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Original Research Article

Study of the Effect of Nanosilica (SiO_2 NPs) on the Gene Expression of Reproductive Hormones and Fertility in Female Rats

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Abstract: The present research was carried out in the animal facility of the Department of Biology, College of Science, University of Al-Qadisiyah, from January 20, 2023, until June 27, 2023. This study sought to observe the effect of varying dosages of nano-silica (SiO2 NPs) on the gene expression of the genes encoding follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in female rats. The findings indicated marked reduction ($P<0.05$) in the gene expression of both FSH and LH within the treatment groups (T1: 100 mg/kg, T2: 150 mg/kg, and T3: 200 mg/kg) relative to the control group. The most marked reduction was noted within the T3 group, suggesting a dose-dependent response. Histopathological exam of the ovaries, oviducts, and uterus established various structural changes within the dose groups. The ovaries of the T2 and T3 experimental groups had granulosa cell degeneration, massive congestion, and follicular cell deterioration. The oviducts of the T1 experimental group had epithelial lining destruction and considerable congestion, but the uterine sections of the T2 and T3 experimental groups were considered histologically unremarkable. The results imply that the administration of nano-silica may cause widespread alterations in the gene expression of reproductive hormones, potentially resulting in compromised reproductive function and fertility in female rats. Further research is needed to clarify the fundamental mechanism and long -time effects of nano-silica exposure on the female reproductive system.

Keywords: Nano-silica, FSH, LH, gene expression, reproductive toxicity, female rats.

INTRODUCTIONS

Silica nanoparticles, also known as SiO_2 NPs, with a size usually much less than 100 nanometers, have generated considerable attention due to their distinct physical and chemical characteristics. SiO_2 NPs exhibited several advantageous properties along with as a large surface area, biocompatibility, chemical stability, and ease of functionalization. These properties make SiO_2 NPs highly suitable for a wide variety of applications in several sectors [1]. Nevertheless, due to their widespread use, they may have adverse effects and penetrated the body through numerous routes. The small size, capacity to penetrate without difficulty, biocompatibility, and potential to break placental obstructions make NPs source of apprehension regarding their toxicity to humans. This problem mainly relates to the health of the foetus and the reproductive structures of each women and females [2]. Growing public apprehensive surrounded the potential for chemical compounds to adversely enter biological systems, in particular with regards to reproductive and developmental toxicity. This issue arises from the fact that reproductive physiology includes elaborate biological presses that may be disrupted through publicity to environmental contaminants. Additionally, living organisms are most vulnerable to negative environmental influences during their early developmental stages. Nanoparticles can reach the reproductive system through many routes, such as skin contact, oral ingestion, or intestinal exposure, among others [5]. Prior research has demonstrated that the gastrointestinal tract is a significant route for the absorption of nanoparticles. Multiple papers have documented that many nanoparticles may be assimilated from the gastrointestinal system into the circulation and accumulated in tertiary organs. Nanoparticles are often employed in the production of food and drinks. Since 2007, over 72 food and beverage items have been identified as containing nanoparticles. Various nanoparticles, including silver nanoparticles, silica nanoparticles [SiO2], TiO2 nanoparticles, and ZnON

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nanoparticles, are included into meals and medications as constituents [6]. Nanoparticles have had adverse effects on the uterus and ovaries due to their secondary deposition following circulation. Studies have demonstrated that smaller nanoparticles have a greater propensity to collect in the uterus. (7) Pregnant women and their foetuses may face health concerns if they are exposed to zinc oxide nanoparticles before and during pregnancy and breastfeeding. (8) A research discovered the buildup of nanoparticles, Nano capsules, and nanolipid emulsions in certain locations within the ovaries of rodents(2). Several research have explored the immediate and prolonged harmful effects of nanoparticles on the reproductive health of females. These studies have specifically examined the toxicity of nanoparticles on cells, genomes, and organs, which frequently produce reactive oxygen species (ROS) (9,10). Nevertheless, the specific way in which they operate is still not understood and needs more research.

MATERIAL AND METHODS

Experimental Animals

A total of 40 female rats with white fur were utilized. Acquired from the College of Veterinary Medicine at the University of Al-Qadisiyah. The age of the subject is within the range of 90 days, while their weight ranges from 250 gm.

Nano-Silica

The study employed nano silica material sourced from the Department of Biology at the College of Science, University of Al-Qadisiyah. Multiple doses levels (100mg/kg, 150mg/kg, and 200mg/kg) were dosed orally to the experimental models at a dosage of 1ml per animal.

Experiment Animals

The research investigated the influence of silica nanoparticles on the reproductive system of female rats at the University of Al-Qadisiyah. Forty female white rats were maintained in specialized plastic enclosures with optimal environmental conditions, water, and food.

Experiment Design

The current investigation examined the impact of administering nano-silica orally at different concentrations on the efficacy of the female reproductive system in rats. A total of 40 female rats were comprised in the experiment. The rats were placed into four groups, with three rats in each group. Over a duration of four weeks.

- The first group: the control group (C) was not treated with nano-Silica.
- The second group was treated with nano silica at a concentration of 100 mg/kg (T1) at 1 ml per rat per day throughout the experiment period.
- The third group: treated with nano-Silica with a different concentration than the second group. 150 mg / kg (T2) and also given 1 ml per animal throughout the experiment period.
- Fourth group: treated with nano-Silica at a concentration of 200 mg/kg (T3) at 1 ml for each animal throughout the experiment period.

