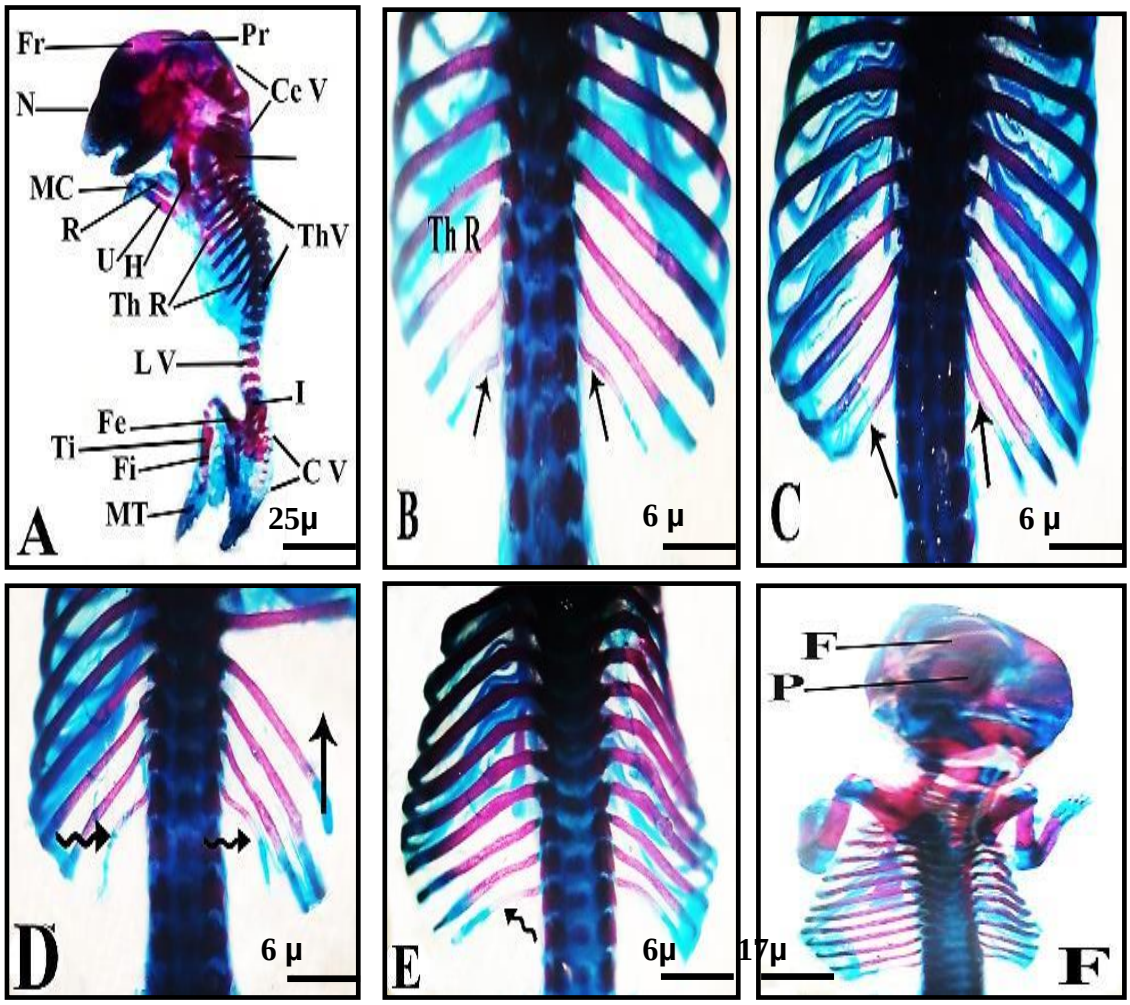

Fig 4: Photographs of a skeleton of a fetus.
From control group show A) Well ossifies skeletal system. Fr= frontal, Pr= parietal, N= nasal, Ce V= cervical vertebrae, Th V thoracic vertebrae, LV= lumbar vertebrae, CV= caudal vertebrae, S= scapula, H= humerus, U= ulna, R= radius, MC= metacarpals, I= ilium, Fe= femur, Ti= tibia, Fi= fibula and MT= metatarsus.
Treated group show (B) Wavy ribs (arrows). (C,D) Incomplete ossification of ribs. (E) Costal separation between thoracic ribs (arrow) and curved rib (wavy arrow). (F) Lack ossified frontal (F) and parietal (P) bone of the skull roof. Th R= thoracic rib.

