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# The Investigation into the Effect of Flouxetine on Quantity of Ovarian Follicles in Adult Female Rats

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**ABSTRACT**

Flouxetine is one of the antidepressants, which have been turned into one of the most frequently prescribed overdosing drugs in the world and millions of people throughout the world are inclined to pay a lot of funds for flouxetine and similar drugs. Flouxetine under Trade Name Prozac, which has been introduced at the end of 1980s, is one of the latest psychotropic drugs, which has made a lot of hue and cry in medical world. With respect to overdose of this drug and inadequate knowledge about quantity of ovarian follicles, it can be implied that the present research is intended to explore the effect of flouxetine drug on number of these follicles. 40 female rats (Vistar race) were divided randomly into 5 groups with equal size. The first group (control group) did not receive any drug. The second group (sample) was infused by distilled water. The experimental group I received 5mg/kg flouxetine per day; the experimental group II also received 10mg/kg flouxetine daily and the experimental group III received 20mg/kg flouxetine by intraperitoneal method per a kilogram of their body weight. After the end of this period, the rats were anesthetized and operated under biopsy and ovaries (left and right) were removed from their bodies and number of ovarian follicles was counted. The data that derived by means of SPSS software were analyzed and the results were expressed in some tables. The quantity of prenatal, secondary and atresia follicles showed no significant difference compared to control group, but the amount of prenatal and graph follicles and corpus luteum (yellow body) indicated significant reduction in comparison with control group in experimental group III, which received the maximum dose of drug. The results show that dose of flouxetine drug may reduce number of graph and prenatal follicles and corpus luteum, which reflect trauma in ovarian tissue.

**Key words:** Flouxetine, Ovarian follicles, Female rat

## INTRODUCTION

Unfortunately today, depression disorder is one of the contagious diseases among social classes of the people. To treat it, drug therapy is the best method of cure. Antidepressants are some group of drugs, which are taken by depressed patients so that the spiritual status has been highly improved in most of depressed patients by taking these drugs[1]. Antidepressants may reduce some chemical substances under title of neurotrans mitters in brain. The brain needs to these neurotransmitters for its normal activity. These drugs may extremely help the depressed patients by putting these neurotransmitters at their brain disposal[2]. Today, several types of antidepressant drugs have been made. The most common pharmaceutical groups are as follows: 1) Tricyclic Antidepressant (TCA); 2) Selective Serotonin Reuptake Inhibitor (SSRI) antidepressants; 3) Monoaminess Oxidase Inhibitors (MAOIS); and 4) Other drug groups (3). SSRI drugs may only affect on a kind of neurotransmitter called serotonin. These drugs are very effective in treatment of depression and compared to TCA drugs, these drugs have fewer side effects. The tranquilizing effect is little in these drugs and they do not cause

