Assessment of the Potential Genotoxicity and Cardiac Teratogenicity of Venlafaxine on Embryos of Pregnant Black Mice

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ABSTRACT

Background: Depression during pregnancy is a very common problem worldwide, so the possibility of intake antidepressant medications during pregnancy is high. In Egypt, about 60% of pregnant women experience some forms of antenatal depression. The most widely prescribed antidepressants worldwide are Selective serotonin and serotonin–norepinephrine reuptake inhibitors (SSRIs and SNRIs). The mechanism of action is poorly understood but in general, these drugs act by blocking the serotonin and/or norepinephrine transporters.

Aim: The aim of this study is to investigate the effect of venlafaxine- one of the most widely prescribed SSRI (Selective serotonin reuptake inhibitors) on DNA, and also study its possible teratogenic effect on cardiac development.

Methods: The present study was carried out on fifty pregnant black mice (C57BL/6). The mice were randomly assigned to one of two groups: a control and venlafaxine-treated groups receiving (3mg, 10mg, 30mg and 100mg/kg/day). The fetuses were dissected for the evaluation of their cardiac structure. The micronucleus test was used to detect the ability of venlafaxine to induce DNA damage.

Results: The present work showed that administration of increasing concentrations of venlafaxine resulted in significant increase in the incidence of embryo heart anomalies in black mice as VSD, pulmonary trunk dilatation and right ventricle enlargement as compared to the control group. Also, this study showed an increase in the frequency of micronuclei in the blood of the adult mice after exposure to increasing dose of venlafaxine.

Conclusions: Physicians should make a proper decision regarding prescription of SSRI in general and venlafaxine, in particular, to treat depression during pregnancy weighing the risks and benefits for both mother and fetus.

Received: 07 July 2019, Accepted: 20 September 2019

Key Words: Cardiac anomalies; genotoxicity; micronucleus; pregnancy depression; venlafaxine.

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ISSN: 1110-0559, Vol. 43, No.3

INTRODUCTION

Serotonin is one of the neurotransmitters that is involved in transmission of nerve impulses in the central and peripheral nervous system[1]. It is considered as an important signaling molecule during embryo and fetal development. During craniofacial development, serotonin stimulates dental development[2]. It is also involved in shaping of the tempromandibular joint and in retinogenesis[3].

During early stages of embryogenesis, in cardiac development, serotonin is involved in the establishment of right/left laterality via the stimulation of fibroblast growth factor 8 (FGF8)/Nodal/ pituitary homeobox 2 (PITX2) pathways[4].

Studies have shown that disruption of the laterality pathway causes many different types of heart anomalies such as ventricular septal defect (VSD), atrial septal defect (ASD), dextrocardia, outflow tract defect (OTD) and pulmonary stenosis (PS)[5].

Sites of early serotonin biosynthesis during embryogenesis have not been detected, it has been suggested that serotonin may be probably of maternal origin[6].

Depression during pregnancy is a very common problem worldwide, so the rate of the exposure to antidepressant medications during pregnancy is very high. Studies revealed that it is marvelously increasing; for example 3-folds in the United States from 1998 to 2005[7], and 16-fold in Europe from 1997 to 2010[8]. In Egypt, about 60% of pregnant women experience antenatal depression[9].

The FDA considered venlafaxine as category C with regarded pregnancy risk which means that venlafaxine is
suspected to cause harmful effects on the human fetuses or neonates\cite{11}.

During the past decade, studies showed that treatment with SSRI/SNRIs during pregnancy has been associated with an increased risk of miscarriage, preeclampsia, preterm birth, decreased fetal body weight and head growth, congenital malformations, and behavioral disorders in offspring\cite{12}.

Recent work showed great debates in the increase of possibility of congenital heart defects associated with SSRI/SNRIs treatment. Also the available studies are not enough with respect to an association between treatments with SSRI especially venlafaxine and the increase in the incidence of congenital heart defects\cite{13}.

**Micronucleus Test and Genotoxicity**

The mammalian in vivo micronucleus assay is a mutagenicity test system used for the detection of chemicals that induce the formation of small membrane-bound DNA fragments known as micronuclei in the cytoplasm of interphase cells as a measure of genotoxicity. The test evaluates the formation of micronucleus in erythrocytes sampled either in the bone marrow or peripheral blood cells of animals, usually rodents\cite{14}.

Micronuclei are small, extranuclear chromatin bodies surrounded by a nuclear envelope. When a bone marrow erythroblast develops into a polychromatic erythrocyte (PCE) or reticulocyte, the main nucleus is extruded; any micronucleus that has been formed may remain behind in the cytoplasm. Visualization of micronuclei is facilitated in these cells because they lack the main nucleus. An increase in the frequency of micronucleated immature erythrocytes in treated animals is an indication of induced chromosomal damage\cite{15}.

Recently the micronucleus test – especially the direct assay- has become the most widely used test for genotoxicity as it is capable of assessing clastogenic, aneugenic, and epigenetic effects. It is simple, accurate and applicable. It can be done on any dividing cell population and its end point which is the frequency of micronucleated immature erythrocytes is easy to identify, so accurate data can be obtained\cite{16}.

**A Test Chemical is Considered Positive if**\cite{17}

I. At least one of the doses exhibits a statistically significant increase in the frequency of micronucleated immature erythrocytes compared with the concurrent control.

II. The increase in the frequency of micronucleated immature erythrocytes is dose-related.

An increase in the frequency of micronucleated immature erythrocyte in treated animals reflects chromosomal damage induced by the test substance.

The available studies are not enough with respect to an association between treatments with SSRI especially venlafaxine and the increase in the incidence of chromosomal aberrations and congenital heart defects.

**AIM OF THE WORK**

The aim of the present work was to study the possible effects of venlafaxine treatment on cardiac development and DNA in black mice.