Histopathological studies

Placenta

Histologically, the placenta is divided into a fetal part and a maternal part [25]. The maternal part consists of the decidua and metrial gland. The decidua basalis was composed of cellular and fibrous elements. It was separated from the basal zone by single layer of giant cells. The fetal part of consists of the basal zone and labyrinth zone. According to [26] the basal zone is composed of giant trophoblast cells, which represent the first trophoblast layer of the placenta, glycogenic trophoblasts and a highly packed basophilic spongiotrophoblast cells. The labyrinth zone contains giant trophoblast cells and syncytiotrophoblasts (Fig. 5).

Light microscopic examination in the placenta of rats treated with 30.8 mg/Kg, in the basal zone, severe reduction in number of giant cells. If their present showed irregular nuclei shape and vacuolated cytoplasm, numerous apoptotic spongiotrophoblast cells were scattered, hemorrhagic areas were present inbetweenspongiotrophoblast cells of the basal zone. Cystic degeneration of glycogen cells was observed. In the labyrinth zone, degeneration and necrosis of the trophoblasts, a diminution in thickness of the trophoblastic septa with a deposition of calcium and irregular dilation of the maternal blood space containing some thrombi were scattered. Histological changes in labyrinth area showed decreased trophoblastic septa (T)

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had lost their cellular architecture which act as a barrier that separates the maternal blood from embryonic capillaries; resulting in admixing of maternal and fetal blood and decreased vessels formation. Degeneration of the fetal blood vessels in the labyrinth zone also revealed (Fig. 5).

