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Role Of Cadmium In Inhibiting Female Fertility In Wistar Rats

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Abstract:

The heavy metal cadmium is widely dispersed in environment and has no known advantages to humans. Cadmium exposure has been associated with adverse toxic effects in various target organs like liver, kidneys including the ovaries. It is now recognized that exposure of Cadmium to animals and humans must be minimized. Despite the effect of cadmium exposures on female reproduction in animals, only a few studies have been conducted on this topic. The purpose of the present study was to evaluate the effect of vitamins C and E supplementation on Cadmium-treated female wistar albino rats. Therefore, the rats were orally administered different concentrations of cadmium chloride (3/5/7mg/ltr) with vitamins C and E (100mg/kg b.w.) to assess the effect of the vitamins in combating Cadmium-induced cytotoxicity and other manifestations. The tissue and blood samples were taken from the rats for histological evaluation and biochemical analyses after 14 days. Haematological analysis, serum biochemical analysis, histopathology of ovarian, kidney, liver tissues and serum hormonal assays were investigated. Histology of ovary, kidney and liver tissues of the group of female rats treated with 3/5/7mg/ltr showed evident ovary damage. All the experimental groups that were recovered with Vitamin C and E along with cadmium showed significant protective effect on all the biochemical and histological parameters studied. The results obtained in the present study clearly demonstrate that co- administration of vitamin C and E had nearly the same protective effects against Cadmium toxicity at the tissue level. They both have beneficial effects in the amelioration of Cadmium toxicity.

Keywords : heavy metals, cadmium, ovary, cytotoxicity,wistar rat

Introduction:

Heavy elements are present in natural components of the earth's crust, among which the environmental pollutants are the most prevalent. The heavy elements are toxic to humans and animals because they enter and are transmitted to humans through the food chain indirectly. When introduced into the body by ingestion or inhalation in sufficient quantities, they cause various toxic effects (Godt, 2006). These effects arise when biochemical reactions are altered sufficiently and adversely.

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Cadmium was discovered in 1817 in Germany as a by-product of the zinc refining process in an ore. The name cadmium is derived from the Latin word cadmia and the Greek word kadmeia that are ancient names for calamine or zinc oxide. Cadmium (Cadmium; atomic number 48; relative atomic mass 112.40, density 8.64 g/cm3 melting and boiling points 321 and 765°C, respectively) is a rare, toxic non-essential heavy metal, potent environmental pollutant and endocrine disruptor. It has 8 stable isotopes- 106Cadmium, 108Cadmium, 110Cadmium, 111Cadmium, 112Cadmium, 113Cadmium, 114Cadmium and 116Cadmium. Amongst these, the most common are 112Cadmium and 114Cadmium. Cadmium makes up about 0.1 ppm of Earth's crust. It is a member of the family of elements known as transition metals, rare earth metals, and amphoteric oxides and metalloids, which are further divided into lanthanides and actinides. It is a soft, ductile, silvery white with bluish coloured element with lustrous and electropositive properties. It does not have any odour or taste and is very poisonous. It remains considerably in the environment.

The accumulation of Cadmium in the atmosphere is a result of natural and human activities. It naturally settles on Earth through rain or air, enters water through industrial wastes, and gets into soil through the leaching of sewage sludge. Once it touches the ground various green vegetables, root crops, cereals, and grains allows it to move up the food chain. Due to its ductility, good anti-corrosion qualities, and significant properties for the use of metals, such as low melting temperature, cadmium is utilised widely. Forest fire, erosion, withering and abrasion of rocks and soil can release cadmium in atmosphere. Volcanic activity is also the reason for increased Cadmium concentration in air, soil and water. It is one of the main sources of Cadmium's release in atmosphere. It is estimated that the amount of Cadmium released by volcanic activity is between 100-500 tons. Another natural source of Cadmium is the deep-sea volcanic activity. Cadmium is capable of travelling a great distance through water transport. According to Friberg et al., 1974, 1979 the natural water bodies carry less than 1 µ g cadmium per litre and seawater bodies reportedly contains 0.04 to 0.30 µg cadmium per litre. Some metals like Zn, Cu and Pb also contribute in release of Cadmium in environment. It is naturally found in the earth crust mainly in association with the sulphide ores of zinc (Zn), lead (Pb), and copper (Cu). As a byproduct of the breakdown of zinc ore, cadmium is produced. Although topsoil in some paddy-growing regions of Japan is known to contain between 1 and 69 mg/kg of cadmium, natural soil typically has less than 1 mg/kg. Approximately 0.006 to 0.036 µg/m3 cadmium is known to be present in air.