increased weight in patients and they have not adverse effect on heart the same as TCA drugs. Like TCA drugs, dose of these drugs should be taken cautiously by the patients, who suffer from epilepsy[4]. Similarly, these drugs may create some alimentary disorders at the beginning of treatment period. It may be seen some symptoms of diarrhea, nausea, and vomiting along with headache, restlessness (neurasthenia), and anxiety in the persons, who have taken these drugs. If these drugs are overdosed once, they may have fewer side effects than TCAs with fewer risks[5]. Flouxetine (HCL), with Trade Name of Prozac that was introduced at the end of 1980s, is the latest version of psychotropic drugs, which made a lot of hue and cry in medical world. This antidepressant has become as one of the most frequently prescribed overdosed drugs in the world and millions of people are ready to pay exorbitantly for it and similar drugs. In fact, the effect of flouxetine does not highly differ from TCA drugs but at the same time it is unique for this reason that it does not affect on a large range of neurotransmitters like TCA drugs, but it affects only on serotonin and to some extent on dopamine[6]. The most common side effects of flouxetine include headache, anger, anxiety, insomnia, vertigo, narcolepsy and fatigue, sense of excitation and lack of control in speech, behavior and emotions, concentration disorder, abnormal dreams, abnormal moves in face and or body, dry mouth, vomiting, constipation, diarrhea, anorexia, weight loss, abdominal pain, change in gustatory perception, symptoms of hypoglycemia, cardiac arrhythmia, inflammation, rash, itching, lumbago (backache), articular and muscular pains, sexual action disorder, urinary system infection, diuresis, menstrual cramps (dysmenorrhoea), mastoid pain or abnormal mastoid inflammation, abnormal lactation (milk secretion) in women, upper respiratory tract infection, coughing, asthma, bronchitis, sinusitis, fever, and nasal congestion. One can refer to some of paramount lesions caused by this drug including hyponatremia (due to syndrome of inappropriate secretion of antidiuretic hormone), increased risk of suicide, spasm (convulsion especially in old people), and widespread vasculitis involved in liver, kidney, and lung along with dermal rash. Likewise, it has been identified that flouxetine causes tremor, stimulation, invasive behaviors, hyperthermia, hidrosis, cardiac arrhythmia, vision loss, hair loss (trichotillomania), and disordered menstruation[7]. With respect to the abovementioned issues and unwanted side effects by this drug, the present investigation is conducted in order to explore the effect of flouxetine drug on quantity of ovarian follicles.

## MATERIALS AND METHODS

The current study has been carried out in vitro with fully randomly method. All the relevant professional ethics versus experimental animals have been observed in this investigation. 40 heads of adult female rats (Vistar race) with average weight (200g ± 5%) and age 100-120days were prepared from Jahrom Researches Center. These rats were placed in vitro in the animal house from Islamic Azad University in Jahrom Branch for period of 21days under experimental conditions including temperature 21±2 ºC and 12 hours under light and 12 hours in darkness cycles. The rats consumed standard nourishment (pellet). Similarly, the water was given to them in special glass bottle. Their cages were sanitized by alcohol (70%) thrice a week. 40 mg volume was attained as lethal dose of drug. Accordingly, the quantities of minimum, average, and maximum doses were determined in such a way that the maximum dose was identified as a half of lethal dose, the average dose as a half of the maximum dose, and also the minimum dose was characterized as a half of average dose.

### Flouxetine is a soluble drug in water

In this study, distilled water was used as solvent. All the solutions were prepared freshly every morning and infusion was done for 30 days.
The rats were divided into 5 groups with 8 members for each one as following:

### Control group (A)

This group did not receive any drug while they are similar to other groups in terms of all conditions for maintenance and their nutrition.

### Sample group (B)

They received distilled water daily based on weight of rat.

### Experimental group I ($C_1$)

This group received one capsule of 20mlg of the solved flouxetine in 4cc distilled water through intraperitoneal infusion per day.

**Experimental group II ($C_2$)**

They received one capsule of 20mlg of solved flouxetine in 2cc distilled water via intraperitoneal infusion every day.

**Experimental group III ($C_3$)**

This group received one capsule of 20mlg of solved flouxetine in 1cc distilled water through intraperitoneal infusion per day. (Table 1)

After the end of 21days period, the rats in all groups were anesthetized after weighting and operated under biopsy. The left and right ovaries were removed and stained by H&E method and then number of ovarian follicles was counted. One-way Analysis of Variance (ANOVA) was employed to compare among treatments and in order to conduct multiple comparisons among several groups; it was followed by t-test and Duncan test. ($P<0.05$) was considered as significance level. To analyze data and conducting statistical tests, SPSS software (version.18) was used.

## RESULTS

The results derived from variance number of prenatal, secondary, and atresia follicles indicated that there is no significant difference between experimental, sample, and control groups (Table 2).

Compared to control group, the experimental group III with concentration of flouxetine 20mg/kg flouxetine to indicated significant reduction in number of prenatal and graph follicles and corpus luteum ($P<0.05$).

