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Study of the effect of fluoxetine on liver enzymes in the blood serum of pregnant albino rats

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***Abstract*---**The current study examined the effect of fluoxetine on liver enzymes in pregnant female rats. 42 rats, including ten males, were used for inoculation only, while the number of females was 32 rats. Female rats were divided into two groups, the control group consisted of 8 rats. The fluoxetine-treated group of 24 females was divided into three groups. The first group included 8 pregnant female rats injected with fluoxetine at a concentration of 20 mg/kg of body weight from day 0 of gestation until day 7 or 18, and the second group also included 8 pregnant females injected with fluoxetine at a concentration of 40 mg/kg. of body weight from day day 0 of gestation until day 7 or 18, and the third group included 8 pregnant females injected with fluoxetine at a concentration of 60 mg/kg of body weight from day 0 of gestation until day 7 or 18, blood samples were collected on the 7 or 18 days From pregnancy from all animal groups to measure the following parameters: ALT, alkaline phosphatase, ALP, and aspartate aminotransferase (AST). The results showed that fluoxetine caused an increase in liver enzymes in pregnant rats, especially at a dose of 60 mg/kg of body weight. We conclude from the foregoing that fluoxetine caused an increase in liver enzymes because it is distributed throughout the body with higher levels in the liver, which may cause oxidative stress, which in turn increases these enzymes, and therefore caution should be taken against using the drug during pregnancy.

***Keywords*---**fluoxetine, liver enzyme, pregnancy.

Introduction

Fluoxetine (FLX) is the most common treatment used in depression, which has a prevalence of about 6.5 to 21% worldwide. Fluoxetine was first manufactured in 1971 by Eli Lilly & Company and was disclosed in 1974 as LY110140, also approved It was approved by the Food and Drug Administration in 1987 and introduced in the treatment of depression in early 1988. It is considered a popular drug in the treatment of depression [1,2]. It is classified as a selective serotonin reuptake inhibitor (SSRI), and its antidepressant effect is explained by its ability to desensitize serotonin receptors in the brain Presynaptic HT [3,4]. Depression is one of the most common medical complications during pregnancy and after pregnancy, i.e. childbirth, as it affects one in seven pregnant women, as the proportion of depressive symptoms in pregnant women reaches about 25% in developing countries, while it reaches 15% in developed countries [5] , and untreated depression during the period Pregnancy has negative effects on maternal and infant outcomes, including an increased risk of spontaneous abortion, low birth weight, growth retardation, and short gestational age [6,7]. Selective serotonin reuptake inhibitors (SSRIs) are generally recommended for the treatment of prenatal depression as they are widely used Broad [8]. Therefore, the current study aimed to show the effect of fluoxetine on pregnancy in general and on liver enzymes in particular, and whether the use of fluoxetine during pregnancy is safe or not.

Materials and working methods

In this experiment, 42 white rats were used, including ten males for insemination only, while 32 sexually mature females were brought from the College of Pharmacy - University of Karbala with ages of more than (9) weeks and weights (160) g and more for both sexes. Males and females were placed in separate cages and monitored for two weeks before starting the experiment in order to acclimatize and ensure that they are healthy and not pregnant. The floor of the cages was spread with sawdust, and the animals were placed under appropriate conditions in terms of temperature, ventilation, and lighting. All-female rats were divided into two main groups: the control group and the fluoxetine treatment groups: the control group included 8 female rats injected with normal saline 0.9% by intraperitoneal injection from day 0 to day 7 or 18. The group treated with fluoxetine consisted of 24 female rats and was divided into four groups. Females of the first group (G1) (8 rats) were injected with fluoxetine at a concentration of 20 mg/kg of body weight. The second group (G2) (8 rats) was injected with fluoxetine at a concentration of 40 mg/kg of body weight. The third group (G3) (8 rats) was injected with fluoxetine at a concentration of 60 mg/kg of body weight. Pregnant rats were sacrificed on the 7th or 18th day of gestation to see the effect of the drug on the fetuses. The level of ALT and AST enzyme activity in rats' blood serum was measured using method [9], while ALP enzyme activity level was estimated according to method [10].

Results and Discussion

Table (1) showed that the treatment of pregnant female rats with fluoxetine at doses of 20, 40, and 60 mg/kg of body weight led to a significant increase

(P<0.05) in the concentration of the aminotransferase enzyme in the blood serum compared with the control group, in contrast between The same table, showed that there was no significant difference in the dose of 40 mg/kg compared to the dose of 60 mg/kg. Table (1) showed that there was a significant effect (P<0.05) for the duration of pregnancy in the concentration of AST aminotransferase enzyme in the blood of pregnant female rats, where it was a significant increase (P<0.05) in the eighteenth day compared to the seventh day of pregnancy.