Cadmium is a powerful and harmful heavy metal for female reproduction. (Tchounwou et al, 2012). Many workers have reported its harmful effect on the reproductive system. (Thomson and Bannigan, 2008; Lafuente 2013 and Byrne 2009). Exposure to Cadmium decreases female fertility by inhibiting the function of ovary and development of oocytes, altering ovulation, steroidogenesis, pituitary function, and fertilization. (Sengupta, 2015; Leoni, 2002; Paksy, 1997; Pillai 2002). It is known to negatively impact estrogen. (Stoica, 2004; Ali, 2010) including toxic effects to the ovary (Iavicoli, 2009; Pillai 2010). It is also known to affect the control and synthesis of hormones. Pregnancy rates are decreased. Mammalian's folliculogenesis is harmed by

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Cadmium, which leads to a decrease in the quantity and quality of ovulated oocytes and the failure of fertilisation. Cadmium impairs female fertility via influencing the shape of granulosa cells and the synthesis of steroids, which directly affect progesterone production.

Cadmium hinders synthesis of progesterone by inhibiting the expression of steroidogenic acute regulatory protein StAR and cytochrome P450 cholesterol side chain enzyme P450scc, both of them have an integral role in acute in steroidogenesis. The mitochondrial membrane's ability to transport cholesterol is controlled by the StAR protein (i.e. from the outer to the inner membrane) and The mitochondrial membrane enzyme P450scc transforms cholesterol into pregnenolone. The granulosa cells of the ovary also accumulate cadmium, which causes a large drop in the gonadotropins and a disruption in the function of the steroidogenic enzymes. When high concentrations of cadmium compounds were administered to animals at a late stage of pregnancy, severe placental damage and foetal death were seen. Exencephaly, hydrocephaly, cleft lip and palate, microphthalmia, micrognathia, club foot, and dysplastic tail were among the severe teratogenic consequences caused by cadmium. After taking low amounts orally, there were no teratogenic side effects reported. (WHO, 1992).

Cadmium reduces progesterone's ability to maintain pregnancy, especially during the first 13 weeks of pregnancy, which causes miscarriages. Through its capacity to breach the placental barrier and accumulate in foetal tissues, cadmium can cause miscarriages by impeding the placenta's ability to perform several of its essential activities, including signalling, transporting nutrients, promoting cellular growth and maturation, and secreting hormones and enzymes. Premature births and low birth weights have also been connected to maternal exposure to high levels of cadmium. When cadmium is absorbed by the body, it is deposited in the placenta. If this material gets into the foetal circulation, it may restrict nutrition and blood flow, which will delay growth. The toxicity of cadmium can result in ovarian bleeding and necrosis. In addition to this, it is the cause of spontaneous abortion, longer pregnancies, and fewer live births.

Material and Methods:

1. Experimental animals

For the purpose of study 65 albino rats (7- 8 weeks old) of wistar strain were procured from the animal house of Delhi University, India. Healthy adult female albino rats of 100- 180 grams were selected for the study. The rodents were given the balanced mice diet consisting of carbohydrates (69%), proteins (16%), fats (7%), fibre (6%), mineral salt mixture (2%). The water was given ad libitum. Rodents were maintained in the standard sized polypropylene cages in well-ventilated room. The laboratory conditions were as follows: temperature 23 ± 20 °C; relative humidity 50 ± 10%, Light: Dark cycle 12:12. Before separating the animals into experimental groups, they were acclimatized in the laboratory for about a week. The present experiments were conducted under the supervision of lAEC (Institutional Animal Ethics Committee) of the College. The study was carried out in compliance with the international guidelines for the use and care of laboratory animals in research.