**Table 1: The way of classification of animals**

| Grouping | Drug type and dose | Period of blood sampling |
|---|---|---|
| Control group | - | End of 30 days |
| Sample group | 1cc/kg distilled water | End of 30 days |
| Experimental group I | 5mg/kg flouxetine | End of 30 days |
| Experimental group II | 10mg/kg flouxetine | End of 30 days |
| Experimental group III | 20mg/kg flouxetine | End of 30 days |

**Table 2: The results derived from variance number of prenatal, secondary, and atresia follicles**

| Parameter | Control | Sham | Experimental I | Experimental II | Experimental III |
|---|---|---|---|---|---|
| Prenatal follicle (%) | 2.6±0.24 a | 2.1 ± 0.47a | 2.2 ± 0.36a | 2 ± 0.26 a | 1.8 ± 0.63 a |
| Primary follicle (%) | 9.2±0.58 a | 9.5 ± 1.5 a | 8 ± 1.6 a | 7 ± 2.3 a | 4.1 ± 1.1b |
| Secondary follicle (%) | 2.8±0.58 a | 2.1 ± 0.65 a | 2.9 ± 0.91 a | 2.4 ± 0.52 a | 1.2 ± 0.6 a |
| Graph follicle (%) | 6.4±0.87 a | 6.8 ± 0.79 a | 6.8 ± 0.40 a | 5.2 ± 1.4 a | 1.7 ± 0.28 b |
| Corpus luteum | 7.4 ± 1.2 a | 7.3 ± 1.3 a | 8.1 ± 1.3 a | 6.5 ± 0.78 a | 3.5 ± 0.86 b |
| Atresia follicle | 00 ± 00 a | 00 ± 00 a | 0.14 ± 0.14 a | 0.14 ± 0.14 a | 0.42 ± 0.29 a |

## DISCUSSION

Flouxetine drug has been widely prescribed to treat depression in the world during three recent decades. Due to long period of depression disorder, this drug may be taken by the patient during period of pregnancy as well[8]. The derived results from this study show that in comparison with control group, the rate of prenatal, secondary, and atresia follicles did not indicate significant difference, but a significant difference was seen in prenatal and graph follicles and corpus luteum compared to control group in experimental group III, which received the maximum dose of drug. With adhesion to very specialized Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) receptors, FSH and LH hormones may stimulate their target oocytes in membrane of target oocytes in ovary. The activated receptors may in turn accelerate the speed of secretion of these cells as well as growth and reproduction of these

cells. Approximately all these stimulating effects arise from activation of cyclic Adenosine Mono Phosphate (AMP) secondary messenger system in cellular cytoplasm. The gonadotropic hormones, particularly FSH, may accelerate follicular growth. The growth of follicles is under the influence of FSH and LH hormones and especially FSH hormones[9]. In this investigation, with respect to possible reduction in FSH hormone it can be concluded that as rate of FSH was reduced significantly, the quantity of primary and graph follicles was also significantly decreased. Secretion of LH hormone from hypophysis has been increased clearly before ovulation and doubled 6-10 times and after ovulation, the granulosa cells and the rest theca internal cells are quickly converted into corpus luteum cells under the influence of LH. These cells become bigger ten folds and are filled with lipid inclusions, which make them yellowish color appearance[10]. In the present research, number of corpus luteum cells has been generally reduced but this reduction is not significant in experimental groups I and II while a significant reduction is seen in experimental group III. With respect to the above-said issues, LH hormone is the major agent for creation of corpus luteum cells.

Successful differentiation of follicles depends on the presence of steroid and growth factors, which stimulate follicular differentiation and at the same time they cause protection of cells from apoptosis. The growth and differentiation of ovarian follicles are caused by trend of reproduction and differentiation of granulosa cells. Estrogenic hormones play the most essential role in regulation of growth, homeostasis, and planned apoptosis in ovary[11]. But due to insignificant nature of such an increase and probably due to time period for drug injection and with increase in time period of infusion, one could expect to see significant increase in quantity of atresia follicles.

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