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Experimental Research Article

The impact of adolescent fluoxetine administration on reproductive abilities and *VASA* gene expression

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ABSTRACT

Introduction: Fluoxetine (FLX) is a commonly used antidepressant drug prescribed to treat psychiatric disturbances. According to the findings of several studies, the present work is designed to assess the influences of treating FLX during adolescence on reproductive hormone levels, ovarian and testicular tissues, and *VASA* gene expression in both sexes.

Methods: FLX was administered (5mg/kg/day, gavage) during adolescence (on postnatal days 21-60). After the treatment duration, blood samples were collected to measure sexual hormones. Ovarian and testicular samples were taken for histological and PCR studies.

Results: Our results indicated that FLX decreased the level of progesterone in female rats, while the level of estradiol was not changed through FLX administration. The testosterone level was decreased in FLX-treated male animals. FLX also decreased the *VASA* gene expression in both sexes, but this effect was significant in female rats. Besides, our findings showed the potency of FLX in inducing tissue damage, degeneration of follicles, and hypospermatogenesis.

Conclusion: Therefore, treatment with FLX during adolescence leads to a decrease in reproductive activities during adolescence.

Keywords:
Fluoxetine
Sexual hormones
VASA gene
Sex differences
Adolescence

Introduction

Fluoxetine (FLX) and other selective serotonin reuptake inhibitors (SSRIs) are prescribed as preferred drugs for several mental health conditions, such as obsessive-compulsive behavior, anxiety, major depression, panic disorder, etc. Side effects of long-term use of these drugs have been shown on several body organs and reproductive abilities (Karimipour et al., 2020; Safarinejad, 2008).

Adolescents have a much higher prevalence of anxiety

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disorders than adults, indicating a susceptibility to the onset of various types of psychopathology during this life span. Adolescence is considered a sensitive period for developing cognitive disorders due to several deviations that can occur during the normal maturation of the adolescent brain and some of its behavioral characteristics (Kryst et al., 2022). The transition from puberty to adulthood is linked to gonadal and behavioral maturation. The development of the biological clock, together with permissive signals that provide information about physical growth, energy balance, and seasonality, regulates the rise time in activity of gonadotropin-releasing hormone neurons at puberty onset, which leads to gametogenesis and improves gonadal steroid hormone secretion (Sisk and Foster, 2004).

Anti-depressants are widely used because depression is the most common psychiatric disorder identified by physicians, especially in adolescents (Zhang et al., 2018). Although there is a wide range of medications that are useful for treating depression in adults, only SSRIs are currently approved by the Food and Drug Administration for the treatment of major depressive disorder in children (Kryst et al., 2022). Antidepressants such as FLX have several curative effects and side effects, for example, sexual disorders and body weight alterations that limit the use of this drug. The FLX administration also changes male hormones and testicular factors that are vital for sperm creation and male fertility (Ferguson, 2001; Monteiro Filho et al., 2014; Sadegzadeh et al., 2020). Experimental investigations have revealed that the prescription of FLX for mothers leads to the creation of side effects of the drug on the male reproductive organs' abilities (Karimipour et al., 2020; Ramos et al., 2016). The activity of the hypothalamic-pituitary-adrenal system was changed through adolescent treatment with SSRIs, and following that, the blood levels of sexual hormones, for example, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone hormone decreased (Pawluski et al., 2012). In other documents, it has been revealed that the administration results in the induction of toxicity in maternal and fetal tissues and the reduction of male sexual behaviors (Harris et al., 2012; Müller et al., 2013). Similarly, the FLX administration results in a decline in FSH and testosterone hormones. These hormonal changes lead to spermatogenesis impairment and sperm motility reduction. In addition, the reproductive organs' weight decreases (Bataineh and Daradka, 2007; Beeder and Samplaski, 2020). FLX administration causes different side effects in the testicular and body systems. Significant testicular atrophy and spermatogenesis reduction can also occur with the treatment of FLX (El Sayed et al., 2021).