**METHODS**

The present study was carried out on fifty pregnant black mice (C57BL/6), obtained from the Animal House Center of Anatomy Department, Faculty of Medicine, Alexandria University. Mice were housed two per cage in a room temperature maintained at twenty degrees (20°C) on a 12:12 hour light: dark cycle, average weight 18-22 gram.

Diet was administrated following the Egyptian Institute of Nutrition (EIN) recommendations. The animals were given food and water ad libitum during the experimental period.

All adult female mice (50) were mated with adult male mice (2:1) in standard caging conditions. The female mice were examined twice daily for the presence of vaginal plug.

Appearance of vaginal plug was the sure sign of mating and the day considered gestational day one (GD1)\cite{18}. The pregnant females were isolated with daily follow up for miscarriage or any other conditions. The mice were left caged in appropriate circumstances from expected GD 1 to GD 8.

Efixor XR 75 mg (Venlafaxine hydrochloride) - extended release capsules manufactured, packed and released by Pfizer Ireland Pharmaceuticals, Little Connell, Newbridge, Co. Kildare, Ireland. Obtained from Dawae pharmacies, Alexandria, Egypt.

**Grouping and start of treatment at GD8 as following**

- **Group I:** (Control group) Included ten pregnant black mice received saline by gavage daily from GD8 to GD18.

- **Group II:** (Experimental group) Included forty pregnant black mice divided into:
  - **Subgroup IIa:** Included ten pregnant black mice received Venlafaxine hydrochloride from GD8 to GD18 by gavage daily at dose of 3 mg/kg/day in saline.
  - **Subgroup IIb:** Included ten pregnant black mice received Venlafaxine hydrochloride from GD8 to GD18 by gavage daily at dose of 10 mg/kg/day in saline.
  - **Subgroup IIc:** Included ten pregnant black mice received Venlafaxine hydrochloride from GD8 to GD18 by gavage daily at dose of 30 mg/kg/day in saline.
  - **Subgroup IID:** Included ten pregnant black mice received Venlafaxine hydrochloride from GD8 to GD18 by gavage daily at dose of 100 mg/kg/day in saline.
Sacrification and removal of uterine horns were carried on GD18 (Full term pregnancy) to exclude effects associated with delivery complications such as prolonged gestation and stillbirth.

1. **Morphological study**[19]
   - The uterine horns were dissected and the number of pups and resorptions were recorded.
   - The pups were separated from the placenta and evaluated for their sex, body weight and external morphology and After preservation in a preservative solution for one day, the pups were dissected for evaluation of cardiac structures under the Olympus SZ Dissecting Stereo Microscope:

   The heart was separated from the lung and to get it out of the thoracic cage and divided into an anterior and a posterior halves using sharp scalpel followed by careful examination of its internal structure. The thickness of the right ventricular wall and pulmonary trunk diameter were measured using the Stereo Microscope.

   The morphological study was done in Experimental embryology lab of the human Anatomy and Embryology department, Faculty of medicine, Alexandria University

2. **Genetic study**[20]
   - DNA assessment with direct micronucleus test
     - The tissues assessed for frequency of micronuclei were bone marrow and peripheral blood.
     1. Two blood samples were obtained from adult pregnant black mice of the control and venlafaxine treated groups at GD 14 from tail vein and at scarification day (GD18) by cardiac puncture.
     2. The blood samples were collected in EDTA treated tubes. Blood film stained with giemsa stain was done. The slides were examined under the Olympus CX41 Binocular LED – Sample Microscope.

   - Bone marrow assay
     1. The samples were collected from the femur of the animal at scarification day was preserved in EDTA tube then fixed by immersing them immediately in 4F1G (4% Formaldehyde and 1% Glutaraldehyde) in phosphate buffer solution (PH=7.2) at 4℃ for 3 hours. Slides were made and Stained by uranyl acetate for 5 minutes then lead citrate for 2 minutes. Finally the sections were examined under the Olympus CX41 Binocular LED – Sample Microscope.

   The genetic study was done at Experimental embryology lab of the human Anatomy and Embryology department, Faculty of medicine, Alexandria University

2. **Statistical analysis of the data:**

   Data were fed to the computer using IBM SPSS software package version 20.0. For normally distributed data; comparison between more than two populations was analyzed by F-test (ANOVA). Significance test results were quoted as two-tailed probabilities. Significance of the obtained results was judged at the 5% level, where values ≤ 0.05 are significant.

**RESULTS**

A. **Resorption Sites**

The present work revealed an increase in the frequency of spontaneous abortion manifested as resorption sites marked in subgroups IIc and IId. The mean number of resorption sites in subgroup IIc was 1.60±1.647 and in subgroup IId was 1.00±1.333 which was significantly different (p < 0.05) from the control group, subgroup IIa and subgroup IIb. There was no significant difference between subgroup IIc and subgroup IId. In subgroup IIa and subgroup IIb, the mean value of the number of resorption sites was non-significant compared to the control group (p > 0.05). (Table 1, Figure 1)

B. **Cardiac Anomalies**

The results of the present work showed that venlafaxine has teratogenic effect on the heart of the pups of black mice. The number of pups of the control group was 120; the pups of venlafaxine treated groups were 375. Subgroup IIa consisted of 110 pups, subgroup IIb consisted of 100 pups, subgroup IIc consisted of 80 pups and subgroup IId consisted of 85 pups. The cardiac anomalies were significantly increased (p < 0.05) in venlafaxine treated groups in comparison with control group. The observed cardiac anomalies were: VSD, enlargement of the right ventricle and dilatation of pulmonary trunk. The percentages of cardiac anomalies were higher in subgroup IId than other venlafaxine treated groups and control group which means that the dose of 100mg/kg/day was highly toxic. (Table 2; Figures 2-6)