Following the conclusion of the experiment, the ultimate weights of female rats subjected to silica treatment were documented. Subsequently, the rats were euthanized after being anaesthetized with chloroform. Subsequently, the animals underwent dissection, during which the ovaries, uterine tubes, and wombs were extracted and transferred to sterile tubes filled with a solution of formalin (10% concentration). The tissues remained in the formalin solution until the tissue cutting procedure was carried out.

Primers

The primers used in this study are GAPDH gene primer as a Housekeeping gene, LHr, and FSHr genes primers as target genes for LH, FSH and Testosterone gene expression. These primers are designed by using NCBI- Gene Bank data base and Primer 3 plus design online. The primers are used in the quantification of gene expression levels by using qRT-PCR technique based SYBER Green DNA binding dye, which supported from (Bioneer company, Korea), as in the table (1).

Primer	Sequence		Amplicon	NCBI- Reference Sequence
LH receptor	F	ATTTCCTTCTGCTGCTGCTGAGC	110 bp	NM_ 012978.1
	R	TCCTGGGAAGCCATTTTTGC		
FSH receptor	F	AAGTTTTCGCGCTGATGCAG	84 bp	NM_ 199237.1
	R	AAGAATGCCAGCAAGGAGAC		
GAPDH	F	ATGCCCCCATGTTTGTGATG	83 bp	NM_ 017008.4
	R	TCCACGATGCCAAAGTTGTC		

Statistical Analysis

The analyses of data were expressed as mean ± SE. The comparisons between each studied groups were performed with Least Significant differences (LSD). P<0.05was considered probability level using. All the statistical analyses were done by using Pentium-4 computer through the (SPSS program) Statistical Package for Social Sciences (version-21).

RESULTS

Gene Expression

FSH Gene Expression

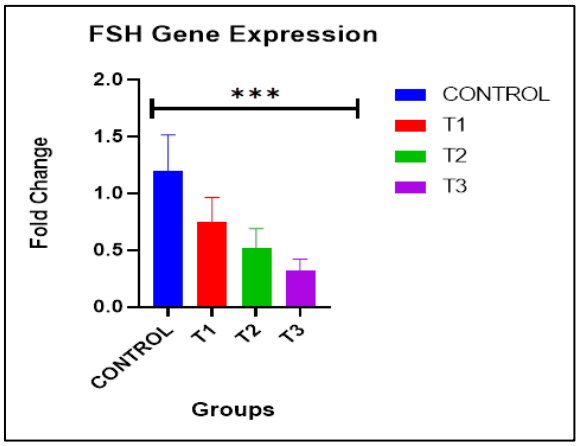
The results of the present study, shown in Table (1) and following figures, showed significant differences in the study of the different genes. The current study showed a significant decrease (P <0.05) in the level of gene expression of the FSH gene in the group of animals

treated with nano-Silica in in T1, T2, and T3 were markedly decreased compared to the control group, with T3 exhibiting the most substantial reduction.

Table 1: Effect of different dose of Nano-Silica on FSHGene expression in female's rats

Groups	FSH mIU/mL
C	1.195 ± 0.321^{A}
T1	0.754 ± 0.210^{B}
T2	0.521 ± 0.172^{C}
T3	0.321 ± 0.101^{D}
LSD	0.012

Numbers Denotes mean ± standard error. Different letters indicate significant differences (P<0.05) between groups. C: Control; T1: SiO2 NPs 100 mg/kg, T2: SiO2 NPs 150 mg/kg, T3: SiO2 NPs 200 mg/kg.



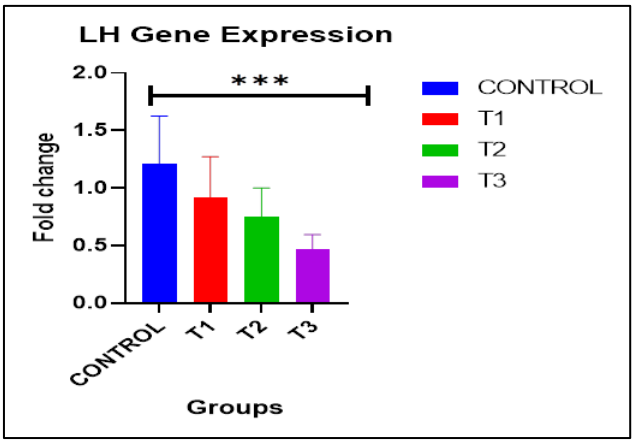
LH Gene Expression

The results of the present study, shown in Table (2) and following figures, showed significant differences in the study of the different genes. The current study showed a significant decrease (P <0.05) in the level of gene expression of the LH gene in the group of animals treated with nano-Silica in in T1, T2, and T3 were markedly decreased compared to the control group, with T3 exhibiting the most substantial reduction.

Table 2: Effect of different dose of Nano-Silica on LHGene expression in female's rats

Groups	LH mIU/mL
C	1.214 ± 0.412^{A}
T1	0.921 ± 0.352^{B}
T2	0.755 ± 0.245^{C}
T3	0.474 ± 0.122^{D}
LSD	0.0214

Numbers Denotes mean ± standard error. Different letters indicate significant differences (P<0.05) between groups. C: Control; T1: SiO2 NPs 100 mg/kg, T2: SiO2 NPs 150 mg/kg, T3: SiO2 NPs 200 mg/kg.