Table 1
Effect of fluoxetine on the concentration of AST (IU/L) AST in the blood of pregnant albino rats

groups / Duration	Control	Reciprocity Fluoxetine 20 mg/kg	Reciprocity Fluoxetine 40 mg/kg	Reciprocity Fluoxetine 60 mg/kg	average duration
Seventh day of pregnancy	83.8 2.95 ±	122.6 3.62 ±	129.4 5.84 ±	131.2 4.56 ±	116.7 2.23± a
Day 18 of pregnany	105.0 3.30 ±	116.6 3.72 ±	129.2 4.02 ±	139.6 2.73 ±	122.6 6.72± b
average totals	94.4 6.70± A	119.6 1.89± B	129.3 0.06± C	135.4 2.65± C	

Mean ± standard error
Different lowercase letters indicate the presence of significant differences vertically at the probability level (P < 0.05).
Different capital letters indicate a horizontal significant difference at the probability level (P < 0.05).

The results of the study showed that the treatment of pregnant rats with fluoxetine caused an increase in the enzyme transporter of the amino group AST, and these results were in agreement with the study [11,12]. This enzyme is in the bloodstream. Fluoxetine has been shown to alter energy metabolism in the liver mitochondria and cause potentially toxic effects when taken in high doses. [14] of the effects associated with fluoxetine doses of liver enzymes were also verified by giving (8 and 24 mg/kg) of the drug and indicated that the doses caused a significant increase in liver enzymes. On the other hand, study [15] disagreed with our results, as it showed that fluoxetine did not cause changes in liver enzymes in pregnant rats. Our results also contradicted study [16], which treated rats (males and females) by injecting fluoxetine at a concentration (5-10 mg/kg), which caused a decrease in liver enzymes. Especially the enzyme AST.

The study also indicated that the duration of pregnancy had a significant effect on the concentration of AST in the serum of pregnant rats. This study agreed with [17,18] who indicated that AST concentration levels increase slightly or moderately in the third trimester of pregnancy. Minor, which may be due to placental secretions. Study 19 also indicated an increase in AST concentration during labor (delivery), which may be caused by contractions of the uterine muscles. Table (2) showed that there was no significant difference (P<0.05) in the concentration of

ALT transporter enzyme for groups of pregnant female rats treated with fluoxetine at the doses of 20 and 40 mg/kg of body weight compared to the control group, and there was also a significant increase ($P < 0.05$) in the concentration of ALT transporter enzyme in the blood of pregnant female rats treated with fluoxetine at the dose of 60 mg/kg of body weight compared with the control group, while the same table showed that there was no significant difference in the dose 40 mg/kg compared to the dose 60 mg/kg. Table (2) also showed a significant effect ($P<0.05$) for the duration of pregnancy in the concentration of ALT transporter enzyme in the blood of pregnant female rats, where it was a significant increase ($P<0.05$) on the eighteenth day compared to the seventh day of pregnancy.

Table 2
Effect of fluoxetine on the concentration of ALT (IU/L) aminotransferase in the serum of pregnant albino rats

groups / Duration	Control	Reciprocity Fluoxetine 20 mg/kg	Reciprocity Fluoxetine 40 mg/kg	Reciprocity Fluoxetine 60 mg/kg	average duration
Seventh day of pregnancy	38.2 1.39±	40.6 1.21±	46.2 1.76±	45.2 5.82±	42.55 1.96± a
Day 18 of pregnany	40.8 1.04±	47.6 3.48±	50.4 4.34±	55.8 3.20±	48.65 2.79± b
average totals	39.5 0.82± A	44.1 2.21± A	48.3 1.32± AB	50.5 3.35± B	

Mean ± standard error
Different lowercase letters indicate the presence of significant differences vertically at the probability level ($P < 0.05$).
Different capital letters indicate a horizontal significant difference at the probability level ($P < 0.05$).

