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Study the possibility of the effect of fluoxetine on the process of implantation of the blastocyst in the uterus of pregnant albino rats?

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***Abstract*---**The current study dealt with knowing the effect of fluoxetine on the process of implantation of the blastocyst in the uterus of pregnant rats, which occurs in the rat on the sixth day of pregnancy because the implantation of the blastocyst is a very critical period of pregnancy. 26 females and male rats were used. Female rats were divided into two groups, the control group, and included 4 rats injected with the physiological solution inside the peritoneal cavity from day zero of pregnancy. The treatment group of 12 females was divided into two groups, the first included 4 females who were injected from day 0 of pregnancy with fluoxetine 20 mg/kg of body weight, and the second also included 4 females who were injected from day 0 of pregnancy with 40 mg/kg of body weight, and the third also included 4 females. From day 0 of pregnancy, she was injected with fluoxetine 60 mg/kg body weight. The histological technique was applied to uterine sections on the 7th day of pregnancy, and samples were stained with hematoxylin-eosin stain. The results on the seventh day of pregnancy for the control and fluoxetine groups showed the same results through implantation and formation of decidual tissue in the endometrium first in the anti-mesoeterium region, which is an indicator of the success of implantation, while the decidual tissue was in the highest degree of growth and development. We conclude this study. The use of fluoxetine does not affect the process of implantation within the endometrium. However, it may have negative effects, which are expected to occur in later periods of pregnancy.

***Keywords*---**blastocyst, fluoxetine, implantation, pregnant, albino rats.

Introduction

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) antidepressant approved in 1987 by the Food and Drug Administration (FDA) and introduced in the treatment of depression in early 1988 and is used in the modern treatment of major depression, including pediatric depression [1,2] . Fluoxetine and its receptor norfluoxetine have a long half-life, with a half-life of fluoxetine from 2 to 4 days after a single dose, while its active metabolite norfluoxetine has a longer half-life of 7 to 9 days [3]. Fluoxetine is used for the prevention and treatment of many disorders, including premenstrual dysphoric disorder, anxiety disorders, eating disorders, as well as premature ejaculation in men [4,5,6]. While the most common use of fluoxetine is depression, and in general, untreated depression during pregnancy has negative effects on maternal and infant outcomes, including increased risk of spontaneous abortion, prematurity, low birth weight, small gestational age, and fetal growth retardation [7,8]. Therefore, the aim of the current study is to know the effect of fluoxetine on the stages of implantation of the blastocyst in pregnant egg rats on the seventh day of pregnancy, and is its use considered safe for pregnant women? The implantation period of the blastocyst is a very critical period of pregnancy. 15% of pregnancy loss cases are attributed to non-implantation of the blastocyst [9,10]. Successful implantation depends on a balance between the stage of development of the embryo itself and the complex series of cellular molecular events that occur in the uterus [11].