VSD was significantly higher (p < 0.05) in venlafaxine treated groups in comparison with control group. It was noted that the percentage of VSD anomaly among animals of subgroup IId was significantly lower than subgroups IIa, IIb and IIc. (Table 2, Figure 2)

Right ventricular hypertrophy was observed in zero pups out of 120 (0%) in the control group. In subgroup IIb, it was observed in 5 pups out of 100 (5%). In subgroup IIc, it was observed in 10 pups out of 80 (12.50%). In subgroup IId, it was observed in 12 pups out of 85 (14.12%). (Table 2, Figures 3, 4)

The mean thickness of the right ventricular wall in the control group was 112.5±10.85µm, while the mean thickness of the hypertrophied right ventricular wall was 280.5±26.92µm. (Table 2, Figures 3, 4)

Right ventricular wall enlargement was observed in subgroups IIb, IIc and IId and significantly higher (p < 0.05) in subgroups IIc and IId in comparison with the control group. There was no significant difference between subgroups IIa and IId. (Table 2, Figures 3, 4)

Pulmonary trunk dilatation was observed in 1.67% in the control group. In subgroup IIa, it was observed
in 13.64%. In subgroup IIc, it was observed in 6.25% and in subgroup IIId, it was observed in 23.53%. (Table 2, Figures 5, 6)

The mean of normal pulmonary trunk diameter in the control group was 134.2±12.5µm, while the mean of dilated pulmonary trunk was 198.5±20.04µm. (Table 2, Figures 5, 6)

Pulmonary trunk dilatation was significantly higher ($p < 0.05$) in subgroups IIa and IIId in comparison with the control group. It was significantly higher in subgroup IIId than IIc. (Table 2, Figures 5, 6)

**D. Other Defects**

The present work showed a significant decrease ($p < 0.05$) in the placental weight at low doses of venlafaxine in subgroup IIa (mean: 0.101±0.047 mg) and subgroup IIb (mean: 0.078±0.057mg) in comparison with the control group and a consequent increase in the placental index (fetal weight / placental weight) in the same groups. (Table 3).

The external morphology of the placenta did not differ in the control group rather than the venlafaxine treated groups.

The present work also revealed that pups’ body weights were significantly reduced ($p < 0.05$) in subgroup IIId (Table 4) in comparison with the control group. In subgroups IIa, IIb and IIc, the pups’ body weights were non-significantly different ($p > 0.05$) in comparison with the control group.

Major anomalies as anophthalmia (10.58%, Figure 7) and anencephaly (14.11%, Figure 8) were observed in subgroup IIId.

**2. Genotoxicity of Venlafaxine**

The present work showed that administration of venlafaxine treatment induces DNA damage in black mice using the direct micronucleus test. The damaging effect of venlafaxine on DNA of the black mice increased with increasing the dose and the duration.

a) Peripheral blood assay: (Tables 5, 6, 8; Figures 9-10)

There was significant increase ($p < 0.05$) in the number of micronucleated erythrocytes in venlafaxine treated groups in comparison with control group.

There was significant increase ($p < 0.05$) in the number of micronucleated erythrocytes with increasing dose of venlafaxine.

The number of micronucleated erythrocytes was significantly higher ($p < 0.05$) in subgroup IIId than subgroup IIc, which means that the dose of 100 mg/kg/day was highly toxic.

b) Bone marrow assay: (Tables 7-8; Figures 11-13)

The bone marrow samples were collected at GD 18. There was significant increase ($p < 0.05$) in the number of micronucleated immature erythrocytes in venlafaxine treated groups in comparison with the control group.

There was significant increase ($p < 0.05$) in the number of micronucleated immature erythrocytes with increasing dose of venlafaxine.

The number of micronucleated immature erythrocytes was significantly higher ($p < 0.05$) in subgroup IIId than subgroup IIc, which means that the dose of 100 mg/kg/day was highly toxic.

**Fig. 1:** A photograph of uterus of adult female mouse from subgroup IIId. The photo shows one ovary and resorption site (RS).

**Fig. 2:** A photograph of dissected heart of 18 days pup of black mouse of subgroup IIId (anterolateral view) showing VSD. (x 16)IVS: Interventricular septum. VSD: Ventricular septal defect.LV: Left ventricle. RV: Right ventricle.
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Fig. 3: A photograph of dissected heart of 18 days pup of black mouse of the control group (anterior view) showing the thickness of right ventricular wall measured using the Olympus SZ Dissecting Stereo Microscope. (x 16) IVS: Interventricular septum. LV: Left ventricle. RV: Right ventricle. LA: Left atrium. RA: Right atrium.

Fig. 4: A photograph of dissected heart of 18 days pup of black mouse of subgroup IIc (anterior view) showing the thickness of right ventricular wall measured using the Olympus SZ Dissecting Stereo Microscope. (x 12.5) IVS: Interventricular septum. LV: Left ventricle. RV: Right ventricle. LA: Left atrium. RA: Right atrium.

Fig. 5a: A photograph of dissected heart of 18 days pup of black mouse of the control group showing a normal shaped heart with the atria brownish in color. Right atrium (RA). Left atrium (LA).

Fig. 5b: A photograph of dissected heart of 18 days pup of black mouse of the control group (anterior view) showing pulmonary trunk diameter measured using the Olympus SZ Dissecting Stereo Microscope. (x 16) PT: Pulmonary trunk. Ao: Aorta. LV: Left ventricle. RV: Right ventricle. LA: Left atrium. RA: Right atrium.

Fig. 6: A photograph of dissected heart of 18 days pup of black mouse of subgroup IId (anterior view) showing pulmonary trunk diameter measured using the Olympus SZ Dissecting Stereo Microscope. (x 16) PT: Pulmonary trunk. Ao: Aorta. LV: Left ventricle. RV: Right ventricle. LA: Left atrium. RA: Right atrium.