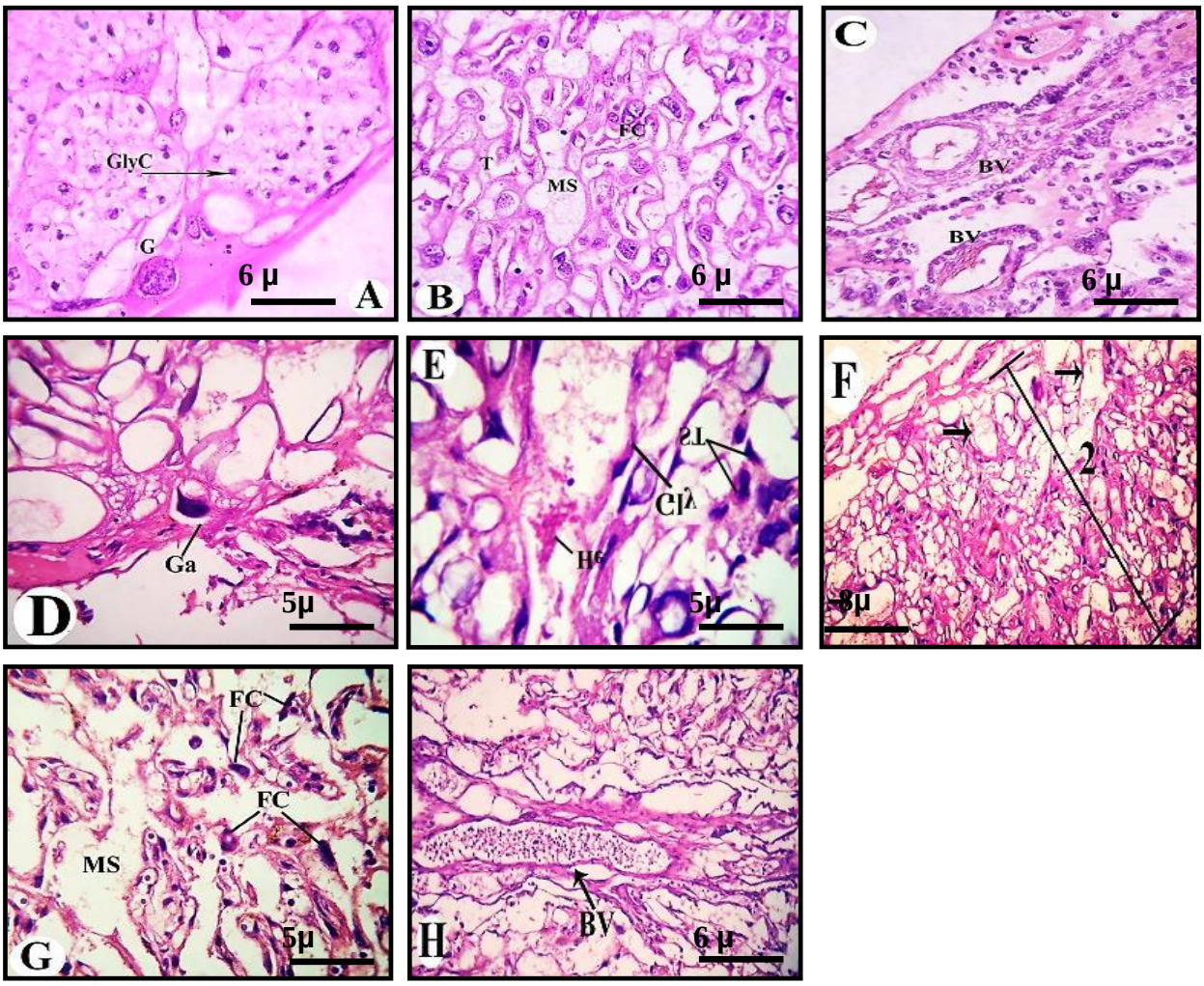

Fig 5: Photomicrographs of a section of placenta of pregnant rat. H&E stain.
From control mother show A) Basal zone; Ga= giant cell, GlyC= glycogen cell. B) Labyrinth zone; showing trophoblastic trabeculae (T) consisting of trophoblasts and syncitiotrophoblast, fetal capillaries (FC) lined by endothelial cells containing fetal erythroblast and maternal sinusoid (MS) containing maternal erythrocytes. C) Normal appearance of blood vessels lined with epithelial cells (BV).

From treated group show D) Giant cell with irregular shape nuclei and cytoplasm. E) Pyknoticspongiotrophoblast (ST), hemorrhage (He) and cytolysis glycogen cell (Gly). F) Basal zone of fetal part (2) reveal decrease in number of giant cells. G) Histological changes in labyrinth area showed decreased trophoblastic septa (T), irregular dilatation of maternal sinusoids (MS) and poor developed fetal capillary (FC). H) Congested blood vessel (BV).