The DEAD-box protein, as a member of the RNA helicases family, is characterized by motifs in various cellular processes, for instance, transcription, processing of pre-mRNA, biogenesis of ribosomes, translation initiation, and organelle functions (Rocak and Linder, 2004). *VASA* is an associate of the DEAD box protein family and was first indicated to be important for female germ cell progress in Drosophila (Lasko and Ashburner, 1988). Another study revealed that *VASA* is required to develop male germ cells in mice. Genetic omission of the *VASA* gene leads males to display reproductive insufficiency with a loss of sperm production (Tanaka et al., 2000). In addition, this gene is responsible for a wide range of molecular activities. One of the main functions of the *VASA* protein is to determine germ cells and their functions, which remain stable during germ cell growth and are found in spermatids and oocytes after mitosis in adult rats (Chen et al., 2022; Gustafson and Wessel, 2010; Onohara et al., 2010). It is considered an ideal molecular marker for detecting primordial germ cell (PGC) signaling, germ cell development, specification, and function (Zhiquan et al., 2016).

Although studies of pharmacological treatments for psychiatric disorders in children and adolescents have expanded significantly in the last few years, there are major gaps in our knowledge of the adverse effects of these medications on sexual abilities. However, information from adult research on psychiatric disorders can increase our understanding of pharmacological treatments for psychiatric disorders in children and adolescents. Insufficient research is seen on these medications' safety, side effects, and effectiveness in prepubertal individuals. Consequently, the present investigation is designed to assess the impact of prolonged FLX administration, the prototypical serotonin reuptake inhibitor during adolescence, on serum levels of gonadal steroid hormones, histopathology, and *VASA* gene expression in rats' ovaries and testes.

Materials and Methods

Animals

We obtained male and female Wistar rats from the

Iranian Pasteur Animal House (Tehran, Iran). The rats were housed at a standard temperature (23 ± 1°C) and a 12-hour light-dark cycle. They had access to sufficient food and water. The males and females were housed in a large cage for breeding, and after that, each pregnant female animal was kept individually in a standard cage. After the birth of the puppies, they were culled to 5male and 5 female pups. The females were weaned on PND 21 and were kept together in a large cage for matching. Based on the method used in our previous research, most female rats have the same estrous cycle (Sadegzadeh et al., 2020). This study was approved by the Ethics Committee of Ardabil University of Medical Sciences (Ethics code: IR.ARUMS.REC.1399.314).

Laboratory animals and drug administration

Thirty-two healthy male and female puppies were organized into 4 groups and were used in the present work: two groups of males and females were treated with FLX hydrochloride (5mg/kg/day, gavage). The other two groups of male and female pups underwent oral gavage of distilled water once daily from postnatal day (PND) 21 to PND 60 (N = 10 in each group) and were assigned as controls. FLX was freshly prepared daily by dissolving it in distilled water. We chose the FLX dose based on the previous work protocol and stated oral drug management, but rats received FLX daily by gavage to ensure precise medication administration.

FLX provides the most effective results in humans when administered at a dose of 20 mg (approximately 0.3–0.9 mg/kg). However, due to variations in liver metabolism, drugs are typically prescribed at 10-fold higher doses in rats. Therefore, the appropriate clinical dose of FLX is 3–9 mg/kg. A FLX dose of 5 mg/kg is commonly used in rat experimental studies and is effective in inhibiting serotonin reuptake. After 40 days of exposure to FLX, the rats were euthanized under deep anesthesia (Sadegzadeh et al., 2020).

Determination of serum levels of sexual hormones

Blood samples were obtained on postnatal day 61. The blood samples were collected by venous sinus perforation and placed in a gel coagulant tube (HEBEI XINLE SCI & TECH CO, China). After collection, the blood samples were centrifuged (2000 x g for 15 min at 4ºC), and the serums were stored at -70 °C. The concentration of estrogen, progesterone, and testosterone was analyzed by Enzyme-Linked Immuno-Sorbent Assay (ELISA) (Estrogen ELISA, DIA.METRA S.R.L DKO 003), (Progesterone ELISA, DIA.METRA S.R.L DKO 004), (Testosterone ELISA, DIA.METRA S.R.L DKO 002) using absorbance reading (Epoch Microplate Spectrophotometer, United States, 450 nm).

Histopathological analyses

The ovary and testis tissues were fixed in neutral formalin 10%, embedded in paraffin, and dehydrated in ascending grades of alcohol. Sections of 5 µm were prepared, stained with hematoxylin eosin, and examined by a pathologist using a light microscope in a blinded manner (Monteiro Filho et al., 2014).

Molecular examinations

For molecular studies, the animals were anesthetized using a low-pressure flow of CO2 in a specific jar. After euthanizing, the ovaries and testis tissues were rapidly isolated on a block of ice, and one of them was frozen in liquid nitrogen. The frozen tissues were stored at -80 ˚C until homogenization for RT-PCR examination, and another one was stored in 10% formalin for pathological studies (Sadegzadeh et al., 2020).