Fig. 7a: A photograph of 18 days pup of black mouse of the control group showing normal morphology with the eyes, ear, fore limb and hind limb are well seen. The photo was taken using Olympus SZ Dissecting Stereo Microscope (x 8).
Fig. 7b and c: Two photographs showing anophthalmia (Congenital absence of the eye) in 18 days pup of black mouse of subgroup II d. The photos was taken using Olympus SZ Dissecting Stereo Microscope (x 8).

Fig. 8a: A photograph of 18 days pup of black mouse of the control group showing normal morphology of head containing the eyes anears. The photo was taken using Olympus SZ Dissecting Stereo Microscope (x 8).

Fig. 9: Bar chart comparing different studied groups: the control group and venlafaxine treated groups regarding the number of micronucleated erythrocytes in peripheral blood samples at GD 14 and GD 18 and the number of immature micronucleated erythrocytes in bone marrow samples at GD 18.

Fig. 8b: A photograph showing anencephaly (congenital absence of cranial vault with part of neural tissues due to neural tube defect) in 18 days pup of black mouse of subgroup II d. The photo was taken using Olympus SZ Dissecting Stereo Microscope (x 5).

Fig. 10a: A photograph of a peripheral blood sample stained with Giemsa from adult pregnant black mouse of the control group showing normal RBC’s. (x 1000)
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Fig. 10b: A photograph of a peripheral blood sample stained with Giemsa from adult pregnant black mouse of subgroup IId at GD18 showing RBCs containing micronucleus (MN) indicating genotoxicity of venlafaxine. (x 1000)

Fig. 11: A photograph of a bone marrow sample stained with uranyl acetate then lead citrate from the femur of adult pregnant black mouse of the control group at GD 18 showing nucleated polychromatic erythrocyte (PCE) and non-nucleated PCE. (x 1000)

Fig. 12: A photograph of a bone marrow sample stained with uranyl acetate then lead citrate from the femur of adult pregnant black mouse of subgroup IIc at GD18 showing polychromatic erythrocytes (PCEs) and normochromatic erythrocytes (NCEs) containing micronucleus (MN) indicating genotoxicity of venlafaxine. (x 1000)

Fig. 13: A photograph of a bone marrow sample stained with uranyl acetate then lead citrate from the femur of adult pregnant black mouse of subgroup IId at GD18 showing normochromatic erythrocytes (NCEs) containing micronucleus (MN) indicating genotoxicity of venlafaxine. (x 1000)

Table 1: Comparison between different studied groups; the control group and venlafaxine treated groups regarding the number of resorption sites

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<td></td>
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<td></td>
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p1 comparison between the control group and group IIa.
p2 comparison between the control group and group II b.
p3 Comparison between the control group and group II c.
p4 Comparison between the control group and group II d.
p5 Comparison between group II c and group II d.

*= statistically significant at p ≤ 0.05

F: ANOVA test
Table 2: Comparison between different studied groups: the control group and venlafaxine treated groups regarding the percentages of cardiac congenital anomalies (Pulmonary trunk dilatation, VSD, and right ventricular hypertrophy)

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<th>Gp. II a “n=110”</th>
<th>Gp. II b “n=100”</th>
<th>Gp. II c “n=80”</th>
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<td>No. %</td>
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p1 Comparison between the control group and group II a.  p2 Comparison between the control group and group II b.
p3 Comparison between the control group and group II c.  p4 Comparison between the control group and group II d.
p5 Comparison between group II c and group II d.
X^2: Chi-Square test
* = statistically significant at p \leq 0.05

Table 3: Comparison between different studied groups: the control group and venlafaxine treated groups regarding placental weight

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</tr>
<tr>
<td>p3</td>
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<td></td>
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<tr>
<td>p4</td>
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<td></td>
<td></td>
<td></td>
<td>0.103</td>
</tr>
</tbody>
</table>

p1 comparison between the control group and group II a.  p2 comparison between the control group and group II b.
p3 Comparison between the control group and group II c.  p4 Comparison between the control group and group II d.
p5 Comparison between group II c and group II d.
F: ANOVA test
* = statistically significant at p \leq 0.05
### Table 4: Comparison between different studied groups: the control group and venlafaxine treated groups regarding the pups’ weight

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Range</td>
<td>0.78–1.6</td>
<td>0.65–1.4</td>
<td>0.63–1.5</td>
<td>0.54–1.6</td>
<td>0.53–1.08</td>
<td></td>
</tr>
<tr>
<td>Mean± S.D.</td>
<td>1.11±0.402</td>
<td>0.94±0.211</td>
<td>1.05±0.226</td>
<td>1.01±0.251</td>
<td>0.75±0.183</td>
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<td>F</td>
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<td></td>
<td></td>
<td>15.33</td>
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<td></td>
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<td>0.004*</td>
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<td></td>
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<td>0.043*</td>
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</table>

p1 comparison between the control group and group II a.  
p2 comparison between the control group and group II b.  
p3 Comparison between the control group and group II c.  
p4 Comparison between the control group and group II d.  
p5 Comparison between group II c and group II d.  
F: ANOVA test  
*= statistically significant at $p \leq 0.05$

### Table 5: Comparison between different studied groups: the control group and venlafaxine treated groups regarding the pups’ weight