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2. Experiment design

In order to study the effect of Vitamin C and E on Cadmium's toxicity in female reproductive system of albino rats, the following 10 experimental groups were made (table 1). The number of rats in each group was 06. The animals were given different doses of Cadmium chloride and Vitamin C and E orally according to their groups. Distilled water (control)- The animals of this group served as control. Only distilled water was administered orally for 14 days till the end of the experiment. Cadmium chloride (3mg/lit)- The animals of this group were administered orally with Cadmium chloride solution of 3mg/lit concentration ad libitum in drinking water for 14 days till the end of the experiment. Cadmium chloride (5mg/lit)- The animals of this group were administered orally with Cadmium chloride solution of 5mg/lit concentration ad libitum in drinking water for 14 days till the end of the experiment. Cadmium chloride (7mg/lit)- The animals of this group were administered orally with Cadmium chloride solution of 7mg/lit concentration ad libitum in drinking water for 14 days till the end of the experiment.

Table- Number of rats, groups, treatment and doses in the experiment

S.No.	Groups	Treatment	Doses	No. of rats
1	Control Group	Distilled water	Ad libitum	06
2	Experimental group 2	Cadmium chloride only	3mg/ltr	06
3	Experimental group 3	Cadmium chloride only	5mg/ltr	06
4	Experimental group 4	Cadmium chloride only	7mg/ltr	06

DISCUSSION:

Cadmium is a toxic pollutant of the environment that is known to cause cyto-toxic effects in animals. In the present study the effect of Vitamin C and E is seen on female Wistar Albino mice treated with different Cadmium chloride concentrations. Vitamin C and E was used for recovery from Cadmium toxicity. The experimental groups of rats were treated with 3/5/7 mg/ltr of Cadmium for 14 days. The result of this study showed less toxicity of Cadmium in experimental group of rats treated with 3 mg/ltr cadmium whereas severe cadmium toxicity was recorded in experimental groups with 5/7 mg/ltr dose. In contrast the experimental groups administered with

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3/5/7mg/ltr cadmium along with Vitamin C and E showed recovery from cadmium toxicity. No cadmium toxicity was recorded in control group of rats.

The control group had a slight weight gain whereas experimental group treated with 3 and 5mg/ltr cadmium showed weight loss ($p < 0.05$) at the end of the experimental period. The experimental groups of rats treated with high dose of cadmium i.e. 7mg/ltr showed significant ($p < 0.05$) weight loss at the end of experiment. With Vitamin C and E as a supplement along with cadmium chloride water, the animals showed a recovery in weight gain. Similar results were reported by Omonkhua et al. 2007 where cadmium toxicity was induced at low doses (1 to 3 µg/kg b.w.) to rats for four weeks where the administration of Vitamin C and E prevented Cadmium induced weight loss, significantly. Our results are in accordance with Omonkhua et al. 2013 where they have reported that vitamin C prevented the effects of Cadmium on the treated rats, indicating that vitamin C may have protective effect, even against low dosage of Cadmium. Similar body weight change was reported by Nna et al, 2017 where the body weight significantly decreased ($p < 0.001$) in all the treated groups, compared to the control. Since cadmium toxicity causes an animal to feel a great deal of discomfort and distress, this directly affects the animal's food and weight loss. Additionally, cadmium exposure can cause anorexia or an animal's refusal to eat. Induction of oxidative stress by cadmium results in changes in antioxidant status, which cause significant metabolic problems and weight loss. Renuka et al, 2021 also reported that inflammation causes weight loss ranges between 1–20% due to Cadmium induced toxicity or treatment.