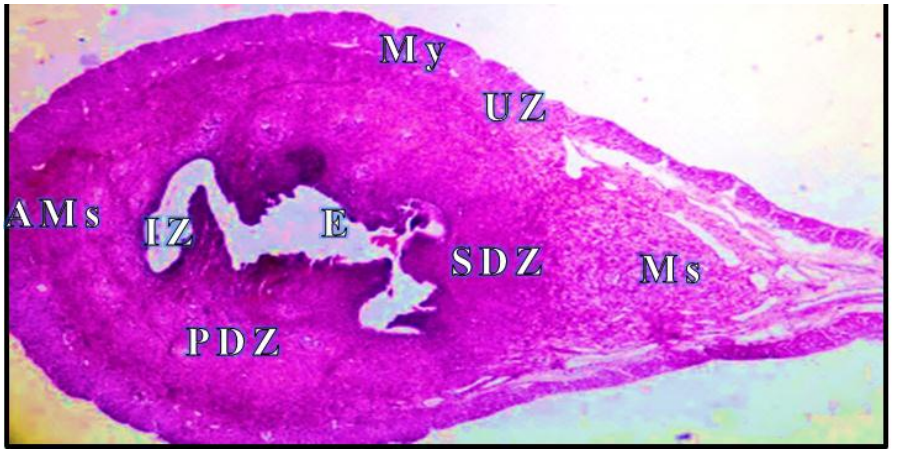
Materials and working methods

The anesthetic chloroform was used when sacrificing pregnant females from the control and treatment groups. After anesthesia, pregnant rats were placed in a dissection dish and a longitudinal incision was made with sharp scissors in its abdomen to extract the two uterine horns containing the embryos for the purpose of collecting them, then the fetal membranes were removed by autopsy tools, a sample was saved The uterus containing the embryos in the beginning after their removal from the animal in a 10% formalin solution for 48 hours. Then the samples were placed in solutions with increasing concentrations of ethyl alcohol. The implanted blastocysts and embryo samples were placed with two types of stabilizers: 10% formalin solution. The samples were passed according to the method of histological technology for embedding in paraffin wax. Tissue sections, cut to a thickness of 5 microns, were colored with hematoxylin and eosin.

Results and Discussion

The results of histological slicing taken from the implantation site of female white rats of the control group, colored with hematoxylin-eosin for the seventh day of pregnancy, showed the results of the normal pregnancy with regard to the formation of the decidual tissue. Four main areas can be identified first: the primary decidual zone (PDZ), which are decidual tissue cells that are compact and tightly compressed, and they surround the blastocyst and the endometrium, as no blood vessel was observed between the cells of this zone. Secondary decidual zone (SDZ) This zone is located between the primary decidual tissue and the zone Undifferentiated zone (UZ) This area is characterized by the presence of blood vessels and interstitial space. Third, the implantation zone (IZ) is a small

area surrounding the fetus and adjacent to it on the side of the endometrium. Fourth, is the undifferentiated zone (UZ) The cells of this zone are small in size and located between the secondary decidual tissue zone and the muscular layer of the uterus, as shown in the picture(1).

