Evaluation of the Teratogenic Effects of the Antidepressant Drug Sertraline on Fetuses of Albino Rats

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ABSTRACT--- ***Teratogenesis refers to the production of defects in the fetus. A teratogenic agent is responsible for producing such a defect. The term teratogen usually is cited in the context of causing anatomical defects in an embryo that was previously differentiating normally.***
Sertraline is an often used antidepressant drug; however insufficient information is available regarding its safety during pregnancy. Therefore, this work was initiated to study the effect of prenatal exposure of mirtazapine (Sertraline) on fetuses of rats. The study was conducted on pregnant rats to observe the safety profile of sertraline 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. Results showed significant reduction in placental weight of pregnant rats treated with sertraline. Treated group showed incidence of pregnancy loss and abortion. Fetal growth retardation during gestational period was recorded also some skeletal anomalies were observed, these abnormalities included weak ossification of the skull bones roof and bones forming girdles and limbs. Histopathological studies of fetuses during gestation revealed changes in liver histology such as presence ofclumping of the hepatocytes with hyperchromatic nuclei and an increase in the number of megakaryocytes, kidney tissue revealed numbers of mitotic activity in the nuclei of the tubular lining epithelium and coagulative necrosis in the lining tubular epithelium of the proximal convoluted tubules at the cortex. The cerebrum showed ill developed wall of the blood vessels also the matrix of striatum in cerebrum showed vacuolization and neuronal cells in the substantia nigrashowed degeneration with loss of the cytoplasmic granules. Our findings suggest the need for great caution to handle sertraline especially during pregnancy.

Keywords--- Sertraline, Teratogenicity, Gestation.

1. INTRODUCTION

Teratology the study of abnormal prenatal development and congenital malformations induced by exogenous chemical or physical agents.A birth defect or a congenital malformation is a structural abnormality of any type present at birth. It may be macroscopic or microscopic, on the surface or within the body (Moore, 1988). Major structural anomalies occur in 2-3% of live born infants, and an additional 2-3% is recognized in children by age 5 years making a total of 5-6% (Sadler, 2000). The most vulnerable period for malformation to take place is the period of organogenesis. Agents given duringthis period are more likely to cause birth defects. This critical time of fetal development in rats and mice is from 6-12 days of their gestation (Somer, 1962; Farris, 1967).
The transplacental transfer of drugs from the maternal to the fetal blood and tissues, leading to potential effects on the fetus, is a major concern. Thus, both mother and fetus must be included in the risk/benefit assessment to ensure a rational decision, weighing the therapeutic benefits of the treatment to the mother against its potential harm to the fetus (Marcela and Mar´ıa, 2010).
Recent studies suggest that the adverse fetal effects are associated with antidepressant drug exposure during pregnancy (Jasmita*et al.,* 2010). However, further studies are necessary to measure the consequences of newer antidepressants fetal exposure such as sertraline.

Women are at an increased risk of becoming depressed during pregnancy, especially when they have pre-existing psychiatric illnesses. During pregnancy, ~20% of women report symptoms of depression (Patkar*et al.*,2004), and 4–7% of pregnant women suffer from major depressive disorder (Anderssone*t al.*,2003; Gorman *et al.*,2004; Melville *et al.*,2010). Biological and psychosocial factors, such as the genetic setup of the mother, hormonal/reproductive history,

current stressors, and life experiences, are known to be risk factors for development of antenatal depression (Miller and LaRusso, 2011). Antenatal depression has been associated with higher rates of poor pregnancy outcomes (such as pre-eclampsia and premature delivery), impaired fetoplacental function, decreased fetal growth, and neonatal complications (Orr and Miller, 1995; Kurki*et al.*,2000; Bonari*et al.*,2004; Jablensky*et al.*,2005; Wisner *et al.*,2009; El Marroun*et al.*,2012; Olivier *et al.*, 2013).