The mean ovary weight of the rats of the control group was found to be 38. 87+ 0.28. The ovary weight in group of rats administered cadmium at various doses were found significantly varying. The maximum weight loss (173.84 + 0.72) in ovary was recorded in the group treated with high cadmium dose i.e. 7mg/ltr. The ovary weight was recorded to improve slightly in the group treated with cadmium and Vitamin C and E. Particularly, the group treated with Vitamin E showed a slight better improvement in weight gain of ovary. The relative weights of the ovary decreased significantly ($p < 0.05$) in Cadmium chloride treated group as compared to control but increased in group treated with Cadmium chloride and Vitamin C and E ($p < 0.05$).

The significant histopathological changes in the structure of ovaries observed after oral administration of various cadmium doses especially in the experimental group 4 of rats with the highest cadmium dose, is similar to the changes reported by many other authors (Wang et al, 2015; Samuel et al, 2011; Massanyi et al, 1997). The Cadmium exposed group showed significant ovary damage. It is proved that Cadmium administration leads to degeneration of corpus lutea, damage and less numerous oocytes, and degeneration of granulosa cells. In our study marked degradation of ovary tissues were recorded due to cadmium induced toxicity. The observation of ovary sections of group of rats treated with high cadmium dose i.e. 7mg/ltr shows severe congested blood vessels, follicles and the corpora Lutea. The degeneration of granulosa cells and damaged oocytes were also recorded. According to our findings, the cytoarchitecture of the follicular cells in the ovary of cadmium-treated rats exhibited distortion, but minor or no distortion was observed in the ovaries of cadmium and Vitamin C and E-treated rats. Our findings are entirely consistent with those of a

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related study by Oyewopo et al. From 2020, in which the rats treated with cadmium and Hibiscus sabdariffa recovered and showed a high rate of improvement. In our study, the histopathology of the ovarian tissues with high cadmium doses revealed significant decrease in follicle number as well which is similar to results reported by Nna et al, 2017. No degenerative changes in the ovary histopathology were reported in rats of control group. Significant Cadmium pathological changes in the kidney and liver structure were observed in mice after three months of Cadmium administration. Long-term exposure to cadmium causes kidney pathology. Proximal tubular epithelial cell degeneration is the first sign of morphological changes, which thereafter lead to glomerular sclerosis, interstitial fibrosis, and cellular atrophy. A similar study was reported by Fingerle et al in 1982 where cadmium was given in the drinking water to male and female rats at a dose of 0, 5, 13, 32, or 50 mg/L to for 92 and 84 weeks. It was discovered that dosage increased kidney weights and the frequency of histological alterations in the renal tubules. Bernard et al 1992 reported that cadmium reduces glomerular anion depletion, which is caused mostly by sialic acid loss, and hence improves glomerular filtration. The rats exposed to Cadmium showed histopathological abnormalities in the liver, including severe degeneration, necrosis, depletion, and necrosis of hepatocytes with noticeable nuclear expansion.

A significant decrease ($P < 0.05$) in red blood count (RBC), packed cell volume (PCV) and haemoglobin (Hb) was recorded with animals treated with cadmium as compared to control. RBC, PCV and Hb showed improvement when animals were treated with cadmium and Vitamin C and E. WBC count was increased in cadmium treated animals. Platelet counts decreased in experimental group treated with cadmium. Haematological results of our study are in coordination with the results reported by Alsudani, 2022 where forty adult male rats were divided into five equal groups. There was a significant decrease ($P < 0.05$) in RBC count, Hb concentration, Packed cell volume and a significant increase ($P < 0.05$) in WBC count in cadmium treated animals as compared to control group.

Bernard et al. (1981) produced proteinuria in rats by exposing them to cadmium in drinking-water at a dose of 200 µg/L for up to 11 months. Thus, cadmium produces renal tubular dysfunction in non-human mammalian species that is analogous to the effect in humans of exposure to low concentrations of cadmium. Serum alkaline phosphatase and acid phosphatase were also increased when cadmium at different doses were given to rats. Study indicated that vitamin C and E may have protective effect, even against low dosage of Cadmium (Omonkhua et al. 2013). Our study also suggested that Cadmium toxicity causes significant elevation in liver enzymes like SGOT, SGPT clearly indicating liver dysfunction.