The results of the study showed that the treatment of pregnant rats with fluoxetine caused an increase in ALT transporter enzyme, especially the dose of 60 mg/kg, despite the approval of its safety. The use of high doses of fluoxetine was associated with many adverse effects, including insomnia, anxiety, nausea, vomiting, diarrhea and balance disorders, bipolar disorders, as well as liver and kidney failure[20]. Our results are consistent with the study[21], which showed an increase in ALT concentration in rats induced by fluoxetine, and our study is consistent with study [22], which indicated the occurrence of necrosis and ischemia induced by fluoxetine in the liver of rats when taken in different doses. This is due to the oxidative stress that causes the drug, or potentially fluoxetine and its receptor norfluoxetine, to be toxic at high doses and to have several effects on energy metabolism in rat liver mitochondria. Also, study[21] indicated that increased production of reactive oxygen species (ROS) by fluoxetine can damage cellular macromolecules such as proteins, DNA, and lipids that produce lipid peroxide. During pregnancy, fluoxetine crosses the placenta and is distributed within the fetus during organ formation and post-organ formation. It also acts on the ovary or hypothalamus-pituitary axis, leading to alterations in follicle growth

and ovulation[23]. Therefore, administration of the drug during pregnancy causes liver failure and damage. The results also indicated that there was a significant effect for the duration of pregnancy in the concentration of ALT aminotransferase enzyme in the blood of pregnant female rats, which was a significant increase on the eighteenth day. In the third trimester of pregnancy, this is due to the building of the enzyme and its release into the blood circulation by the placenta because the placenta contains high concentrations of this enzyme after birth, its concentration decreases and reaches normal values within two weeks [26,27].

Table (3) showed that treatment of pregnant female rats with fluoxetine at doses of 20, 40, and 60 mg/kg of body weight led to a significant increase ($P<0.05$) in the concentration of ALP in the serum compared to the control group. The same table also showed that there was no significant difference ($P<0.05$) for the duration of pregnancy in the concentration of alkaline phosphatase enzyme ALP in the serum of pregnant female rats on the eighteenth day compared to the seventh day of pregnancy.

Table 4-8
Effect of fluoxetine on the concentration of alkaline phosphatase (IU/L) ALP in the serum of pregnant white female rats

groups / Duration	Control	Reciprocity Fluoxetine 20 mg/kg	Reciprocity Fluoxetine 40 mg/kg	Reciprocity Fluoxetine 60 mg/kg	average duration
Seventh day of pregnancy	182.8 13.26±	227.0 13.58±	262.0 10.78±	255.6 10.76±	231.8 16.12±
Day 18 of pregnany	198.4 13.26	238.0 13.54±	254.2 10.91±	270.2 7.18±	240.2 13.77±
average totals	190.6 4.39± D	232.5 3.47± C	258.1 2.46± B	262.9 4.61± A	

mean ± standard error
Different capital letters indicate a horizontal significant difference at the probability level ($P < 0.05$).

The results of the study showed that fluoxetine caused an elevation of the alkaline phosphatase enzyme ALP. The alkaline phosphatase enzyme is an indicator of the bile duct and any change in it causes biliary liver damage or cholestasis. Our results correspond to [28] that showed an increase in the concentration of alkaline phosphatase in females treated with fluoxetine and the dose of 10 -20 mg/kg of body weight. He also showed that the drug caused damage to vital organs such as the liver, kidneys, and ovaries. [29] also indicated that giving fluoxetine to female rats leads to effects on liver enzymes and ovarian hormones, and the reason for this is that fluoxetine is distributed throughout the body with higher levels in the liver, causing oxidative stress, which in turn increases the concentration of alkaline phosphatase. ALP in the blood, and our results contradicted study [30,] which indicated that fluoxetine caused a decrease in the basal phosphatase enzyme ALP in the ovaries and uterus.

The results also indicated that there was no significant effect during pregnancy on the concentration of alkaline phosphatase enzyme ALP in the blood serum of pregnant female rats. ALP alkaline phosphatase is secreted by the placenta in the second and third trimesters through syncytiotrophoblasts, and this enzyme plays an important role in cell division. The cell is also responsible for the effective transport of phosphate and the transfer of globulin IgG from the mother to the fetus and helps in the absorption of nutrients, and this is important for the growth and formation of the fetus. The effectiveness of this enzyme in the serum by delaying the formation of the fetus in the womb, premature rupture of the membrane, and premature birth[31]. It also participates in the mobilization of carbohydrates and fat metabolites for use by the oocytes [32,33].

Conclusions

We conclude from the foregoing that fluoxetine caused an increase in liver enzymes in pregnant rats, especially at a concentration of 60 mg/kg, as it is distributed throughout the body with higher levels in the liver, which may cause oxidative stress, which in turn increases these enzymes. Be careful not to use the drug during pregnancy.

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