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CORRELATION BETWEEN CHRONIC TRAMADOL ADMINISTRATION AND DISTURBANCES ACTIVITY OVARIAN FOLLICLES AND ENDOMETRIUM IN FEMALE RATS

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ABSTRACT: Researchers on toxic effects of tramadol on female reproductive system are limited and need to be extended for more confirmations and results So the purpose of this study was to detect the possible correlation between chronic tramadol administration and disturbances activity of ovarian follicles and endometrium in female rats. The study was involved twenty-five adult female rats divided into 4 experimental groups(A, B, C&D); received tramadol by different doses and methods and control group (CON) received normal saline. Histopathological examination was done for ovaries and uterus to all groups. The result in group A showing mild and moderate decreased number of growing follicles and ovulated oocytes with cystic changes and hyper cellular stroma with recovery in 80% in group C. In group B showing moderate and severe decreased of ovulation with recovery in 40% of growing follicles in group C. Also in group A showing moderate atrophied endometrial gland with obvious recovery in the group C. While in group B showing severe atrophy of endometrial gland with recovery in 60 % in group D. In conclusion; positive correlation between chronic tramadol administration and disturbances activity of ovarian and growing follicles in female rats. which is not permanent as it can be reversed after withdrawal of the tramadol. It is recommended that; clinical studies are needed to approve present results about the effect of tramadol on male and female genital system.

Keywords: Tramadol, Rats, Reproductive Function, Histopathology

INTRODUCTION

Drug abuse has existed throughout human history, all over the world. The prevalence of drug abuse has increased dramatically, with the easier access to these drugs particularly tramadol, which produces an enormous burden on many societies1. Tramadol abuse has been heavily demonstrated in the Egyptian community in the last 9 years 2. Tramadol, is synthetic codeine analog, it's a weak μ-receptor agonist and centrally acting analgesic. It has received widespread acceptance in human medicine since it was first introduced in 1977 in Germany3. This opioid pain-killer medication was known as having safe and low abuse liability and widely used throughout the world. After a while, it shows significant risk when an overdose

occurs and the Food and Drug Administration (FDA) has received hundreds of reports of tramadol-associated abuse, dependence, and withdrawal4. Tramadol is associated with a wide range of abuse and illegal transactions that made it easily accessible and readily provided at cheap cost despite of it being scheduled5. The alleged usages of tramadol contributed greatly to its popularity and massive use especially among youth and middle-aged groups as a remedy for premature ejaculation and for extended orgasm and to increase sexual pleasure as promoted in online drug stores and media4. The phenomenon of tramadol abuse has been heavily noticed in the last few years. It is available without a prescription, although it is scheduled, make it easily accessible and very popular5. The mechanism by which tramadol delays ejaculation has not been identified; numerous laboratory studies have shown that tramadol acts as a mild mu-opioid agonist, 5 hydroxytryptamine (5-HT2C) receptor antagonist, and a serotonin and norepinephrine modulator. It's possible that one or a combination of these effect leads to a delay in ejaculation6.

Tramadol as a one of chronic opioid users are susceptible to develop a change in the hypothalamic–pituitary–gonadal axis, which can lead to hypo gonadotropic hypogonadism. These users experience reduced libido, erectile dysfunction, fatigue, depression, hot flashes, and reduced life quality7. As regards developmental or reproductive toxicity, endogenous opioid peptides are located in different tissues on the reproductive system, which suggests that they might be involved in the reproductive function8,9. As peptides induce their effects on opioid receptors (κ, λ, and μ) so, it causes loss of libido and erectile and ejaculatory dysfunctions among men and inhibition of uterine cell proliferation which was mediated mainly by the mu opiate receptor10. It was reported that chronic administration of tramadol caused reproduction dysfunction and increased average of sterility11. Opiate abuse may lead to hypogonadism, primarily by decreasing the release of gonadotropin-releasing hormone (GnRH), testosterone deficiency and infertility. It was reported that chronic administration of tramadol caused reproduction dysfunction and increased average of infertility12. Several studies have demonstrated that long-term administration of tramadol had dose-dependent adverse effects on testicular tissues13. Other studies showed that rats received subcutaneous injections of tramadol (40mglkg body weight) three times per week for 8 weeks showed reduced plasma levels of luteinizing hormone, follicle-stimulating hormone14. In addition, tramadol caused a concentration-dependent inhibition of potassium chloride-induced myometrium contractility15.

So the purpose of this study was to detect the possible correlation between chronic tramadol administration and disturbances activity of ovarian follicles and endometrium in female rats

SUBJECTS AND METHODS

A. Experimental animals

After free informed consent from institute of animal house of medical experiments in the Faculty of Medicine Al-Azhar University (New Damietta). Twenty adult female albino rats weights approximately 1500 gm (± 500 gms) were used in this study. Animals were housed in clean cages with softwood chips for bedding and fed on a commercial basal diet and water ad libitum and exposed to a12h light/dark cycle for two weeks before the experiment for acclimatization and to ensure normal growth and behavior. The animals were randomly divided into 5 experimental groups. According to1617, as follows:

-Group A: Five females received 30 mg/kg tramadol for two months.

-Group B: Five females received 60 mg/kg tramadol for two months.

-Group C: Five females received 30 mg/kg tramadol for two months, followed by withdrawal in two weeks.

-Group D: Five females received 60 mg/kg tramadol for two months, followed by withdrawal in two weeks.

-Group CON: Five females as a control group, received normal saline.

B. Drug

Tramal (Tramadol HCl), 50 mg capsules, were obtained from Mina-Pharm, Egypt. Its chemical name is (+) cis-2- [(dimethylamino) methyl]-1-(3-m ethoxyph-enyl) cyclohexanol hydrochloride.

C. Method

The study was performed in animal house laboratory of medical experiments in the Faculty of Medicine Al-Azhar University (New Damietta). Applied tramadol HCL doses (30 mg /Kg body weight) for groups A & C and (60 mg/kg body weight) for groups B & D were suspended in saline solution and daily orally administered for 60 days with stoppage of the treatment for further 15 days in groups C and D for recovery. At the end of experiment, the animals in each group of the experiment were anesthetized intraperitoneally by sodium pentobarbital (40 mg/kg). The abdomen and thoracic cavities were opened. The uterus and ovaries from female rats were dissected out and fixed in Bouin's fixative at room temperature and processed to obtain five µm thick paraffin sections18.

According to19,20, each finding was classified to mild, moderate and severe as follow:

0-10% negative

20-50% mild

50-70% moderate

70-100% severe

STATISTICAL ANALYSIS

The collected data were organized, tabulated and statistically analyzed using SPSS software computer package version 16 (SPSS Inc. Chicago, IL). For quantitative data, all the values were expressed as that the values P<0.05 were considered statistically significant. For qualitative data, number and percent distribution were calculated and Chi-square test ($\chi 2$) was used for comparison between two groups.

RESULTS

Table (1a): Degree of damage of ovarian growing follicles

Changes/Groups	A		B		C		D		CON	
	No	%	No	%	No	%	No	%	No	%
Negative	1	20%	0	0%	4	80%	2	40%	5	100%
Mild	2	40%	0	0%	1	20%	3	60%	0	0%
Moderate	2	40%	1	20%	0	0%	0	0%	0	0%
Severe	0	0%	4	80%	0	0%	0	0%	0	0%

Group A: female rats received 30 mg/kg tramadol oral daily for two months

Group B: female rats received 60 mg/kg tramadol oral daily for two months

Group C: female rats received 30 mg/kg tramadol oral daily for two months, then withdrawal for 2 weeks

Group D: female rats received 60 mg/kg tramadol oral daily for two months, then withdrawal for 2 weeks

Group CON: control group, female rats received oral saline daily for two months

As regards damage of growing ovarian follicles revealed that; 40% of rats in group A, showed mild and moderate damage, while 20% of rats in group B showed moderate damage and 80% showed severe damage. Group C showed mild damage in 20% of rats while rest of the rats 80% had normal growing follicles with no damage, 60% of rats in group D showed mild damage of growing follicles (Table 1a).

Table (1b): Comparison of damage of growing follicles in different groups

	A		B		C		D	
	$\chi 2$	P	$\chi 2$	P	$\chi 2$	P	$\chi 2$	P
A			7.167	0.025*	8.100	0.004*		
B							11.000	0.001*
CON	11.000	0.001*	11.000	0.001*	3.400	0.121	11.000	0.003*

* Significant P < 0.05

Table (1b) showed that there was significant differences in comparison of damage of growing follicles in group A and group B to control group (p value=0.001 each). Also there was a significant differences and decrease in the damage of growing follicles as regard comparing group C (withdrawal) to group A and also comparing group D (withdrawal) to group B (p value=0.004 and 0.001 respectively).

Table (2a): Degree of increased number of atretic follicles

Changes/Groups	A		B		C		D		CON	
	No	%	No	%	No	%	No	%	No	%
Negative	0	0%	0	0%	4	80%	3	60%	5	100%
Mild	4	80%	1	20%	1	20. %	2	40%	0	0%
Moderate	1	20%	4	80%	0	0%	0	0%	0	0%

Group A: female rats received 30 mg/kg tramadol oral daily for two months

Group B: female rats received 60 mg/kg tramadol oral daily for two months

Group C: female rats received 30 mg/kg tramadol oral daily for two months, then withdrawal for 2 weeks

Group D: female rats received 60 mg/kg tramadol oral daily for two months, then withdrawal for 2 weeks

Group CON: control group, female rats received oral saline daily for two months

As regards increased number of atretic follicles, 80% in group A showed mild increase in number of atretic follicles and 20% showed moderate increase, while in group B 20% showed mild increase number of atretic follicles and 80% showed moderate increase. In group C (withdrawal) showed 20% only mild increase in number of atretic follicles, while in group D (withdrawal) showed 40% moderate increase in the number of atretic follicles (Table 2a).

Table (2b): Comparison of increased the number of atretic follicles in different groups

	A		B		C		D	
	$\chi 2$	P	$\chi 2$	P	$\chi 2$	P	$\chi 2$	P
A			11.000	0.003*	8.000	0.024*		
B							11.000	0.002*
CON	11.000	0.002*	11.000	0.003*	3.300	0.121	11.000	0.002*

* Significant P < 0.05

Table (2b) showed that there was a significant differences in comparison of increase number of atretic follicles in group A, B and D to control group (p P<0.05) while a non-significant differences in comparison of increase number of atretic follicles in group C to control group (P=0.121).

Table (3a): Degree of ovarian cyst formation

Changes/Groups	A		B		C		D		CON	
	No	%	No	%	No	%	No	%	No	%
Negative	1	20%	0	0%	5	100%	4	80%	5	100%
Mild	4	80%	1	20%	0	0%	1	20%	0	0%
Moderate	0	0%	4	80%	0	0%	0	0%	0	0%

Group A: female rats received 30 mg/kg tramadol oral daily for two months

Group B: female rats received 60 mg/kg tramadol oral daily for two months

Group C: female rats received 30 mg/kg tramadol oral daily for two months, then withdrawal for 2 weeks

Group D: female rats received 60 mg/kg tramadol oral daily for two months, then withdrawal for 2 weeks

Group CON: control group, female rats received oral saline daily for two months

Regarding ovarian cyst formation 80% in group A showed mild degree, in group B 20% showed mild degree and 80% showed moderate degree while in group C all rats were negative and only 20% in group D showed mild degree Table (3a).

Table (3b): Comparison of ovarian cyst formation in different groups

	A		B		C		D	
	χ^2	P	χ^2	P	χ^2	P	χ^2	P
A			11.000	0.001*	5.000	0.001*		
B							11.000	0.001*
CON	11.000	0.011*	11.000	0.002*	11.000	0.031*	11.000	0.011*

* Significant P < 0.05

Table (3b) and Figure (2a): showed that there was a significant differences between all groups and control group as regarding ovarian cyst formation (P<0.05) and also a significant differences in comparison between group A and group C and group B and D (P<0.05).

Table (4a): Degree of pyknosis of ovarian atretic follicles granulosa cells

Changes/Groups	A		B		C		D		CON	
	No	%	No	%	No	%	No	%	No	%
Negative	1	20%	0	0%	5	100%	4	80%	5	100%
Mild	4	80%	0	0%	0	0%	1	20%	0	0%
Moderate	0	0%	5	100%	0	0%	0	0%	0	0%

Group A: female rats received 30 mg/kg tramadol oral daily for two months

Group B: female rats received 60 mg/kg tramadol oral daily for two months

Group C: female rats received 30 mg/kg tramadol oral daily for two months, then withdrawal for 2 weeks

Group D: female rats received 60 mg/kg tramadol oral daily for two months, then withdrawal for 2 weeks

Group CON: control group, female rats received oral saline daily for two months

As regards pyknosis of ovarian atretic follicles granulosa cells revealed that; in group A 80% showed mild pyknosis of granulosa, while all rats in group B showed moderate pyknosis, in group C improvement and return to normal in all rats and in 80% in group D (Table 4a).

Table (4b): Comparison of pyknosis of atretic follicles granulosa cells in different groups

	A		B		C		D	
	$\chi 2$	P	$\chi 2$	P	$\chi 2$	P	$\chi 2$	P
A			11.000	0.002*	11.000	0.003*		
B							12.000	0.001*
CON	11.000	0.002*	11.000	0.002*	11.000	0.002*	11.000	0.002*

* Significant P < 0.05

Table (4b): showed that there was a significant pyknosis of atretic follicles granulosa cells as regard comparing group A and group B to control group (p value= 0.002 each). Also significant pyknosis in comparison between groups C and A and in comparison between groups D and B as well (P = 0.002 each).

Table (5a): Degree of decreased number of ovulated oocytes

Changes/Groups	A		B		C		D		CON	
	No	%	No	%	No	%	No	%	No	%
Negative	0	0%	0	0%	5	100%	2	40%	5	100%
Mild	0	0%	0	0%	0	0%	0	0%	0	0%
Moderate	4	80%	1	20%	0	0%	3	60%	0	0%
Severe	1	20%	4	80%	0	0%	0	0%	0	0%

Group A: female rats received 30 mg/kg tramadol oral daily for two months

Group B: female rats received 60 mg/kg tramadol oral daily for two months

Group C: female rats received 30 mg/kg tramadol oral daily for two months, then withdrawal for 2 weeks

Group D: female rats received 60 mg/kg tramadol oral daily for two months, then withdrawal for 2 weeks

Group CON: control group, female rats received oral saline daily for two months

As regarding decreased number of ovulated oocytes, in comparing with control group 80% in group A showed moderate and 20% severe decrease in the number of ovulated oocytes and in group B showed 20% moderate and 80% severe decrease in number of ovulated oocytes while in group C all rats return to normal as

control group and in group D showed 60% moderate decrease in number of ovulated oocytes and return of 40% to normal as control group (Table 5a).

Table (5b): Comparison of decreased number of ovulated oocytes in different groups

	A		B		C		D	
	$\chi 2$	P	$\chi 2$	P	$\chi 2$	P	$\chi 2$	P
A			11.000	0.003*	11.000	0.003*		
B							11.000	0.001*
CON	11.000	0.002*	11.000	0.002*	11.000	0.002*	11.000	0.002*

* Significant P < 0.05

Table (5b) showed that there was a significant differences in comparing the number of ovulated oocytes of group A and group B to control group (P<0.05), also showed a significant differences in comparison between groups C and A and in comparison between groups D and B (P<0.05).

Table (6a): Degree of ovarian stromal hyper cellularity and fibroblast activity

Changes/Groups	A		B		C		D		CON	
	No	%	No	%	No	%	No	%	No	%
Negative	0	0%	0	0%	4	80%	3	60%	5	100%
Mild	0	0%	0	0%	1	20%	1	20%	0	0%
Moderate	4	80%	1	20%	0	0%	1	20%	0	0%
Severe	1	20%	4	80%	0	0%	0	0%	0	0%

Group A: female rats received 30 mg/kg tramadol oral daily for two months

Group B: female rats received 60 mg/kg tramadol oral daily for two months

Group C: female rats received 30 mg/kg tramadol oral daily for two months, then withdrawal for 2 weeks

Group D: female rats received 60 mg/kg tramadol oral daily for two months, then withdrawal for 2 weeks

Group CON: control group, female rats received oral saline daily for two months

As regarding ovarian stromal hyper cellularity and fibroblast activity; in group A 80% showed moderate changes in the stromal cellularity and fibroblast activity, in group B showed 20% moderate and 80% severe changes in the stromal cellularity and fibroblast activity. In group C showed mild changes in stromal hyper cellularity and fibroblast activity in 20% in all rats, while in group D showed mild and moderate changes in stromal hyper cellularity and fibroblast activity in 20% each (Table 6a) and Figure (2B).

Table (6b): Comparison of ovarian stromal hyper cellularity and fibroblast activity in different groups

	A		B		C		D	
	$\chi 2$	P	$\chi 2$	P	$\chi 2$	P	$\chi 2$	P
A			11.000	0.003*	11.000	0.003*		
B							11.000	0.002*
CON	11.000	0.002*	11.000	0.002*	11.000	0.002*	11.000	0.002*

* Significant P < 0.05

Table (6b) revealed that there was a significant differences in stromal hyper cellularity and fibroblast activity as regard comparison of group A and group B with control group (P = 0.002 each). Also significant differences in the stromal cellularity and fibroblast activity in comparing group C to group A, as well as comparing group D to group B (P<0.05).

Table (7a): Degree of atrophy and decrease secretory function of endometrial glands

Changes/Groups	A		B		C		D		CON	
	No	%	No	%	No	%	No	%	No	%
Negative	0	0%	0	0%	4	80%	3	60%	5	100%
Mild	0	0%	0	0%	1	20%	2	40%	0	0%
Moderate	4	80%	1	20%	0	0%	0	0%	0	0%
Severe	1	20%	4	80%	0	0%	0	0%	0	0%

Group A: female rats received 30 mg/kg tramadol oral daily for two months

Group B: female rats received 60 mg/kg tramadol oral daily for two months

Group C: female rats received 30 mg/kg tramadol oral daily for two months, then withdrawal for 2 weeks

Group D: female rats received 60 mg/kg tramadol oral daily for two months, then withdrawal for 2 weeks

Group CON: control group, female rats received oral saline daily for two months

Table (7a), Figure (4A) and figures (4B): showed atrophy and decrease secretory function of endometrial glands; in group A moderate atrophy in 80% and severe atrophy in 20%, while in group B 20% showed moderate atrophy and 80% showed severe atrophy while in group C 20% was showed mild atrophy and in group D only 40% was showed mild atrophy of endometrial glands and decrease secretory function in all rats.

Table (7b): Comparison of atrophy and decrease secretory function of endometrial glands in different groups

	A		B		C		D	
	$\chi 2$	P	$\chi 2$	P	$\chi 2$	P	$\chi 2$	P
A			11.000	0.002*	11.000	0.001*		
B							12.000	0.001*
CONF	11.000	0.001*	11.000	0.001*	5.000	0.011*	3.400	0.121

* Significant P < 0.05.

Table (7b), showed a significant differences in atrophy and decrease secretory function of endometrial glands as regard comparing group A and group B to control group (p value= 0.001 each) and also there was a significant differences in atrophy and decrease secretory function of endometrial glands as regard comparing group C to group A and also in comparing group D to group B (P < 0.05).

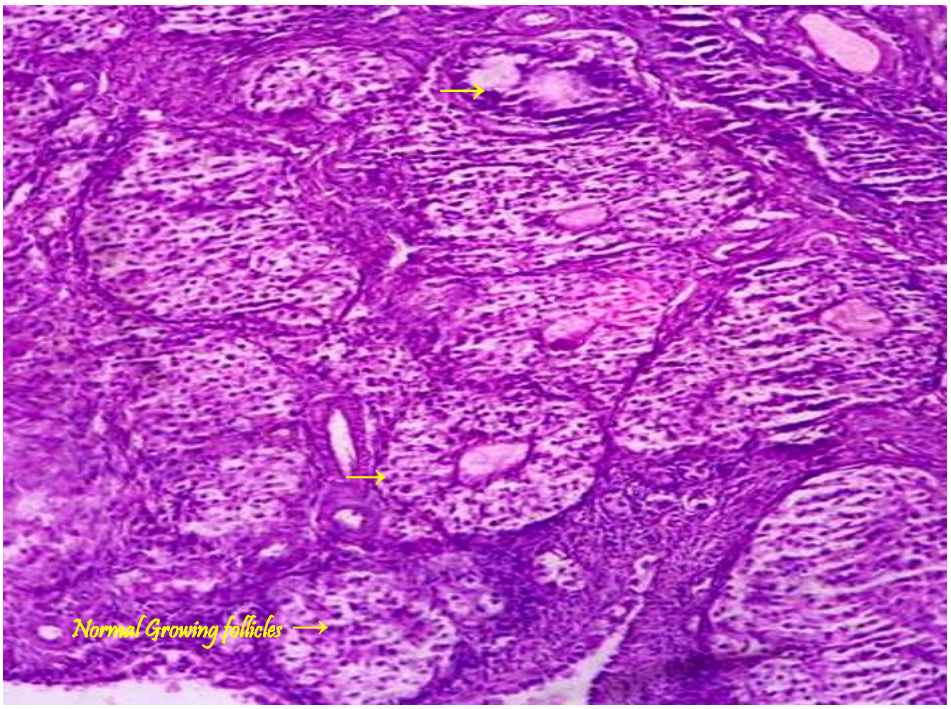

Fig 1: A photomicrograph of a section from the ovary of a rat from control group showing normal structure with different stages of growing follicles. Hematoxyline & Eosin (H&E X200).

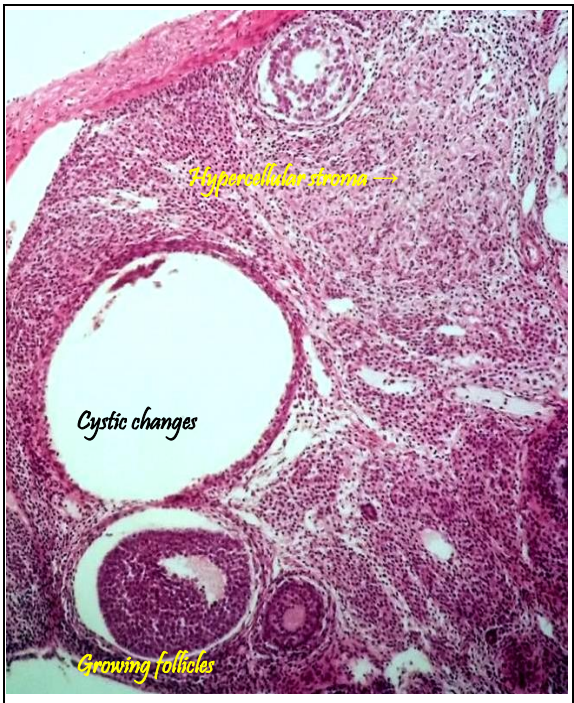

Figure (2a): A photomicrograph of a section from the ovary of a rat from group A showing decreased number of growing follicles and ovulated oocytes with cystic changes and hyper cellular stroma. (H&E X200).

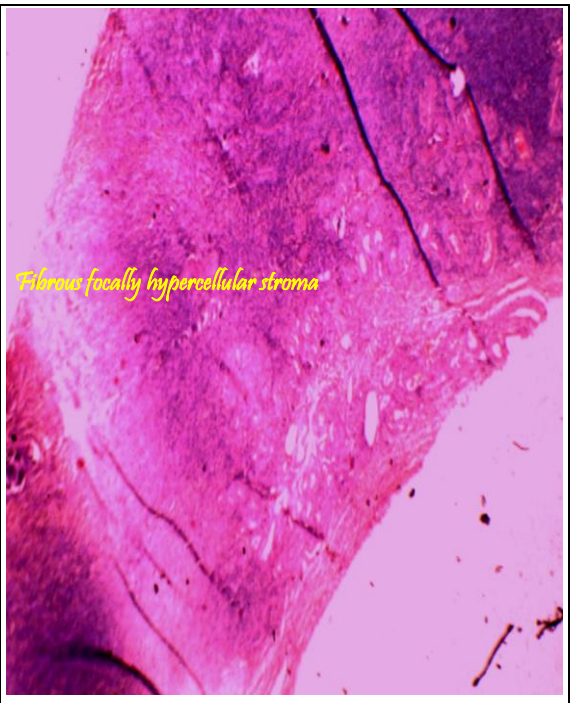

Figure (2b): A photomicrograph of a section from the ovary of a rat from group B complete absence of ovulation with replacement by fibrous focally hyper cellular stroma. (H&E X200).

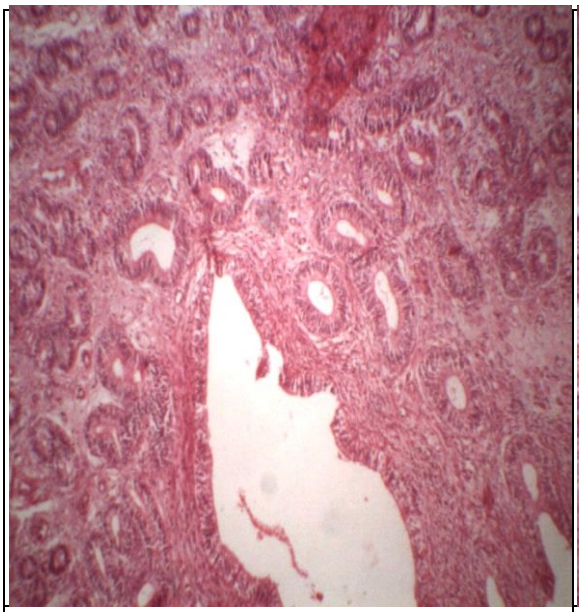

Figure (3A): A photomicrograph of a section from a normal uterus of rat showing normal endometrial gland. (H&E X200).

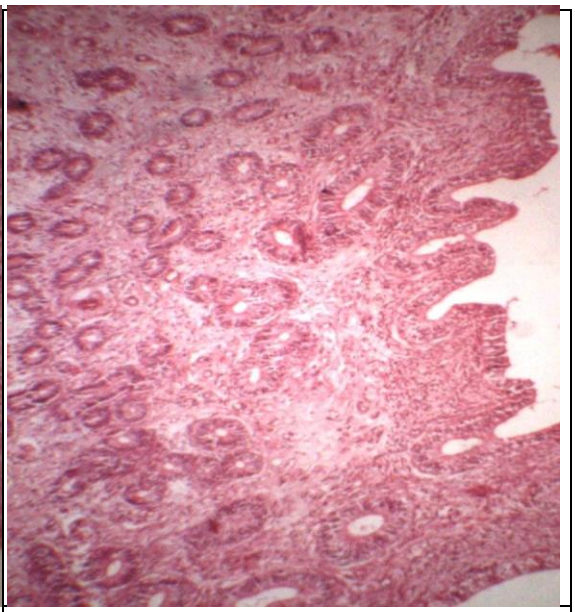

Figure (3B): A photomicrograph of a section from a normal uterus of rat showing normal endometrial gland. (H&E X200).

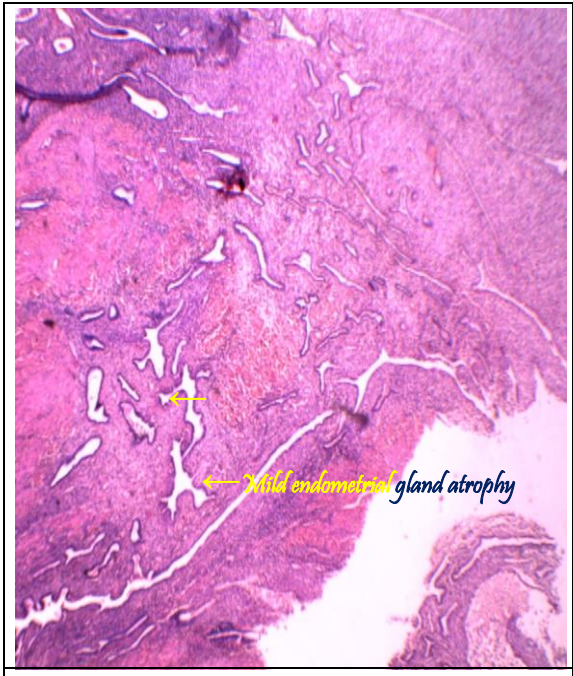

Figure (4A): A photomicrograph of a section from the uterus of a rat from group A showing mild atrophied endometrial gland (small widely spaced endometrial glands lines by single layer). (H&E X200).

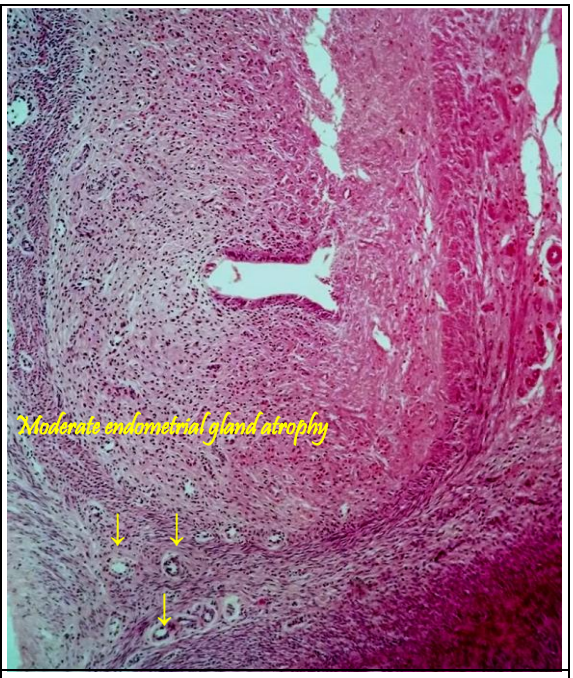

Figure (4B): A photomicrograph of a section from the uterus of a rat from group B showing moderate atrophy of endometrial gland. (H&E X200).

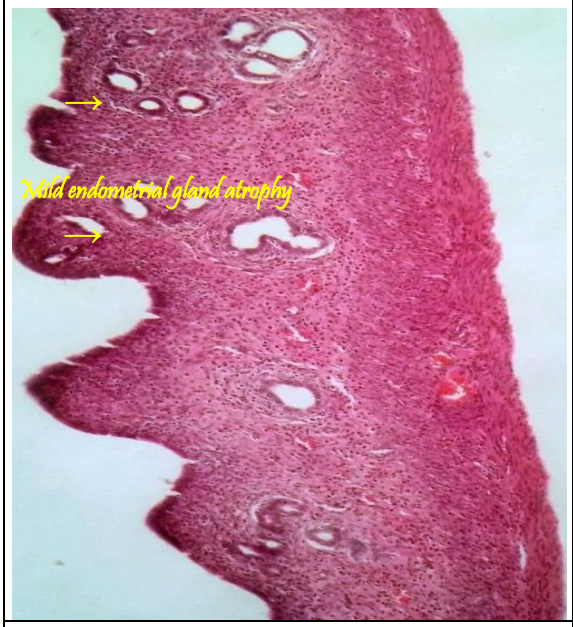

Figure (5A): A photomicrograph of a section from the uterus of a rat from group A showing mild atrophy of endometrial gland. (H&E X200).

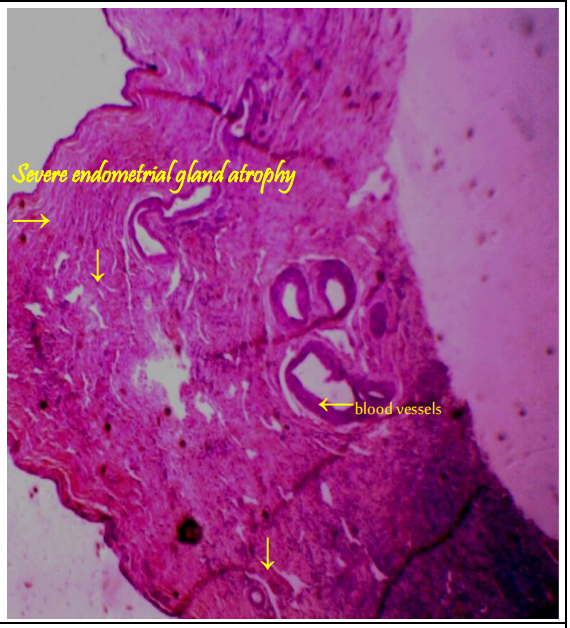

Figure (5b): A photomicrograph of a section from the uterus of a rat from group B showing severe atrophy of endometrial gland. (H&E X200).

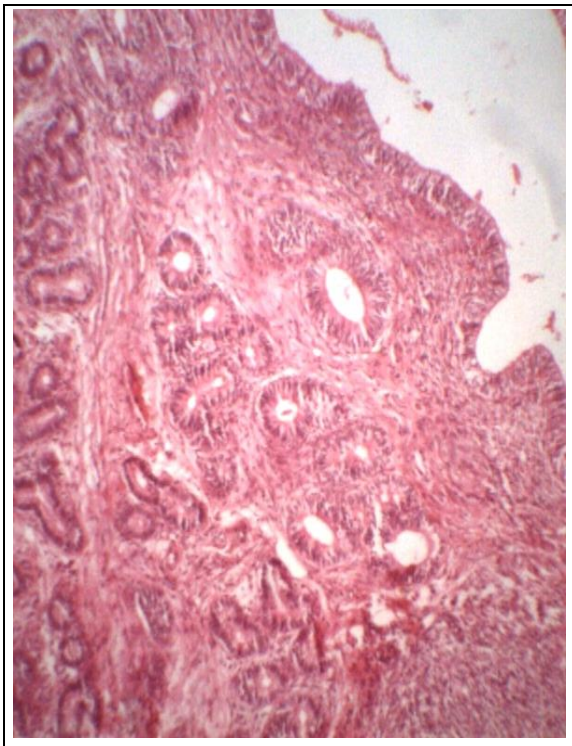

Figure (6A): A photomicrograph of a section from uterus of group C rat showing moderate to obvious recovery of endometrial gland. (H&E X200).

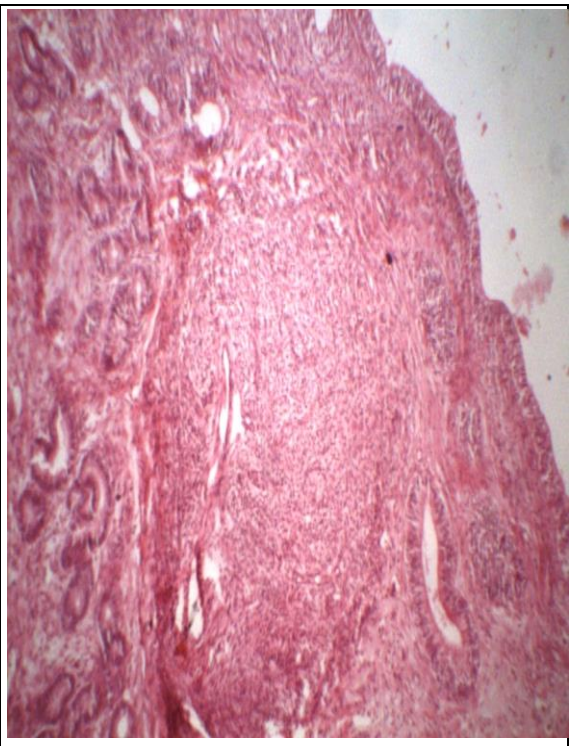

Figure (6B): A photomicrograph of a section from uterus of group D rat showing mild recovery of endometrial gland. (H&E X200).

DISCUSSION

The purpose of this study was to detect the possible correlation between chronic tramadol administration and disturbances activity of ovarian follicles and endometrium in female rats

from the animal house of Medical Experimental Research Center (MERC), Faculty of Medicine Al-Azhar University (New Damietta).

In the present study, there was significant damage of ovarian growing follicles with different degrees in each group (tables 1a& 1b) and figure (2a), as seen in group A (which received 30 mg/kg tramadol for 60 days), increasing the dose to 60 mg/kg as seen in group B caused more damage of the growing follicles figure (2). This result of diminished ovarian follicle count was also recorded also by Abbas and Paulis[21], who gave also two groups of female rats tramadol at doses 40 and 80 mg/kg for 8 weeks for assessment of ovarian function.

As regard ovarian cyst formation figure (2a), tramadol could increase ovarian cysts formation which increases by increasing the dose from 30 mg/kg in group A to 60 mg/kg in group B,

as seen in (tables 3a). These results are agreements with El-Ghaweet[11] who, stated that many of the mature follicles appeared in the form of cystic-like structure in tramadol treated female rats (40 mg/kg).

As regard the atretic follicles seen in the ovaries possessed pyknosis of their granulosa cells (tables 4a), but with rapid and full recovery to all rats to normal after withdrawal for only two weeks in group C, and recovery for 80% to normal in group D like control group. This is in accordance with Zhou et al[22], who reported that ovarian follicles is an effective way to estimate ovarian toxicity in female rats that have been exposed to tramadol.

As regard impaired ovarian functions suggested by marked decrease in number of ovulated oocytes, as in group A and showed more affection in group B. in group C showed improvement in all rats but in group D showed return to normal in 40%. These results may suggest that the reversible toxic pathological effect of tramadol on female reproductive system could be time dependent rather than dose-dependent, or it may be also related to female cyclic hormonal and physiological changes in reproductive system which need more researchers for confirmation. This is in accordance with Abbas and Paulis[21]; Zhou et al[22] who, stated that ovulated oocytes or antral follicles are more sensitive to toxic effect of tramadol and a histological examination of the ovaries, went in the same line as hormonal, estrous cycle and oxidative stress changes.

As regard atrophy and decrease secretory function of endometrial (Tables 7a) and Figure (5A), (5B): showed that 80% of rats in group A showed moderate degree and 20% showed severe degree of endometrial glands atrophy which significantly improved after stoppage of the drug for two weeks, as 80% of rats in group C revealed normal endometrial glands. Also 20% of rats in group B showed moderate degree and 80% showed severe degree of endometrial glands atrophy which significantly improved after stoppage of the drug for two weeks as 60% of rats in group C revealed normal endometrial glands. These results are in corresponding with El-Ghaweet[11] who reported that massive atrophy and decreased secretory function of the endometrial glands in the study of tramadol caused a concentration-dependent inhibition of potassium chloride-induced myometrial contractility[23]. However, the opioid-induced inhibition of uterine cell proliferation which was mediated mainly by the mu opiate receptor [24].

There were a significant difference in different groups as regard; damage of growing follicles and their replacement by atretic ones; also cysts like structures formation, pyknosis of atretic follicles granulosa cells, decreased the number of ovulated oocytes and stromal hyper cellularity as well as the atrophy of uterine endometrial glands (Tables 1-6b). these results are in agreements and corresponding with Abd El-Twab[25] who showed that obvious deterioration, degeneration and necrosis of ovarian follicles and endometrial damages in

tramadol-administered rats are dose-dependent and could be reversed to some extent after stoppage of the drug.

CONCLUSION

The results of the present study revealed a significant correlation between tramadol administration and disturbances in fertility function in adult female rats, as observed from a histopathological examination of ovaries and uterus, which could affects the activity of ovarian and growing follicles in female rats. These hazardous effects can be completely or incompletely reversed after withdrawal of the tramadol, which means that these effects are not permanent.

RECOMMENDATION

1- Further human studies are necessary to explain and confirm the findings of this study.
2- Clinical studies are needed to approve our results about the effect of tramadol on male (testis) and female genital system (uterus and ovary), especially with no obvious causes of infertility.
3- Any female with delayed fertility and under long-term treatment with tramadol, should undergo regular screening for their fertility.

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العلاقة بين التعرض المزمن لعقار الترامادول وحدوث اضطرابات في نشاط جريبات المبيض والرحم في أنثى الفئران.

الملخص: إن دراسة الباحثين للتأثير السمي لعقار الترامادول على الجهاز التناسلي للإناث لازال محدودا ويحتاج لمزيد من الجهد لمعرفته وتأكيده، لذا كان الهدف من هذا البحث هو دراسة العلاقة بين التعرض المزمن لعقار الترامادول و إمكانية حدوث اعتلال في نشاط المبيض والرحم لإناث الفئران، اشتملت الدراسة على عدد خمسة وعشرون من إناث الفئران البالغين قسموا إلى أربع مجموعات للدراسة (A,B,C,D) تم إعطاؤهم جرعات مختلفة من عقار الترامادول وبطرق مختلفة والمجموعة الضابطة (CON) تم إعطاؤها محلول ملح للمقارنة، تم تشريح الفئران و استئصال المبيض والرحم وذلك لعمل التحليل النسيجي لهن.

وأسفرت نتائج الدراسة عموما عن وجود نقص بسيط ومتوسط في عدد بويضات المبيض مع وجود حويصلات بالرحم نتيجة التعرض المزمن لعقار الترامادول، وأن هذا الضرر يزداد ليصبح شديداً بزيادة جرعات الترامادول، كما أسفرت الدراسة- أيضاً- عن حدوث اعتلال في أنسجة المبيض ونقص في عدد الجريبات المتزايدة في المبيض و تم استبدالها بجريبات تالفة و تكيسات كما وجد خلل و ضمور في غدد و بطانة الرحم، وأن هذه الآثار السلبية تتزايد بزيادة جرعات الترامادول، كما حدث تعافي لهذه التغيرات الخلوية (المبيض والرحم) سواء كان جزئيا أو كليا وذلك عند وقف إعطاء عقار الترامادول للفئران. لذا بناءً على ما سبق نوصى بمزيد من الدراسة لتوضيح هذه النتائج وتطبيقها على الإنسان ودراستها إكلينيكيا لمعرفة تأثير هذا العقار على الجهاز التناسلي للذكور(الخصية) والإناث (الرحم والمبيض) وخصوصا في الحالات التي لا يوجد لديها سبب واضح للعقم أو لتأخر الإنجاب.

الكلمات المفتاحية: الترامادول، الوظيفة الإنجابية، الفئران، التحليل النسيجي.