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RESULTS:-

Group 1 served as the control group and photograph below represents ovarian histology of Wistar rats administered only distilled water throughout the experiment. The photograph shows a normal ovary with follicles (F), blood vessels (BV) and corpora lutea (CL) (indicating ovulation).

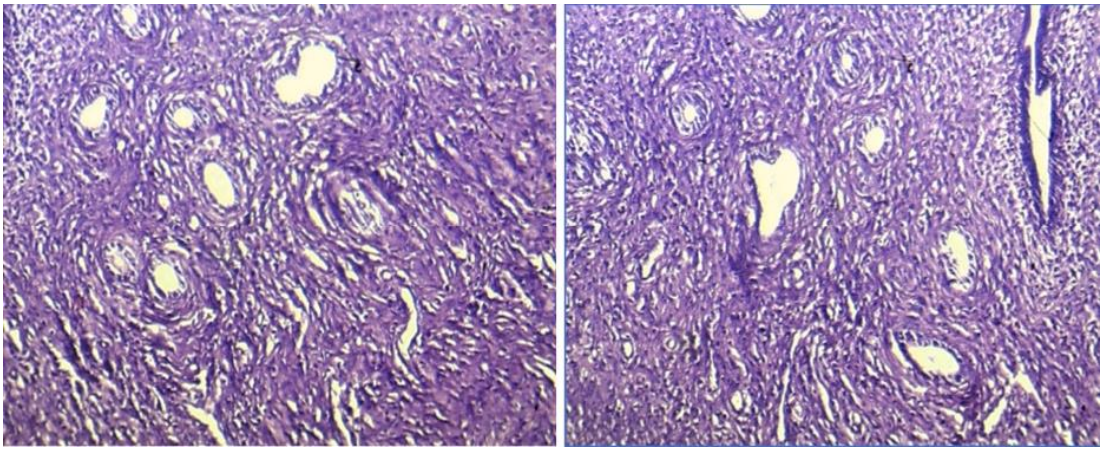

Fig- Group 1 (Control) Histological section of ovarian tissue of rats administered only distilled water for 14 days. Photomicrographs of ovary sections stained with hematoxylin and eosin (magnification ×100). The image shows normal ovary with follicles (F) at varying stages of development, blood vessels (BV), and Corpora Lutea (CL).

II. Experimental group 2- Experimental group 2 was the group of female Wistar rats that were administered 3mg/ltr Cadmium chloride for 14 days.