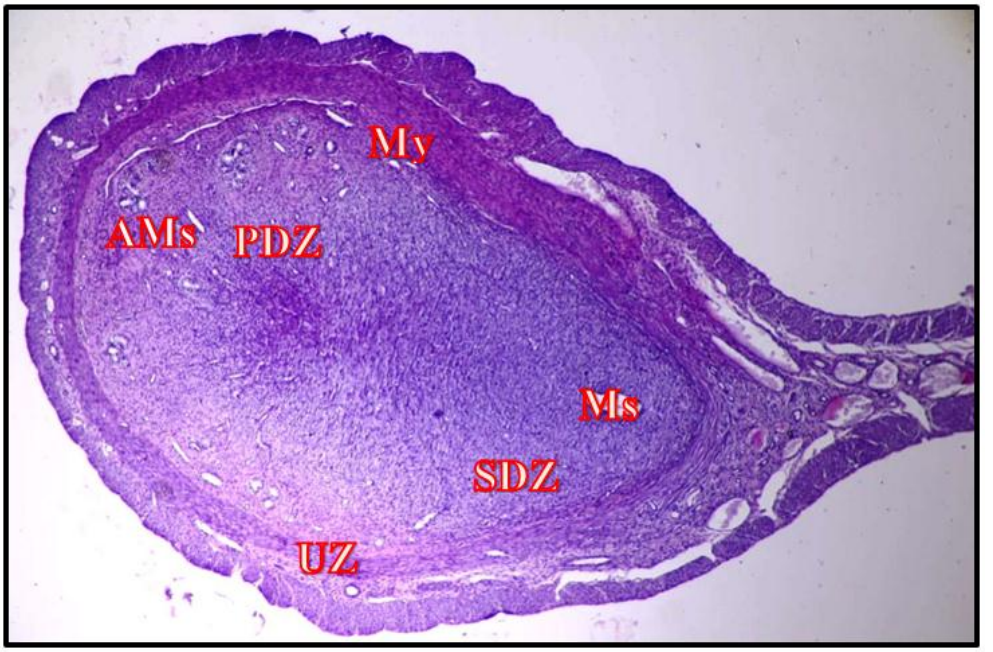


Picture 1: Transverse sections of the uterus of a pregnant female rat on the seventh day of pregnancy showing the distribution of the main areas of decidual tissue in the endometrium and the occurrence of the decidual reaction, (PDZ) primary decidual tissue region (SDZ) secondary decidual tissue region (IZ), implantation region, Undifferentiated area (UZ), (E) fetal, (Ms) mesometrium side, (AMs) anti-mesometrium side, (My) tunica myometrium, color H&E - 4 X

While the results of the groups treated with fluoxetine at a concentration of (60,40,20) mg/kg showed the normal formation of decidual tissue compared with the control group (Picture 1). It shows that the stromal cells in the endometrium have undergone modifications to turn into decidual tissue, which is an important indicator of the success of implantation in the anti-mesometrium part of the uterus. The four main regions of the decidual tissue can be identified as shown in pictures (2), (3), and 4).

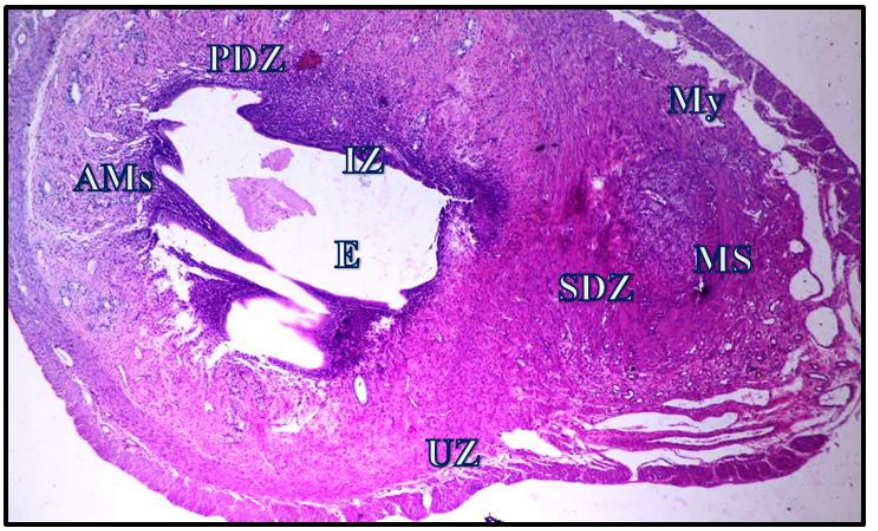
Picture 2. Cross-sections of the uterus of a pregnant female rat on the seventh day treated with fluoxetine at a concentration of 20 mg/kg.

The distribution of decidual tissue regions in the endometrium is noted, (PDZ) primary decidual tissue region (SDZ) secondary decidual tissue region (IZ), implantation region, UZ Undifferentiated area (E) fetal, (Ms) mesometrium side, (AMs) anti- mesometrium side, (My)) tunica myometrium, H&E - 4 X.



Picture 3. Cross-sections of the uterus of a pregnant female rat on the seventh day treated with fluoxetine at a concentration of 40 mg/kg

The distribution of decidual tissue regions in the endometrium is noted, (PDZ) primary decidual tissue region (SDZ) secondary decidual tissue region (IZ), implantation region, (UZ) undifferentiated area (E) fetal, (Ms) mesometrium side, (AMs) anti- mesometrium side, (My) tunica myometrium, H&E - 4 X.