<table>
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<tr>
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</thead>
<tbody>
<tr>
<td>Range</td>
<td>0–4</td>
<td>0–10</td>
<td>0–17</td>
<td>0–52</td>
<td>20–156</td>
<td></td>
</tr>
<tr>
<td>Mean± S.D.</td>
<td>0.60±1.188</td>
<td>4.10±3.007</td>
<td>5.60±4.935</td>
<td>19.70±17.045</td>
<td>61.05±35.782</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>38.5</td>
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<td>P</td>
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<td></td>
<td></td>
<td>0.0001*</td>
</tr>
<tr>
<td>p1</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td>0.001*</td>
</tr>
<tr>
<td>p2</td>
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<td></td>
<td></td>
<td></td>
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<td>0.001*</td>
</tr>
<tr>
<td>p3</td>
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<td></td>
<td></td>
<td></td>
<td>0.0001*</td>
</tr>
<tr>
<td>p4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.001*</td>
</tr>
<tr>
<td>p5</td>
<td></td>
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<td></td>
<td></td>
<td>0.001*</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>0.106</td>
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<td></td>
<td>0.003*</td>
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<tr>
<td>p8</td>
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<td></td>
<td>0.005*</td>
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<td>p9</td>
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<tr>
<td>p10</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>0.001*</td>
</tr>
</tbody>
</table>

p1 Comparison between the control group and group II a.  
p2 Comparison between the control group and group II b.  
p3 Comparison between the control group and group II c.  
p4 Comparison between the control group and group II d.  
p5 Comparison between group II c and group II d.  
p6 Comparison between group II a and group II b.  
p7 Comparison between group II a and group II c.  
p8 Comparison between group II a and group II d.  
p9 Comparison between group II b and group II c.  
p10 Comparison between group II b and group II d.  
F: ANOVA test  
*= statistically significant at $p \leq 0.05$
### Table 6: Comparison between different studied groups: the control group and venlafaxine treated groups regarding the number of micronucleated erythrocytes in peripheral blood samples at GD 18

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Range</td>
<td>0.0-4.2</td>
<td>0.0-10.0</td>
<td>0.0-20.3</td>
<td>5.0-65.0</td>
<td>30.0-172.0</td>
</tr>
<tr>
<td>Mean± S.D.</td>
<td>0.61±0.901</td>
<td>7.98±5.65</td>
<td>14.6±5.65</td>
<td>42.6±22.8</td>
<td>98.0±22.8</td>
</tr>
<tr>
<td>F</td>
<td>42.6</td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p1</td>
<td>0.0021*</td>
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<td></td>
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<tr>
<td>p2</td>
<td></td>
<td>0.001*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p3</td>
<td></td>
<td></td>
<td>0.0001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p4</td>
<td></td>
<td></td>
<td></td>
<td>0.0001*</td>
<td></td>
</tr>
<tr>
<td>p5</td>
<td></td>
<td></td>
<td></td>
<td>0.001*</td>
<td></td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>0.062</td>
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<td>0.0014*</td>
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<tr>
<td>p8</td>
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<td></td>
<td></td>
<td>0.0001*</td>
<td></td>
</tr>
<tr>
<td>p9</td>
<td></td>
<td></td>
<td></td>
<td>0.005*</td>
<td></td>
</tr>
<tr>
<td>p10</td>
<td></td>
<td></td>
<td></td>
<td>0.001*</td>
<td></td>
</tr>
</tbody>
</table>

- p1 Comparison between the control group and group II a.
- p2 Comparison between the control group and group II b.
- p3 Comparison between the control group and group II c.
- p4 Comparison between the control group and group II d.
- p5 Comparison between group II c and group II d.
- p6 Comparison between group II a and group II b.
- p7 Comparison between group II a and group II d.
- p8 Comparison between group II b and group II c.
- p9 Comparison between group II b and group II d.
- F: ANOVA test

* = statistically significant at \( p \leq 0.05 \)

### Table 7: Comparison between different studied groups: the control group and venlafaxine treated groups regarding the number of micronucleated erythrocytes in bone marrow samples at GD 18

<table>
<thead>
<tr>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>0-3</td>
<td>3-14</td>
<td>9-30</td>
<td>10-100</td>
<td>70-200</td>
</tr>
<tr>
<td>Mean± S.D.</td>
<td>0.60±0.966</td>
<td>8.10±4.067</td>
<td>15.70±6.343</td>
<td>45.80±27.300</td>
<td>104.80±38.476</td>
</tr>
<tr>
<td>F</td>
<td>34.65</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p1</td>
<td>0.001*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p2</td>
<td></td>
<td>0.001*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p3</td>
<td></td>
<td></td>
<td>0.0001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p4</td>
<td></td>
<td></td>
<td></td>
<td>0.0001*</td>
<td></td>
</tr>
<tr>
<td>p5</td>
<td></td>
<td></td>
<td></td>
<td>0.001*</td>
<td></td>
</tr>
<tr>
<td>p6</td>
<td></td>
<td></td>
<td></td>
<td>0.021*</td>
<td></td>
</tr>
<tr>
<td>p7</td>
<td></td>
<td></td>
<td></td>
<td>0.001*</td>
<td></td>
</tr>
<tr>
<td>p8</td>
<td></td>
<td></td>
<td></td>
<td>0.0001*</td>
<td></td>
</tr>
<tr>
<td>p9</td>
<td></td>
<td></td>
<td></td>
<td>0.0021*</td>
<td></td>
</tr>
<tr>
<td>p10</td>
<td></td>
<td></td>
<td></td>
<td>0.0001*</td>
<td></td>
</tr>
</tbody>
</table>

- p1 Comparison between the control group and group II a.
- p2 Comparison between the control group and group II b.
- p3 Comparison between the control group and group II c.
- p4 Comparison between the control group and group II d.
- p5 Comparison between group II c and group II d.
- p6 Comparison between group II a and group II b.
- p7 Comparison between group II a and group II d.
- p8 Comparison between group II a and group II d.
- p9 Comparison between group II b and group II c.
- p10 Comparison between group II b and group II d.
- F: ANOVA test

* = statistically significant at \( p \leq 0.05 \)
Table 8: Comparison between different studied groups: the control group and venlafaxine treated groups regarding the number of micronucleated erythrocytes in peripheral blood samples at GD 14 and GD 18 and the number of immature micronucleated erythrocytes in bone marrow (BM) samples at GD 18