Histopathological changes

Upon the release of the results The histological analysis of the ovaries in female rats revealed that both the control group and the first treatment group (with a concentration of 100 g/kg body weight) had a normal ovarian cortex with a healthy pool of follicles and a significant presence of blood vessels in the interstitial tissue. The treatment groups indicated are T2 and T3. The mature follicle shows degeneration of granulosa cells with mild congestion in the ovaries of the second group T2 females (at a dose of 150 mg/kg of body weight). As seen in Figure 3, there is a noticeable presence of severe congestion and degradation of follicular cells. Figure 4 demonstrates the ovaries of female subjects in the third group, who were administered a dosage of 200 mg/kg body weight, denoted as T3. The histological analysis of the oviduct sections from the control group revealed a normal layer structure, as seen in Figure (5). In addition to experiencing a little hemorrhage. In Figure 6, the group that received a concentration of 100 mg/kg (TI) showed damage to the epithelial lining with severe congestion. Regarding the second and third groups, denoted as T2 and T3 respectively in Figure 7 and 8, The histological analysis of the uterine sections revealed a histologically normal structure. Figure 9 shows a small amount of congestion in control group C. The initial treatment group consisting of 10 individuals will be closely monitored for changes in height. Regarding epithelial cells and severe congestion. Regarding the second and third groups, denoted as T2 and T3 respectively Refer to Figures 11 and 12.

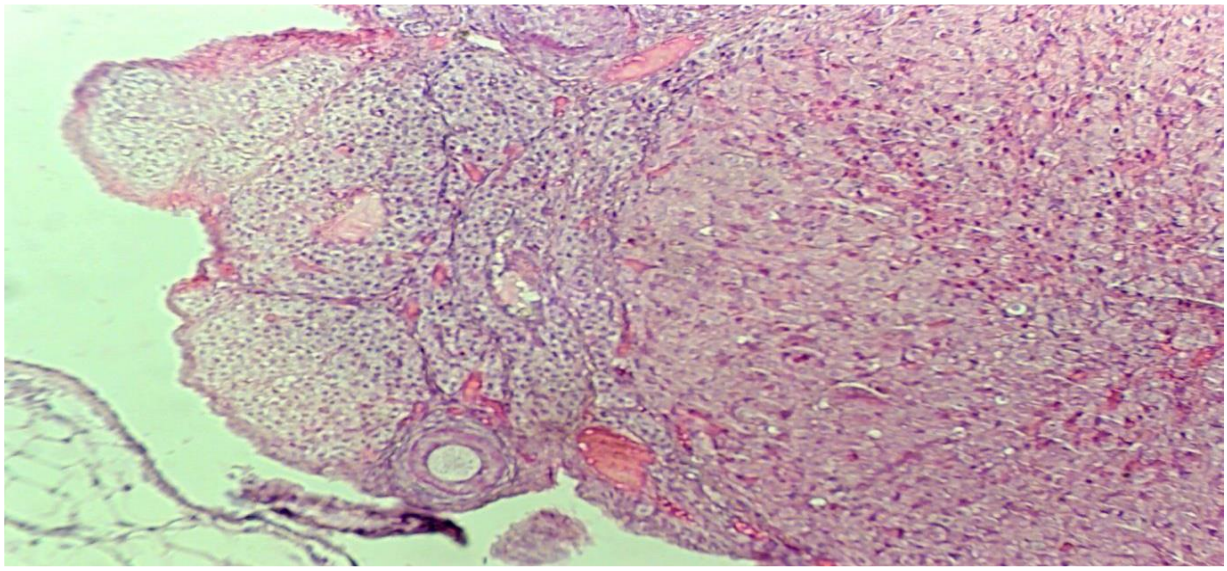


Figure 1: Histological sections of control female's rat's ovaries stained with (H&E) (magnification: ×100) appears normal ovarian cortex with normal pool of follicles and high vascular in interstitial tissue

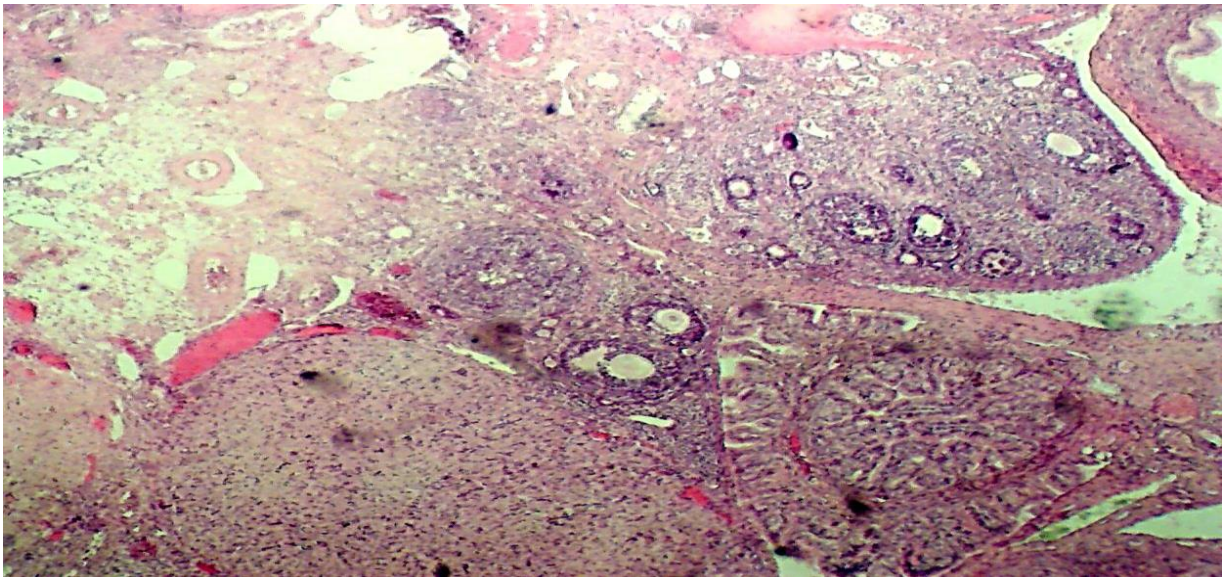


Figure 2: Histological sections of control female's rat's ovaries stained with (H&E) (magnification: ×100) that treated(T1) 100 mg/kg of nanosilica for 4weeks and show normal normal ovarian structure