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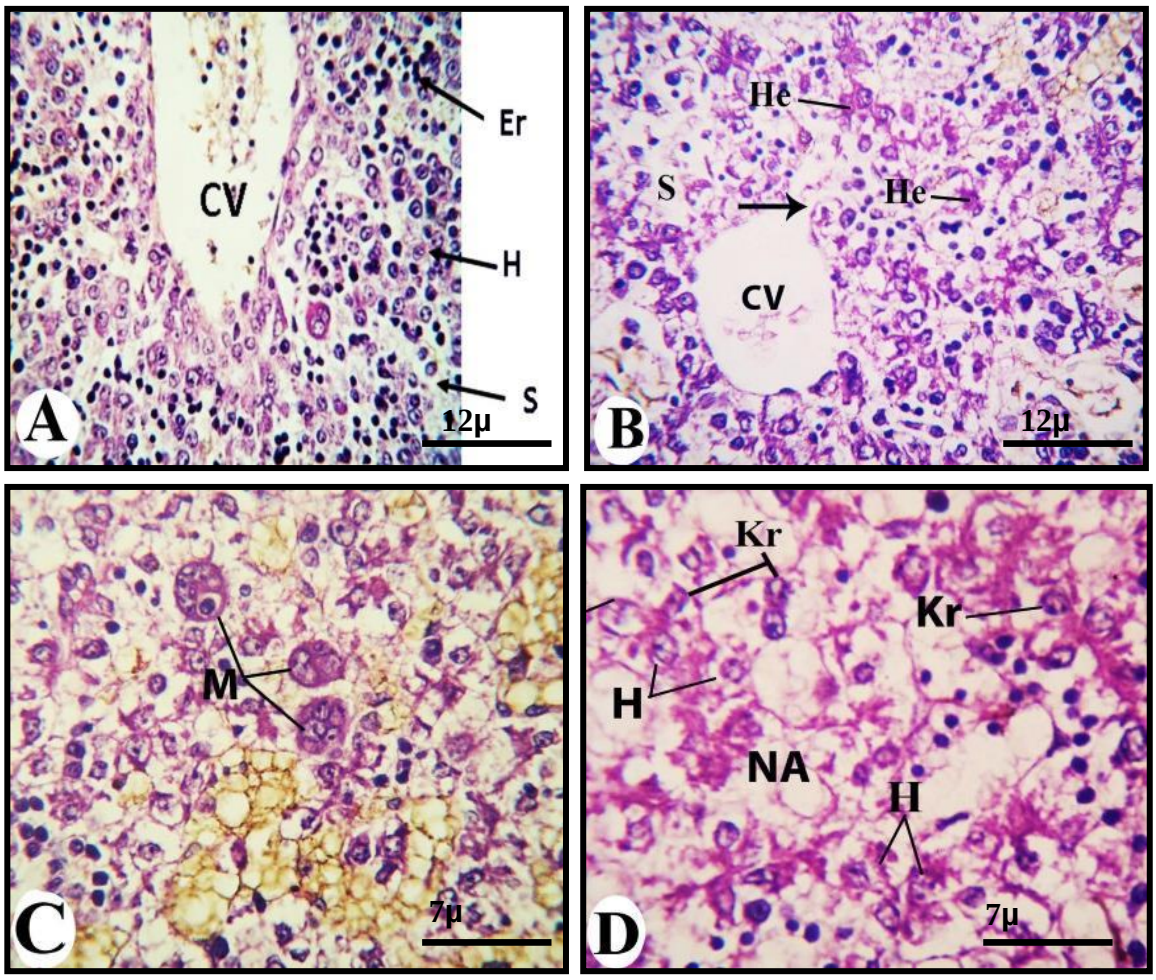

Fig 6: Photomicrographs of a section of liver of a fetus. H&E stain.
From control mother show A) Normal architecture of the liver tissue.The hepatic lobules that can be only distinguished by their central vein (CV), hepatocytes (H), sinusoids (S) and numerous erythroblasts (Er). From treated group show B-D) Dilation of central vein (CV), cytoplasmic vacuolization and hepatocyte degeneration (H), pyknotized or karyolysed cells. He= hemorrhagic area, M= megakaryocytes, Er= erythroblasts, Kr= karyolysis, and NA= necrotic area.

Liver

In liver sections of livers of fetuses on day 20 of gestation, normal hepatic structure was found (Fig. 6). The hepatic cells are large, polygonal in shape and possess coarsely granulated cytoplasm. They represent the different types of blood forming cells, namely the lymphocytes and erythroblasts. Liver sections of fetuses obtained from rats maternally receiving therapeutic doses of Trazodone Hcl, exhibited dilatation of central veins and detached of endothelial cells that lining the central vein wall and lumen of vein continuous with the sinusoid. Increase in number of megakaryocytes and decrease of erythroblasts number. Also some cells showed signs of pyknotic nuclei and vacuolization of cytoplasm that might be attributed to lipolytic degeneration and in some cases the histopathological alterations in fetal liver sections showed pathological responses in the nuclei of liver cells ranging from karyolysis to almost complete necrosis (Fig. 6).

Kidney

Examination of the kidney of control fetus revealed that it is differentiated in to outer cortex and an inner medulla, which is formed of conical pyramids. Each medullary pyramid with the corresponding part of the cortex represents a renal lobe which consists of the uriniferous tubules and stromal tissue. The uriniferous tubule is composed of the nephron which is formed of the Malpighian corpuscle, the proximal convoluted tubule, the descending and the ascending limbs of Henle's loop and the distal convoluted tubule. Each

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corpuscle consists mainly of a tuft of blood capillaries, or glomerulus and a Bowman's capsule which is a double walled cup formed of two layers, an outer parietal layer and an inner visceral layer separated by a clear, distinct capsular space (urinary space) (Fig. 7).

Examination of the kidney of fetus maternally treated with 30.8 mg/Kg, revealed degeneration in the tubular lining epithelium with swelling in the endothelial cells lining the tufts of the glomeruli within the Bowman's capsule as recorded in (Fig. 7).

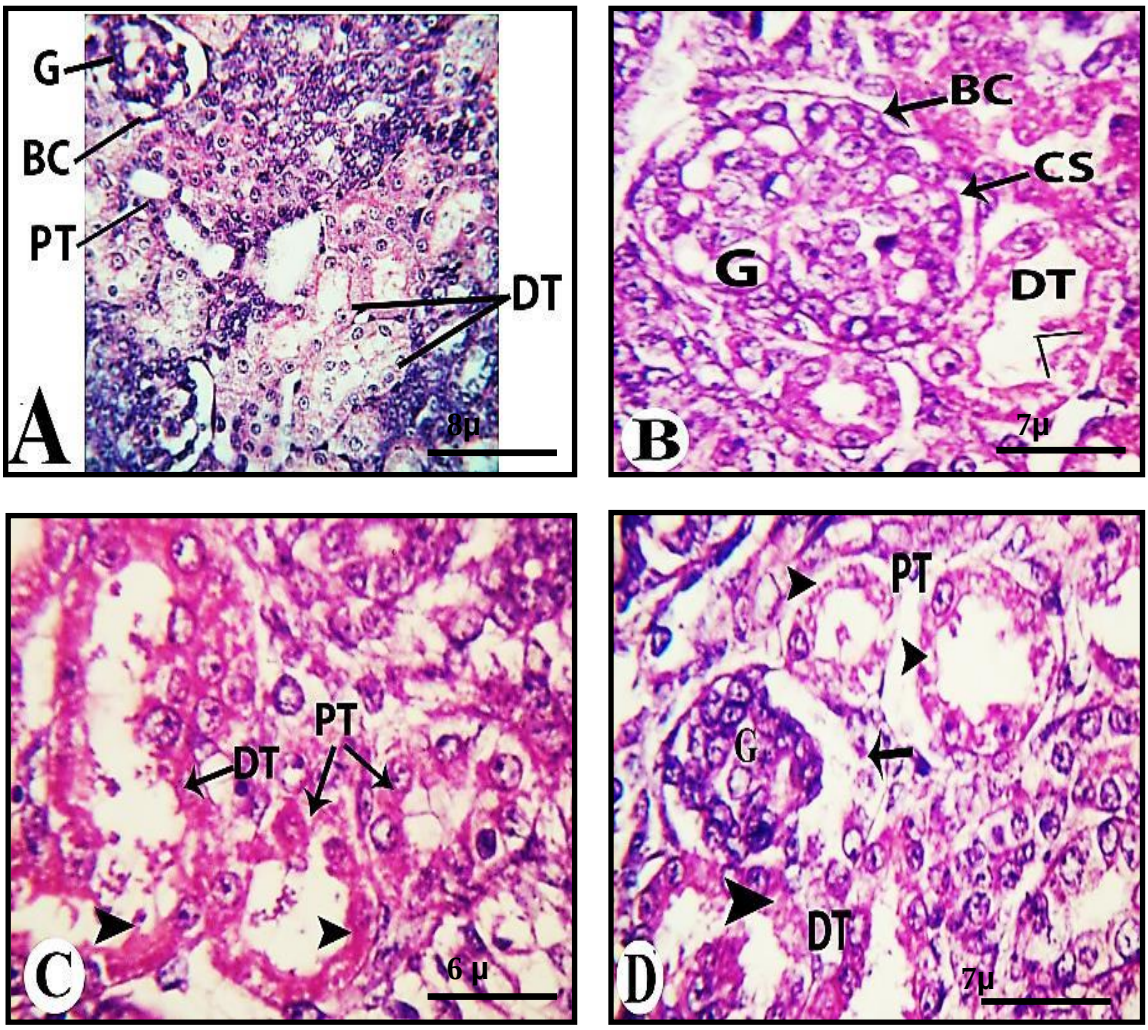

Fig 7: Photomicrographs of a section of kidney of a fetus. H&E stain.
From control mother show A) Apart of the cortical region containing, a glomeruli (G) within Bowman's capsule (BC) and tubules (T).PT=proximal tubule and DT= distal tubule. Scale bar value= 8µ.
From treated group show B-D) Degeneration of epithelium lining renal proximal tubules (PT) and distal tubule (DT) also swelling of glomeruli (G) inside Bowman's capsules (BC) without capsular space (CS). Shrinked glomeruli (G) shown in photo (D). Scale bar value: B)= 6.6µ, C)= 5.7µ and D)= 6.6µ.

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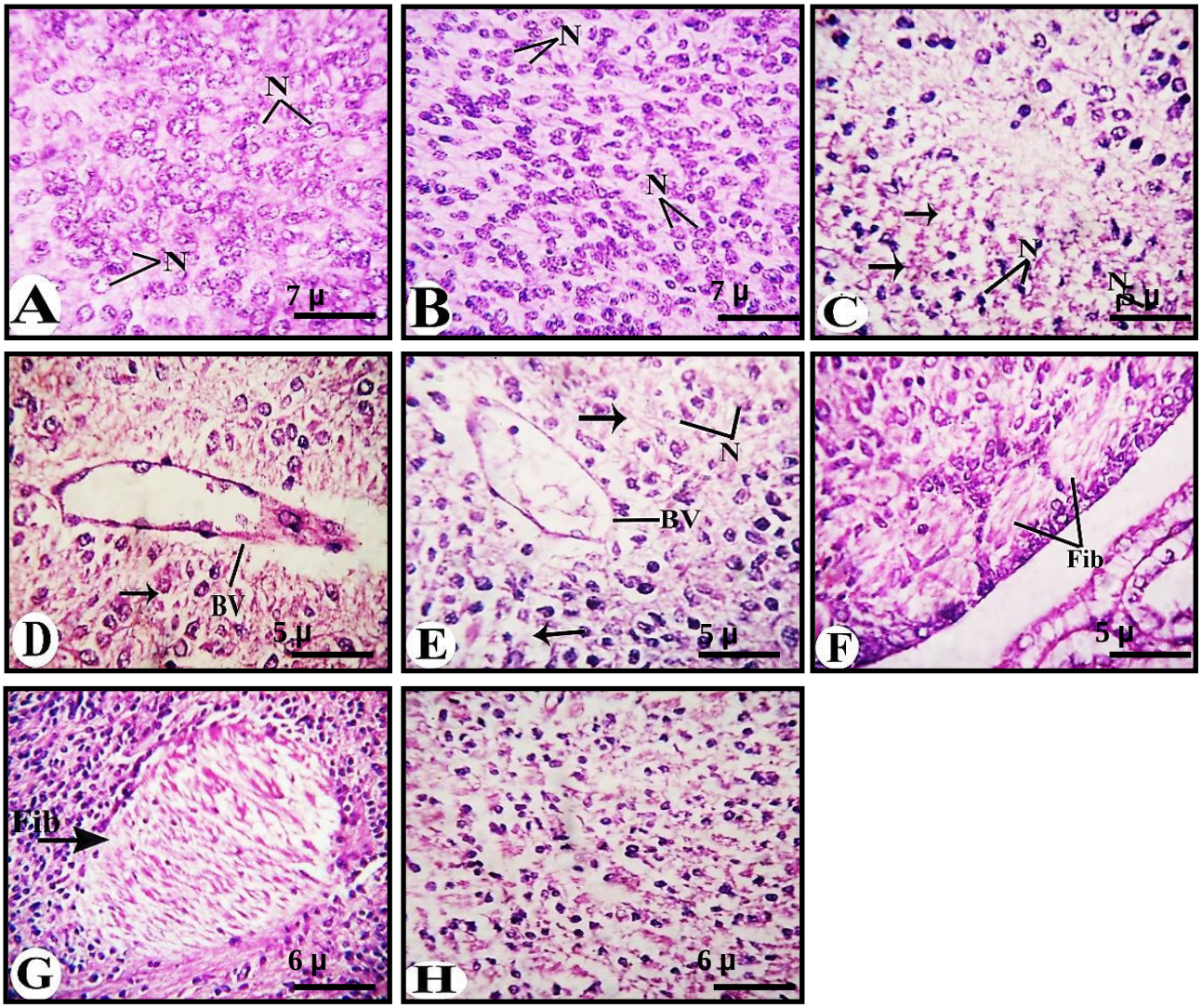