<table>
<thead>
<tr>
<th>Group</th>
<th>Peripheral blood at GD 14</th>
<th>Peripheral blood at GD 18</th>
<th>BM samples at GD 18</th>
<th>BM samples at GD 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.60±1.188</td>
<td>0.61±0.901</td>
<td>0.656</td>
<td>0.60±0.966</td>
</tr>
<tr>
<td>Gp. II</td>
<td>4.10±3.007</td>
<td>7.98±3.65</td>
<td>0.003*</td>
<td>8.10±4.06</td>
</tr>
<tr>
<td>Gp. II*</td>
<td>5.60±4.93</td>
<td>14.6±5.65</td>
<td>0.001*</td>
<td>15.70±6.34</td>
</tr>
<tr>
<td>Gp. IIc</td>
<td>19.7±17.04</td>
<td>42.6±22.8</td>
<td>0.001*</td>
<td>45.8±27.3</td>
</tr>
<tr>
<td>Gp. II*</td>
<td>61.05±35.75</td>
<td>98.0±22.8</td>
<td>0.001*</td>
<td>104.8±38.47</td>
</tr>
</tbody>
</table>

P1 comparison between number of micronucleated erythrocytes at peripheral blood samples at GD 14 and GD 18.

P2 comparison between number of micronucleated erythrocytes at peripheral blood at GD 18.

* = statistically significant at \( p \leq 0.05 \)

DISCUSSION

The doses of venlafaxine used in the present work (3, 10, 30 and 100 mg/kg/day) were in the range of the therapeutic doses of this drug used in humans (i.e., 37.5, 75, 150 and 225 mg/day), and they were scaled to adjust for the difference in body surface area between human and black mice according to the study done by Nair AB et al.,[21] which demonstrated the equation of animal equivalent dose (AED).

The present work revealed an increase in the frequency of spontaneous abortion at venlafaxine doses of 30mg and 100mg /kg/day treated groups. This could be explained by either the serotonin theory which suggests that serotonin has abortive properties, or the adrenergic/noradrenergic theory, which suggests that catecholamines are associated with tocolytic properties. Since venlafaxine inhibits reuptake of both serotonin and noradrenaline, so both theories are acceptable[20].

A review by Broy P. and Berard A.,[21] including reviews, published from 1975 through 2009 for studies that examined the relation between poor pregnancy outcomes and in utero exposure to antidepressants with data on spontaneous abortions, agreed with the result of the present work and suggested that in utero exposure to antidepressants in general, paroxetine and venlafaxine in particular, increase the risk of spontaneous abortion.

The present work showed that administration of increasing concentrations of venlafaxine resulted in significant increase in the incidence of congenital heart anomalies in pups of black mice as ventricular septal defect (VSD), pulmonary trunk dilatation and right ventricular enlargement as compared to the control group.

VSD anomaly was significantly higher in subgroups IIa, IIb, IIc and IId in comparison with the control group. It was noted that the percentage of VSD anomaly among animals of subgroup IId was significantly lower than subgroups IIa, IIb and IIc. This may be due to genetic constitution of the tested animals of subgroup IId.

Pulmonary trunk dilatation was significantly higher in subgroups IIA and IID in comparison with the control group. This anomaly was not observed in subgroup IIb and non-significant in comparison to the control group in subgroup IIC. This anomaly may be due to the low dose of venlafaxine (3, 10 mg/kg/day) which was given to subgroups IIa and IIb. There was no significant difference between subgroups IIC and IID which means that this anomaly appeared with high doses and the dose of 30 mg/kg/day is toxic. It was noted that it appeared in the animals that had another anomaly as VSD or pulmonary trunk dilatation or animals had both VSD and pulmonary trunk dilatation.

Pulmonary trunk dilatation is a very rare congenital anomaly that may be explained as follows: in presence of other anomalies as interventricular septal defect which may cause left to right shunting. This shunting will lead to increase in pulmonary artery blood flow and shear stress leading to pulmonary artery dilatation[22].

Pulmonary trunk dilatation is significant clinically as it can predict pulmonary hypertension[24]. Based on this information, if pulmonary trunk dilatation is a sign of pulmonary hypertension, we can consider that the cause of right ventricle hypertrophy might be due to pulmonary hypertension.

A study done by Laurent et al.,[23] was in total agreement with the findings in the present work and stated that prenatal exposure to venlafaxine leads to an increase in cardiac anomalies including VSD, pulmonary trunk dilatation, absence of the innominate artery, and enlargement of one of the atria or the right ventricle, in 506 fetuses of rats which were examined under stereomicroscope.

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A recent population-based cohort study included over 2.3 million births from Denmark, Finland, Iceland, Norway, and Sweden between 1996 and 2010 also agreed with the findings of the present work, stated that in utero exposure to antidepressants with effects on serotonin reuptake is associated with a 13% increased prevalence of major birth defects and a 15% increased prevalence of cardiac defects in a covariate controlled analysis. Furthermore, a population-based cohort study done by Pedersen et al. agreed with the findings of the present work. There was an increased prevalence of septal heart defects among children who were exposed in utero to SSRI.

Another population-based study by Colvin et al. included 123,405 pregnancies from 2002 to 2005. The study results showed an increased risk of cardiovascular defects and confirmed that in utero exposure to SSRI leads to an increase in the prevalence of cardiovascular defects.

A previous cohort study by Vasilakis-Scaramozza disagreed with the result of the present work and suggested that the exposure to tricyclic antidepressants (TCAs) and SSRIs during the first trimester of pregnancy was not associated with a significant increase of the risk of congenital anomalies in the offspring of mothers exposed to these drugs. The lack of association between in utero exposure to SSRI and congenital malformations in that study may be due to the small sample size.