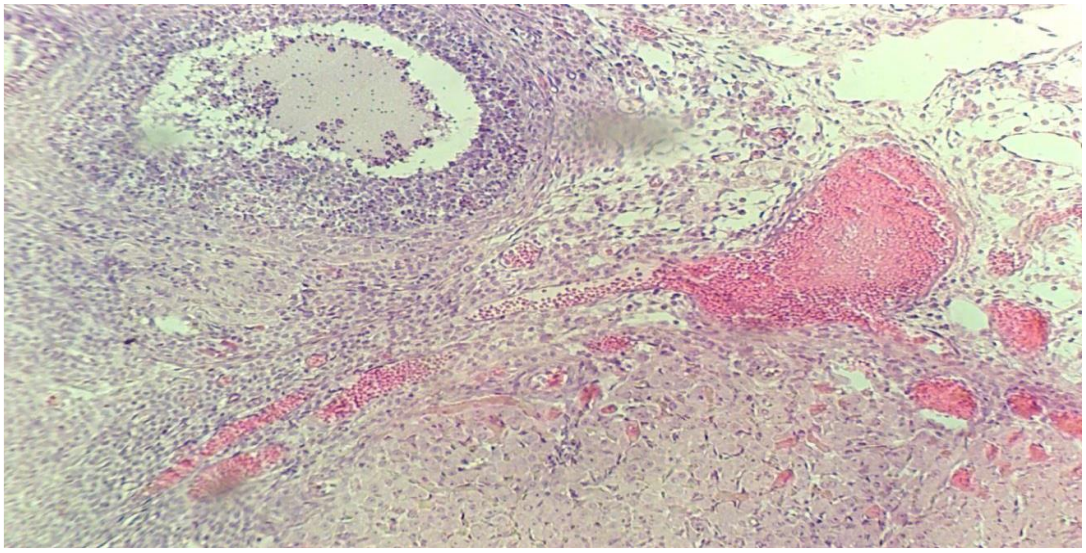


Figure 3: Histological sections of control female's rat's ovaries stained with (H&E) (magnification: ×100) that treated(T2) 150 mg/kg of nanosilica for 4weeks and show degeneration of granulose in mature follicle with slight congestion

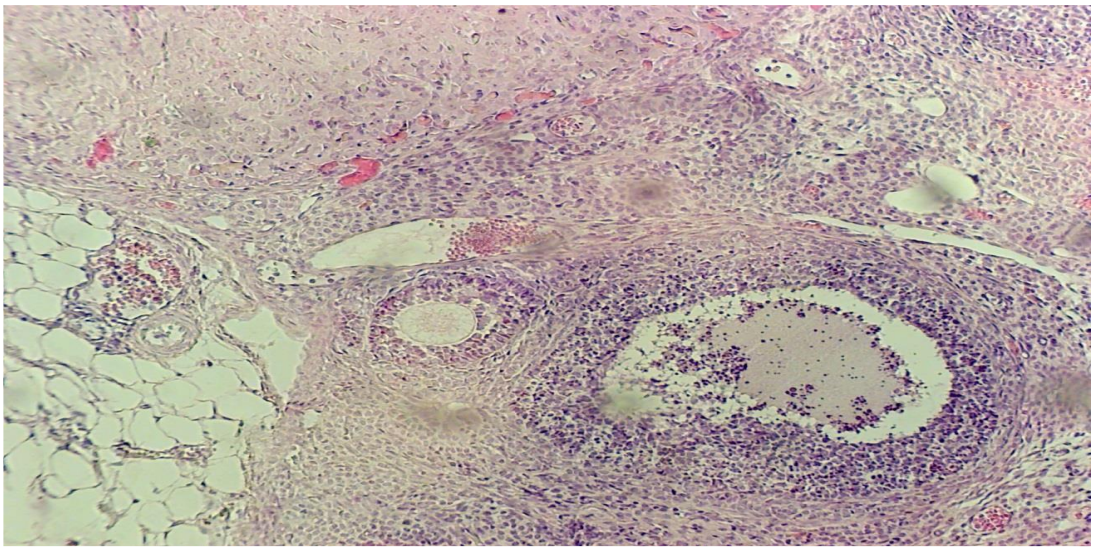


Figure 4: Histological sections of control female's rat's ovaries stained with (H&E) (magnification: ×100) that treated(T3) 200 mg/kg of nanosilica for 4weeks and show sever a congestion and degeneration of follicles cells