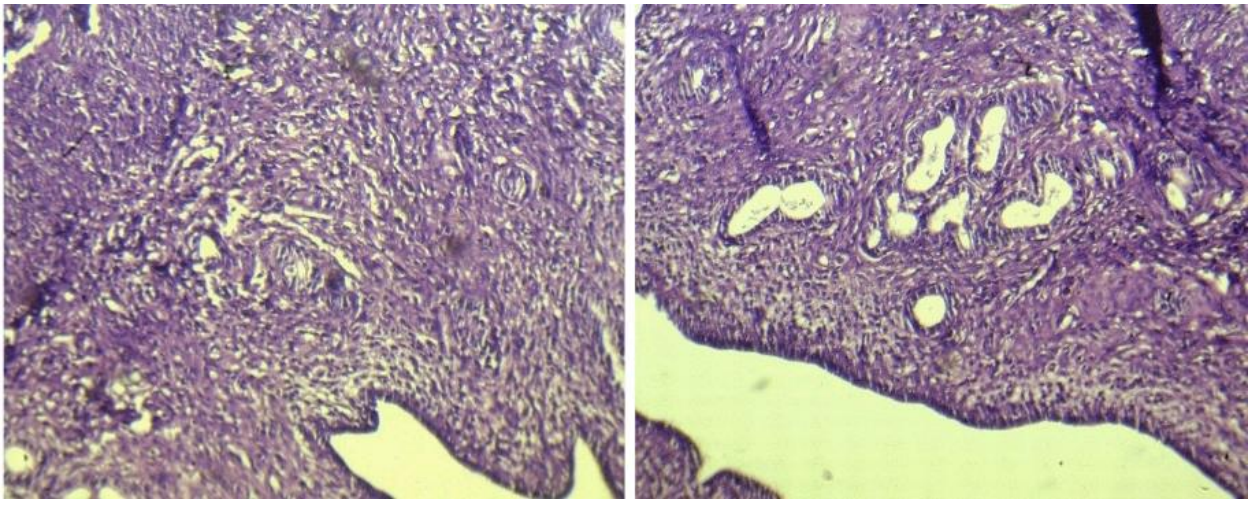

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Fig- Group 2 (Experimental group) Histological section of ovarian tissue of rat administered 3mg/ltr Cadmium chloride for 14 days. The section shows slightly congested blood vessels (CBV), follicles (F) at varying stages of development, and the corpora Lutea (CL)

III. Experimental group 3- Experimental group 3 was the group of female Wistar rats that were administered 5mg/ltr Cadmium chloride for 14 days.

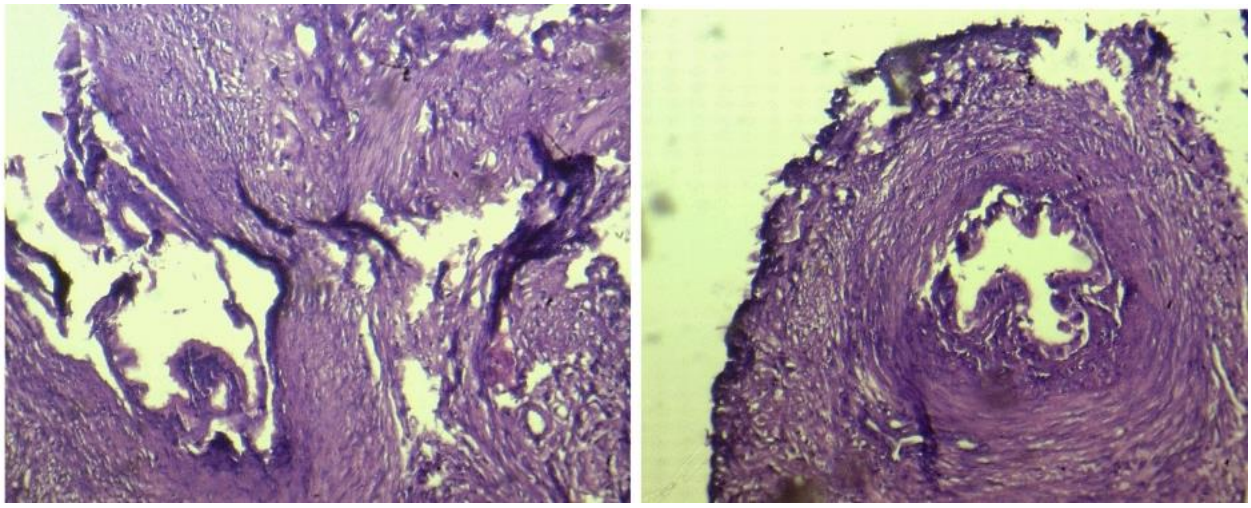

Fig- Group 3 (Experimental group) Histological section of ovarian tissue of rat administered 5mg/ltr Cadmium chloride for 14 days. The section shows characteristic congested blood vessels (CBV), follicles (F) at varying stages of development, and the corpora Lutea (CL)

IV. Experimental group 4- Experimental group 4 was the group of female Wistar rats that were administered 7mg/ltr Cadmium chloride for 14 days. The stronger necrosis and inflammation have been observed in group received 7 mg/ltr Cadmium compared to group with 3 mg/ltr Cadmium ($P<0.05$).