The results of the present work revealed major anomalies as anophthalmia and anencephaly in subgroup IIb.

Anencephaly can be explained as follows: serotonin influences neurogenesis and plays an important role in brain development. Serotonergic neurons appear as early as 5 weeks and by 15 weeks, the raphe nuclei already contain a typical arrangement of serotonin neurons. Disturbance of serotonin level by SSRI can lead to defective brain development as anencephaly.

Anophthalmia can be explained as follows: serotonin has an undeniable role in retinogenesis and in development of periocular mesenchyme. SSRIs affect serotonin level and may lead to anophthalmia.

A study done by Laurent et al. stated that prenatal exposure to venlafaxine was associated with an increase in the incidence of major anomalies as anophthalmia and anencephaly.

Polen KN et al. in an earlier study suggested a relation between prenatal venlafaxine exposure and major congenital anomalies as anencephaly which agreed with the findings in the present work.

The findings in the present work differ from an earlier study done by Adrienne Einarson et al. on 150 women who were exposed to venlafaxine during pregnancy. They stated that there were no significant differences between the women of the control group and the women who took venlafaxine during their pregnancy in the comparison group. The study suggested that the use of venlafaxine during pregnancy does not increase the rates of major malformations above the baseline rate of 1%-3%.

The present work showed a decrease in the placental weight at low doses of venlafaxine (3, 10 mg/kg/day) and a consequent increase in the placental index in the same groups. This can be explained as serotonin is important for placenta development, acts as a vasoconstrictor in the placenta, and increases placental chorionic vein and umbilical artery vasoconstriction.

Previous studies demonstrated that activation of the serotonin receptor 5-HT2A in trophoblast cells activates intracellular signals that are known to regulate survival, differentiation, migration and invasion, suggesting a role for serotonin in placentaion. As a result, SSRI can affect the development of the placenta. SSRI treatment of pregnant women also alters gene expression in the placenta which could lead to an altered placental function, which in turn could affect the development of the fetus.

It was noted that the placental weight did not decrease at high doses of venlafaxine (30, 100 mg/kg/day). The explanation is unknown; this might need further study with large number of animals.

A study by Barak Y et al. discovered the existence of a functional link between the placenta and the developing heart. They were able to achieve a complete reversal of the cardiac phenotype of PPARγ of embryos through selective replacement of their trophoblast lineage by tetraploid chimera methodology. This may link the alteration of the placenta and congenital cardiomyopathies.

The present work showed a decrease in the fetal body weight at high doses of venlafaxine (100 mg/kg/day). The decrease in the fetal body weight can be explained by either alteration of placental function or by the possible toxic effect of venlafaxine.

Da Silva et al. detected decreased fetal and neonatal weight upon using venlafaxine and fluoxetine during gestation period in rodents at 40 and 80 mg/kg of venlafaxine. They explained these results by the potential toxic effects of SSRI on the rodents’ embryos when administered during pregnancy.

A study by Singh M. and Singh KP. reported that the fetal body weights of prenatally exposed rats to venlafaxine were significantly reduced especially in high doses treated group. Their results showed fetal body weight reduction by 18.13, 25.31 and 30.94 % at respective doses of 25, 40 and 50 mg venlafaxine.

Another study by Gregory E. Simon et al. stated that in utero exposure to SSRIs was associated with earlier delivery and consequent lower birth weight. Exposure to SSRIs was associated with a 0.9 week decrease in mean gestational age, a 175g decrease in mean birth weight. They also demonstrated that third-trimester SSRI exposure was also associated with lower Apgar scores.
A study done by Laurent et al.,[25] stated that prenatal exposure to venlafaxine alters the placenta with a consequent effect on fetal body weight and length. As a result, the placental index (fetal weight / placental weight) was increased.

In contrast, a cohort study by Nordeng et al.,[41] revealed that in utero exposure to antidepressant was not associated with low birth weight. The study included 63,395 women from the Norwegian Mother and Child Cohort Study. Of the 63,395 women, 699 (1.1%) reported using antidepressants during pregnancy, most frequently SSRIs (0.9%). There were 2887 infants born preterm (4.6%) and 1652 infants with low birth weight (2.6%), so the association between SSRI use throughout pregnancy and preterm and low birth weight was non-significant.

The present work showed that administration of increasing concentration of venlafaxine treatment induces DNA damage using the direct micronucleus test. The direct micronucleus test is simple, accurate and applicable and its end point which is the frequency of micronucleated immature erythrocytes is easy to identify, so accurate data can be obtained.

In both peripheral blood and bone marrow assays, there was significant increase in the number of micronucleated erythrocytes in venlafaxine treated groups in comparison with control group.

There was significant increase in the number of micronucleated erythrocytes with increasing the dose of venlafaxine.

The number of micronucleated erythrocytes was significantly higher in subgroup IId than subgroup IIc which means that the dose of 100 mg/kg/day is highly toxic.

There was significant increase in the number of micronucleated erythrocytes in blood samples collected at GD 18 in comparison to blood samples collected at GD 14.

The DNA damage can be explained by the theory that serotonin is capable of inducing DNA cleavage with increasing the dose and duration of treatment.

The significant increase in the number of micronucleated immature erythrocytes in peripheral blood sample at GD 18 more than GD 14 is due to longer duration and exposure to venlafaxine.

The number of micronucleated immature erythrocytes in the bone marrow and the number of micronucleated erythrocytes in peripheral blood sample at GD 18 is explained by the theory stating that the spleen in mice does not remove micronucleated erythrocytes[43].

A previous study by Safarinejad MR,[45] agreed with the findings of the present work and stated that SSRI can impair semen quality and damage sperm DNA integrity.