Continuing or starting pharmacological therapy during pregnancy is often unavoidable. Cohen *et al.* (2006) showed that 68% of depressed women who discontinued treatment relapsed during pregnancy, while only 26% of those who continued treatment did so. Twenty-five percent of women on antidepressants continue treatment during pregnancy and 0.5% of pregnant women who have not been treated with antidepressants previously begin treatment (Verver*et al.*, 2006). As antidepressant medications cross the placenta and are evident in breast milk, questions have been raised about their developmental safety (Heikkinen*et al.*, 2003; Noorlander*et al.*, 2008). However, exposure to antenatal depression similarly increases the risk of child psychopathology (affective, anxiety, and disruptive behavior disorder; Weissman*et al.*, 2006). Therefore, the question arises as to whether children exposed to maternal antidepressants are at risk and, if so, whether the risks are due to medication or to the underlying depression.

There is little information available on the safety of sertraline usage during pregnancy.

2. MATERIALS AND METHODS

Experimental animals

The present experimental study is carried out on the albino rat (*Rattusnorvegicus*). The standard guidelines of the Institutional Animal Care and Use Committee (IACUC) were used in handling animals.
Females of 11-13 weeks old were selected for the present study and vaginal smears were prepared every morning and examined under light microscope (according to the method of **Snell (1956)**) for 5 days to select the female with regular estrus. Two females with regular estrus cycle were selected in the pro-estrus stage and caged together with one male overnight under controlled environmental conditions of temperature, humidity and light. The first day of gestation was determined by the presence of sperms in the vaginal smear **(McClain & Becker, 1975)**.

Experimental design

Serpass (sertraline) Drug was manufactured by GLOBAL NAPI PHARMACEUTICALS (GNP) – Egypt.
The Route of administration was Oral. The time of administration was scheduled from the 5^{th} day of gestation, daily until the end of gestation.

Experimental groups

Group A: Control group received distilled water from 5^{th} day of gestation to 19^{th} day of gestation.

Group B: Treated group received 20.5 mg/kg of Sertraline from the 5^{th} day of gestation, daily until the end of gestation.

Developmental observations

On the 20^{th} day of gestation, all pregnant rats of groups A and B were sacrificed and total implantation sites, fetal mortality rate (resorped or still birth) and living fetuses were recorded. Fetal body weight, body length, tail length and external malformation were also recorded.

Skeletal examination

Fetuses were preserved in 95% ethyl alcohol and were stained with double staining of fetal skeletons for cartilage (blue) and bone (red) according to the method described by **Deinz*et al.*, (1995)**.

Histological examination

Autopsy samples were taken from liver, kidney and brain of fetuses in different groups at the 20th day of gestation. They were fixed in 10% formal saline for twenty four hours. Washing was done in tap water then serial dilutions of alcohol (methyl, ethyl and absolute ethyl) were used for dehydration. Specimens were cleared in xylene and embedded in paraffin at 56 degree in hot air oven for twenty four hours. Paraffin bees wax tissue blocks were prepared for sectioning at 4 microns thickness by sledge microtome. The obtained tissue sections were collected on glass slides, deparaffinized, stained by hematoxylin & eosin stain for routine examination then examination was done through the light electric microscope **(Bancroft *et al.*, 2002).**

3. RESULTS

A. Morphological studies

The average weight of placenta of all treated pregnant rats groups was decreased as compared to control (Table 1& Fig. 1). There was significant ($P \leq 0.05$) reduction in placenta weight of animals that received Sertraline.

Fig. 1: Histogram showing effect of Sertraline on placenta weight (P.W) at 20th day of gestation.

Values are expressed as Mean. The statistical differences were analyzed by Duncan's test. a= $P \leq 0.05$ compared with control.

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 20.5 mg/Kg showed normal shape and sometimes with asymmetrical distribution of fetuses in the two uteri, completely resorbed uterus also revealed (Fig. 3).