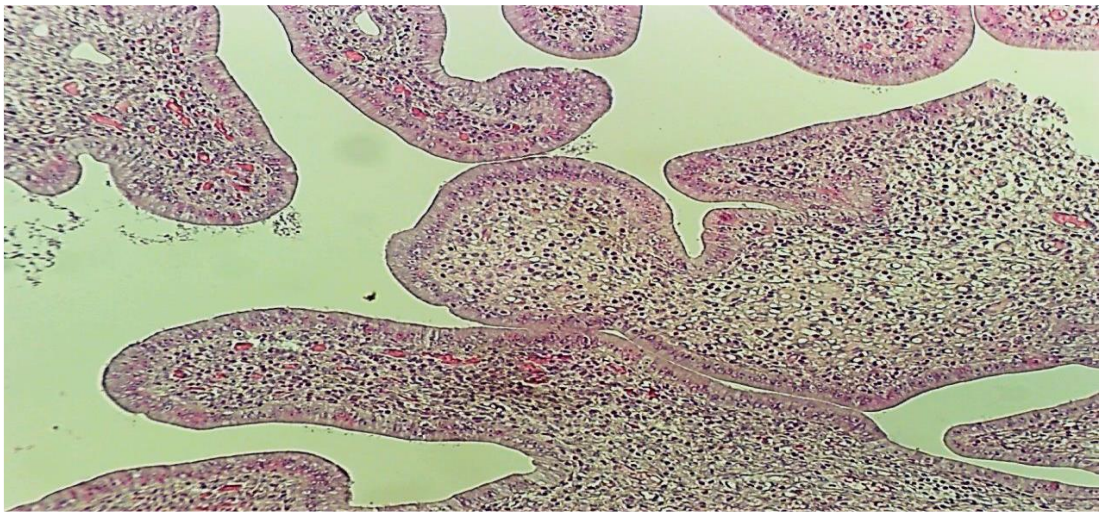


Figure 5: Histological sections of control female's rat's ovaduct stained with (H&E) (magnification: ×40) appear normal structure of layer

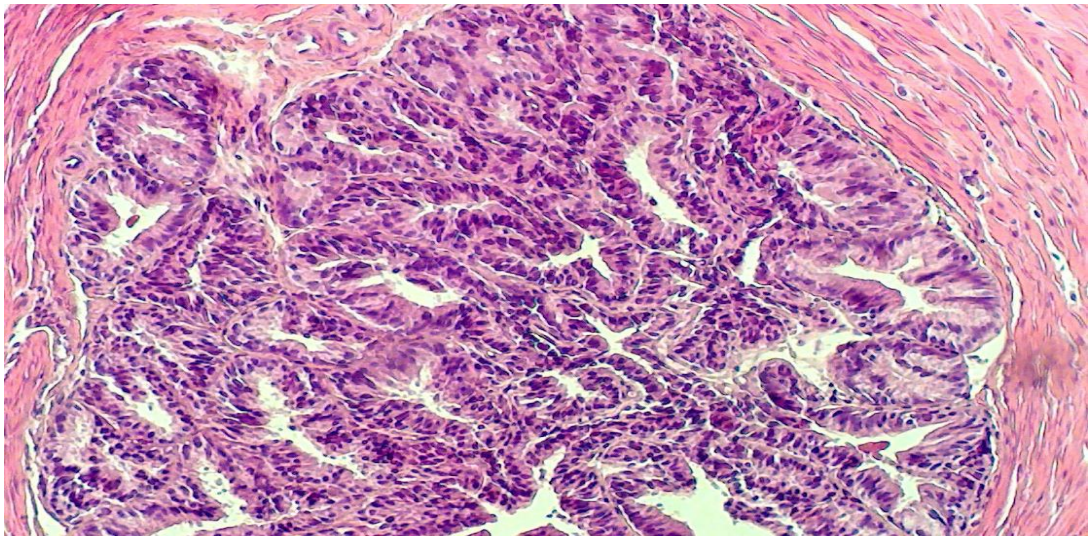


Figure 6: Histological sections of female's rat's ovaduct stained with (H&E) (magnification: ×100) that treated(T1) 100 mg/kg of nanosilica for 4weeks and show slight hemorrhage

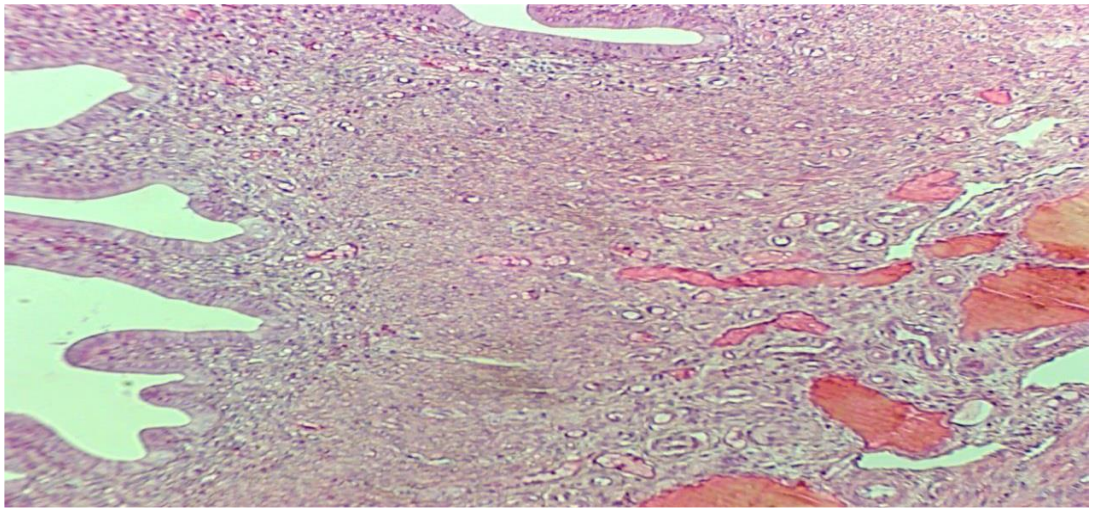


Figure 7: Histological sections of female's rat's ovaduct stained with (H&E) (magnification: ×100) that treated(T2) 150 mg/kg of nanosilica for 4weeks and show sever congestion