Semi-Quantitative PCR

The entire ovary and testis RNA were extracted using the guanidine isothiocyanate-phenol-chloroform method with RNX + reagent following the manufacturer's protocol, as described in a previous study (Sadegzadeh et al., 2020). The RNA samples were treated with 50 µl of RNase-free water to remove DNA contamination. The concentration of purified RNA was determined using spectrophotometry (Thermo-Nano Drop 2000c-spectrophotometer, United Kingdom). Finally, the RNA samples intended for cDNA synthesis were stored at -20 °C.

The reverse transcription reaction was carried out with a first-strand cDNA

synthesis kit (SinaClonBioScience, Cat. No: RT5201) as stated in the manufacturer's instructions. Reactions were completed using selective forward and reverse primers for the *VASA* and *GAPDH* genes.

The Sinaclon synthesizes all sequences of the primer. The amplification protocol included an initial denaturation step of 5 minutes at 95 °C, followed by 34 cycles of PCR (30 seconds at 95 °C, 30 seconds at 62 °C, and

TABLE 1. The PCR primer sequences

VASA	Forward	5′- GGATGTTCCTGCGTGGTTAGA 3′
	Reverse	5′- GTGTTCAGTGTGTTCTTGCCC-3′
GAPDH	Forward	5′- CCAATGTATCCGTTGTGGAT-3′
	Reverse	5′- CATCAAAGGTGGAAGAATGG-3′

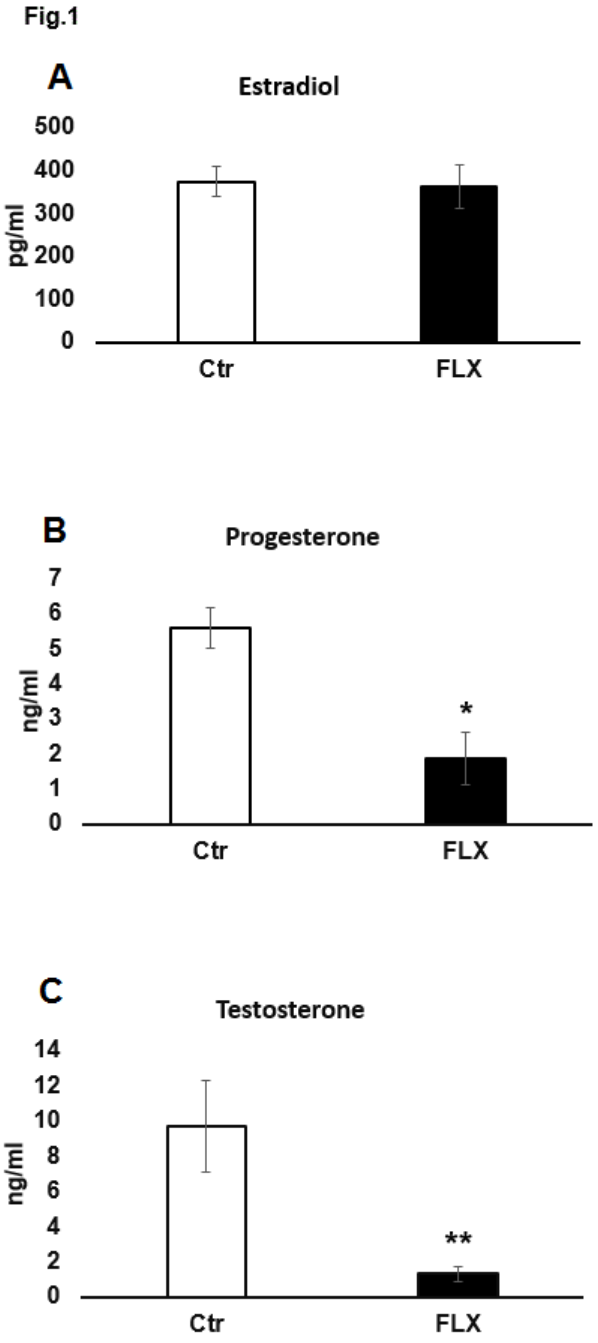

FIGURE 1. The effect of FLX on serum levels of estradiol (A), progesterone (B), and testosterone (C) in FLX-treated rats. Female rats treated with FLX showed no change in estradiol levels (A), but progesterone levels were significantly decreased in FLX-treated rats compared to the control group (B). In addition, testosterone levels in male rats were significantly reduced in the FLX-treated group versus the control group (C). *P< 0.05 and **P < 0.01 versus the control group. Data represent the mean ± SD (n = 8 rats per group). Ctr: Control, FLX: Fluoxetine.