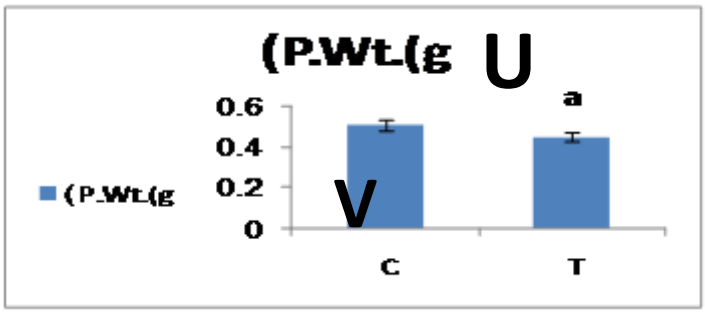

Fig. 2: A photograph of uterus of control pregnant rat at the 20th day of gestation.

Showing normal symmetrical distribution of fetuses in the two uteri horns. U= Uterus, V= Vagina.

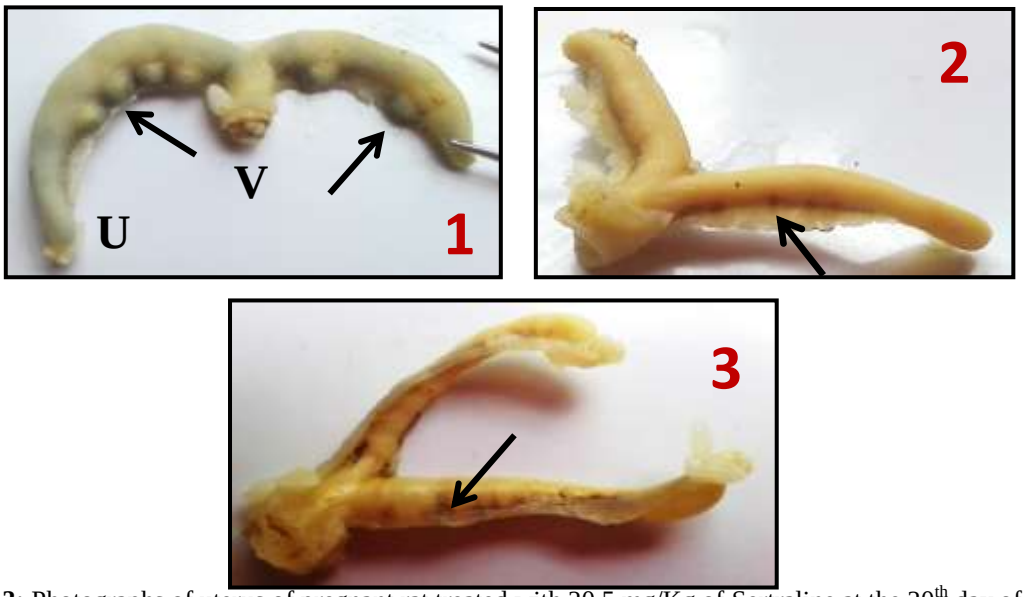

Fig. 3: Photographs of uterus of pregnant rat treated with 20.5 mg/Kg of Sertraline at the 20th day of gestation.

Table 1: Showing effect of Sertraline on fetus weight, fetus length, tail length and placenta weight at 20th day of gestation.

Group	Fetus weight (F.WT)	Fetus length (F.L)	Tail length (T.L)	Placenta weight (P.WT)
Control (A)	4.875± 0.11	6± 0.06	1.6833± 0.05	0.5083± 0.008
20.5 mg/Kg (B)	2.4667± 0.07	4.8167± 0.03	1.0333± 0.02	0.45± 0.015

The morphological examination of the fetuses showed that the Sertraline caused growth retardation represented by a decrease in fetal body weight and body length (Table 1 & Fig. 4). There was a significant (P≤ 0.05) reduction in fetus weight and fetus length in treated group when compared with the control group (A).