Fig 8: Photomicrographs of a section of brain of a fetus. H&E stain.
From control mother show A) Normal structure of brain tissue, neuron (N) of the cerebral cortex.
From treated group show B-H) Dark neuron (N) and degenerated area (arrow), dilated blood vessel and fibrin deposition (Fib). While F,G) Reveal disorganization of cerebral cortex appearance.

Brain

The brain tissues of fetuses from control pregnant rats showed, showed normal feature under microscopic observation (Fig. 8).

Examination of the brain of fetus maternally treated with 30.8 mg/Kg, revealed several histopathological alterations as pyknotic and degenerated neurons, fibrin deposition (fibrosis), cerebral cortex showed disorganization appearance and dilated and enlarged blood vessels (Fig. 8).

DISCUSSION

Antidepressant medications particularly selective serotonin reuptake inhibitors (SSRI) now rank as the most every now and again endorsed sedates in drug. These medications not just utilized for the treatment of major and minor despondency additionally for the alleviation of queasiness and spewing showed up in pregnant ladies during early pregnancy. Many articles have been distributed concerning the impact of psychotropic medications on the babies and also pregnant moms. The present work expected to concentrate the impact of the therapeutic doses of TrazodoneHCl on the pregnant rats and their descendants [27].

Trazodone hydrochloride is an antidepressant synthetically inconsequential to tricyclic, tetracyclic, or other known antidepressant agents. The mechanism of trazodone's antidepressant activity in man is not completely caught on. In animals, trazodone specifically hinders serotonin take-up by brain synaptosomes and potentiates the behavioral changes instigated by the serotonin antecedent, 5-hydroxytryptophan. Trazodone is not a monoamine oxidase inhibitor and, not at all like amphetamine-sort drugs, does not empower the center nervous system.

Our results did not reveal any signs of maternal toxicity as vaginal bleeding or abortion also no dead cases were observed while the study showed that there was a marked increase in the embryonic toxicity (number of resorption) and decrease in the fetal body weight and length when compared with the control. It can be said that, the previous prevailing phenomenae of teratogenicity may attributed to toxicity of TrazodoneHCl due to accumulation of this drug in certain organs, placental barriers, endometrial layer of uteri as well as placental dysfunction.

In the previous studies by [28] and [29] detailed that, the utilization of Psychotropic medications amid pregnancy may bring about three complications:1-Teratogenicity, 2-pre-birth disorders (neonatal toxicity), and 3-postnatal behavioral squalae behavioral danger. They additionally included, the presentation to certain psychotropic medications in utero may build the hazard for some particular congrntial anomalies, and the intrauterine exposure to the Psychotropic medications amid the second and third trimester can prompt to postnatal inconveniences; for instance, floppy-baby disorder instigated after organization of Benzodiazepines (Tranquilizers) to pregnant dams [27].

Malformation of fetuses considered a major part of the results of the present work. Oral administration of the therapeutic doses of TrazodoneHCl to female rat from 5th day up to 19th days of gestation induced several fetal malformations. These malformations represented by subcutaneous hematoma as well as deformed limbs. These results were similar to those described by [27, 30&31] who worked on antid-epressant drugs as Fluoxetine Hcl, Cipralex and Valdoxan, respectively. In our study skeletal defects of foetuses have been observed. These defects included incomplete ossification of some skull bones, irregular shaperibs and incomplete ossification of ribs.

In the study carried by [27] he reported similar result using antidepressant drugs namely Fluoxetine Hcl. Also, these results confirmed by those of [32 and [33] when described a delay or incomplete ossification of skull and sternum of rat foetuses treated with Thalidomide (Tranquilizer).