TABLE 2. The impact of FLX on the testicular and ovarian weight of treated rats

Groups	Control	FLX
Testicular weight (g)	1.281±0.027	1.380±0.026*
Ovarian weight (g)	0.041±0.003	0.048±0.002

The results were reported as mean ± standard deviation. Treatment with FLX increased the weight of the testis in rats. *P < 0.05 versus the control group (n = 10 rats per group).
FLX; Fluoxetine

30 seconds at 72 °C), and a final extension step of 3 minutes at 72 °C. This was analyzed using Lab Works analyzing software from UVP in the UK.

Statistical analysis

Our results were expressed as mean ± SD The Kolmogorov-Smirnov test was used to assess the normality of the data. The data are approximately normally distributed. Therefore, we used an unpaired independent sample t-test to compare the mean of quantitative variables such as estradiol, progesterone, testosterone, and *VASA* gene expression between the control and FLX groups. A p-value < 0.05 was considered statistically significant.

Results

The effect of FLX on ovarian and testicular weight

As shown in Table 2, the ovarian and testicular weights in the FLX group were higher than those in the control group. However, this change was significant in the testes of FLX-treated rats compared to the control group (P<0.05).

The influence of FLX on estradiol, progesterone, and testosterone levels

The FLX-treated female rats showed no changes in estradiol levels (Figure 1A). But, the levels of progesterone were significantly reduced in FLX-treated rats compared to the control group (P< 0.05, Figure 1B). Additionally, testosterone levels in male rats decreased significantly in the FLX-treated group compared to the control group (P< 0.01, Figure 1C).

The effect of FLX on the VASA gene expression in testicular and ovarian tissues

FLX reduced *VASA* gene expression in testicular tissues of males, but this difference was not significant (Figure 2A). Furthermore, this drug significantly down-regulated *VASA* gene expression in ovarian tissues when compared to the control group (***P < 0.001, Figure 2B).

The effect of FLX on histopathological alterations in ovarian and testicular tissues

Photomicrographs of the testicular and ovarian parenchyma in control and FLX-treated rats are shown in Figures 3A and 4A. Histopathological examinations showed normal ovarian and testicular tissue structures in the control group (Figures 3A, 4A). Our results also indicated that administering FLX during adolescence caused tissue damage and degenerated follicles in females. Seminiferous tubules cross-section and lymphatic space in the testis of the control and FLX groups are indicated in Figures 3B and 4 B. Treatment with FLX also led to the detachment of the cell organization of the germinal epithelium. As a result, there was incomplete maturation and hypo-spermatogenesis in male animals (Figures 3B, 4B).

Discussion

The results of the present work revealed that administration of FLX during adolescence decreased progesterone levels in female rats, while the effect of FLX on estradiol levels was insignificant. FLX also decreased *VASA* mRNA expression in ovarian tissue and destroyed ovarian follicles. Administration of FLX in adolescent male rats resulted in decreased testosterone levels, immature sperm production, and hypospermatogenesis. In addition, treatment with FLX decreased the thickness of the germinal epithelium. These findings are in agreement with those stated by Ramos et al.(2016). They have shown that maternal administration of FLX reduces the number of Sertoli cells in weanling and pubertal animals, and this study recommends that this change may be associated with consequent impacts on spermatogen-