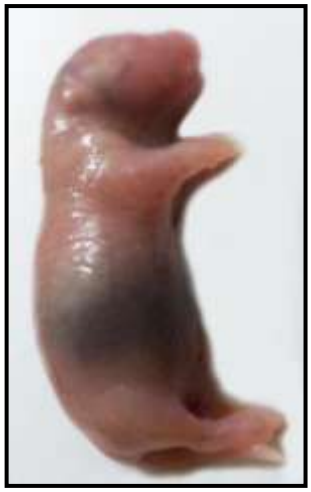

Fig. 4: Histogram showing effect of Sertraline on fetus weight (F.W) and fetus length (F.L) at 20th day of gestation.

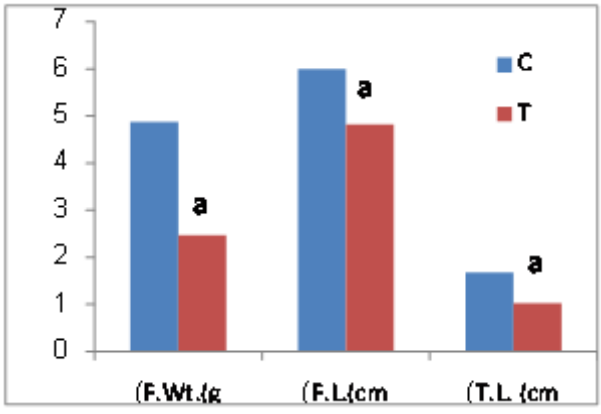

Fig. 5: A Photograph of fetus of control mother at 20th day of gestation.Fetus exhibited normal morphology and normal length.

Values are expressed as Mean. The statistical differences were analyzed by Duncan's test. a= P ≤ 0.05 compared with control.

Values are expressed as Mean. The statistical differences were analyzed by Duncan's test. a= P ≤ 0.05 compared with control.

The fetus from control animals appeared with normal shape, correct weight and length (Fig. 5), also appeared straight dorsally. The malformations are not recorded in fetuses from treated group except (Fig. 6).

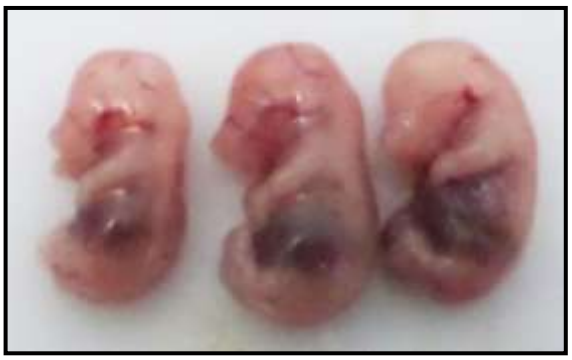

Fig. 6: Photographs of fetuses of maternally treated with 20.5 mg/Kg of Sertraline at 20th day of gestation. Showing fetal growth retardation.

Fetal mortality:
Total mortality rate included resorbed fetuses and stillbirth (dead fetuses at birth) and was recorded for both control and treated groups in table 2.

Table 2: Effect of Sertraline on fetal mortality at the 20th day of gestation.

Groups	Total no. of pregnant rats	No. of implantation sites	No. of live fetuses		No. of resorbed fetuses		No. of dead fetuses	
Control (A)	6	54		100%	0	0 %	0	0 %
Treated Groups (5th-20th) mg/Kg (B)	4	24	6	25 %	18	75 %	0	0 %

Values are expressed as Mean ± SEM. The statistical differences were analyzed by independent samples T test. a= P ≤ 0.05 compared with control.

Skeletal anomalies
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. 7). On the other hand, fetuses maternally treated with 20.5 mg/Kg of Sertraline showed lack of ossificationof the skull roof (frontal and parietal), delay ossification of the fore and hind limbs, pectoral and pelvic girdles, vertebrae and ribs (Fig. 8).

Fig. 7: A Photomicrograph of a skeleton of a fetus from control mother. H&E stain. Showingcomplete ossification in all parts of the axial and appendicular skeleton.