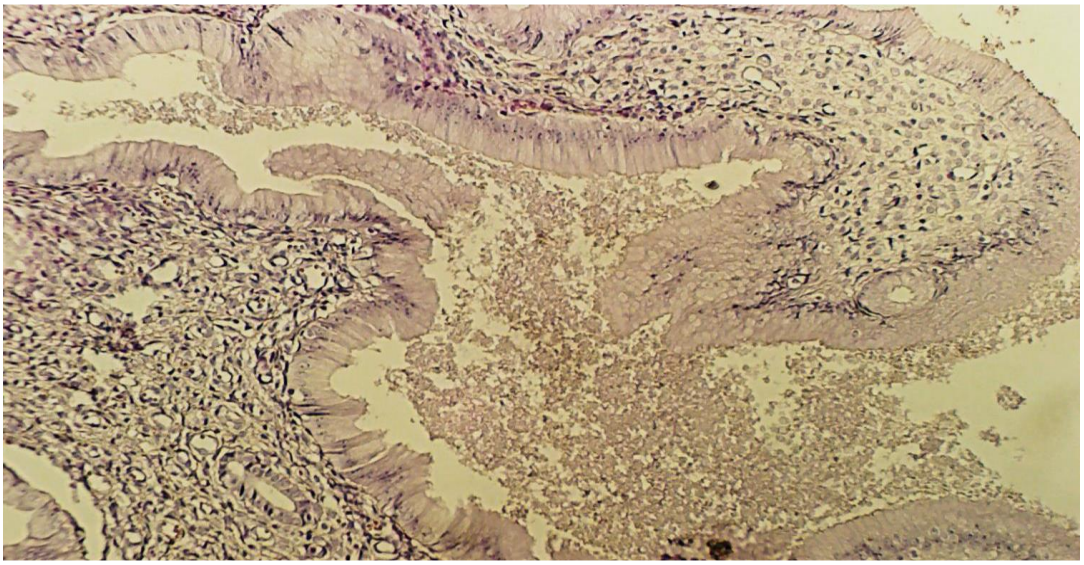


Figure 8: Histological sections of female's rat's ovaduct stained with (H&E) (magnification: ×200) that treated(T3) 200 mg/kg of nano silica for 4weeks and show damage in epithelium lining with sever congestion

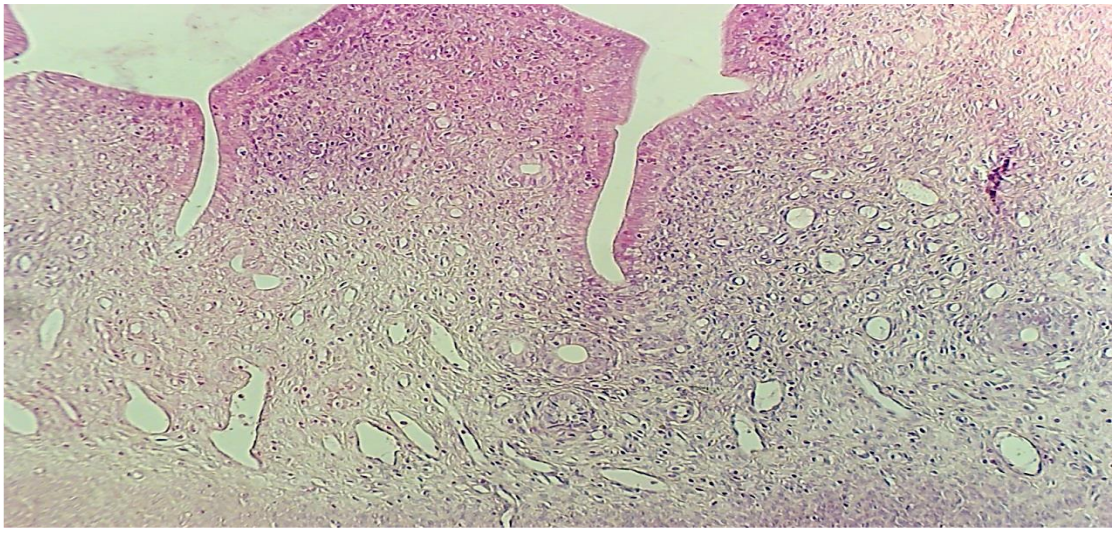


Figure 9: Histological sections of control female's rat's uterus stained with (H&E) (magnification: ×100) observe normal histological structure