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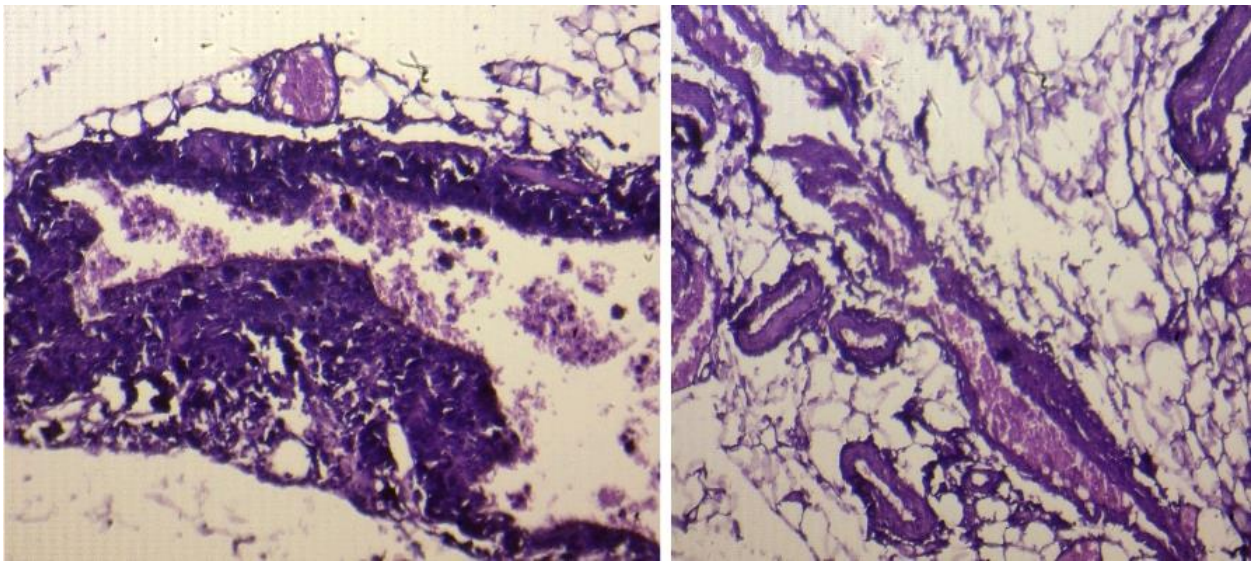

Fig- Group 4 (Experimental group) Histological section of ovarian tissue of rat administered 7mg/ltr Cadmium chloride for 14 days. The section shows severe congested blood vessels (CBV), follicles (F) at varying stages of development, and the corpora Lutea (CL). The photomicrograph exhibits a trogen concentration was observed in female rats receiving the high dose of cadmium chloride (7mg/ltr) Similar results were reported by Oyewopo et al, 2020. There are numerous published results that show cadmium promotes both genomic (Brama et al. 2007; Garcia-Morales et al. 1994; Stoica et al. 2000; Johnson et al.degeneration of granulosa cells and damaged oocytes.

Our results showed that exposure to different cadmium concentrations produced a significant decrease ($p<0.05$) in estrogen, progesterone, FSH and LH levels in female rats as compared to the estrogen, progesterone, FSH and LH levels for female rats in the control groups. These findings revealed endocrine disruption caused by excessive cadmium exposure may predispose organisms to reproductive dysfunctions by reducing sex hormone levels in female rats. In our study a significant reduction in the serum level of Luteinizing and follicle stimulating hormone of the rats were observed that were treated with cadmium (group 2,3,4) when compared with control rats (group 1) In 2004 revealed that vitamin C could be protective against the steroidogenesis by reducing lipid peroxidation when there is cadmium-induced damage. According to experimental investigations on female rats, Cadmium directly affects the shape of granulosa cells and steroid biosynthesis to suppress ovulation and reduce progesterone production (Peter et al, 1995). Another in vivo study on female rabbits reported that when Cadmium chloride was administered at a dose of 1.5 mg/kg, there was a decrease in the number of primary follicles and an increase in the number of atretic follicles in the ovary (Massanyi 2007). Cadmium toxicity prevents ovulation, which causes a tiny amount of corpus luteum to be formed and further lower progesterone levels. Low levels of LH serum, which are linked to the development of large cystic antral follicles, can

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interfere with ovulation. Cadmium has been found to disrupt the hormonal function (Pollack et al, 2014) and is able to inhibit the ovulation.

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