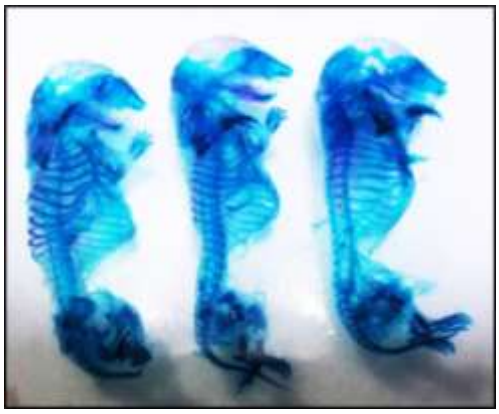

Fig. 8: A Photomicrograph of a skeleton of a fetus from treated mother. H&E stain. Showing Incomplete ossification of the all parts comprise the skeletal system.

Histological studies of fetuses

Liver

Light microscopic examination of sections of the fetal livers of control group using H&E stain showed ill-defined demarcation of hepatic lobules and the interlobular connective tissue was poorly developed. In each hepatic lobule, hepatocytes were arranged as irregular, branching and interconnected cords originating from a central vein and goes peripherally. Blood sinusoids were seen between the hepatic cords. The cytoplasm was abundant, granular and stained acidophilic. The nucleus was euchromatic, located centrally, rounded, and contained one or more nucleoli (Fig. 9).

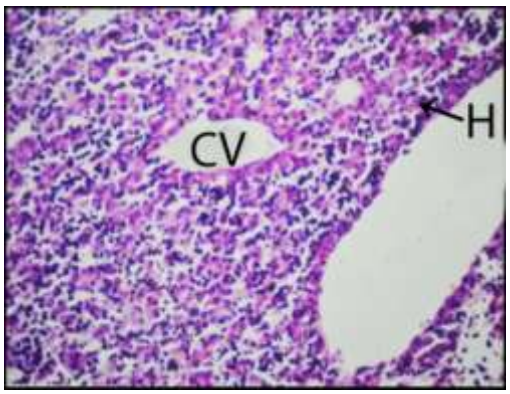

Fig. 9: A Photomicrograph of a section of liver of a fetus from control mother. H&E stain. Showing normal architecture of the liver tissue, the hepatic lobules that can be only distinguished by their central veins (CV) and hepatocytes (H) and numerous erythroblasts (arrow).100X

In liver tissuemultiple numbers of multinucleated megakaroblasts were detected in the hepatic parenchyma in the groups receiving Sertraline during the pregnancy (Fig. 10).

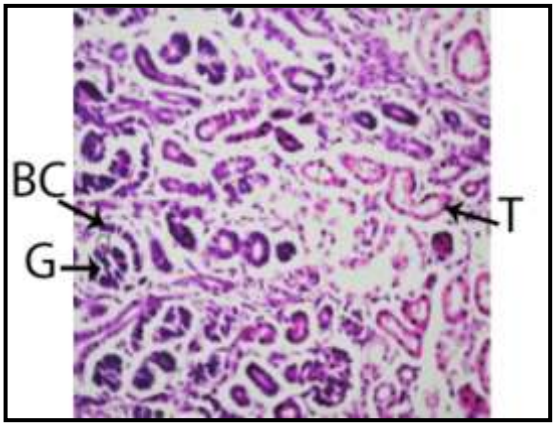

Fig. 10: A Photomicrograph of a section of liver of a fetus from treated mother. H&E stain. Megakaryoblasts (M) were detected in between the degenerated hepatocytes (H) in diffuse manner all over the parenchyma and numerous shapes of erythroblast (Er) were present. 400X

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 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. 11).