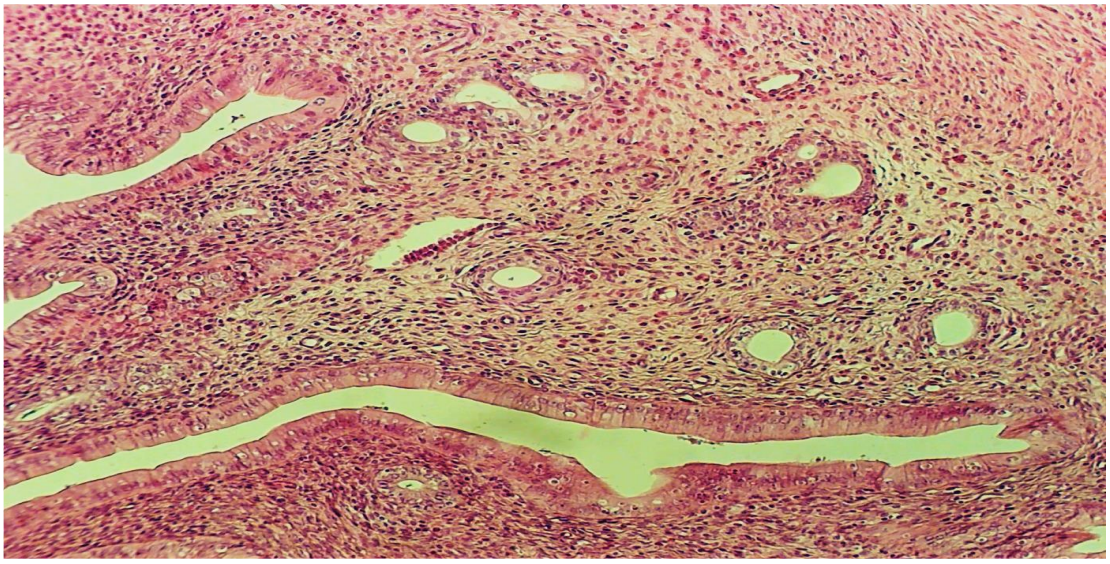


Figure 10: Histological sections of female's rat's ovaduct stained with (H&E) (magnification: ×100) that treated(T1) 100 mg/kg of nano silica for 4weeks show slight congestion

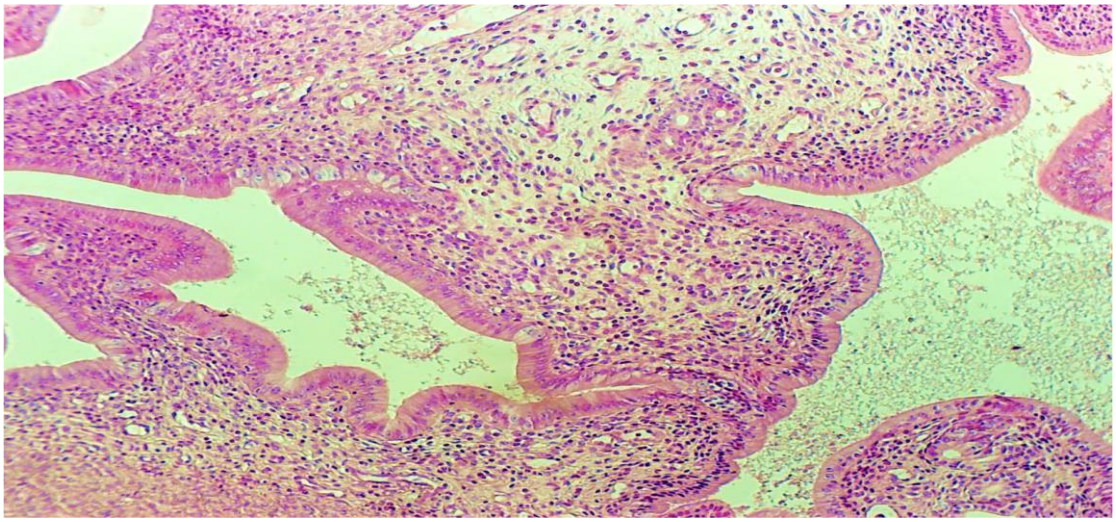


Figure 11: Histological sections of female's rat's ovaduct stained with (H&E) (magnification: ×100) that treated(T2) 150 mg/kg of nano silica for 4weeks show height of epithelial cells and congestion

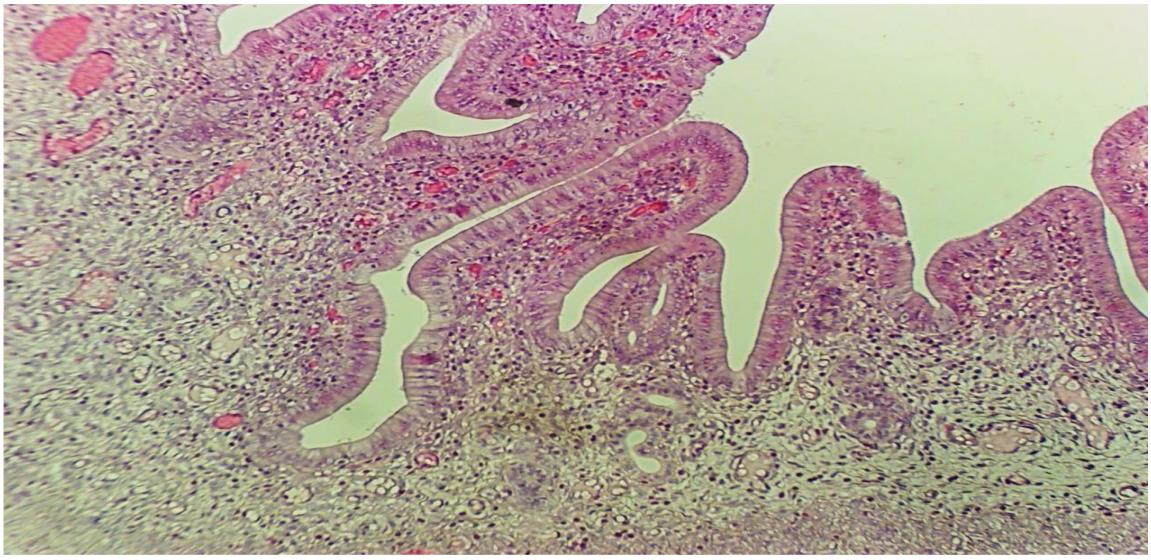


Figure 12: Histological sections of female's rat's ovaduct stained with (H&E) (magnification: ×100) that treated(T3) 200 mg/kg of nano silica for 4weeks show height of epithelial cells and sever congestion

DISCUSSION

This study's results indicate a notable reduction in the gene expression of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in female rats with varying dosages of nano-silica (SiO_2 NPs). This discovery aligns with previous studies examining the effects of nanoparticle exposure on reproductive hormones. Nano-silica is a commonly utilised nanomaterial across several sectors, including cosmetics, electronics, and biological applications. Concerns have been expressed about its possible detrimental consequences on human health, especially affecting the reproductive system [13]. In addition to its clear impact on the female reproductive system, the results of another study conducted by [20] have manifest that silica nanoparticles have also a notable impact on the male reproductive system, as shown in a significant downregulation in sperm concentration, dynamics and viability. In addition, the ratio of abnormal and non-viable sperms in treated groups of mice was much higher than in the control group. The effect of silica nanoparticles on germ cells, which causes an imbalance in spermatogenesis and sperm quality, is presumably.

This work provides significant insight into molecular changes due to nano-silica risk for regulating two essential hormones, FSH and LH in the female reproductive cycle. The decline marked in FSH genes that are listed in treated cohorts in particularly the highest dose group (T3) indicates that the exposure of nano-silica may interfere with the hypothalamic-pituitary-gonadal axis, which controls synchronized production and secretion of these hormones [14]. This is in line with previous research as evidenced by [15], which indicates that the FSH levels in offspring have reduced due to exposure to silicon dioxide nanoparticles during pregnancy in mouse, possibly ovarian function and fertility have been compromised. In addition, prior studies has shown that silica -nanopartical has created reactive oxygen species (ROS), causing oxidative stress and imbalance between antioxidants and free radicals. The dysfunction and cellular damage to the vital organ follow it. Severe degenerative changes associated with high concentrations of this nanopathy and tissue overload supported the harmful effects depending on their dosage [18, 19, 21]. These mechanisms can also explain the side effects seen on the reproductive system in the current study.

LH gene expression mentioned in treated groups, especially important in the T3 group, confirms the concept that the exposure of Nano-Silica interferes with general hormonal control in the female reproduction system. Luteinizing hormone (LH) is essential for ovulation and the sustenance of corpus luteum function; its disturbance can profoundly affect female fertility. The dose-dependent characteristics of the observed effects indicate that the highest dosage (T3) produces the most significant decreases in FSH and LH gene expression, implying a clear correlation between nano-silica toxicity and the given dose. This conclusion corresponds with the increasing data suggesting that the detrimental effects of nanoparticles are frequently dose-dependent [13].

The methods by which nano-silica exposure affects FSH and LH gene expression remain inadequately clarified in the present investigation. Recent study offers insights into possible paths. Nano-silica has been demonstrated to provoke oxidative stress, inflammation, and death in several cell types, including reproductive organs. These cellular and molecular alterations can interfere with normal hormonal signalling pathways, resulting in the dysregulation of FSH and LH synthesis and release. Furthermore, nano-silica may traverse the blood-testis/blood-ovarian barrier and directly engage with the reproductive organs, possibly disrupting the normal operation of the hypothalamus-pituitary-gonadal axis [14]. Nano-silica may also display

oestrogenic or anti-estrogenic characteristics, hence exacerbating the breakdown of the intricate hormonal equilibrium necessary for optimal reproductive function [13].

Through the results shown above, we note the histological effects of nano-silica, and we note that the group with a low concentration has less effect than in the higher concentration, where we notice the second group T2 with a concentration. 150 mg / kg degeneration of granulose in mature follicle with slight congestion, while the third group T3 (with a concentration of 200 mg / kg of body weight) sever a Congestion and degeneration of follicles cells. We note a slight hemorrhage. In the oviduct of the first group TI (with a concentration of 100 mg / kg of body weight) and damage in epithelium lining with sever congestion. In the third and second group T2 and T3. And height of epithelial cells and sever congestion. In the tissues of the uterus of rats of the second and third group T2 and T3The results of increasing in vitro studies showed that the cytotoxicity caused by silica nanoparticles depends on the amount of dose, the duration of exposure, the size of the particles, as well as the type of cells [16]. One study found that NPs are Accumulation of NPs in rodent ovaries was observed, and this accumulation was determined to be size dependent and limited to special regions of the ovaries [17], NPs can enter the female reproductive system and damage the female reproductive organs and cells, thereby compromising their fertility and fetal development. This study demonstrates that exposure to nano-silica significantly reduces the gene expression of FSH and LH in female rats, with the most substantial effects noted at the highest dosage. These findings have significant significance for comprehending the possible reproductive toxicity of nano-silica and underscore the necessity for more study to clarify the underlying processes and long-term effects of such exposures. Given the increasing use of nano-silica across diverse sectors, it is imperative to prioritise safety evaluations and devise measures to limit possible dangers to human health, especially concerning reproductive health. Continued research, with the establishment of rigorous regulatory frameworks and the integration of safer-by-design methodologies, will be crucial for the responsible advancement and utilisation of nano-silica and other nanomaterials.

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