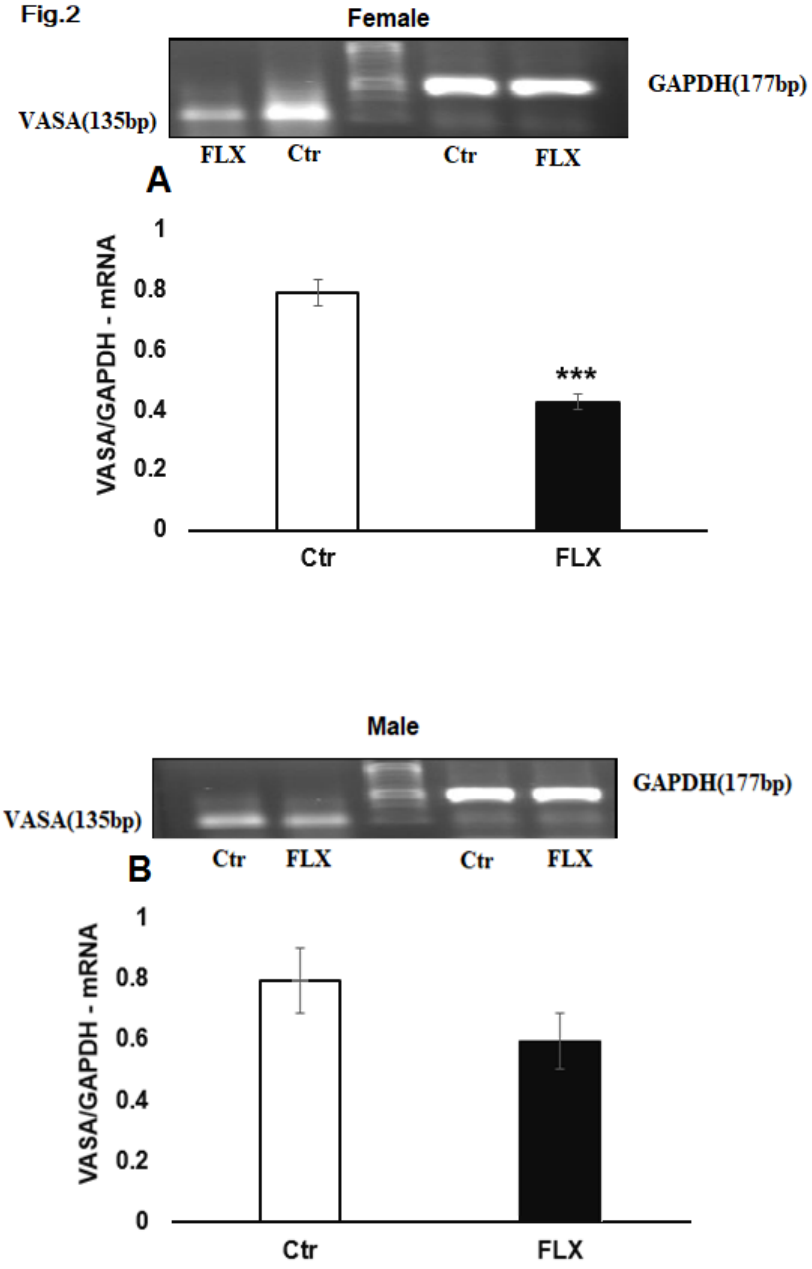

FIGURE 2. The effect of FLX on *VASA* gene expression in testicular and ovarian tissues of male and female rats. Administration of FLX in adolescent male rats decreased the *VASA* gene expression compared to the control group, but this difference was not significant (A). The effect of treatment with FLX during adolescence on *VASA* gene expression in ovarian tissue indicated that post-weaning FLX administration down-regulated *VASA* gene expression in ovarian tissue (B). Data represent the mean ± SD. ***P < 0.001 versus the control group (n = 4-5 rats per group). FLX: Fluoxetine

esis (Ramos et al., 2016).

Depressive disorders are the main cause of death in the pediatric age group, with a prevalence of 8.3%. This prevalence is higher in adolescents than in adults (Costello et al., 2003). In addition, antidepressants, serotonin reuptake inhibitors, are the first-choice treatment for most depressed patients. In recent years, the use of this drug in adolescents has been expanding (Edinoff et al., 2021), and there is little information about the sexual side effects of these drugs before puberty. Additionally, human studies in the pediatric population are insufficient due to moral concerns. Thus, along with studies in

Fig3

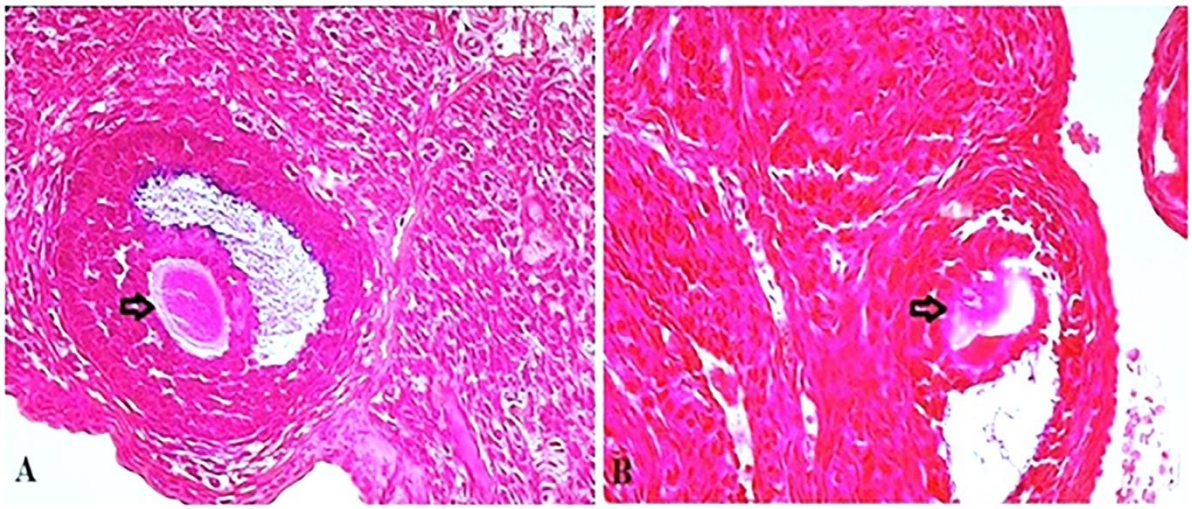

FIGURE 3. Histopathological evaluation of ovarian tissue. Ovarian sections are stained with hematoxylin and eosin (H&E). The normal ovarian tissue structure and the healthy ovarian follicle are shown by the arrow in the control group (A). FLX-administered rats had degenerated follicles shown by the arrow (B) (40 × H&E) (n = 4-5 rats per group). FLX: Fluoxetine

Fig4

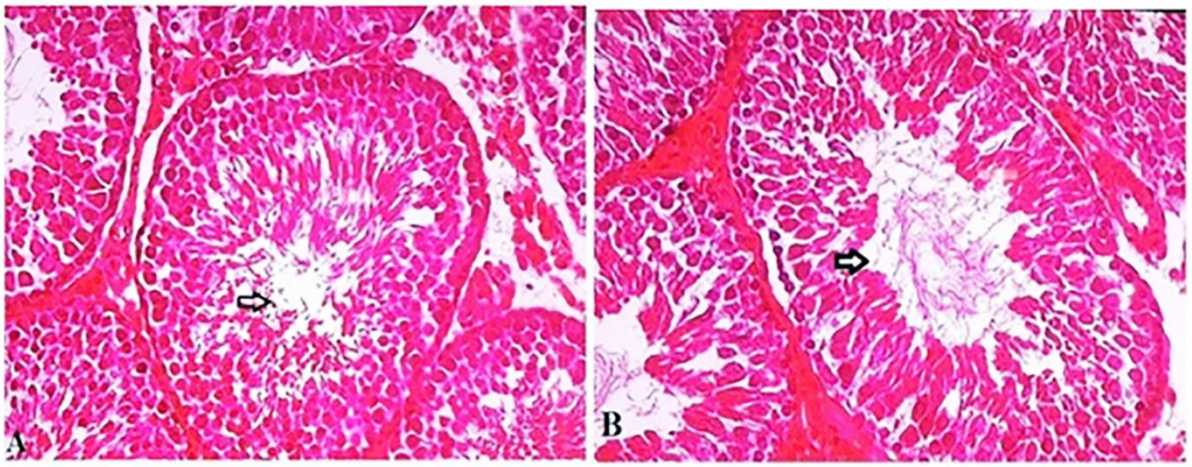

FIGURE 4. Histopathological evaluation of testicular tissue. Testicular sections are stained with hematoxylin and eosin (H&E). The normal spermatogenesis and alive spermatozoa in the control group are shown by the arrow (A). FLX-administered rats had incomplete maturation of sperm and hypo-spermatogenesis. FLX also caused a decrease in the thickness of the germinal epithelium, shown by the arrow (B) (40 × H&E) (n = 4-5 rats per group). FLX: Fluoxetine

humans, the impacts of SSRIs on adolescents have to be examined in experimental animals (Kryst et al., 2022). Besides, the previous findings show that compared to humans, rats grow rapidly and reach sexual maturity around the sixth week (Sengupta, 2013). Accumulating evidence suggests that treatment with FLX and other antidepressant drugs negatively affects semen parameters and shows a spermicidal effect. In addition, chronic intake of FLX led to a reduction in reproductive organ weights, spermatogenesis, FSH, and testosterone levels in rats (Beeder and Samplaski, 2020; Kumar et al., 2006; Milosavljević et al., 2022). Sexual impairments such as

loss of libido, delayed or absent ejaculation, impaired orgasm, damaged testicular organization, and decreased Sertoli cell numbers are probable adverse effects of antidepressant therapy such as FLX, which may cause infertility in adults (Taylor, 2006). Evidence suggests that the toxic effects of antidepressants can affect redox imbalance, disrupt cellular energy status, reduce total ATP production, and impair mitochondrial function. The side effects of antidepressants may be related to the effect on ATP synthesis by inhibiting oxidative phosphorylation in mitochondria (Arimochi and Morita, 2006; Sołek et al., 2021).

Testicular destruction affected by FLX was related to free radicals and antioxidant imbalance. The decrease in testosterone may result from the impact of FLX on Leydig cells or the influence of ROS on testicular steroidogenesis (Bataineh and Daradka, 2007). Besides, administration of this drug prompts alterations in the pituitary-adrenal system in young animals and diminished serum levels of LH, FSH, and testosterone hormones. FLX also causes reproductive toxicity and reduces sexual behavior in animals. In addition, it disrupts spermatogenesis, reduces sperm motility and viability, lowers sex hormone levels, and leads to hypospermatogenesis and infertility (Karimipour et al., 2020).

In the present study, an appropriate dose (5 mg/kg) of FLX was administered to adolescent (PNDs21-60) rats to explore the impacts of this drug on sexual glands, reproductive hormones, and *VASA* gene expression in male and female rats. FLX is effective at doses of 20–60 mg/day, equivalent to approximately 0.3–0.9 mg/kg. In animal studies, administration of FLX at 3 to 10 mg/kg/day leads to serum levels of FLX within the range detected and suggested in adolescents and adult humans treated with FLX. Consequently, doses between 3 and 5 mg/kg/day in experimental animals were comparable to plasma levels of FLX reported in adolescent subjects treated with FLX at a dose of 20 mg/day; however, doses up to 10 mg/kg/day resulted in serum levels of FLX and its metabolite reaching the ranges recommended for therapeutic doses in patients (Kryst et al., 2022). Chronic administration of FLX at 5, 10, and 20 mg/kg/day alters the Sertoli cell population and all testicular factors during the critical period of testicular development (Amorim et al., 2008). On the other hand, FLX at 40 mg/kg/day was a toxic dose for animals, resulting in muscle contractions, slow movements, and loose stools after 2 weeks of treatment, and most experimental animals failed to survive beyond four weeks (Aggarwal et al., 2012).

According to the results of another study, FLX reduces serum estrogen levels. It suggests that this estrogen deficiency may be due to a reduction in estrogen receptor (ER) β1 mRNA expression in both the telencephalon and hypothalamus and ERα mRNA expression in the telencephalon because ERα mediates both negative and positive feedback of estrogen on LH levels in female goldfish. Therefore, FLX administration can impact the neuroendocrine axis of females (Mennigen et al., 2008). In our work, chronic treatment with low doses of FLX (5mg/kg) did not decrease estradiol levels, but serum levels of progesterone were decreased compared to the control group. This difference may be attributed to the fact that our study samples were in the adolescent stage, and the physiological characteristics of this period differ from those of adulthood, which was previously studied.

According to the findings of another document, FLX administration at a dose of 20mg/kg results in degenerative changes in the ovaries of female rats and causes a prominent decline in the levels of estradiol and progesterone (Achary and Rohini, 2021). Another study demonstrated the potency of FLX to interfere with estrogen signaling by increasing 17β-estradiol levels (Lupu et al., 2017). However, the document is inconsistent with several investigations indicating an increase, some reduction, or no effect. Our findings highlight the need for further research to improve our understanding of the changes that FLX exposure may cause in the development of sexual ability, sexual organs, and hormones. Different effects resulting from different doses, treatment periods, and developmental stages of the rats have influenced these results and require further research in this area.

The *VASA* gene, isolated in recent studies, is an extreme germ cell marker and is useful for studying the determination and function of human and mammalian germ cells. *VASA* mRNA codes for a cytoplasmic protein that plays a vital role in germ cell growth and fertility (Gustafson and Wessel, 2010).

The *VASA* gene is considered an ideal molecular marker for exploring Primordial Germ Cell signals and development (Gustafson and Wessel, 2010). This is used to investigate the effects of various drugs and chemicals on the testis, ovary, and fertility of rats (Zhang et al. ,

2017). Deleting the *VASA* gene exhibits reproductive insufficiency with damage to spermatogenesis. The *VASA* expression in the center of the testicular cords causes pro-spermatogonia to colonize the basement membrane and begin spermatogenesis during adolescence. Therefore, the VASA protein is the main factor for differentiating testicular germ cells and is also mostly expressed in the adult testis (Azizi et al., 2020).

We observed that the *VASA* gene was downregulated in the ovarian tissues of FLX-treated rats. This decrease in *VASA* expression results in ovarian follicle destruction, documenting the ability of FLX to reduce reproductive activities. However, we did not observe a significant reduction in *VASA* gene expression in FLX-treated male rats. Given this study is the first to investigate the effect of FLX treatment on *VASA* gene expression in rat ovaries and testes, further studies are necessary to clarify the causes of this differential expression in the two sexes. Another study revealed the key role of *VASA* in developing abalone germ cells. They elucidated the molecular mechanism through which photoperiod affected *VASA* expression and regulated gonadal development in abalone (Luo et al., 2024). Based on the results of previous and present studies, although both male and female germ lines contain *VASA*, this gene may have different functional targets or be controlled differently in the two germline types.

The histopathological evaluation of this study indicated degenerative changes in the seminiferous layer, germinal epithelium, and ovarian follicles in the FLX group. These results confirm the disorder of the spermatogenesis process and ovarian follicle development. These changes may be due to endocrine-disrupting abilities and downregulation of *VASA* gene expression by FLX treatment.

Previous studies reported that FLX injection for 14 days decreased the proliferative function of splenocytes compared to the saline-received animals and found that both FLX and its active metabolite norfluoxetine harmed rats' livers by inducing oxidative stress. Free radicals, mediated by oxidative stress donate electrons, resulting in mitochondrial swelling and dysfunction (Kubera et al., 2000). A recent study demonstrated that liver sections from the FLX group showed hepatocytes with vacuolated cytoplasm, congestion of the portal vein and blood extravasation. Therefore, this study concluded that FLX administration could induce liver injury through different mechanisms, including the induction of inflammation, oxidative stress, and apoptosis. They observed hepatocyte necrosis, cytoplasmic vacuolation, swelling, congestion, and hydropic degeneration in the livers of FLX-treated rats (Shaer and Halim, 2023). Thus, FLX administration during the developmental period has negative effects on the development of the body systems that may continue into adulthood regarding dose and exposure period (Fricke et al., 2023; Rayen et al., 2013). The findings are consistent with our findings; FLX-treated animals showed an elevation in ovarian and testicular weight. This overweight may be due to cytoplasmic vacuolation, congestion, and blood extravasation. The induction of oxidative stress, inflammatory cytokines, and apoptosis by FLX treatment likely led to reduced sexual hormones, degeneration of ovarian follicles, and hypospermatogenesis.

Limitations

We did not evaluate the levels of LH, FSH, and sexual behavior, but future studies will investigate these aspects.

Conclusion

In general, this study was designed to provide quantitative evidence for FLX-induced reproductive toxicity. Our results demonstrated that FLX reduces sexual hormones and *VASA* gene expression. Additionally, the destruction of the spermatogenesis process and ovarian follicle development induces a decrease in reproductive activities during adolescence. Low levels of sex hormones can result in decreased germinal epithelium thickness, hypo-spermatogenesis, and ovogenesis, eventually resulting in reproductive disorders and infertility. Further investigations are essential to clarify the exact mechanisms mediating the impact of FLX therapy.

The findings of the present work provide information on the histological changes caused by FLX in the testes and ovaries of male and female animals. Therefore, any human being at any stage of life and gender may experience or develop a period of mental disorders and depression, and consequently be treated with this drug. There is an urgent need to know their safe dose and duration. More investigations are necessary to understand whether induced modifications in the animal reproductive organs are reversible or irreversible. Physicians must be cautious when recommending the dosage and length of

FLX use to their patients.

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Conflict of interest

The authors report no conflicts of interest.

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