The present study suggested that the oral administration of TrazodoneHCl to the pregnant rat induced delaying of the ossification and severs skeletal anomalies which may be due to mesenchymal condensation during embryonic development, or may be due to resorption of cartilage, during embryonic development, which precedes endochondral ossification. These results were also confirmed by [34] they reported that certain Psychotropic drugs inhibitcalcium-calmodulin-system in rat neonates as a systemic action of these Psychotropic drugs (Verapamal, Haloperidol and Penfluridal).

The placenta not only provides a link between the circulation of two distinct individuals (maternal and fetal) but also acts as a barrier to protect the fetus from xenobiotics in the maternal blood [35].

The present results revealed dose-dependent pathological changes in the placenta. This is manifested as severe structural changes in rats of treated group (B), thus, may lead to reduced uteroplacental blood flow which appear to be associated with increased risk of poor outcome (the outcome cannot be predicted but must be empirically determined).

Our study showed that, trophospongium zone was decreased which resulted from degeneration of trophoblasts. Trophoblast giant cells (TGCs) were present that had an increased number of vacuoles. The giant cells act as biological elimination of degenerated trophoblasts and finally cause diminished of trophoblastcells[35].

Our study also illustrated necrotic foci of trophoblasts in the labyrinth. The labyrinth septa had lost their architecture, with fibrin deposition and decreased vessels formation. These changes are might be due to modulation of nutritional and homeostatic conditions in which the embryo depends on in its development and

may influence its viability and growth. Fibrin deposition inhibits maternal perfusion of the placenta, which then causes placental necrosis that is often associated with fetal morbidity and mortality. Placental dysfunction causes the inadequate supply of nutrients and oxygen to support normal growth of the fetus, resulting in fetal blood flow redistribution [36,37] and the mechanisms above affect the physiological development and position of the lower limbs [38].

The results obtained from the present study showed that administration of the therapeutic dose induced various changes in liver of fetuses. These changes varied from fatty changes, haemolysis of the blood in sinusoidal spaces and dilatation of central vein and pyknotic nuclei. In addition, a necrotic mass was identified in the liver tissue. This necrotic lesion may either due to progressive degenerative action of cellular enzymes of the injured cells or to a metabolic disturbance and inhibition of protein synthesis in the hepatic cells.

Vacuolation of the cytoplasm was observed in the degenerated hepatocytes in the treated group. Previous authors revealed that these vacuoles represent hydropic degeneration in the affected liver and other considered the cytoplasmic vacuolization in the animal cells as a result of the breakdown of lipoprotein complexes in the affected cells [39].

The present study tends to adopt the idea that cytoplasmic vacuolization is mainly a consequence of considerable disturbance in fat metabolism occurring under such pathological conditions. This speculation is based on the observation that such vacuoles are usually well defined and corresponded-- to a large extent-- to the areas previously occupied by lipid droplets before the pathological impact. In addition, the damage observed in the liver cells of treated group could be related to the disturbance of enzymatic activities since some vacuoles were observed containing inclusions probably remnants of digestive materials. This observation coincided with the finding of some authors that in cellular injury release of lysosomal enzymes is due to damage of the lysosomal membranes, thus the lysosomal hydrolases were setting free leading to cell death in one way or another [39].

In the present study, the kidney of 20-days-old fetuses maternally treated with TrazodoneHcl showed several histopathological changes. The cortical region showed swelling of the glomerular tufts and reduction of the urinary space. Dramatical changes were noticed in group B, including hypertrophied and congested glomerular tufts, degeneration and vacuolation of the cytoplasm of the cells lining the convoluted tubules. Moreover, the nuclei of some deteriorated cells showed clear signs of pyknosis.

In this experiment, the histopathological changes in the fetal brain of the treated groups were evident in the early stages of development. As already noted, many nerve cell nuclei were pyknosed, presence of many intensely stained “dark” neurons and tissue disorganization with signs of degeneration.

It was evident that the use of antidepressants (TrazodoneHcl) in rat females during the “critical period” of gestation caused fetal growth retardation and histopathological alternations in main fetal tissues. Therefore, more scientific and clinical knowledge, as well specificity and administration of antidepressants in the first trimester of gestation are needed to reduce macro- and microscopic alteration in fetuses.

CONCLUSION

Trazodone Hcl is considered not being safe to the embryos and it should be used during pregnancy only under careful consideration of the risk benefit.

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