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# Research Article
# Histological and Histochemical Alternations in the Fetal Heart Tissue of Maternal Prozac Exposure

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## Abstract

**Background and Objective:** Depression during gestation destructively affects fetal development. Fluoxetine (Prozac) as a selective serotonin reuptake inhibitor (SSRIs) is used for handling of maternal despair. Anti-depressants cross the placenta and are transported to the fetus. This study aimed to determine the effects of fluoxetine on histopathological and histochemical changes in fetal heart tissue maternally treated with Fluoxetine. **Materials and Methods:** Forty pregnant rats were categorized into the following groups: Control group, group of 10 pregnant rats treated daily with 0.72 mg $kg^{-1}$ b.wt. Fluoxetine (treatment started one month before pregnancy and continued till end of gestation), group of 10 pregnant rats treated daily with 1.44 mg $kg^{-1}$ b.wt. Fluoxetine (treatment started from day zero till day 20 of pregnancy), group of 10 pregnant rats treated daily with 2.88 mg $kg^{-1}$ b.wt. Fluoxetine (treatment started from day zero till day 20 of pregnancy). Pregnant mothers were sacrificed on day 19 of gestation and small samples of fetal heart were taken for the histological and histochemical studies. **Results:** Many histological and histochemical alternations were observed in fetal heart of all the treated groups compared with control group. The harshness of these changes increased with increasing the doses of Fluoxetine. **Conclusion:** Maternal fluoxetine exposure caused harmful changes in the fetal heart, therefore the use of this drug during gestation should be under strict precautions and further studies are recommended that it is essential to survey the roles of anti-depressant drugs on fatal development during pregnancy.

Key words: Prozac (fluoxetine), selective serotonin reuptake inhibitor, pregnant rats, fetal heart tissue, antidepressant drugs

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Data Availability: All relevant data are within the paper and its supporting information files.

## INTRODUCTION

The gestational period is a physiologic marvel. It is described by many changes as, physical, hormonal, mental and social changes that can specifically impact a females' mental health. The rise of gravidity hormones level, estrogen and progesterone, can bring about mental issue, which can be less or more viable trusting upon the affectability of every female[1].

During gestation there is a high exposure to medicines. The exposure to medicines during pregnancy have a potential hazard of teratogenic effects[2,3]. Pregnant women often need psychiatric handling in face of emotional illnesses caused by pressure and anxiety[4]. The emotional state during gestation is an important reason in medicine. Pregnancy increases the vulnerability for depression onset or return[5]. Mood disorders are public with prevalence rates for depression reported to be 7.4% in the first trimester, 12.8% in the second trimester and 12.0% in the third trimester[6].

Depression during antenatal period are associated with major effects outcomes for mother, developing fetus and the neonate[7,8].

Selective Serotonin Reuptake Inhibitors (SSRIs) have been studied for antepartum despair based on the severity of state[9]. The SSRI therapy has been aimed to have a relation with neurobehavioral disturbances, preterm birth, lower birth weight, neurotoxic effects and behavior teratogenic effects, cardiac defects, pulmonary hypertension, movement disorders and seizure[10]. Recent studies reported the use of fluoxetine, tricyclic anti-depressants and serotonin reuptake inhibitors in pregnant women[11,12].

Prozac during organogenesis, drug can be considered as a teratogenic influence, thereby causing congenital defects and serious injuries that may lead to abortion[13].

Fluoxetine fits to the pharmacological group of the serotonin reuptake selective inhibitors. Because it does not fix to histamine, acetylcholine and epinephrine receptors, it has less analgesic, anti-cholinergic and cardiovascular properties than the tricyclic anti-depressants[14]. Increase in serotonin levels, thus leading to a passing reduction in uterine blood stream. This drops the oxygen and nutrient supply to the fetus, reduces its growth and leads it to premature birth. Also, it affects the fetus neural development[12]. Fluoxetine was carefully chosen for being the anti-depressant of choice for pregnant women and most studies have focused on fluoxetine because of its high selectivity and negligible affinity for numerous receptor subtypes.

The administration of Fluoxetine to pregnant rats led to variable histopathological alternations on different fetal organs such as lung, heart and kidney[15]. Many histological and histochemical changes were detected in fetal skin maternal exposure to Prozac[2].

Histopathological studies of fetuses during gestational period discovered degeneration of hepatocytes, vacuolization and necrotic areas within the cytoplasm. Swelling of glomeruli and degeneration of cells lining renal tubules were detected in the fetal kidney and degenerative changes were observed in the brain following trazodone administration from anti-depressant of the serotonin antagonist reuptake inhibitor[1].

Some studies have demonstrated that maternal exposure to fluoxetine in early pregnancy was associated with cardiac malformation and congenital heart defects[16], while some studies have shown that there is no linkage between SSRIs and congenital heart defects[17]. Studies have also shown that fluoxetine can lead to ventricular septal defects[18] and atrial septal defects[19].

Placental transfer of antidepressant medications to the fetus and this cause damage the organs of fetuses and the heart tissue of fetuses more sensitive to drugs, so the present study was aimed to evaluate the possible histopathological and histochemical alternations in the heart of fetuses maternally exposed to fluoxetine with three different doses (0.72 and 1.44 and 2.88 mg $kg^{-1}$ b.wt.).

## MATERIALS AND METHODS

**Experimental animals:** A total of 40 female *Albino rattus norvegicus* and 20 male, weight 200-280 g b.wt., were selected. Rats fed on standard diet and some vegetables. Before the research, all rats were waited for 2 weeks in metal cages under standard laboratory environments of light (12 h light /dark cycle), temperature 25±5 in July and August, 2016 and approval for this study was obtained from the ethics committee of Al-Azhar University, Faculty of Science, Egypt.

**Induction of pregnancy:** Estrous cycle was firm according to Taylor[20]. Vaginal smears were collected daily for estrous cycle purpose and then the estrous rats were placed with healthy male in the ratio of 2:1 for coupling. In the following morning, mating was confirmed by presence of sperms in the vaginal slight or presence of the vaginal mass that was considered as day zero of gestation[21]. The pregnant rats were categorized and separated, after one week of coupling, non-pregnant rats were barred.

**Experimental groups:** Forty pregnant rats were used and categorized into four groups after mating, each group was contained 10 rats: group 1 (Control group C), group 2 (pregnant rats were treated daily with 0.72 mg $kg^{-1}$ b.wt., Prozac (T1) treatment started one month before pregnancy and continued till day 19 of gestation, group 3: Pregnant rats were treated daily of gestation with 1.44 mg $kg^{-1}$ b.wt., Prozac (T2), group 4: Pregnant rats were treated daily of gestation with 2.88 mg $kg^{-1}$ b.wt., Prozac (T3). Prozac doses were determined after alteration from human doses according to Paget and Barnes[22].

**Histological and histochemical study:** Pregnant rats from all the treated and control groups were sacrificed on day 19 of pregnancy and small samples of heart were taken for the histological and histochemical studies. These pieces were fixed in 10% neutral buffered for mol solution and Carnoy's fluid for the histological and histochemical studies. Paraffin sections were prepared 5 µm thicknesses and marked with Harris haematoxylin and eosin[23]. Mallory's trichrome stain[24] for staining collagen fibers. Polysaccharides were detected by PAS (periodic acid Schiff) method[25]. Total proteins were spotted by mercuric bromophenol blue technique[26]. The DNA content were perceived by Feulgen method[24].

**Image analysis:** The optical transparency (pexil) of the PAS positive materials, total protein and DNA content were recorded. The analysis of differences between groups were performed with a t test and data measured as statically significant at p-value<0.05.

## RESULTS

Examination of control fetal cardiac tissue stained with H and E showed normal myocytes of heart tissue (Fig. 1a). Cardiac tissue of a fetus of group T1 showed Congested Blood Vessels (CBV) with numerous hemorrhagic areas (h) and numerous faintly stained nuclei (karyolysis, K) as shown in

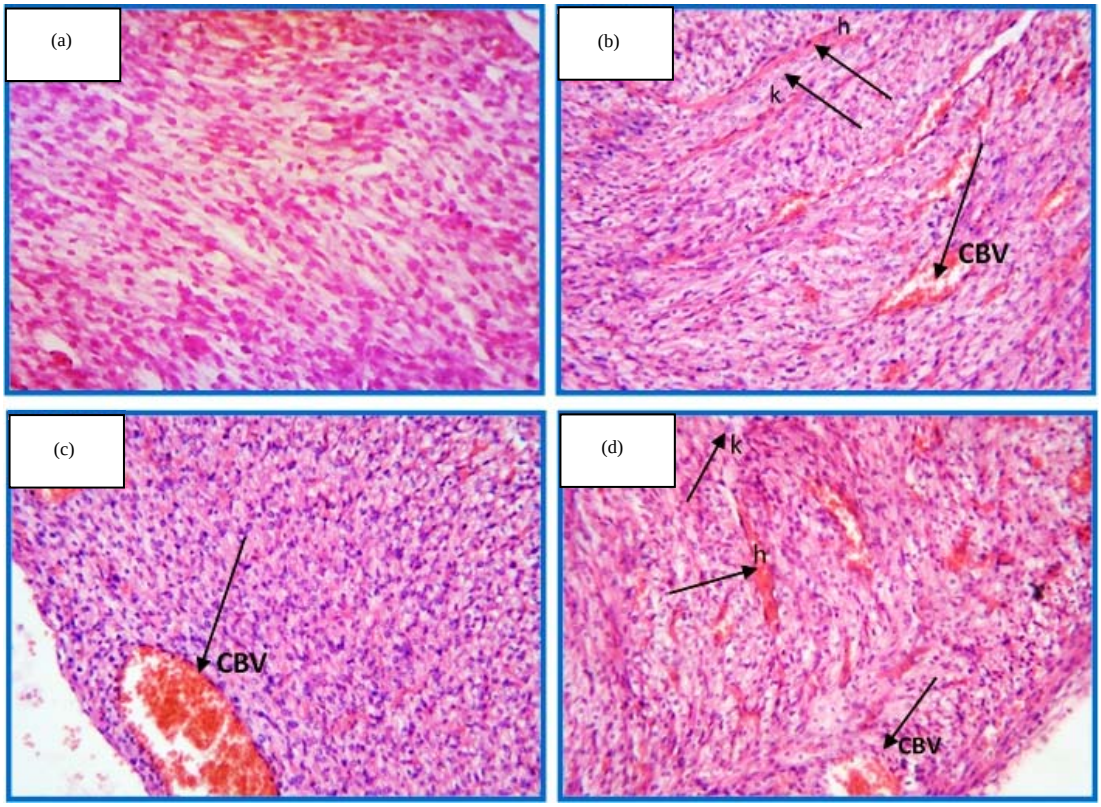


Fig. 1(a-d): Photomicrographs of H and E stained fetal cardiac sections of the (a) Control, (b) T1 group showed Congested Blood Vessels (CBV) with numerous hemorrhagic areas (h) and numerous faintly stained nuclei (karyolysis, K), (c) T2 group showed highly Congested Blood Vessels (CBV) with scattered small pools of blood cells and deeply stained nuclei of myocytes and (d) T3 group showed congested blood vessels, numerous hemorrhagic areas (h) and karyolysis in numerous nuclei of myocytes (k), (X = 200)

Fig. 1b. Cardiac tissue of a fetus of group T2 showed highly Congested Blood Vessels (CBV) with scattered small pools of blood cells and deeply stained nuclei of myocytes (Fig. 1c). Cardiac tissue of a fetus of group $T_3$ showed congested blood vessels, numerous hemorrhagic areas (h) and karyolysis in numerous nuclei of myocytes (k) (Fig. 1d).

Mallory's trichrome stained sections showed thin collagen fibers in between and around the cardiac muscle fibers in control group (Fig. 2a). Highly increased collagen fibers (↑) were noted in between and around the cardiac muscle fibers with numerous brightly red stained hemorrhagic areas (h) in between the muscle fibers in group T1 (Fig. 2b). Mallory's trichrome stained sections in group T2 showed increased collagen fibers with lots of brightly red stained hemorrhagic areas (h) in between the muscle fibers and Congested Blood Vessels (CBV) (Fig. 2c). Highly increased collagen fibers, numerous brightly stained hemorrhagic areas and congested and dilated blood vessels (h) were noted in group T3 (Fig. 2d).

Data in Table 1 and Fig. 3a-d illustrated dense staining affinity of PAS positive materials was detected in fetal cardiac tissue of the control group (Fig. 3a), while Fig. 3b showed highly increased PAS +ve materials (↑) but Some degenerated muscle fibers showed pale staining affinity in the cardiac tissue of group T1 (MOT = 128.29). Group T2 showed reduced staining affinity of PAS +ve materials (↑) (MOT = 123. 36) (Fig. 3c). Decreased staining affinity of PAS +ve materials was observed in the fetal cardiac tissue with exception of some deeply stained Blood Cells (bc) in group T3 (MOT = 116.36) (Fig. 3d).

Table 2 and Fig. 4a-d illustrated fetal cardiac tissue of control group showed moderately stained total protein in the myocytes (MOT = 77.43) (Fig. 4a), decreased total protein in the myocytes with a slight increase in the hemorrhagic areas and the congested and dilated blood vessels were realized in cardiac tissue of $T_1$ group (MOT = 61.7) (Fig. 4b). Decreased total protein was demonstrated in $T_2$ especially in the degenerated muscle fibers but congested and dilated blood

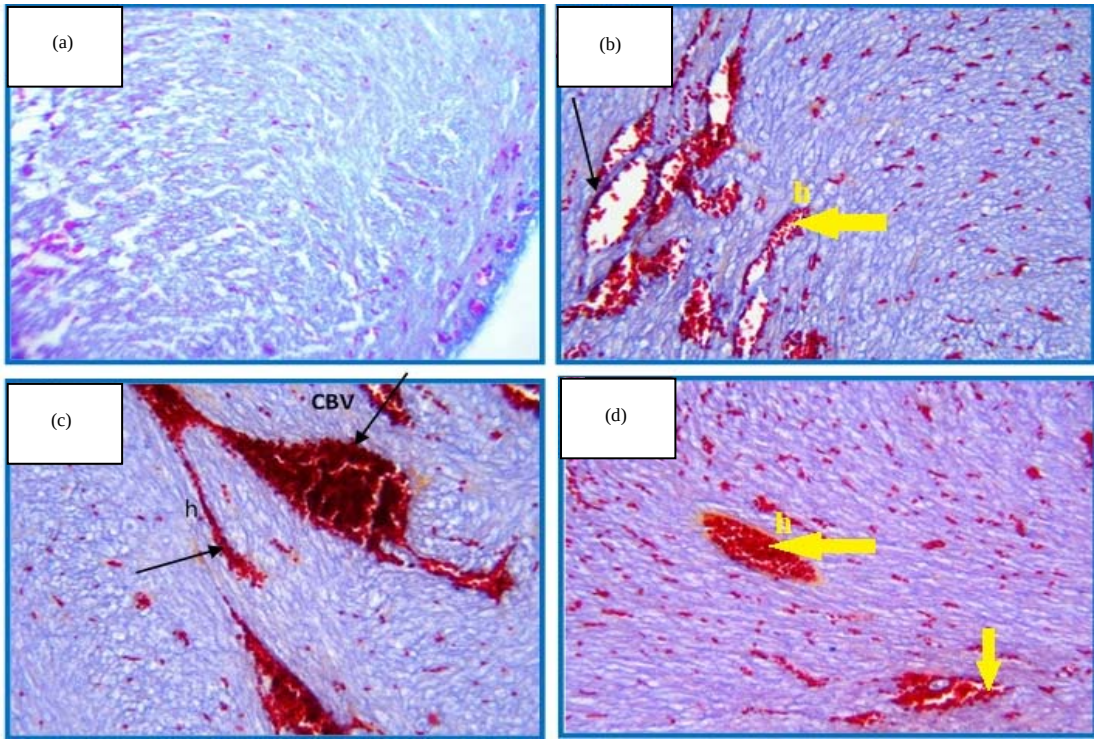


Fig. 2(a-d): Photomicrographs of Mallory's trichrome stained fetal cardiac sections of the (a) Control group showed thin collagen fibers in between and around the cardiac muscle fibers, (b) T1 group showed highly increased collagen fibers (↑) were noted in between and around the cardiac muscle fibers with numerous brightly red stained hemorrhagic areas (h) in between the muscle fibers, (c) T2 group showed increased collagen fibers with lots of brightly red stained hemorrhagic areas (h) in between the muscle fibers and Congested Blood Vessels (CBV) and (d) T3 group showed highly increased collagen fibers, numerous brightly stained hemorrhagic areas and congested and dilated blood vessels (h), (X = 200)

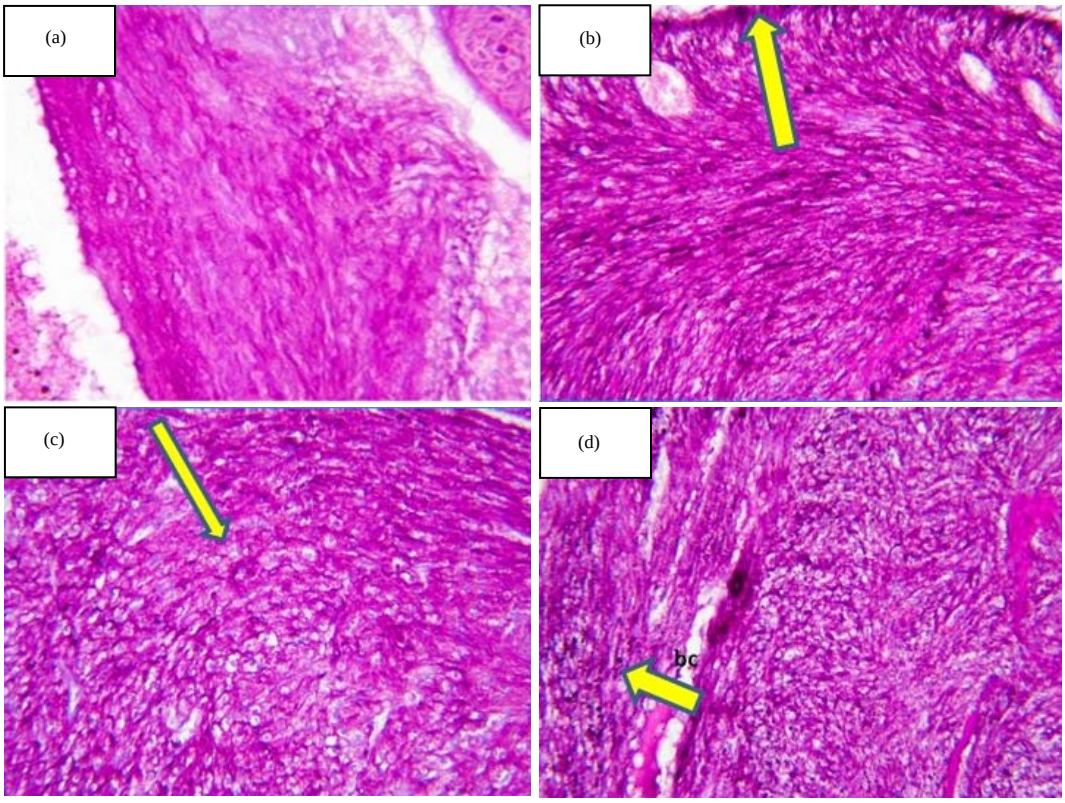


Fig. 3(a-d): Photomicrographs of PAS +ve materials stained fetal cardiac sections of the (a) Control, (b) T1 group showed highly increased PAS +ve materials (↑) but Some degenerated muscle fibers showed pale staining affinity, (c) T2 group showed reduced staining affinity of PAS +ve materials (↑) and (d) T3 group showed decreased staining affinity of PAS +ve materials with exception of some deeply stained Blood Cells (bc), (X = 200)

Table 1: MOT values of PAS positive materials in heart of the control and treated groups

| Parameters | Control | T1 group | T2 group | T3 group |
|---|---|---|---|---|
| Mean | 96.766671 | 128.299998 | 123.366665 | 116.366666 |
| S.D. | 19.27556918 | 28.06273924 | 23.9762645 | 28.17921171 |
| Percentage | | 32.58697098 | 27.48879725 | 20.25490264 |
| t-test | | 0.006594135** | 0.012920576** | 0.077806671 |

*Significant at p<0.05, **Highly significant at p<0.01

Table 2: MOT values of total protein in heart of the control and treated groups

| Parameters | Control | T1 group | T2 group | T3 group |
|---|---|---|---|---|
| Mean | 77.433332 | 61.700003 | 68.066668 | 58.66667 |
| S.D. | 11.38355484 | 15.25377888 | 20.47695216 | 15.43005025 |
| Percentage | | -20.31854835 | -12.0964238 | -24.23589624 |
| t-test | | 0.040214064* | 0.100583206 | 0.000998514** |

*Significant at p<0.05, **Highly significant at p<0.01

Table 3: MOT values of DNA content in heart of the control and treated groups

| Parameters | Control | T1 group | T2 group | T3 group |
|---|---|---|---|---|
| Mean | 44.899997 | 48.166666 | 43.233337 | 43.600003 |
| S.D. | 10.66806111 | 12.75529335 | 8.630445086 | 10.05003088 |
| Percentage | | 7.275432557 | -3.711937887 | -2.89530977 |
| t-test | | 0.25781519 | 0.36883244 | 0.420686738 |

*Significant at p<0.05, **Highly significant at p<0.01

vessels acquired deep staining affinity (MOT = 68.06) (Fig. 4c) and faintly stained degenerated muscle fibers in T3 group (MOT = 58.66) (Fig. 4d).

Table 3 illustrated the changes in DNA content in sections of fetal cardiac tissue of the control and treated groups. The MOT of DNA of the control group reached 44.89. Slightly increased staining affinity of DNA materials was observed in some nuclei of myocytes of group $T_1$ (MOT = 48.16). Nuclei of cardiac tissue of $T_2$ group and $T_3$ group revealed decreased staining affinity of DNA materials (MOT = 43.23 and 43.6), respectively.

## DISCUSSION

Maternal fluoxetine exposure caused many histological and histochemical alternations in fetal heart of treated groups and these harmful changes increase by increasing doses of Fluoxetine. Depression during pregnancy has been lead to higher rates of deprived pregnancy outcomes such as premature delivery, preeclampsia, reduced fetal growth,

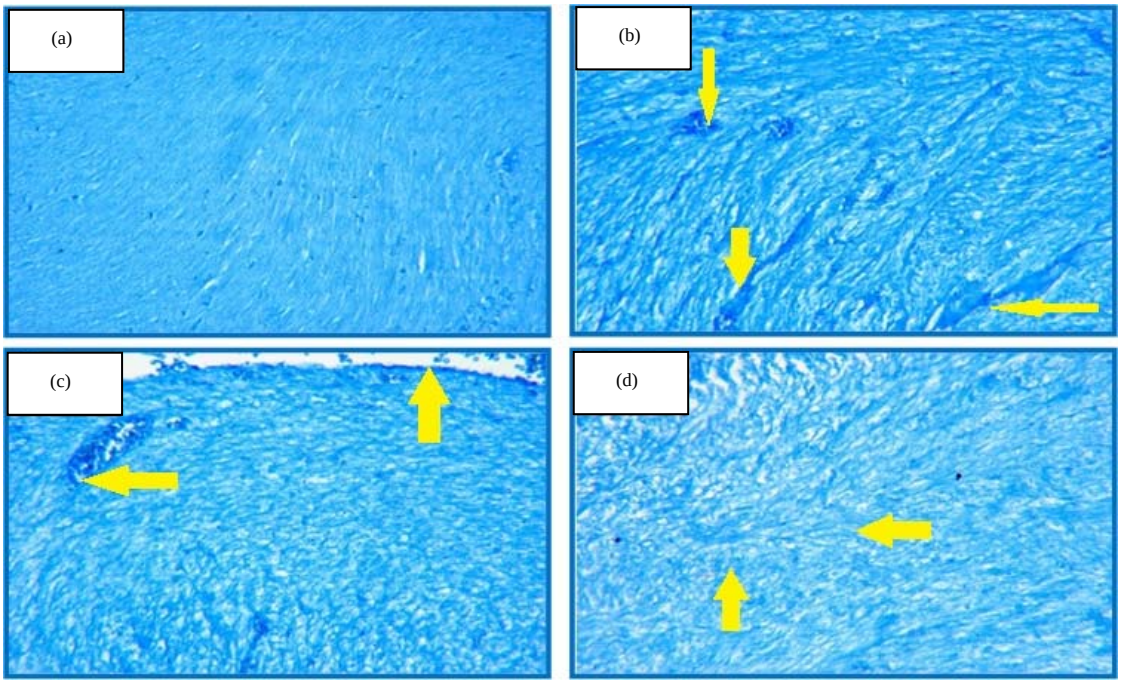


Fig. 4(a-d): Photomicrographs of mercuric bromophenol stained fetal cardiac sections of the (a) Control group showed moderately stained total protein in the myocytes, (b) T1 group showed decreased total protein in the myocytes with a slight increase in the hemorrhagic areas and the congested and dilated blood vessels (↑), (c) T2 group showed decreased total protein in the degenerated muscle fibers but congested and dilated blood vessels acquired deep staining affinity (↑) and (d) T3 group showed faintly stained degenerated muscle fibers (↑), (X = 200)

impaired fetoplacental function and neonatal problems[27,28]. In study completed in the University Hospital of Imam Abdulrahman Bin Faisal University demonstrated that depression are common during gestation[8]. The SSRI exposure in-utero was related with increased neonatal care at delivery and differences in Apgar scores compared with normal[29]. Use of SSRIs during gestation increases the risk of preeclampsia[30]. The development of antenatal depression may cause by some risk factors such as biological and psychosocial factors, hormonal/reproductive past of mother, genetic setup, present stressors and life experiences[31]. By 2020 depression will become the second leading cause of worldwide disability, behind only heart disease and that depression is already the single leading cause of disability for people in midlife and for women of all ages[7]. Fluoxetine is one of the most important SSRIs and researches had focused on it because of its high selectively and negligible affinity for numerous receptors subtypes[12]. Fluoxetine inhibit 5HT reuptake followed by serotonin concentration development in synaptic cleft and that removes symptoms of depression[32]. Fluoxetine effects on the timing of developmental stages of fetuses[33].

In the present study, fetuses maternally treated with fluoxetine (Prozac) showed numerous histopathological and histochemical changes in the fetal heart. Deleterious changes in the fetal heart of group $T_1$ were observed. Congested blood vessels, numerous hemorrhagic areas and numerous faintly stained nuclei. Fetuses of group $T_2$ showed highly congested blood vessels with scattered small pools of blood cells and deeply stained nuclei of myocytes. Congested blood vessels, necrosis in numerous myocytes, numerous elongated hemorrhagic areas and karyolysis in numerous nuclei of myocytes were noted in-group $T_2$.

The SSRI exposure increase oxidative stress leading to creation of the harmful free radicals, which are damaging the fetal cardiac tissue[34]. The expression of serotonin transporter in the fetal heart cells were inhibited by SSRIs and thereby decrease serotonin in the cells and that can disturbs the normal cardiac development[35]. The SSRI induce neonatal adaptation problems of offspring, increase the rate of cardiac malformations, pulmonary hypertension of the newborn[36].

Fluoxetine and paroxetine could result in the enhancement of genetic heart defects[37]. Fluoxetine result in right ventricular outflow tract obstruction and atrial septal defect in the heart tissue[38,39]. Anti-depressant drug in albino rats result in welling of glomeruli and degeneration of cells lining renal tubules in the fetal kidney tissue[1]. While some other studies did not find relation between use of SSRIs and cardiac malformations[40,18]. By histological

analysis, there is no any change in heart development of the fluoxetine exposed group[15].

In the present work, increased collagen fibers were noted in the fetal heart tissue of all the treated groups, this result agree with Al-Nasser[41], Nehal *et al.*[2] in some organs of fetuses and their mothers treated with Prozac. Myofibers were noted in the muscle fibers of Prozac group (0.06 mg Prozac/mouse/day) with variation in size, sarcolemma, amplified collagen deposition and some regions of affected empty of Golgi bodies[42]. There is no change were showed in collagen fibers of periodontal tissue[43].

Results illustrated changes in PAS +ve materials in fetal cardiac tissue of the control and treated groups. Highly increased PAS +ve materials was noted in fetal cardiac of fetuses of group $T_1$ but some degenerated muscle fibers showed pale staining affinity (MOT = 128.29 compared to the control one 96.76). Also, decreased PAS +ve materials was detected in the fetal cardiac tissue of group $T_2$ and $T_2$ with exception of some deeply stained blood (MOT was 116.36 compared to the control one 96.76).

Increased stain affinity of PAS +ve materials was founded by Eid and Al-Nasser[44] in lung tissue of pregnant rats treated with fluoxetine (0.143, 0.286 and 0.572 mg $kg^{-1}$ b.wt.) but they noticed diffused polysaccharides inside the blood vessels of lungs of all the treated groups.

Increased PAS +ve materials were noted in few hair follicles and hypodermal muscle fibers but decreased stain affinity was detected in the different layers of the fetal skin whose mothers received fluoxetine during pregnancy[1].

Sections from rats pretreated with fluoxetine showed strong reaction in the normal hepatocytes, faint stainability in some hepatocytes while the necrotic cells were devoid of stainable materials[45].

Increased polysaccharides in the brain of mice treated with antidepressant drugs[46], this may be dependent on adrenocortical activity[47].

In the present study, decreased total protein was demonstrated in the fetal cardiac tissue of all the treated groups (MOT values reached 61.7, 68.06, 58.66 in $T_1$, $T_2$, $T_3$, respectively compared with the control group 77.43). This study agreed with Song *et al.*[48], they noted decreased protein level in mice brain tissue. On the other hand, increased total proteins was noted by Kim *et al.*[49] and Eid and Al-Nasser[44] in lungs of treated pregnant rats with fluoxetine. Increased stain ability of total protein in the thickened keratin and Malpighian layers of fetal skin whose mothers received fluoxetine during pregnancy[2]. Kim *et al.*[49] stated that fluoxetine has high affinity to bind with proteins.

Decreased stain affinity of DNA was demonstrated in then of cardiac tissue heart of fetuses of groups $T_2$, $T_3$ (MOT values reached 43.23 and 43.6 compared the control group 44.89), in spite of the presence of slightly increased staining affinity of DNA materials was observed in some nuclei of myocytes of group $T_1$ and MOT reached 48.16. Fadladdeen[50] noticed numerous histological and histopathological changes in many fetal organs treated maternally with Prozac. These changes include: Internal hemorrhage in the gastrointestinal tract, destructed muscle fibers and altered PAS+ve materials, total protein and DNA content.

The dissolution of DNA material in the degenerated cell due to two distinct morphological patterns of cells death have been recognized, either by necrosis or apoptosis. Apoptosis happens in both pathological and physiological conditions. It arises due to an elevation of cytosolic free calcium concentration resulting in activation of the nuclear enodonuclease. Activated endonucleases produce oligonucleosome-length DNA fragments. This DNA cleavage can lead to death of cell[51].

There is relation between decreased omega-3 polyunsaturated fatty acid and depression were noted by Su *et al.*[52], so pregnant females must take enough amounts of foods rich with omega-3 for safety of mothers and their fetuses. This drug during gestation should be under strict precautions and further studies are recommended that it is essential to demonstrate the harmful effect of anti-depressant drugs on fetuses during pregnancy.

## CONCLUSION

The results of the present work showed that maternal use of Prozac has been related with dystrophic changes in the fetuses and increased risk of fetal malformation. The result of this study showed that crossing of the fluoxetine from the placenta could exert adverse effects on heart development. These findings should be taken into considerate before using of Prozac during pregnancy and future researches on the placenta can lead to better understanding of the effects of Prozac use during pregnancy to improve public health outcomes. According to the result of this study, it is essential to survey the roles of anti-depressants on fetus during pregnancy.

## SIGNIFICANCE STATEMENT

This study discover the harmful effect of Prozac treatment on the fetal heart tissue, that can be beneficial for prevention use of anti-depression drugs during pregnancy. This study will

help the researcher to uncover the critical areas of Prozac exposure during pregnancy that many researchers were not able to explore. Thus a new theory on injury of selective serotonin reuptake inhibitor on fetal tissues may be arrived at.

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