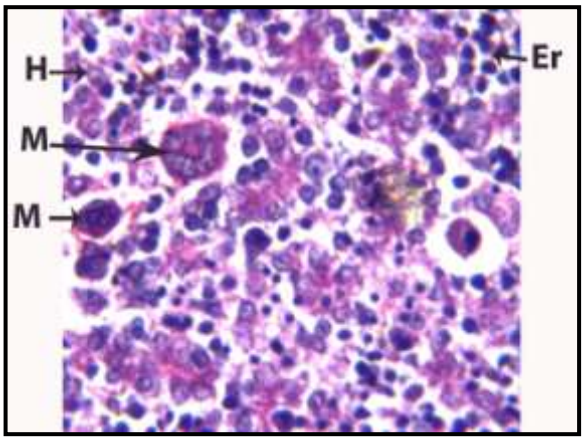

Fig. 11: Photomicrograph of a section of kidney of a fetus from control mother. H&E stain. Showing a part of the cortical region containing, a glomeruli (G) within Bowman's capsule (BC) tubules (T).100X

Examination of the kidney of fetus maternally treated with ---mg/Kg showed numbers of mitotic activity in the nuclei of the tubular lining epithelium as well as the nuclei of the endothelial cells lining the glomerular tuftsin Fig. 12.

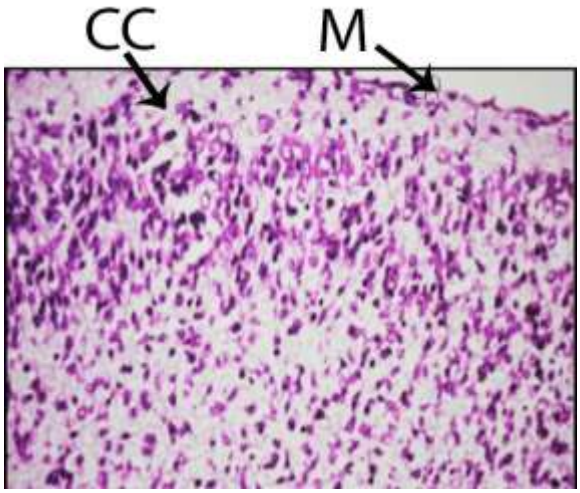

Fig. 12: A Photomicrograph of a section of kidney of a fetus from treated mother. H&E stain. There was degeneration in the tubular lining epithelium (T) with swelling in the endothelial cells lining the tufts of the glomeruli (G) within the Bowman's capsule (BC). 400X

Brain

The brain tissues of fetuses from control pregnant rats showed, showed normal features under microscopic observation (Fig. 13).

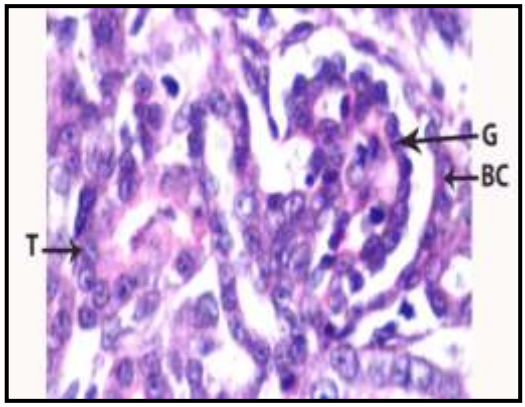

Fig. 13: A Photomicrograph of a section of brain of a fetus from control mother. H&E stain. Showing normal structure of brain tissue, CC= cerebral cortex.400X

Examination of the brain of fetus maternally treated with 20.5 mg/Kg, the cerebrum showed ill developed wall of the blood vesselsas recorded in Fig. 14.

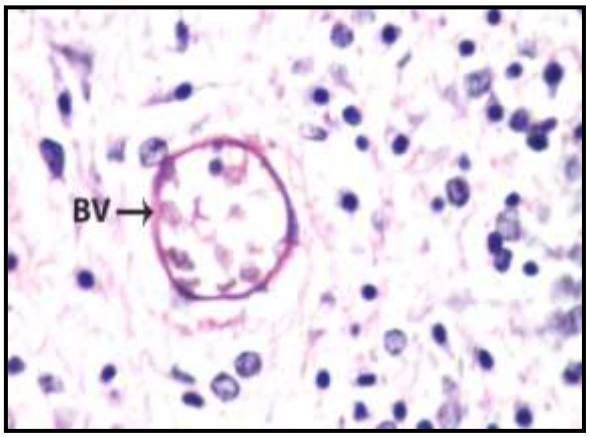

Fig. 14: A Photomicrograph of a section of brain of a fetus from treated mother. H&E stain. The cerebrum showed ill developed wall of the blood vessels (BV). 400X

4. DISCUSSION

The present study is carried out to evaluate the teratogenic potential of Sertraline on the fetuses maternally treated with 20.5 mg/Kg of the used drug during the gestation. However, many of the cardiovascular drugs that are prescribed for a pregnant woman have the potential to cross the placenta and exert a pharmacologic or even teratogenic effect upon the fetus.

Teratology, the study of abnormal prenatal development and congenital malformations induced by exogenous chemical or physical agents, is a growing area of medical research in the quest for the eradication of preventable birth defects. Birth defects are known to occur in huge numbers; roughly 7∼10% of all children require extensive medical care to diagnose or treat a birth defect; this compromises the quality of life of millions of people worldwide **(O'Rahilly, 2001).** Almost all therapeutic agents cross placental barrier and enter fetal circulation. Every agent given during pregnancy therefore has a tendency to produce some sort of structural abnormality in the neonate at birth until proved otherwise **(Schlegel *et al.*, 1991)**. A birth defect or a congenital malformation is a structural abnormality of any type present at birth. It may be macroscopic or microscopic, on the surface or within the body **(Moore, 1988).** During the past few decades, it has become increasingly evident that human and animal embryos are subjected to the toxic effects of many drugs, such as the use of some antibiotics in the treatment of serious diseases occurring during pregnancy.

Pregnancy should be carefully evaluated given that it is a period during which women go through many physical, hormonal and psychic changes which, in turn, influence their mental health **(Camacho*et al.*, 2006).** Lately, it has been recognized that gestation can be complicated by emotional problems such as depression, thus heavily impacting both mother and fetus **(Zinga*et al.*, 2005).** The use of medication during pregnancy requires special attention due to the potential risks to the developing fetus. Pregnant women often need psychiatric treatment in face of emotional disorders caused by stress, anxiety and depression. Antidepressants are capable of crossing the placental barrier, and their use has been evaluated with respect to their biosecurity. Recent researches report the use of tricyclic antidepressants and serotonin reuptake inhibitors in pregnant women. Some authors have proposed new studies to assess the risk-benefit ratio of the use of antidepressants during gestation **(Bellantuono*et al.*, 2006 andLisboa*et al.*, 2007).**

In the present study, oral treatment of pregnant rats with Sertraline during the gestation led to a significant reduction in the weight, length and tail length of fetuses. The observed fetal growth retardation may be arising from the direct action of the used drug on embryos and fetal tissues.

The current work revealed that Sertraline treatment induced complete fetal resorption when rats were given 20.5 mg/kg/day at gestational days during organogenesis period.

The present work showed no cases of external malformations and revealed skeletal abnormalities as un-ossified skull bones and Weakossification of phalanges.

The results obtained from the present study showed that administration of the therapeutic doses in organogenesis period induced various changes in liver and kidney of fetuses maternally treated with 20.5 mg/kg of Sertraline from 5th day to 20th day of gestation. Liver showed degeneration of the cytoplasm of hepatocytes and increases in the number of megakaryocytes. The fetal liver assumes the primary role of blood cell development at mid- and late-gestation. The histopathological changes in liver that were observed with alcohol treatment may affect haematopoietic cell trafficking from the liver to other sites. Kidney revealed degeneration in the tubular lining epithelium with swelling in the endothelial cells lining the tufts of the glomeruli within the Bowman's capsule.

5. CONCLUSION

It was evident that the use of antidepressants (Sertraline) in rat females during the “critical period” of gestation caused fetal growth retardation and histopathological alternations in main fetal tissues.

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