Picture 4. Cross-sections of the uterus of a pregnant female rat on the seventh day treated with fluoxetine at a concentration of 60 mg/kg

The distribution of decidual tissue regions in the endometrium is noted, (PDZ) primary decidual tissue region (SDZ) secondary decidual tissue region (IZ) and implantation region, (UZ) undifferentiated area, (E) fetal, (Ms) mesometrium side, (AMs) anti- mesometrium side,(My) tunica muscularis of the uterus. H&E - 4 X.
The results of the histological sections of the current study showed that the drug fluoxetine at a concentration of (60,40,20) mg/kg did not affect pregnancy in its early stages, specifically on the seventh day. These results are consistent with findings [12,13] which indicated that women treated with fluoxetine during the first trimester had no increased risk of spontaneous pregnancy loss or major fetal abnormalities. In other words, the drug fluoxetine did not interfere with the implantation process that occurred on the sixth day of pregnancy, which is one of the basic processes in the success of pregnancy, especially in its early stages. This is what the researchers indicated [14,15] and that a successful pregnancy consists of coordinating three interrelated processes: the formation of the fetus, the formation of the placenta, and the formation of the decidua from the mother's tissues.

The placenta and the formation of decidual tissue from maternal tissue, which was observed in this study was the proliferation and differentiation of endometrial cells to form decidual cells in both the control group and the group treated with fluoxetine. One of the prominent signs of pregnancy, especially in animals with a placenta of the haemochorial placenta, is that any success of the implantation process and the development of the fetus is directly related to the formation of the deciduous tissue that occurs through morphological and functional differentiation in the endometrium, and this, in turn, leads to the uterus accepting the fetus in it. [16,17]. The comparison of the histological sections of the results of the study of the groups treated with fluoxetine on the seventh day of pregnancy with the variables in the deciduous tissue for the same period in the control group clearly shows us the steps and stages in which the deciduous tissue plays and its important roles in it, as is the case in the normal pregnancy of rats[18] .

The results of the current study also showed that the uterine cross-sections of mice on the seventh day of pregnancy were characterized by an increase in the number of stromal cells in the endometrium, which suffered from morphological and functional changes to turn into a decidual tissue, in addition to a narrowing of the uterine cavity with the absence of bundles of colloidal fibers outside the cells. The decidual tissue cells were characterized by the narrowness of the space between them and the adhesion of cells and their accumulation with each other, and the decidual tissue appeared in both regions of the uterus (the uterine mesenteric and anti- mesometrum uterine regions), but it is more abundant in the mesometrial decidual zone, which is represented as occupying A triangular space in the endometrium located between the implant as a new pole and the muscular layer of the uterus as another pole [18,19].

Whereas the secondary decidual tissue area (SDZ) and as shown in the pictures (2) ,(3) and (4) is characterized by the presence of a large number of blood vessels in this area, and there is also an interspace between the decidual cells and the blood vessels that work on Increasing the arrival of nutrients through it, which helps the fetus in the development and growth and its movement towards the mesenteric region of the uterine lining, in which the formation of the uterine decidual mesenteric tissue will be completed, in which vessels and blood sinuses abound, and their extension with the largest blood vessels in the mesenteric triangle [20,21]. Where the triangle of the uterine mesentery is close to the sources of blood supply and nutrition from the mother's side, which comes through the uterine arteries and the branches of the spiral arteries, so it is important in the period of implantation [9], and this process is planned for the emergence of the decidual tissue, which usually begins with the proper growth and formation of the endometrium through the implantation of the cyst Urumi [17]. And the important balance between the two pregnancy hormones (progesterone and estrogen) works to increase the number of fibroblast cells in the endometrium, which are morphologically and functionally differentiated to be ready for implantation of the blastocyst [22,23].

Conclusions

The drug fluoxetine during this period of pregnancy did not affect the implantation process, despite these results, caution should be taken against the use of drugs during pregnancy, and the drugs can cause many problems for the fetus, including intrauterine growth restriction, premature birth, and preeclampsia.

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