A study by Kálmán J et al.,[45] was parallel with the findings of the present work. They studied the effect of venlafaxine on gene expression in human lymphocytes. They concluded that venlafaxine caused alterations in the expression of genes responsible for rapid adaptations to both external and internal stimuli, which is an important for neuronal plasticity.

In contrast, a study by Abdel-Wahab BA and Salama RH,[46] claimed that Long-term venlafaxine treatment in low therapeutic doses (5, 10, 20 mg/kg/day) can protect against stress-induced oxidative cellular and DNA damage by attenuation of oxidative stress and lipid peroxidation.

CONCLUSION

The present work revealed that in utero exposure to venlafaxine alters the heart development with an increase in the incidence of the cardiac anomalies as VSD, right ventricle hypertrophy and dilatation of pulmonary trunk.

It also induces major anomalies such as anophthalmia and anencephaly, especially in high doses.

A decrease in the placental weight and consequent decrease in the fetal body weight also have been associated with venlafaxine.

Venlafaxine is implicated to cause spontaneous abortion in high doses.

This study also demonstrates that venlafaxine induces DNA damage with increasing the dose and duration of treatment.

CONFLICTS OF INTEREST

There are no conflicts of interest

REFERENCES


الملخص العربي

تقييم السمية الجينية المحتملة وتشوه القلب الناتج عن عقار الفينلافاكسين على أجنة الفئران السوداء الحوامل

ملاحظات: نعيش بقرار قلادة، السيد على متولى، مها ضياء الدين أحمد، لبني محمد محمد علي عبد المطلب
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المقدمة: اكتسب الحمل مشكلة متشرطة عالمياً، ولكن فإن معدل تعاطي الأدوية المضادة للاكتئاب خلال الحمل قد ازداد، حيث أن في مصر تقريباً 20% تقريباً من النساء الحوامل يتعرضنً للاكتئاب خلال فترة حملهن. إن مثبتات إعادة امتصاص السيرتونين الانتقائية و مثبتات إعادة امتصاص النورابينورفين الانتقائية هما الأدوية الأكثر وصفاً عالمياً لعلاج اكتئاب الحمل. إن طريقة عمل هذه الأدوية غير مفهومة تماماً ولكن بصفة عامة فهي تعمل عن طريق منع نواقل السيرتونين و النورابينورفين.

الهدف من البحث: وحيد أن الدراسات المتاحة الآن غير كافية للربط بين العلاج بمضادات إعادة امتصاص السيرتونين الانتقائية ومثبطات عقار الفينلافاكسين، حيث أن زيادة في معدل حدوث خلل في الكروموسومات والتشوهات الخلقية في القلب. لذا كان الهدف من هذه الدراسة هو بحث تأثير الفينلافاكسين على الحمض النووي، وكذلك تأثيره المحتمل على تطور القلب في الجنين.

مواد وطريقة البحث: تم إجراء الدراسة على خمسين من الفئران السوداء الحوامل (C57BL/6) تم توزيع الفئران عشوائياً على احدى المجموعتين:

1. مجموعة تحكم: تم تشريح الاجنة و تقييم تركيب القلب.
2. مجموعة تم أعطائها عقار الفينلافاكسين بتركيزات (2 مجم/كجم، 3 مجم/كجم، 10 مجم/كجم، 100 مجم/كجم/يوم).

وقد تم استخدام اختبار النويات الجينية للكشف عن قدرة الفينلافاكسين في إحداث تلف للحمض النووي.

النتائج: أظهرت الدراسة الحالية أن مع زيادة تركيز عقار الفينلافاكسين وزيادة الجرعة يزيد بشكل ذو دلالة إحصائية معدل التشوهات الخلقية في القلب. في أجهزة الفئران السوداء كوجود ثقب في الحاجز بين البطينين، زيادة قطر الشريان الرئوي و تضخم في عضلة البطين الأيمن. تم تطبيق جميع المجموعات الثلاث، مما أظهرت الدراسة الحالية أيضاً زيادة ذو دلالة إحصائية في معدل تكون النويات الناتجة عن تلف الحمض النووي كنتيجة لتناول عقار الفينلافاكسين بطريقة تعمد.

الاستنتاج: إذا وجب على الأطباء أن يتخذوا قراراً صعباً يخص متطلبات إعادة امتصاص السيرتونين الانتقائية بشكل عام، وعقار الفينلافاكسين بشكل خاص لعلاج الاكتئاب خلال فترة الحمل مع الموازنة بين المخاطر و المنافع العائدة على الأم والجنين.

الملخص الإنجليزي

Evaluation of the Genotoxic Potential and Cardiomyopathy Induced by Venlafaxine on Pregnancy Rats

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Depression during pregnancy is a widespread problem worldwide and therefore the rate of taking antidepressant drugs during pregnancy has increased. In Egypt, about 20% of pregnant women are exposed to depression during their pregnancy. Although the mode of action of these drugs is not fully understood, it is generally accepted that they work by preventing serotonin and norepinephrine reuptake.

The aim of this study was to investigate the genotoxic potential and possible cardiac defects induced by venlafaxine in pregnant rats during pregnancy.

Materials and Methods: The study was performed on fifty pregnant black rats (C57BL/6) distributed randomly into two groups:

1. Control group: the fetuses were examined and their cardiac anatomy was assessed.
2. Group treated with venlafaxine at concentrations of (2 mg/kg, 3 mg/kg, 10 mg/kg, 100 mg/kg/day).

Results: The study showed an increase in the rate of congenital cardiac defects with increasing the concentration of venlafaxine and increasing the dose. The study also showed an increase in the rate of DNA damage as a result of taking venlafaxine at a dosage that exceeded the recommended dosage.

Discussion: Therefore, healthcare providers should take a cautious approach when prescribing selective serotonin reuptake inhibitors and venlafaxine, especially at high doses, considering the risk-benefit ratio for both mother and fetus.

References: