

Effect of Coenzyme Q₁₀ on the reproductive system of female rats (*Rattus norvegicus*) treated with lead acetate

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Abstract

This study was conducted to evaluate the effectiveness of the CoQ₁₀ on the reproductive system of female rats and its ability to reduce the harmful effect of lead acetate. To achieve this goal an experiment was done on 24 mature female rats which are randomly divided into 4 groups, group(1) treated with 1ml/kg corn oil and considered as a negative control group, group(2) treated with CoQ₁₀ at dose 200 mg/kg and considered as a positive control group, group(3) treated with lead acetate at dose 8mg /kg ,and group (4) treated with lead acetate for 30 days then after CoQ₁₀ for another 30 days. Blood samples were taken from all animals after 60 days for biochemical analysis to estimate FSH, LH, estrogen and progesterone hormones .Histological examinations of an ovary and uterus were also involved in this study. Results showed a significant increase ($p < 0.05$) in serum FSH, estrogen and progesterone levels in group(2) compared to other groups while LH level was significantly increased ($p < 0.05$) compared to group (3). Group(3) showed a significant decrease ($p < 0.05$) in serum FSH, LH level in compared to group (1) and group(4),while progesterone and estrogen levels showed no significant difference ($p > 0.05$) compared to group(1) . At the same time, there were no significant difference ($p > 0.05$) in serum LH, estrogen and progesterone levels in group (4) compared to group(1), while there was a significant decrease ($p < 0.05$) in serum FSH level in group(4) compared group(1). The results of ovary sections ,group(2) showed normal structure and distribution pattern of various ovary components, while group (3)showed sever hemorrhage in the ovarian stroma and suppression of ovarian follicles. Group(4) showed particular recovery in ovarian parenchyma. Uterus sections of group(2) showed normal epithelium which lining the uterus and there is destitution uterine glands. Group(3) showed epithelium degenerative, small and non developed uterine glands and hemorrhage in uterine tissue .Other wised uterus in group (4)showed normal columnar epithelium which lining the uterus, and proliferation of uterine glands.

Key words: Coenzyme Q₁₀, lead acetate ,reproductive system

تأثير مرافق الإنزيم Q10 على الجهاز التناسلي لأناث الجرذان المختبرية المعاملة بخلات

الرصاص

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المستخلص

أجريت هذه الدراسة لتقييم فعالية CoQ10 على الجهاز التناسلي لأناث الجرذان و قدرته على الحد من التأثير الضار لخلات الرصاص .ولتحقيق هدف من التجربة أجريت الدراسة على 24 من اناث الجرذان الناضجة والتي قسمت إلى 4 مجاميع ، جرعت المجموعة (1) 1مل / كغم من زيت الذرة واعتبرت مجموعة السيطرة السلبية، المجموعة (2) جرعت CoQ1 200 ملغم / كغم واعتبرت السيطرة الإيجابية ، مجموعة (3) جرعت بخلات الرصاص بجرعة 8ملغم / كغم، مجموعة (4) جرعت خلات الرصاص لمدة 30 يوما ثم CoQ10 لمدة 30 يوما أخرى .جمعت عينات الدم من جميع الحيوانات بعد 60 يوما للتحليل البيوكيميائي لتقدير هرمون المحفز للجريبات وهرمون الاباضة، هرمون الاستروجين وهرمون البروجسترون. الفحوصات النسيجية للمبيض والرحم كانت ايضا من ضمن هذه الدراسة .أظهرت النتائج وجود زيادة معنوية ($P < 0.05$) لهرمون المحفز للجريبات وهرمون الاستروجين والبروجسترون في المجموعة (2) عند المقارنة بالمجاميع الأخرى بينما اظهر مستوى هرمون الاباضة ارتفاع معنوي ($P < 0.05$) مقارنة مع المجموعة (3) . اظهرت المجموعة (3) انخفاضا معنويا ($P < 0.05$) في مصل الدم لهرمون المحفز للجريبات وهرمون الاباضة بالمقارنة مع المجموعة (1) والمجموعة (4) ، في حين لم يظهر مستوى هرمون البروجسترون وهرمون الاستروجين فرق معنوي ($p > 0.05$) مقارنة مع المجموعة (1) .في الوقت نفسه، لم يكن هناك فرق معنوي ($p > 0.05$) في مصل الدم لهرمون الاستروجين و البروجسترون في المجموعة (4) عند مقارنتها مع المجموعة (1)، في حين كان هناك انخفاض معنوي ($p < 0.05$) في مستوى الهرمون المحفز للجريبات في المجموعة (4) مقارنة المجموعة (1) . نتائج التقطيع النسيجي للمبيض، مجموعة (2) تركيب ونمط التوزيع مختلف مكونات المبيض طبيعي ، في حين أظهرت مجموعة (3) نزيف حاد في سدى المبيض وقلة حويصلات المبيض .المجموعة (4) أظهرت إعادة إصلاح جزئي في نسيج المبيض .وأظهرت التقطيع النسيجي للرحم للمجموعة (2) ظهارة طبيعية لبطانة الرحم وهناك انتشار لغدد الرحم .وأظهرت المجموعة (3) انتكاس لبطانة الرحم ، وغدد الرحم صغيرة وغيرمتطورة ونزيف في الأنسجة الرحمية . من جهة أخرى أظهرت المجموعة (4) الرحم مبطن بنسيج ظهاري عمودية طبيعي ، وتكاثر الغدد الرحمية .

الكلمات المفتاحية : مرافق الانزيم Q10 ،خلات الرصاص ،الجهاز التكاثري .

Introduction

Coenzyme Q₁₀ (CoQ₁₀) or ubiquinone is essentially vitamin-like substance (7). CoQ₁₀ is found in small amounts in a wide variety of foods and is synthesized in all tissues. Frederick Crane of Wisconsin, U.S.A., in 1957 Was the first person who isolated CoQ₁₀ from beef heart mitochondria (18). CoQ₁₀ resides primarily on the inner membranes of the mitochondria and it is the coenzyme for at least three mitochondrial enzymes (complexes I, II and III) as well as enzymes in other parts of the cell (23). Coenzyme Q₁₀ is a compound that functions as an electron carrier in the mitochondrial respiratory chain (14). Then ATP production acting as an essential antioxidant and supporting the regeneration of other antioxidants, influencing the stability and permeability of membranes; also, stimulating cell growth and inhibiting cell death (9). CoQ₁₀ is a crystalline powder that is insoluble in water. Absorption of CoQ₁₀ follows the same process as that of lipids and the uptake mechanism appears to be similar to that of vitamin E. The biosynthesis of CoQ₁₀ from the amino acid tyrosine is a 17- step process requiring at least eight vitamins and several trace elements (6), Because of this biosynthesis complexity, defects in some human enzymes or regulatory proteins may cause CoQ₁₀ deficiency in infantile and adult organisms (20). CoQ₁₀ consists of a benzoquinone and a hydrophobic tail that contains isoprenoid units CoQ₁₀ can be reduced to ubisemiquinone (QH) and further reduced to ubiquinol (QH₂). These reducing properties allow CoQ₁₀ to function as an antioxidant or pro-oxidant depending on a number of factors, such as pH, or the presence of other redox couples including: vitamin E, vitamin C, and α -lipoic acid It is possible that CoQ₁₀ may become pro-oxidant (induce oxidative stress) if not given in conjunction with a redox couple previously stated (27). CoQ₁₀ appears to play multiple roles in cells. Therefore the present study aims to evaluate the effectiveness of the CoQ₁₀ on the female reproductive system and the ability to reduce the harmful effect of lead acetate.

Material and Methods

Experimental animal

The study was carried out on twenty four mature Wistar albino female rats at (190 \pm 20) gm average weight, at the age was around 4-5 months). Animals were purchased from animal house of Biology Department, Scientific College, Thi-Qa University. They were placed in individual cages. The rats were fed with standard rodent chow and provided with tap water. The experiment was performed under controlled conditions (temperature 25C^o, and a 12- hour's light-dark cycle).

Experimental design

Female rats were randomly assigned in to four equal groups (6 rats in each group). All the groups were administration orally by gavage needle as follows: group(1) treated with 1ml/kg corn oil and considered as a negative control group, group(2) treated with CoQ₁₀ at dose 200 mg/kg and considered as positive control group, group(3) treated with lead acetate at dose 8mg /kg, group(4) treated with lead acetate for 30 days then CoQ₁₀ another 30 days

Animal sacrificing

The female were sacrificed after anesthetizing by ether (4%) on the day (60) for all groups. The abdominal lumen was opened and blood was collected by heart puncture technique using 10 ml disposable syringe. The collected blood samples were left at room temperature till being clotted. Then sample centrifuged at (300) rpm for (10) minutes, after centrifugation, the Serum was aspirated in to the tube and stored at (- 25⁰ C) until the time to be used for measurement of female sex hormones FSH, LH, estrogen and progesterone (4), the reproductive organs (ovaries and uterus) were also removed, one of the ovaries and uterus were fixed in (10%) formalin for histological study.

ELISA technique was used to measure sex hormones FSH, LH, estrogen and progesterone .

Histological study

The histological sections for ovary and uterus were prepared in the department of Pathological Analysis /College of Science/ University of Thi- Qar by using the method in(2)

Statistical Analyses

Statistical analyses was made by using (SPSS) computer software according (ANOVA) and least significant differences (L.S.D) at P-Value less than (0.05) level of significant was considered statistically significant.

Results

Serum level of follicle stimulation hormone (FSH)

There was a significant increase ($p > 0.05$) in serum FSH Level in group2 compared with group 1, group 3 and group4, While group 3 showed a significant decrease ($p < 0.05$) in serum FSH level in comparable to group 1 and group4. FSH in group 4 showed a significant increase ($p < 0.05$) compared with group 3(table 1).

Serum level of luteinizing hormone (LH)

LH values did not show any significant differences ($p > 0.05$) among group1, group2 and group4. However there was significant decrease ($p < 0.05$) in serum LH level of group 3 compared with other groups (table 1).

Serum estrogen

The results of serum estrogen level clarified in table(1) revealed a significant increase ($p < 0.05$) in group 2 compared to other groups, while group 3 and group 4 showed no significant differences ($p > 0.05$) in serum estrogen level comparable to group1. In contrast, group 4 showed a significant increase ($p < 0.05$) in serum estrogen level compared with group 3.

Serum progesterone

Progesterone level was significantly higher ($p < 0.05$) in group2, compared to other groups, At the same time there were non- significant differences ($p < 0.05$) observed among group1, group 3 and group4.

Table (1): Effect of CO Q₁₀ and lead acetate on Serum Level of FSH, LH, Estrogen and Progesterone in female rats.

Groups	FSH mIU/MI	LH mIU/MI	Estrogen pg /ml	Progesterone ng/ml
Group1	0.591 ± 0.159 B	0.667 ± 0.210 A	22.591 ± 1.456 BC	13.653 ± 1.505 B
Group2	1.416 ± 0.173 A	0.850 ± 0.151 A	49.358 ± 5.397 A	35.511 ± 7.736 A
Group3	0.481 ± 0.111 D	0.186 ± 0.197 B	14.806 ± 0.228 C	7.441 ± 0.770 B
Group 4	0.573 ± 0.154 C	0.482 ± 0.166 A	29.708 ± 1.613 B	15.578 ± 1.546 B
L.S.D	0.01	0.7	13.44	18.62

Values are means ± S.E.

Different superscript refer to significant differences (p<0.05).

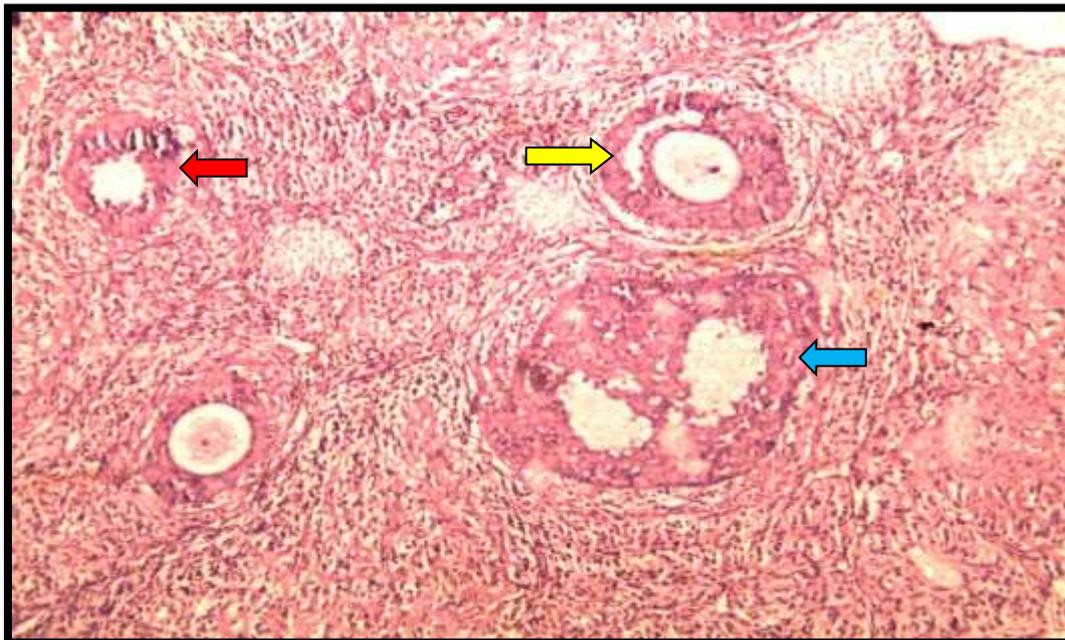
Same superscript refer to no significant differences (p>0.05).

Histological changes of ovary

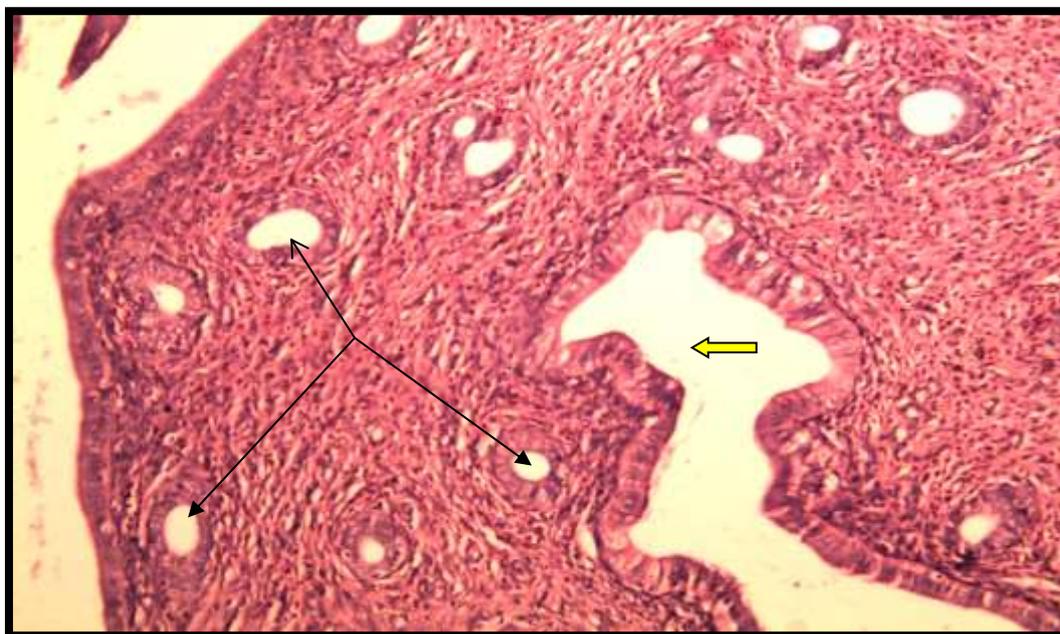
The result of group 2 showed normal structure and distribution pattern of various ovary components, different types of developing follicles, which characterized mature griffin follicular, primary and secondary follicular also there is corpus luteum and ovary showed no pathological lesions. While the results of group 3 showed there was sever hemorrhage in the ovarian stroma and suppression of ovarian follicles. After administration of lead acetate then treated with CoQ₁₀ in group 4 there was particular recovery in ovarian parenchyma. There were primary, secondary follicles and corpus luteum

Histological changes of uterus

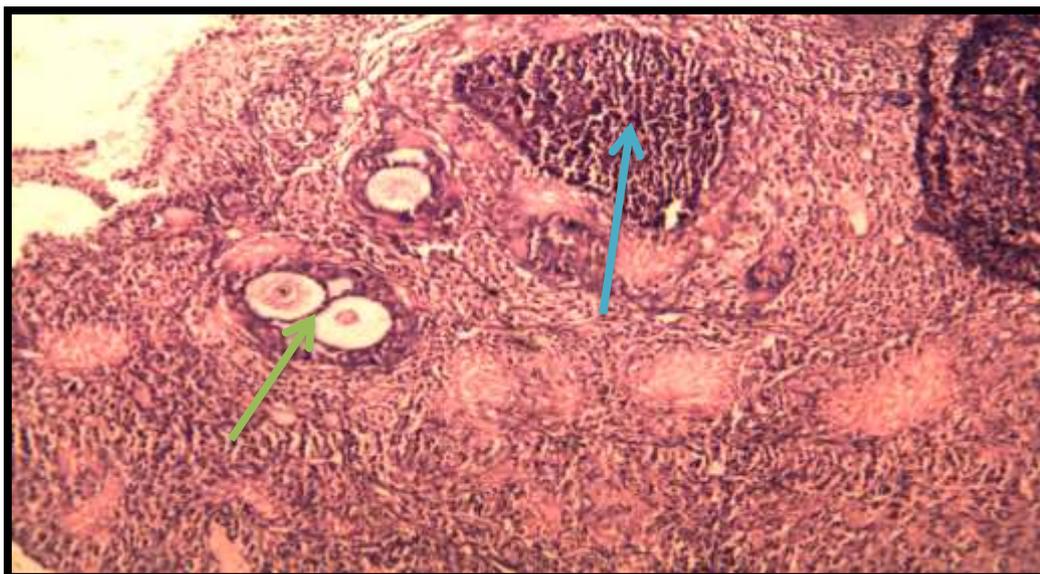
According to result of group 2 there was normal columnar epithelium which lining the uterus and there was destitution uterine glands. While group 3 after administration of lead acetate uterus showed epithelium degenerative, small and no developed uterine glands and there was hemorrhage in uterine tissue. Other wised uterus in group 4 showed normal columnar epithelium, also there was proliferation of uterine glands and there was full thickness of uterus which showed residue of destructed glands and repaired glands.



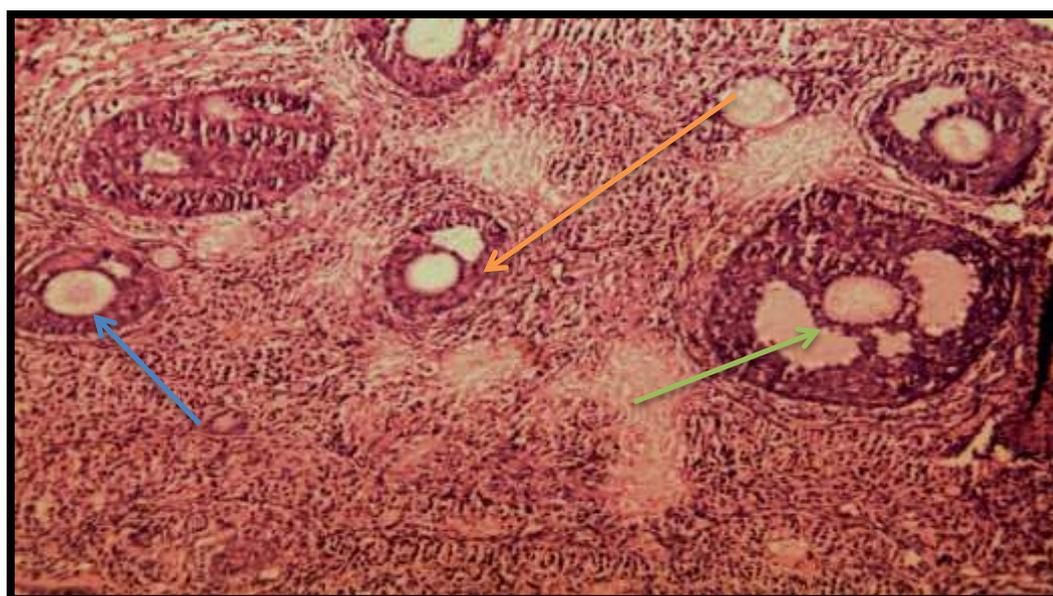
picture (1): Ovarian section of rat administered with corn oil 1ml/kg orally for 2 months group 1. There is primary (red arrow), secondary (blue arrow) and Graafian follicles (yellow arrow). There is no hemorrhage in the ovarian stroma. H&E 10 X.



picture(2): Uterus section of rat administered with corn oil 1ml/kg orally for 2 months group 1. There is normal columnar epithelium which lining the uterus (yellow arrow), also there is normal uterine glands (thin arrows). H&E,10X



picture (3): Ovarian section of rat administered with CoQ₁₀ 200 mg/kg orally for 2 months group 2, There is different follicles at a various stages of development primary, secondary (yellow arrow) and corpus luteum (blue arrow). There are no pathological lesion .H&E,10X



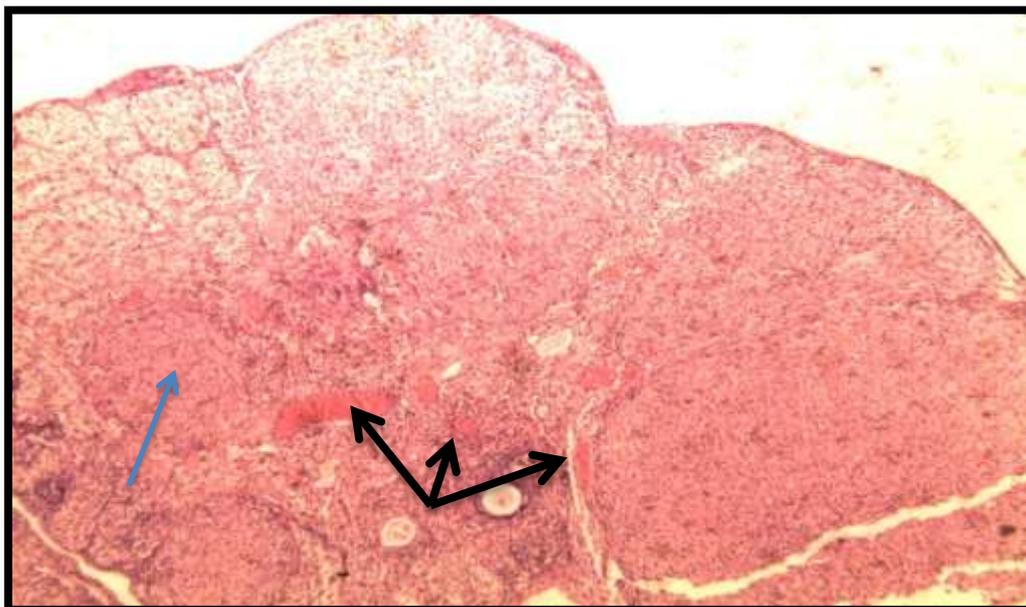
picture (4): Ovarian section of rat administered with Co Q₁₀ 200mg/kg orally for 2 months group 2, There is high follicular growth wave which characterized mature Graavian follicular (yellow arrow), primary (red arrow) and secondary follicles (blue arrow). There are no pathological lesions .H&E .10X



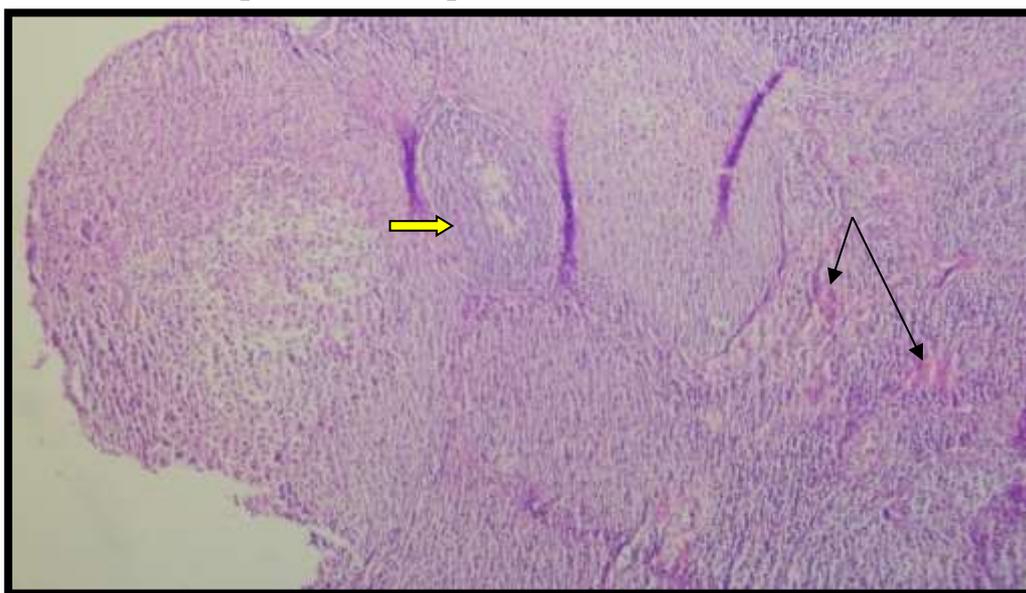
picture (5): Uterine section of rat administered with Co Q₁₀ 200mg/kg orally for 2 months (group 2). There is normal columnar epithelium which lining the uterus (thin arrows) and normal uterine glands (yellow arrow). H&E,10X.



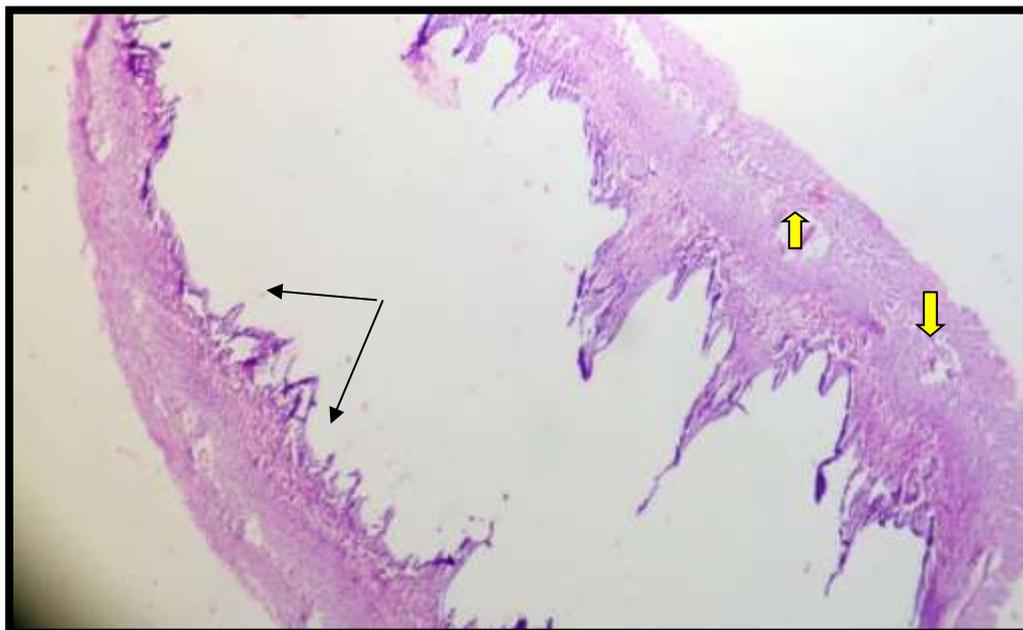
picture (6): Uterine section of rat administered with Co Q₁₀ 200mg/kg orally for 2 months (group 2). There is proliferation of uterine glands (thin arrows) and normal columnar epithelium (yellow arrow). H&E, 10X



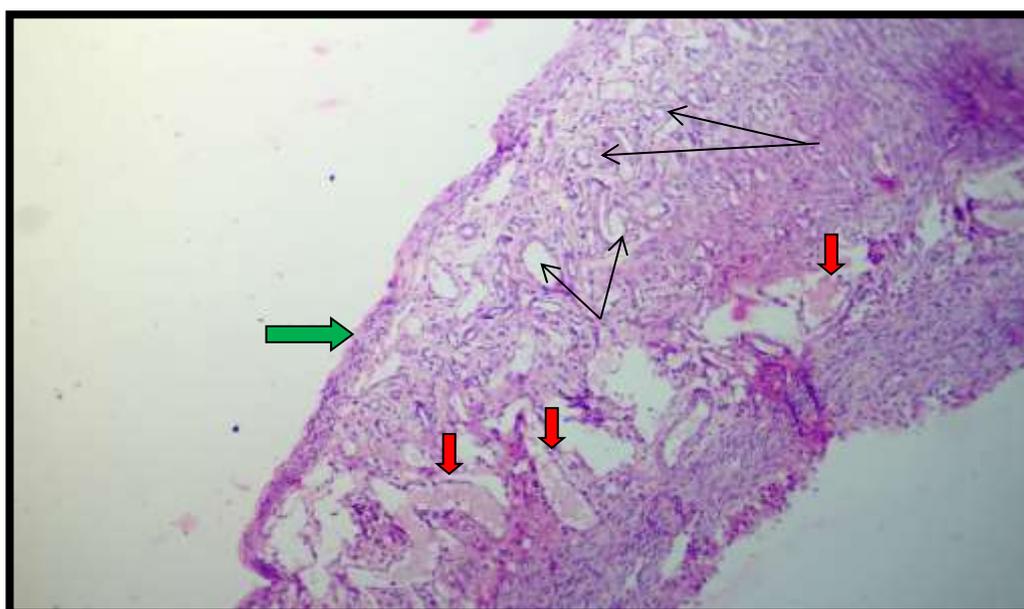
picture (7): Ovarian section of rat administered with lead acetate 8mg/kg orally for 2 months (group 3). There is severe hemorrhage in the ovarian stroma (thin arrows), of ovarian follicles and presence of corpus luteum (blue arrow). H&E,



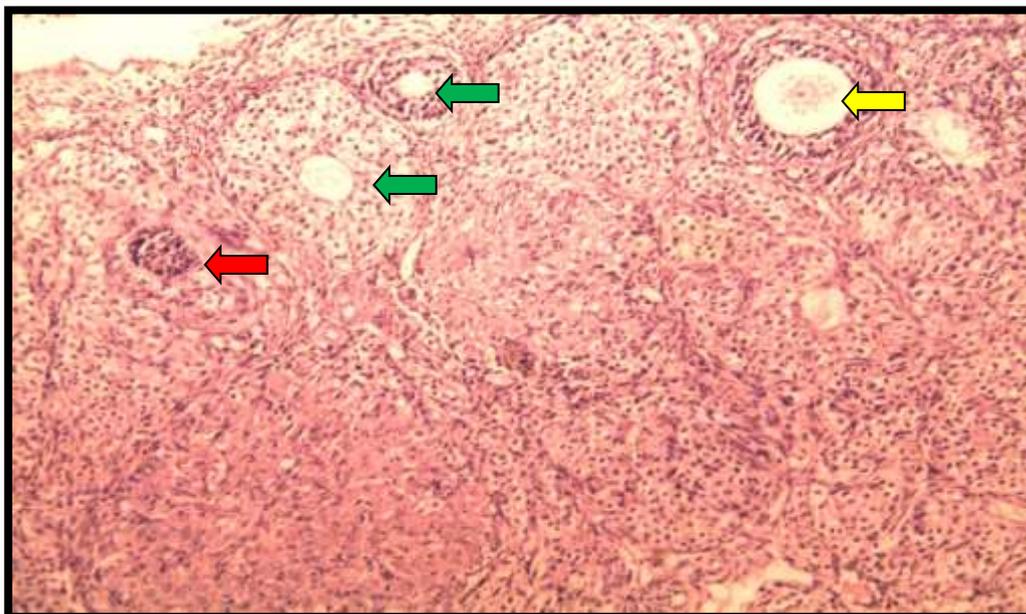
picture(8): Ovarian section of rat administered with lead acetate) 8mg/kg orally for 2 months (group 3) . There is severe hemorrhage in the ovarian stroma (thin arrows) and presence of corpus luteum (yellow arrows). H&E 4 X .



picture (9): Uterus section of rat administered with lead acetate (group 3) orally 8mg/kg for 2 months. There is degeneration of endothelium which lining the uterus (thin arrows) and destroyed endometrial glands (yellow arrow). H&E,4X.



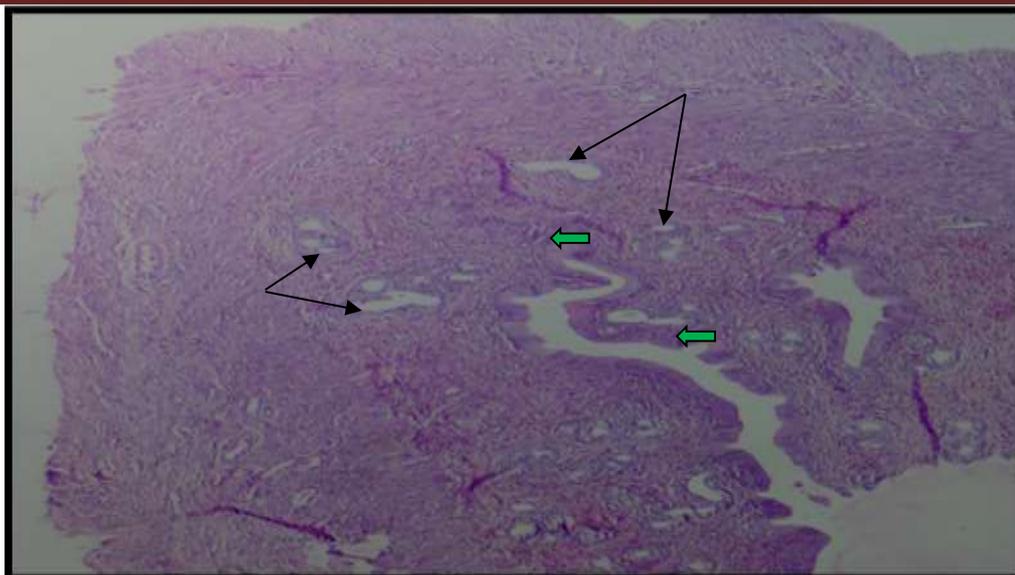
picture (10): Uterus section of rat administered with lead acetate 8mg/kg orally for 2 months (group 3). There is uterine epithelium degeneration (green arrow), small and non-developed uterine glands (thin arrows) and There is hemorrhage in uterine tissue (red arrows). H&E,4X.



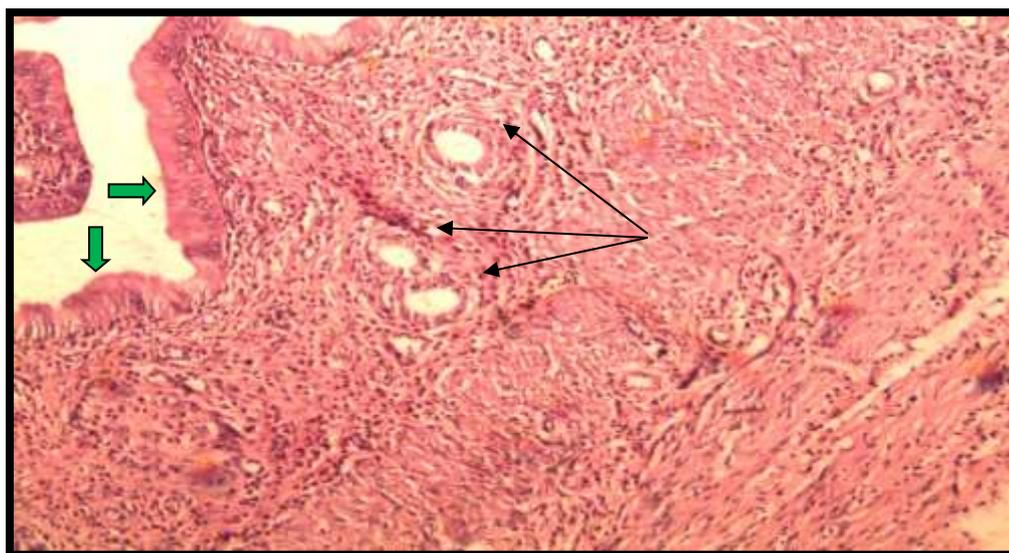
picture. (11): Ovarian section of rat administered with lead acetate 8mg/kg orally for month than treated with Co Q₁₀ 200mg/kg for another month (group 4). There is particularly recovery in ovarian parenchyma. There are primary (green arrows) , secondary follicles (yellow arrow) and corpus luteum (red arrow), H&E, 4X.



picture (12): Ovarian section of rat administered with lead acetate 8mg/kg orally for month then treated with Co Q₁₀ 200mg/kg for another month (group 4). There is marked follicular growth which characterized by mature follicle (green arrow) and other secondary follicle (yellow arrow). H&E ,10 X .



picture (13): Uterus section of rat administered with lead acetate 8mg/kg orally for month then treated with Co Q₁₀ 200 mg/kg for another month (group 4). There is normal columnar epithelium which lining the uterus (green arrow), also there is proliferation of uterine glands (thin arrows).H&E,4X.



Picture (14): Uterus section of rat administered with lead acetate 8mg/kg orally for month then treated with Co Q₁₀ 200mg/kg for another month (group 4). Full thickness of uterine wall, there is proliferation, repair, and development of uterine glands (thin arrows), and presence of normal columnar epithelium (green arrows). H&E,10X.

Discussion

Serum level of female sex hormones

The results of present study indicated sex hormones (FSH, LH, estrogen and progesterone) were significantly changed after CoQ₁₀ administration. These changes may be traced to the effect of CoQ₁₀ on the hypothalamus to induce secretion of GnRH and also its effect on pituitary to secrete FSH and LH which in turn stimulate granulosa cells to secrete estrogen. Also the increase of LH hormone in group 2

compared to other groups may increase the level of progesterone because the high level of LH hormone usually leads to increase of its binding with the receptors on theca cells. The increase of LH hormone is considered as a principle factor to stimulate the theca internal to elevate production of pregnenolone compound which converted by granulose cells to progesterone. There were significant decreases ($p < 0.05$) in serum FSH, LH, estrogen and progesterone levels during lead acetate administration. Lead is being one of the reproductive toxicants which has negative impacts on can affect the gonadal structure and functions and ultimately can cause infertility (21). However, results of the present study are in agreement with (21) in which they found that lead salts can inhibit the FSH release. Several studies demonstrated that lead acetate may have an inhibitory effect on FSH and LH hormonal levels via GnRH from hypothalamus (22). Lead acetate considers as a causative agent for decreasing the follicles numbers and size (17). The significant decrease in a level of estrogen after oral administered by lead acetate may due to the effect of lead acetate on FSH hormone from pituitary gland and then on estrogen secretion from granulose cells (5). Lead can cause a reduction in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) binding, which significantly alters steroid production in vitro and exerts a direct influence on granulose cell function (19). Oxidative damage associated with the presence of lead has been illustrated as one possible mechanism involved in lead toxicity (1). (8) suggests that antioxidant might play a role in the treatment of lead poisoning. Animals have protective mechanism in the form of antioxidant nutrients, vitamins and several enzymes. Antioxidant may play an important role in abating some hazardous effects of lead. The body consists of an elaborate antioxidant defense system that depends on dietary intake of antioxidant vitamins and minerals. (3). Results obtained from the present work that showed CoQ₁₀ ameliorated the negative impact of lead acetate for the level of female rats sex hormones. Administration of CoQ₁₀ many improves the levels of FSH, LH, estrogen and progesterone hormones in the animals intubation with lead acetate. The present findings therefore could suggested the ability of CoQ₁₀ to ameliorate lead acetate induced ovarian and pituitary damage. The effective role of CoQ₁₀ in the present study is in accordance with (24) who reported the therapeutic role of CoQ₁₀ against high magnetic induced testicular toxicity. This results may explained that antioxidant activity of ubiquinone could be due to its ability to scavenge singlet oxygen; and structurally affect the lipid bilayer so as to inhibit hydroperoxide decomposition by metalcatalyzed reactions which promote spontaneous lipid peroxidation. (15) showed a reduction of damaged area of corneal epithelium of rabbit eyes which exposed to a source of UVB when it treated with CoQ₁₀.

Histological Findings Of Ovary And Uterus

In the present study there were a normal histological appearance of ovary and uterus in group 1. The treatment of female rats with 200mg /kg CoQ₁₀ showed an increase in numerous of growing follicles and huge griffin follicles. While treatment with 8 mg /kg of lead acetate resulted in appearance of few number of growing follicles and huge griffin follicles. There is normal columnar epithelium which lining the uterus

and there is destitution uterine. Previous studies reported that CoQ₁₀ is a naturally occurring hydrophobic compound that is not only a critical component of the mitochondrial respiratory chain but also a powerful antioxidant. CoQ₁₀ suppresses the generation of ROS by blunting the expression of NADPH oxidase and scavenges lipid peroxidation products during free radical reactions(26).CoQ₁₀ acts as an antioxidant, preventing lipid peroxidation in biological membranes and in serum low density lipoprotein(16). Lead exposure mainly occurs through the respiratory and gastrointestinal systems Some studies suggested that low doses of lead affect reproduction and sexual development in small mammals either directly or indirectly (11). The results of histological section of ovary figures and uterus figures ,showed decrease in a numbers of follicles (primary , secondary and griffin follicles) after intubation rats with lead acetate and the H&E stained slides of group 3 showed damage in uterus structure and distribution of various components. There is an evident damage in all uterus layers and there was hemorrhage in uterine tissue. Uterine glands decreased in size and lumen of uterus in this group also reduced. Several authors reported that the effect of lead on hypothalamus lead to inhibition of GnRH and FSH from pituitary gland (12).while(13) noted that the harmful effects of lead is the result of its effect on the enzyme called alkaline phosphatase , this enzyme necessary for growth and development of ovarian follicles and any disturbance in enzymatic action may lead to reduction of ovarian follicles development.(25) reported that exposure to high lead concentrations caused considerable damage to rats ovaries From the findings of our study, it is clear that the lead also has negative impacts on the developing follicles but the extent of damage increases with time. Theca cells may also be targeted due to the heavy metal injury. Lead is known to disturb the normal profile of reproductive hormones in animals, both at hypothalamic pituitary and at the gonad levels(12). Similarly(9) noted that lead causes reduction in the number of primordial follicles and decrease the number of follicles that enter the growing phase .this may be a possible explanation regarding to the changes that observed in our study Uterus of lead acetate group showed damage in its structure and distribution of various components. There was also an evident damage in endometrial myometrium and perimetrium .Results obtained from the present work showed that CoQ₁₀ ameliorated some pathological changes of the ovary and uterus produced by lead acetate .Ovarian section of rat administered orally with lead acetate for month then treated with Co Q₁₀for another month (group 4). There was particularly recovery in ovarian parenchyma, the sections of uteri revealed there was a normal histological appearance of uterine wall in group4, similar to that of control group . an increase of uterus thickness and increase the number of uterine glands were the most characteristic feature in Co Q₁₀ group. But depletion of uterine glands for lead acetate groups, these results highlighted the involvement of the oxidative stress in female infertility and confirmed the benefits of the use of antioxidants in the medication of this condition .The present findings therefore could suggested the ability of CoQ₁₀ to ameliorate lead acetate-induced ovary and uterus damage. The effective role of CoQ₁₀ in the present study is in accordance

with (9) who found Coenzyme Q₁₀ improves ovarian function may be due to its antioxidant

Conclusions

Coenzyme Q₁₀ has beneficial therapeutic effects on lead acetate toxicity by potentially having antioxidant capacity. Coenzyme Q₁₀ could also be a positive factor in increasing the reproductive efficiency via its effects on the levels of FSH, LH, estrogen and progesterone hormones

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